UNIVERSITÁ DEGLI STUDI DI PAVIA

DOTTORATO IN SCIENZE CHIMICHE E FARMACEUTICHE

XXXI CICLO

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Pd-Catalyzed regioselective C-H activation for the synthesis of potentially biologically active compounds

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A Mamma, a Papà, a Chicca e alla mia bellissima Moglie,
persone senza le quali non avrei realizzato tutto questo
e non sarei arrivato dove sono.

SUMMARY

1 C–H Bond In Organic And Medicinal Chemistry

1.1 Hystorical evolution and early applications in the synthesis of biologically active substances

From the origins of organic chemistry, researchers dealt with the synthesis of new and complex molecules. Despite the variety of applications of organic synthesis, for a long time, it was based essentially on functional group interconversion.[1, 2]

Since the end of the twentieth century, however, in order to minimize the number of steps necessary for a synthesis, chemists have been committed in the study of new methodologies in order to functionalize molecules starting directly from carbon-hydrogen bonds.

All of the approaches which provide the direct functionalization of C–H bonds are called C–H activations.[3, 4, 5]

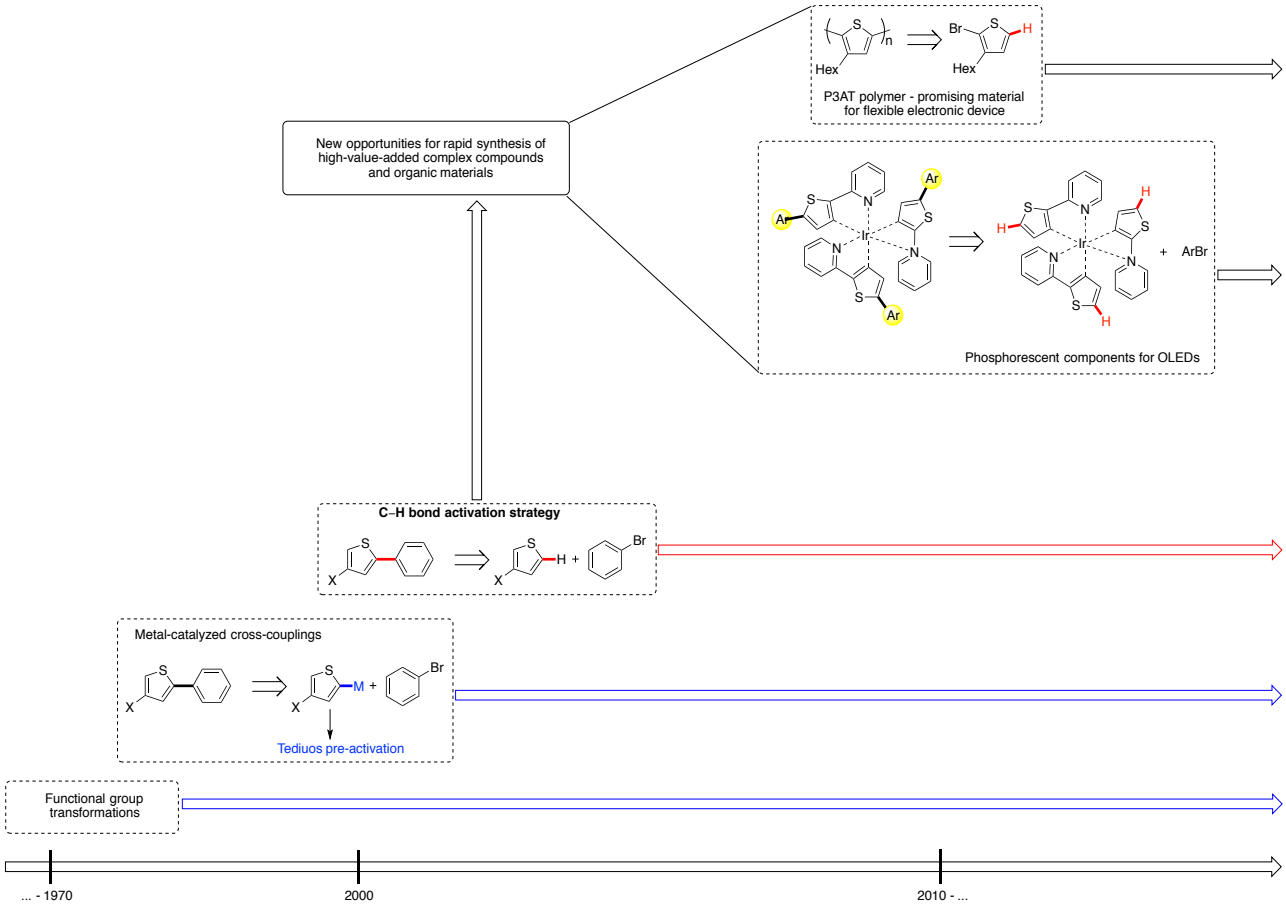

Figure 1 Hystorical evolution of most important reactions in organic chemistry

[1] Corey, E. J.; Cheng, X. M. "The Logic of Chemical Synthesis"; John Wiley & Sons: New York, 1989; pp 1-91
[2] Katritzky, A. R.; Taylor, R. J. K. Comprehensive Organic Functional Group Transformations, 1st ed.; Elsevier: Amsterdam, Netherlands, 2005
[3] Wencel-Delord, J.; Glorius, F. *Nat. Chem.* **2013**, 5, 369-375
[4] Godula, K.; Sames, D. *Science* **2006**, 312, 67-72
[5] Ackermann, L.; Vicente, R.; Kapdi, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826

It is clear that the direct activation of C–H bonds makes the synthesis easier in comparison with a classical one and this is due to shortcuts in the synthetic approach: thus, rendering synthetic routes atom-economical and more straightforward.

For these reasons, the C–H activation has become one of the most popular and rapidly developing fields of organic chemistry in the last twenty years.

The rapid growing of this technique led to the development of an amazing number of reactions that allows the formation of new carbon-carbon and carbon-heteroatom bonds.[6,7]

The impressive growth of these new reactions was further emphasized by their presence in the synthesis of complex biologically active compounds and natural products but also for the applications in different other field including pharmaceuticals, agriculture, food and energy.[8,9]

The capacity to transform a C–H bond in a selective and unequivocal manner opens new routes to virtually unlimited use of this technique and allows the late-stage diversification of different complex molecules.

This new approach, ensuring the diversification of the same starting scaffold, makes it possible to create libraries of compounds to be tested and used especially in medicinal chemistry.

In particular, the C–H activation methodology becomes an important tool for pharmaceutical industries whose goal is the pursuit of new biologically active compounds for use as new drugs.

Thousand research groups, often those from industries, exploit the advantages of C–H activation reactions in order to make the synthesis of this kind of compounds more accessible and scalable to chilogram scale for industrial purposes.

The great advantage of C–H activation strategy is that is not required an organometallic starting material for the transmetallation step whoch is the key step in the traditional cross coupling reactions (we will discuss this aspect in detail in the next chapter). In fact, organometallic reagents are difficult to be prepared and their synthesis is strongly dependent by the substrate that could show complex structural motifs and particular molecular frameworks.

In literature, there are many examples which show the advantages of C–H activation strategy in comparison with classical cross-coupling reactions or other reactions from classical chemistry and the results are strongly in accordance with the state of art in synthetic organic chemistry.

To understand better this phenomenon, a useful example of C–H activation step is exploited in the pharmaceutical research from the Merck laboratories for the synthesis of the GABA α2/3 antagonist, an important compound for the treatment of CNS disorders.[10]

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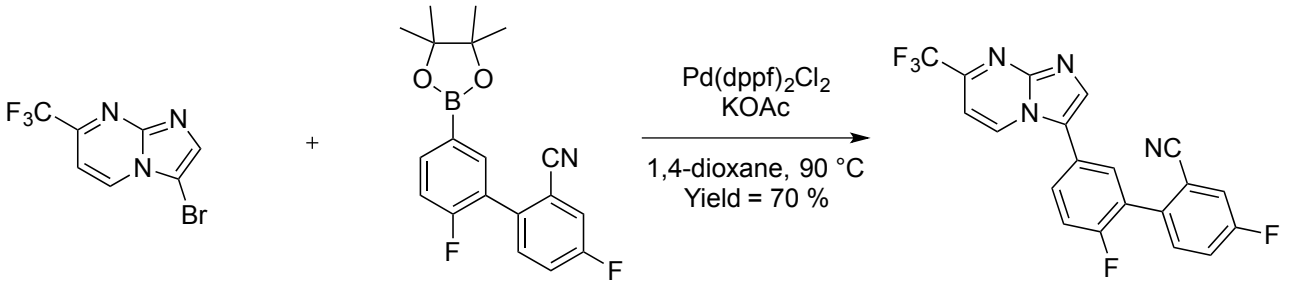
[6] Ackermann, L. *Chem. Rev.* **2011**, 111, 1315-1345
[7] Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, 110, 1147-1169
[8] Yamaguchi, J,; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, 51, 8960-9009
[9] Mcmurray, L.; O'Hara, F.; Gaunt, M. *J. Chem. Soc. Rev.* **2011**, 40, 1885-1898
[10] Cameron, M.; Foster, B. S.; Lynch, J. E.; Shi, Y.-J.; Dolling, U.-H. *Org. Process Res. Dev.* **2006**, 10, 398-402

The main difficulty found in the classical synthetic route is the preparation of the boronate precursor needed for the subsequent Suzuki coupling (Scheme 1).[11]



Scheme 1 Suzuki coupling in the synthesis of GABA α 2/3 antagonist

In according with scheme 3, more than five steps are required for obtaining the desired boronate, and the need of a new strategy that reduce the numbers of steps for this total synthesis is a good chance for the company.

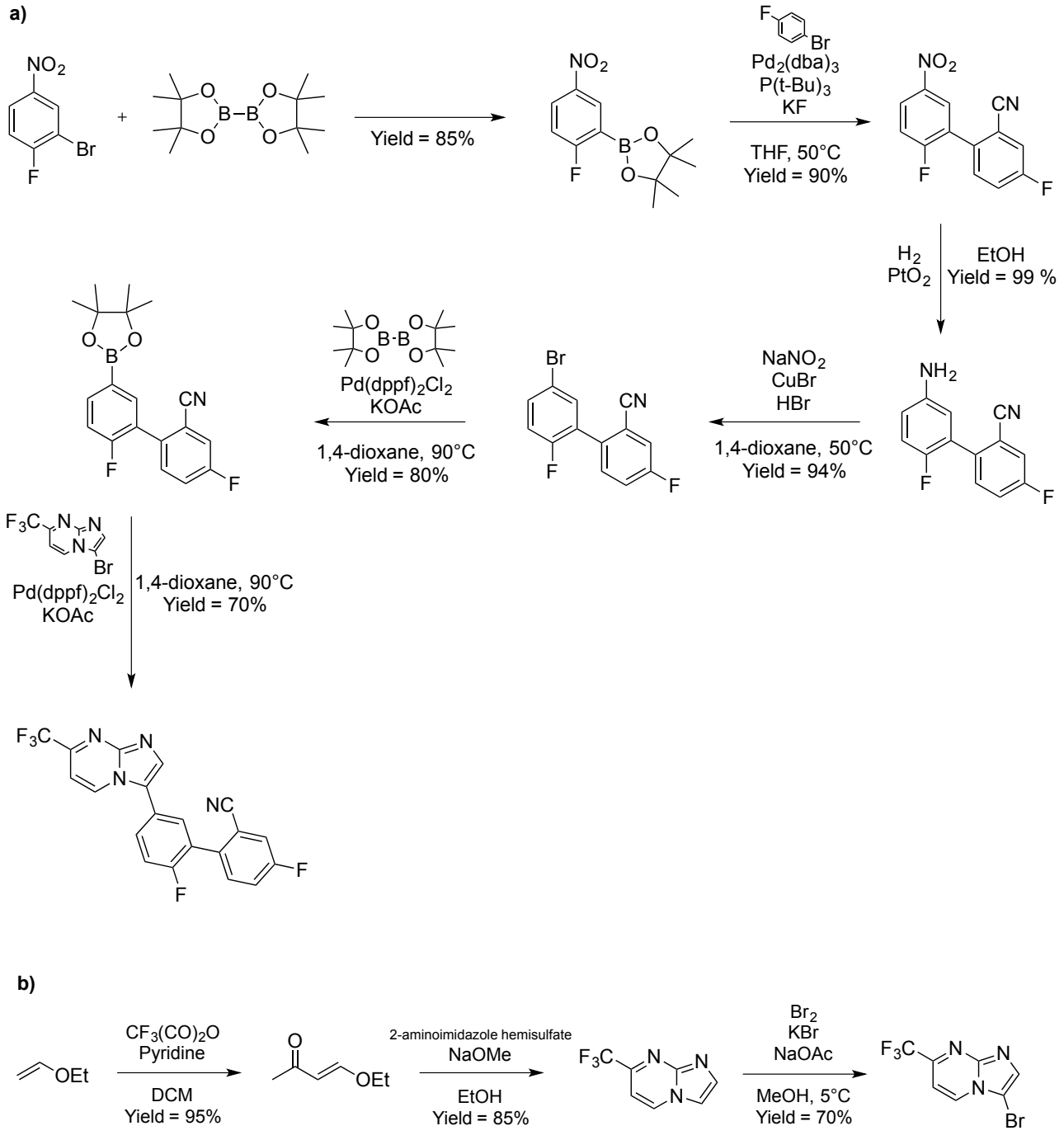
Exploiting the C–H activation methodology, the intermolecular biaryl coupling is performed starting from the (5'-bromo-2',4-difluoro-[1,1'-biphenyl]-2-carbonitrile) which is more easily obtained than the bis(pinacolato)diboron reagent (Scheme 2).

Scheme 2 Synthesis of GABA α 2/3 inhibitor through intermolecular C-H activation

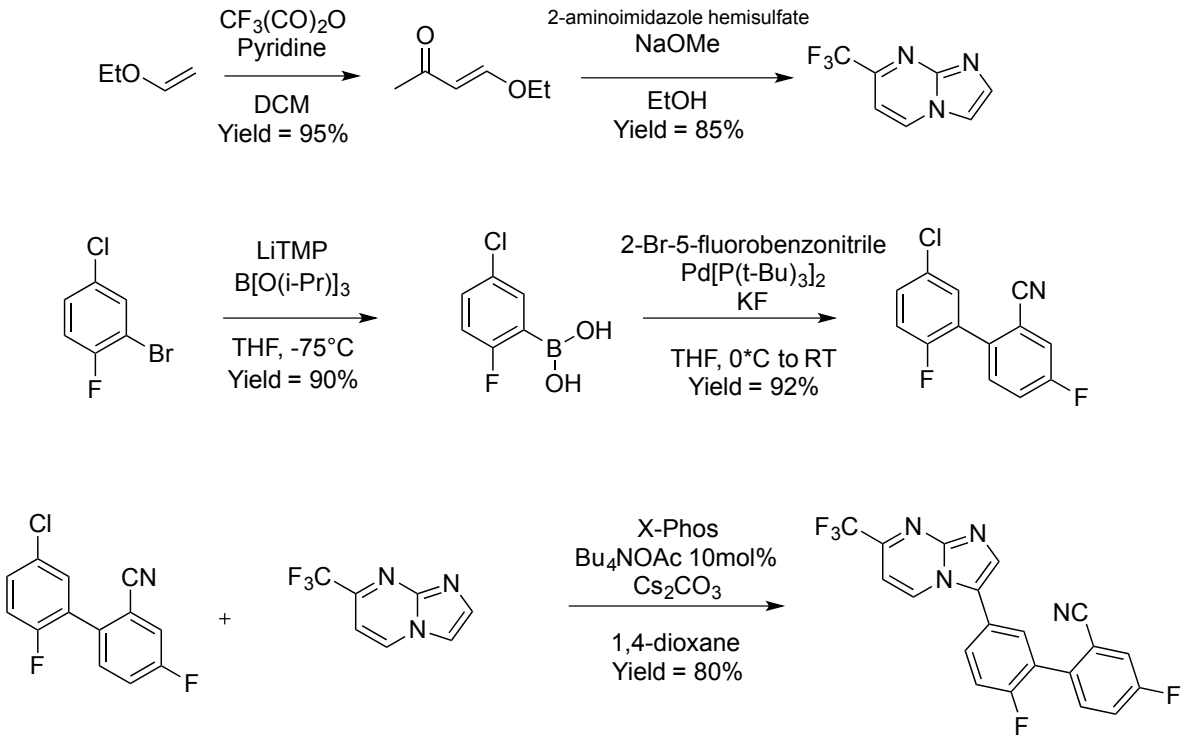
The intermolecular C–H activation reaction affords the target compound in 80% yield and it is suitable for kilogram scale.

In this way, the new synthetic pathway is made only by six steps instead of nine steps necessary with the classic approach performed with the Suzuki cross-coupling (Scheme 3).

[11] Macchia, M.; Cervetto, L.; Demontis, G. C.; Longni, B.; Minutolo, F.; Orlandini, E.; Ortore, G.; Papi, C.; Sbrana, A.; Macchia, B. *J. Med. Chem.* **2003**, 46, 161-168



Scheme 3 a) Synthesis of GABA antagonist with the Suzuki coupling as a key step b) Synthesis of the coupling partner



Scheme 4 Synthesis of GABA antagonist with the intermolecular C-H activation as a key step

The importance of the construction of aryl and heterobiaryl scaffolds, plays a key role in medicinal chemistry: fortunately, a lot of these core structures are easily obtainable with the C–H activation protocol.

The pharmaceutical drug "preclamol" can be synthesized with a C–H activation protocol as described by Yu and coworkers (Figure 2).[12]

Starting from two very simple and cheap commercially available compounds, the authors were able to build the desired heterobiaryl compound, precursor of the synthetic target. The scaffold thus obtained, can be further functionalized and modified with classical transformation well known in organic chemistry (scheme 5).

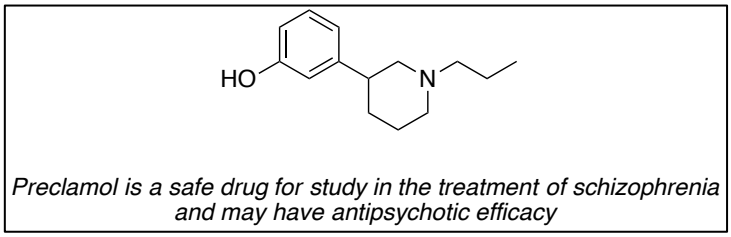
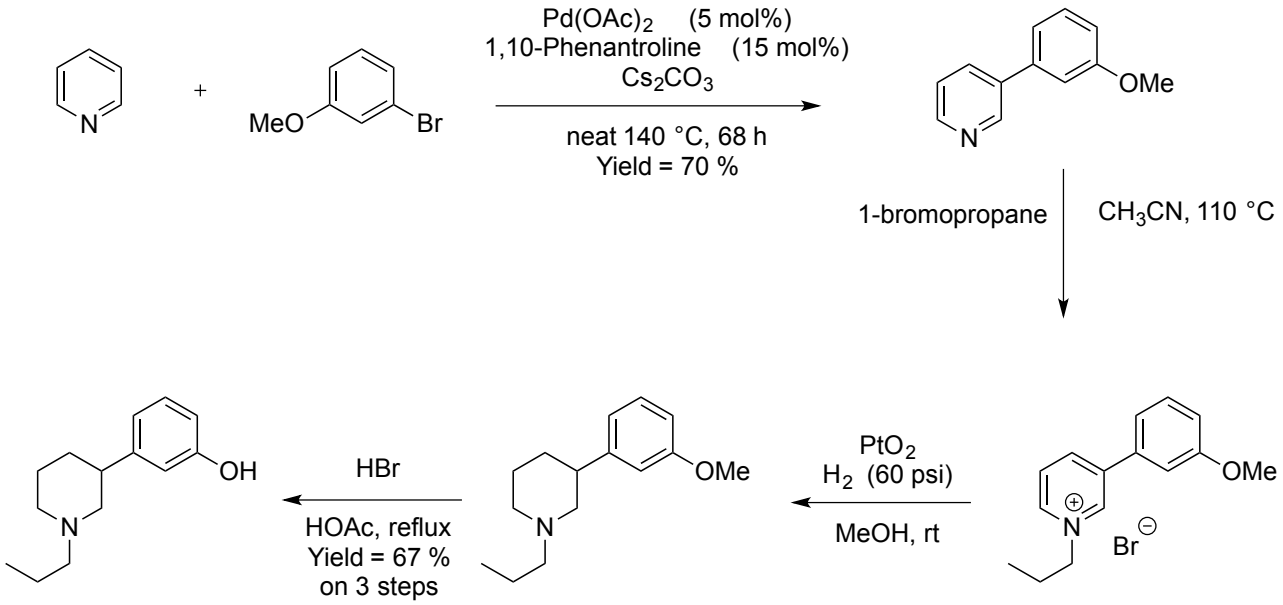


Figure 2 Praclamol drug

[12] Ye, M.; Gao, G.-L.; Edmunds, A. J. F.; Worthington, P. A.; Morris, J. A.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, 133, 19090-19093



Scheme 5 Novel synthesis of the pharmaceutical compound Praclamol

The classical approach for total synthesis of Preclamol needs as starting material directly the expensive heterobiaryl compound: find a procedure like the new one showed above is so a goal for pharmaceutical companies in terms of time and money.

It is clear why, in the last twenty years, the C–H activation methodology has become an important tool not only for the synthesis of new biologically active compounds, but also for the development of new synthetic strategies for the preparation of known molecules with complex scaffolds.

2 From Cross-coupling to C–H activation

2.1 Cross-coupling reactions

Traditional cross-coupling reactions have been, one of the most important synthetic evolution to the classical interconversion approach for carbon-carbon bond formation and in particular for the construction of byaril systems (Figure 3).[13,14,15]

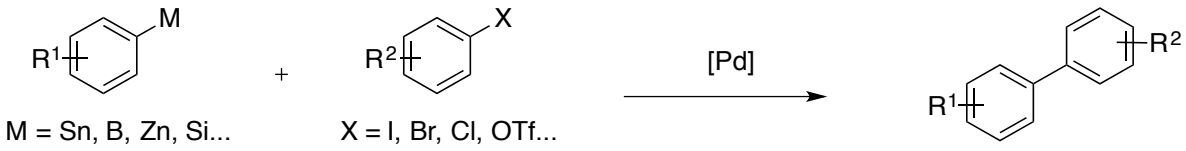
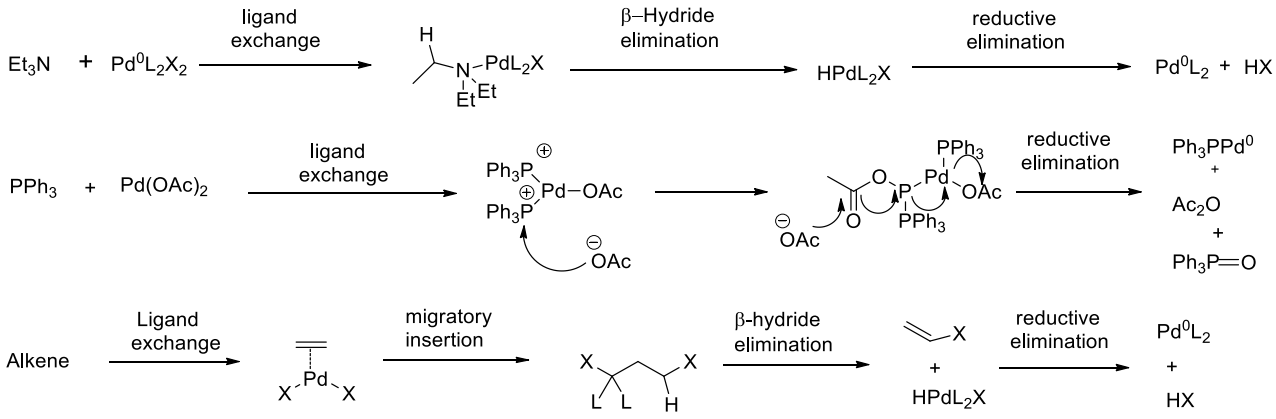


Figure 3 Classical cross-coupling reaction

The first example of these pioneristic coupling reaction was certaintly the Mizoroki-Heck reaction, subsequently, his work led other chemists such as Stille, Negishi, Suzuki and Hartwig to revolutionary discoveries.

In this type of reactions, Palladium is the most widely used metal as catalyst. Palladium chemistry is dominated by two oxidation state: palladium(0) and palladium(II). In a classical cross-coupling reaction, Pd(0) is the catalytic active specie for the process.

In reactions requiring Pd(0), is more convenient to generate it *in situ* from Pd(II) complexes such as $Pd(II)(OAc)_2$ with specifically reducing agents. Any phosphine can be used in the reaction without "*de novo*" synthesis and isolation of Pd(0) species. The reduction of palladium can be achieved also with the cooperative aid of amines, alkenes and some organometallics such as DIBAL-H or BuLi (Scheme 6).



Scheme 6 Mechanisms for in *situ* generation of Pd(0) from Pd(II)

[13] Engelin, C. J.; Fristrup, P. *Molecules* **2011**, 16, 951-969
[14] Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, 48, 5094-5115
[15] Seregin, I. V.; Gevorgyan, V. Chem. Soc. Rev. **2007**, 36, 1173-1193

The mechanism of palladium catalyzed cross-coupling starts, as the Mizoroki-Heck reaction, with the oxidative addition (or oxidative insertion) of Pd(0) in the carbon-halogen bond of the substrate, in order to form the Pd(II) complex (square planar): it can be subsequently functionalized to form the new desired carbon-carbon bond (Figure 4).

In the next step, the transmetalation step, the nucleophile is transferred from the metal (Zn, Cu, Sn etc which depends on the type of cross coupling) in the organometallic specie to the palladium atom: the new palladium(II) complex formed, undergoes a first isomerisation step and then a reductive elimination leading to the desired product.

Palladium(0) is regenerated in the reductive elimination step and is now ready to enter again in the catalytic cycle.

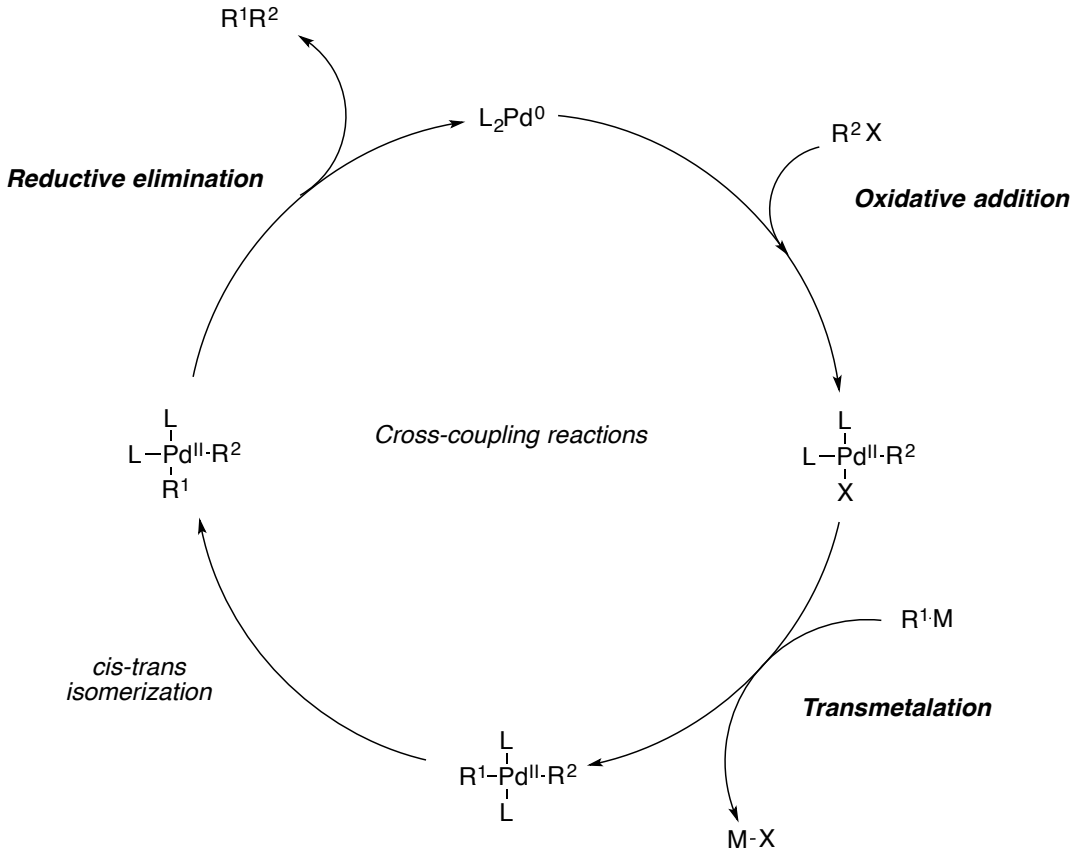


Figure 4 Catalytic cycle for *cross-coupling* reactions

In all the cross-coupling reactions we take advantage of this type of catalytic cycle and the distinction of the various types is due only to the organometallic species used for the transmetalation step.

Thus, the Stille reaction uses the stannanes, Suzuki, the boron derivatives and Negishi the zinc derivatives (Figure 5).

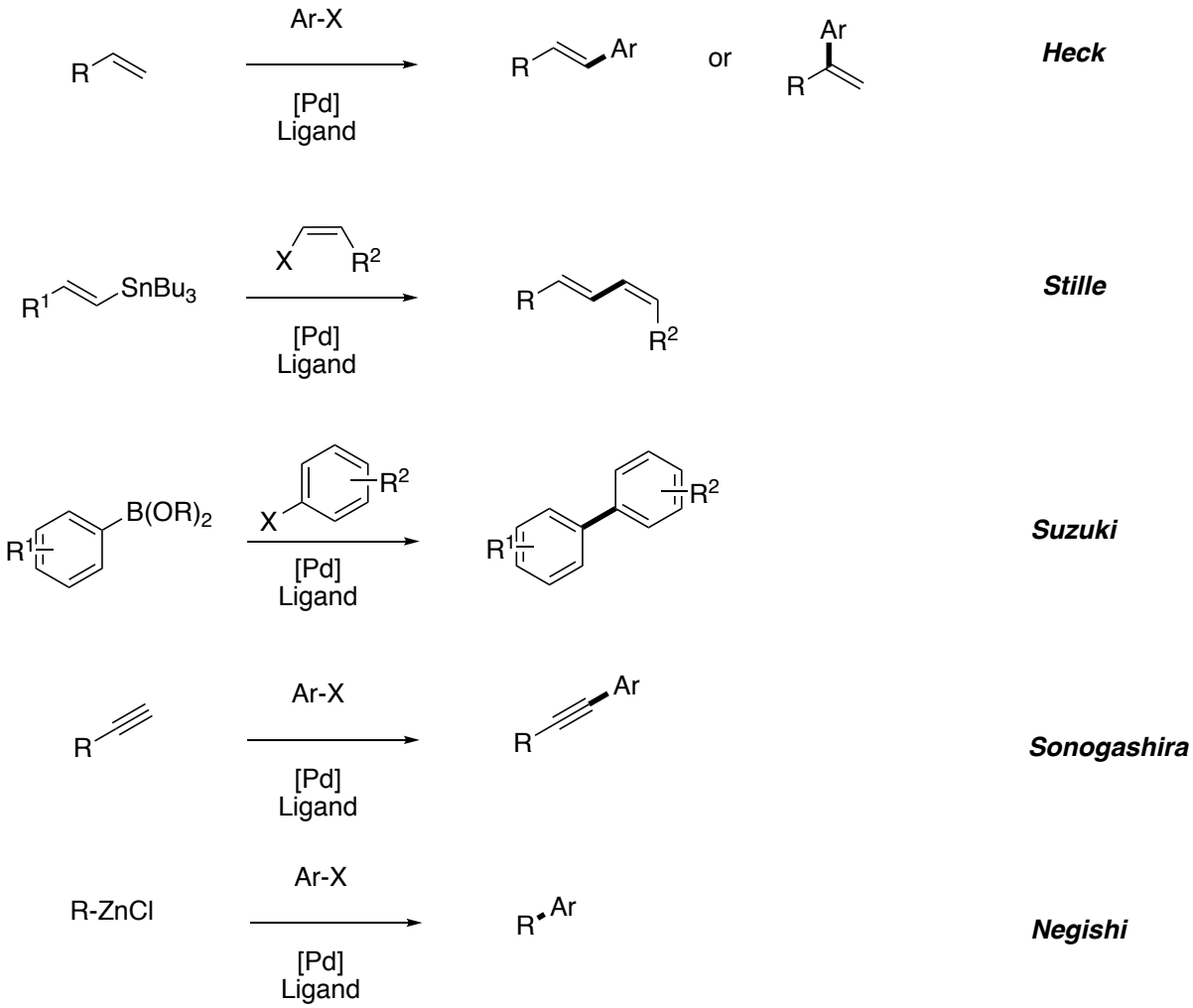


Figure 5 Summary of common palladium catalyzed coupling reactions

It is easy to understand the importance of these organometallic reactions as one of the most important development in the research for new approach for carbon-carbon bond formation, but despite all the potential they have, some limitations still remain a problem.

In particular, these reactions require the formation and use of organometallic species or organic halides often not commercially available and therefore require steps for their preparation and this slows down the synthesis.

Furthermore, some functional groups are not compatible with the reaction conditions required and this makes necessary the use of protection and deprotection strategies that are not in accordance with the principles of atom economy.

2.2 C–H activation reaction

C–H activation reaction represents an evolution among cross coupling reactions, with this methodology is it possible to act directly on the C–H bond without having to first functionalize or modify it.

The term C–H activation means making reactive the C–H bond, which is known to be a particularly stable and inert bond: this is possible thanks to the use of transition metals as catalysts.

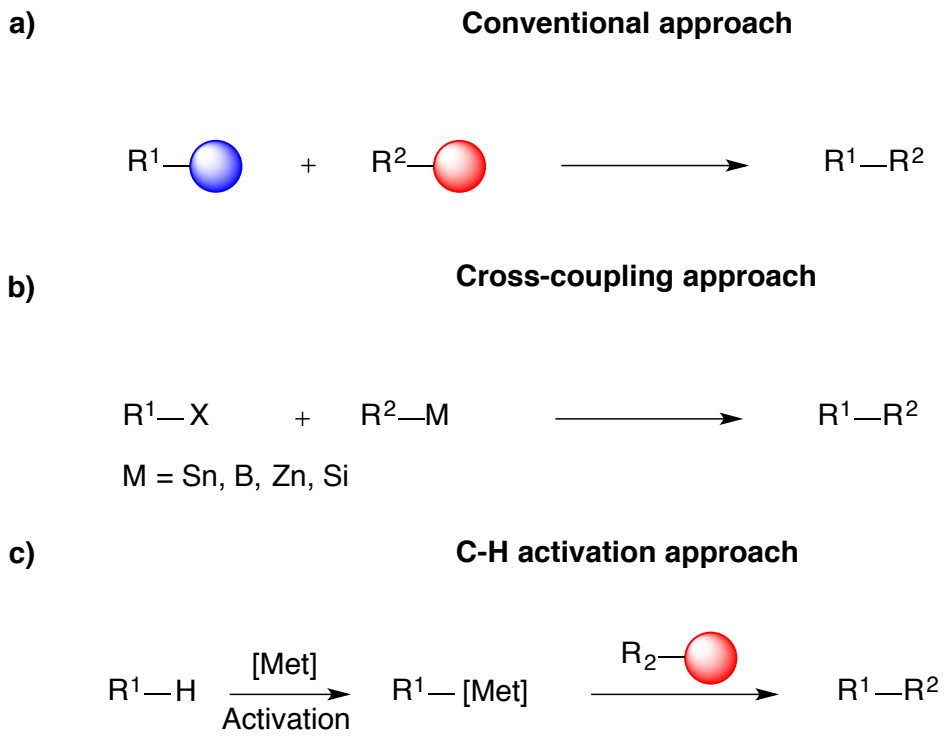


Figure 6 Difference between the installation of functional group by a) conventional interconversion b) classical *cross-coupling* reaction c) C-H activation strategy

It is well known that complexes based on transition metals can react and activate C–H bonds to produce C–M bonds, which undergo functionalization to produce required functional materials.

In particular, in order to activate C–H bond, is quite diffused the use of group 10 metals through the formation of square planar metal complexes.[16]

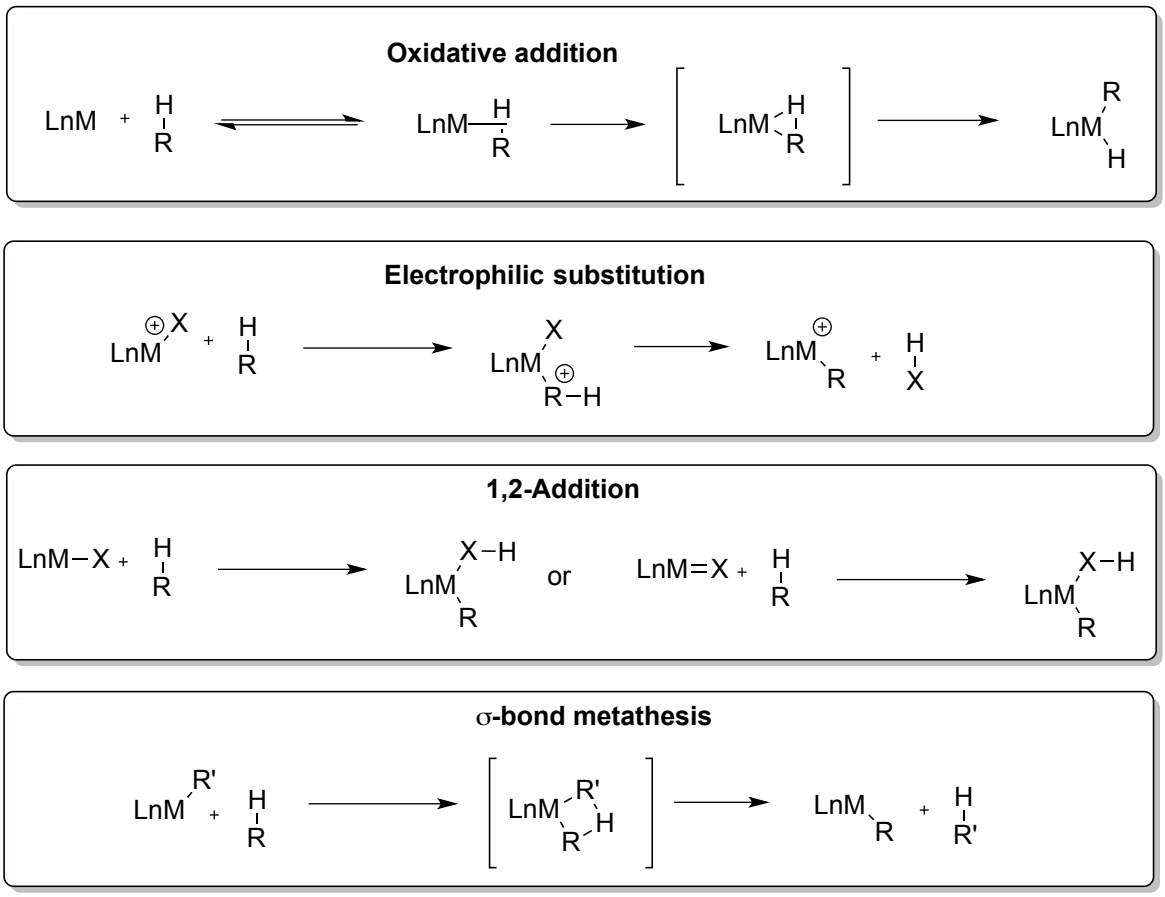
Furthermore, metals of this group have the ability to circumvent the kinetic barrier associated with C–H bond as the activation of the C–H bond is thermodynamically unfavorable.

[16] Engle, K. M.; Mei, T.-S; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, 45, 788-802

In this type of methodology, in the key step of the process, the metal activates directly the desired carbon-hydrogen bond in what is called the metalation step.

This step significantly varies from substrate to substrate, and is also influenced by other factors such as the solvent, additives, the presence of binders and the type of transition metal used.

There are several mechanisms for the activation of C–H bond and over the years were proposed five of these (Scheme 7 and 8).



Scheme 7 Different mechanism for C-H activation

The first and most common mechanism is the oxidative addition which start with the coordination of the C–H bond on a metal vacant site and it ends with the formation of a M–C bond and one M–H bond (it is to be noted that the metal is oxidized, and formally it is a metal oxidative addition in the C–H bond). Shilov and Shul'pin defined this mechanism as a "true metal complex activation" because this metal environment is obtained by a contact between the metal ion and the C–H bond as close as possible. [17]

[17] Shilov, A. E.; Sul'pin, G. B. *Chem. Rev.* **1997**, 97, 2879-2932

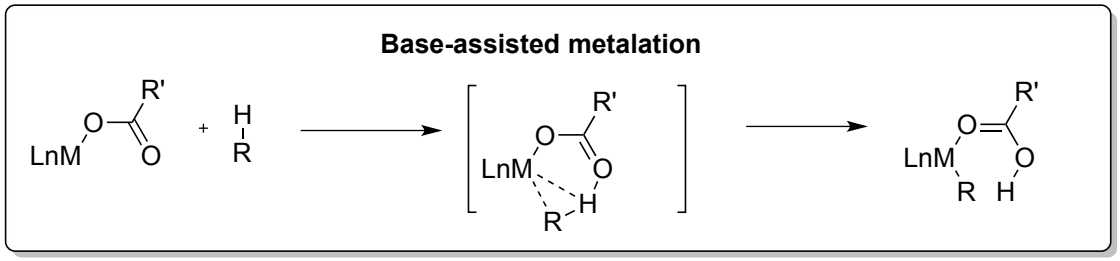
For electron-rich transition metals (called also late transition metals), the oxidative addition is typical because the change of the oxidation state and the change of geometry is not energetically disfavoured. The activation reaction proceeds through the formation of a cycle of three atoms followed by an increase in the oxidation number of the metal of two.

The δ-bond metathesis mechanism is favored with electron-poor transition metals (called also early transition metals) and is characterized by the concerted formation and breaking of the bonds in the transition state of the reaction. In this case, it passes through a transition state with four centers and four electrons with no change of the metal oxidation state.

It is also possible that the metal acts as a Lewis acid and the hydrogen atom of the reagent is replaced by the metal: this mechanism is classified as electrophilic substitution.

The C–H bond can be activated with a 1,2-addition mechanism in which the presence of a couple of electrons on the heteroatom bond to the metal or the metal-heteroatom double bond is fundamental. In this case the new C–M bond is formed without breaking the bond δ M-X.

At least, an important C–H activation mechanism has taken place and takes the name of the base-assisted metalation (Concerted Metalation Deprotonation) (Scheme 8).[4, 18]



Scheme 8 The base assisted metalation process (CMD)

In this process, the bidentate base, acts an important role.

The partecipation of the carboxylate leads to a mechanism in which the metalation occurs in a concerted manner with the deprotonation; the base acts as a proton shuttle helping the formation of the new C–C bond. The base must be bidentate because, in coordination to the metal, take part in the concerted transition state of metalation and dehydrogenation. This mechanism seems to be the more plausible and diffused to explain most of the C–H activation reactions.

In general, palladium (0, II), rhodium (II), nickel (II), copper (II), and ruthenium (II) are widely used in the C–H activation and in literature we found a lot of works that exploit these catalysts in the presence of suitable binders and additives.

[18] Hubrich, J.; Himmler, T.; Rodefeld, L.; Ackermann, L. *ACS Catal.* **2015**, 5, 4089-4093

3 Regioselectivity

The main problem of the C–H activation reactions is that in the same molecule there can be more than one C–H bond and therefore it is important to activate and functionalize only the desired one. Chemists consider regioselectivity the ability of a reaction to proceed with the breaking or the preferential formation of a bond with respect to others.

To solve the regioselectivity problem, three approaches can be exploited (Figure 7).[19, 20, 21]

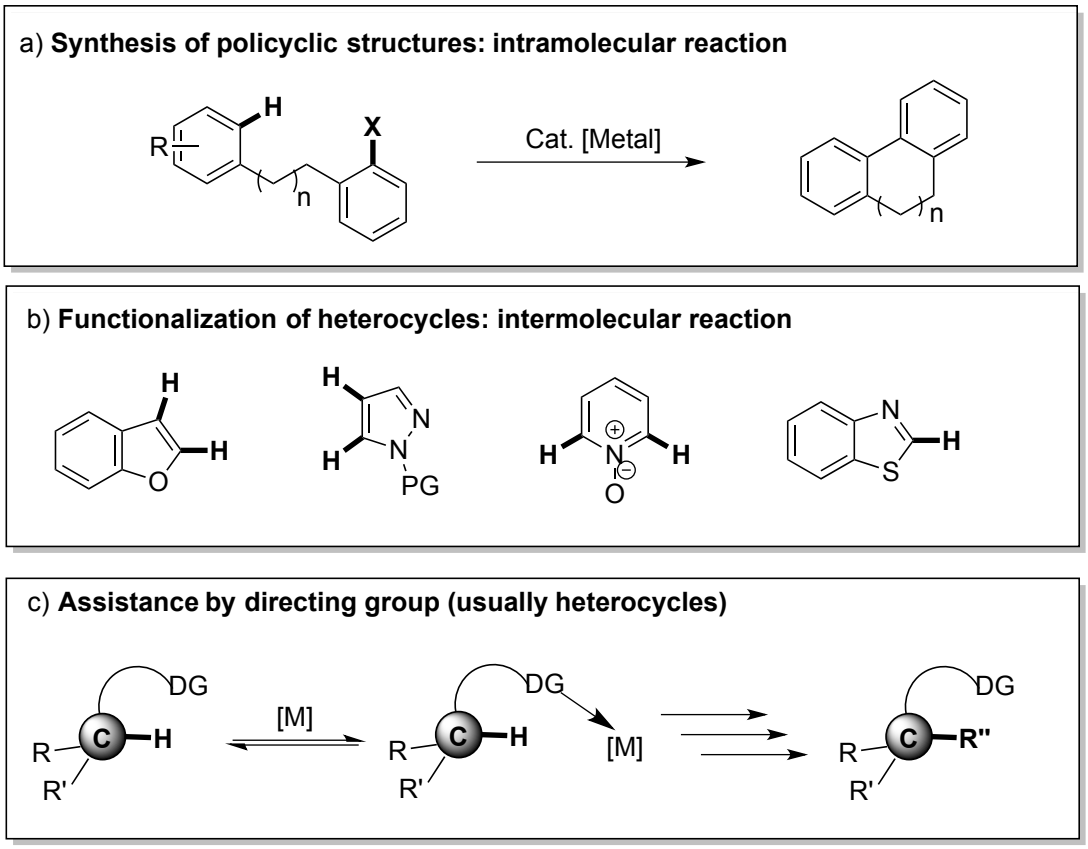


Figure 7 Regioselectivity control

As depicted in Figure 7a, using an intramolecular reaction is possible to force the desired C–H bond to react preferentially due to entropic factor: the substrate should be built in a suitable fashion. In the second case, the reactivity of the heterocycle (or the substrate) itself lead to the functionalized product mainly due to electronic factors; this approach sometimes is present also in the intramolecular reaction and works together with the entropic factors. The last, is an important pathway in molecular functionalization and in particular for the late stage diversification and makes

[19] Althammer, A. *Angew. Chem. Int. Ed.* **2007**, 46, 1627-1629
[20] Althammer, A. Fenner, S. *Angew. Chem. Int. Ed.* **2009**, 48, 201-204
[21] Ackermann, L. *Top Organomet. Chem.* **2007**, 24, 35-60

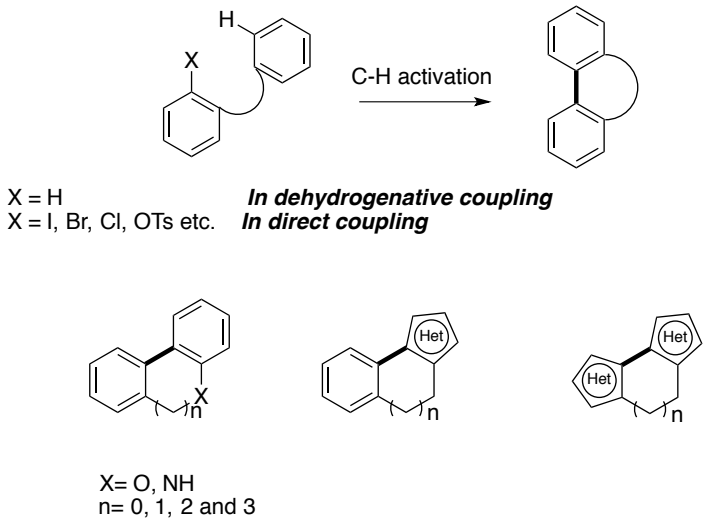
use of directing group, usually heterocycles. In principal, is possible to reach far C–H bonds only by changing the spacer of the directing group.[22, 23]

Is important to underline that the regioselectivity in the C–H activation strategy is firstly influenced by the nature of the substrate which takes part in the reaction, but can be modulated by operating on different parameters.

3.1 Intramolecular C–H Activation

One of the most useful ways to perform a site-selective C–H activation is to exploit the entropically favored intramolecular cyclization.

All the intramolecular reactions are a proof of the synthetic utility of C–H activation reaction: in all these cases for steric and expecially entropic factors, one C–H bond is forced to be involved in the metalation and the formation of the most stable ring results preferred in respect to the other reactions possible. With this approach is possible to obtain five, six and seven membered rings.

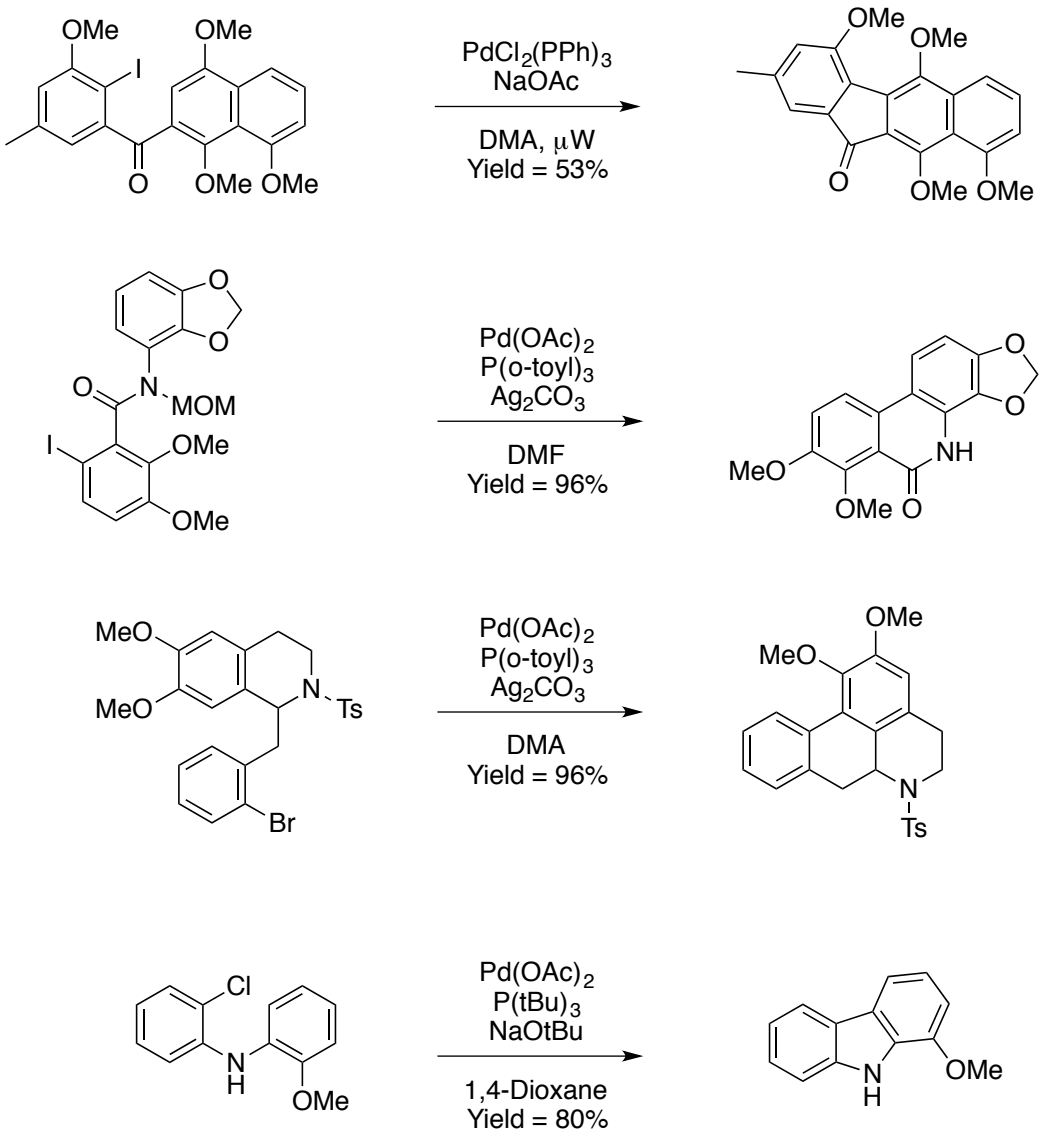


Scheme 9 Examples of intramolecular C-H activation

This methodology is particularly exploited for the synthesis of polycyclic structures containing biaryl systems and heteroatoms: is therefore a classical C(sp^2)–H functionalization.

In literature there are evident examples of this type of reaction that allows to build the core structure of natural products and biologically active molecules already object of investigation (Scheme 10).[24, 25, 26, 27]

[22] Leow, D.; Li, G.; Mei, T.-S.; Yu, J-Q. *Nature* **2012**, 486, 518-522
[23] Lyons T. W.; Sanford M. S. *Chem. Rev.* **2010**, 110, 1147-1169
[24] Quabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, 65, 7187-7194
[25] Harayama, T.; Akamatsu, H.; Okamura, K.; Miyagoe, T.; Akiyama, T.; Abe, H.; Takeuchi, Y. *J. Chem. Soc. Perkin Trans.* **2001**, 1, 523-528



Scheme 10 Examples of intramolecular C-H activation

The effects of the substituents in the intramolecular C–H activation depend on the substrate but is important to underline how in all the reactions there is a great tolerance of different functional group even if are used harsh reaction conditions.

Usually high temperatures are necessary (sometimes also microwave heating) and very concentrated solutions, but in the last years were performed also milder intramolecular C–H activation reactions.

[26] Lafrance, M.; Blaquière, N.; Fagnou, K. *Chem. Commun.* **2004**, 0, 2874-2875

[27] Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, 71, 9403-9410

3.2 Intermolecular C–H activation

In systems such as heteroaromatic rings, the regioselectivity is firstly driven by electronic effects; the basic concept is that the C–H bonds in a molecule present a different reactivity.

This aspect is well desrcibed by some works of Prof. Sames concerning the functionalization of imidazole and pyrazole systems.[28, 29]

Sames and collaborators, showed the different reactivity of the C–H bonds in the case of the pyrazole: is it possible to synthesize 3-substituted pyrazole with complete regiocontrol of the reaction thanks to the SEM protecting group.

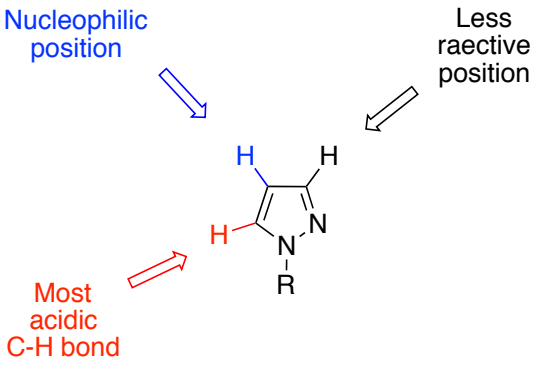
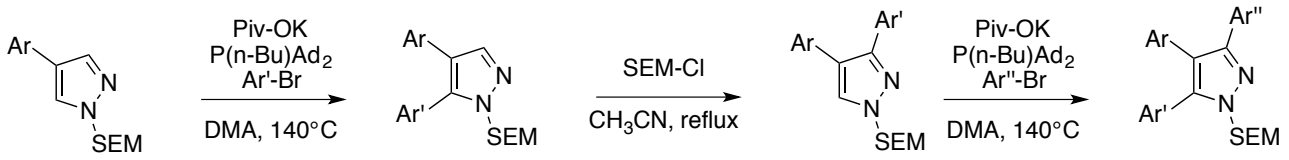


Figure 8 Pyrazole reactivity

In the pyrazole, the C-4 is the most reactive position for the arylation as the most nucleophilic; this is reasonable because of the inductive effect of the nitrogen in position one, which stabilizes the carbon-palladium bond on the C-5 and therefore the metalation to the C-5 appears to be favored by thermodynamic and kinetic factors. The C-5 position is the most acidic and must be activated with the use of strong bases or with the aid of other factors; the C-3 is the least reactive position and also when the arylation is carried out there, the product is difficult to be obtained. The protocol found, allows, first of all, the selective functionalization of the C-5 position, and subsequently the C-3 arylation thanks to the shift of the protective group (Scheme 11).

[28] Joo, J. M.; Tour, B. B.; Sames, D. *J. Org. Chem.* **2010**, 75, 4911-4920
[29] Goikham, R.; Jacques, T. L.; Sames, D. *J. Am. Chem. Soc*. **2009**, 131, 3042-3048



Scheme 11 Examples of transformations on pyrazoles SEM-protected

With this approach is possible to functionalize all the positions with good regioselectivity and permits the preparation of analogous series of compounds.

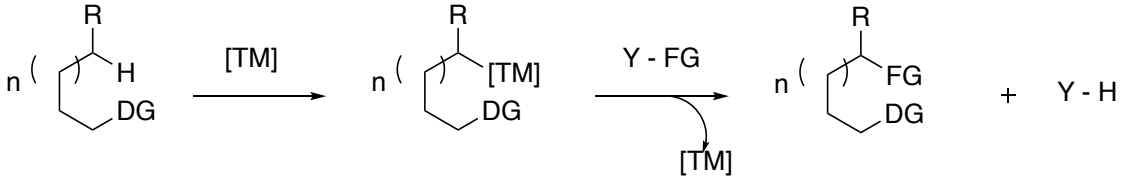
The SEM protecting group's role is fundamental; firstly, it enables the application of the C–H activation protocol to pyrazoles (are not typical substrates for these reactions because of the free NH bond); secondly, through the shift of the same, transforms the unreactive position (C-3) to the reactive one (C-5).

With this example is clear how in the C–H activation strategy the regioselectivity, in absence of directing group or entropic factor, is influenced by electronic factors of the substrate. In literature, there are a lot of examples of this type of C–H functionalization.[30, 31, 32]

3.3 Directing group assisted C–H activation

The regioselectivity can also be controlled by the presence of functional groups in the substrate: the activation of a specific C–H bond is possible due to the presence in the substrate of a chelating or donor group which chelates the transition metal, leading the C–H activation and the subsequent functionalization: this makes the reaction selective. [17]

Directing groups commonly used in C–H activation reactions can be monodentate or bidentate.



Scheme 12 Directing group assisted C-H activation

The monodentate directing groups are those containing a single heteroatom acting as a ligand for the transition metal used to promote the reaction.

The first examples of this regioselective functionalization are those with carboxylic acids and its derivatives as directing group (especially amides). In 2002, De Vries and coworkers took advantage of an amide group for the *ortho* selective olefination of their substrates. [33]

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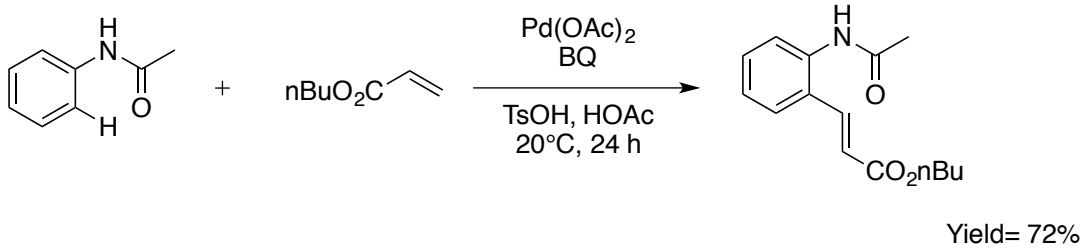
[30] Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *Eur. J. Org. Chem.* **2006**, 3, 693-703
[31] Bellina, F.; Cauteruccio, S.; Mannina, L.; Rossi, R.; Viel, S. *J. Org. Chem.* **2005**, 70, 3997–4005
[32] Bellina, F.; Cauteruccio, S.; Rossi, R. *J. Org. Chem.* **2007**, 72, 8543-8546

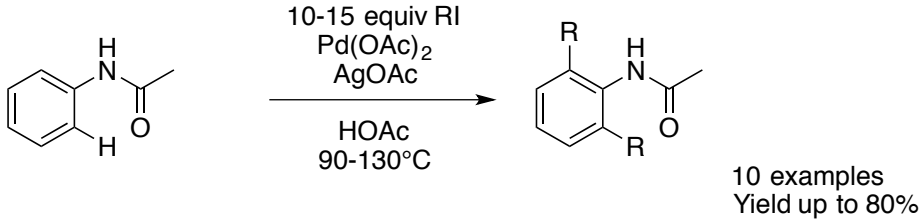


Scheme 13 Ortho-selective arenes functionalization

The studies on the amide group as a directing group in the activation of C–H bonds are also present in the arylation reaction and led to excellent results.

The original Tremont's work shows that a good number of anilides and pivaloyl or acetyl-derivatives were alkylated with alkyliodides to give the corresponding 2,6-dialkylanilides using stoichiometric amounts of silver acetate and palladium as catalyst (Scheme 14). [34]

The products were isolated with very good yields.



Scheme 14 Tremont's ortho-arylation of acetanilides

In both examples showed above, the functionalization is *ortho*-selective and C(sp^2)–H type. In principal, the functionalization tends to occur at the less-hindered C-H bond (and so the *ortho* position to a directing group); to achieve a *meta* and expecially *para* functionalization is necessary a longer and usually different chain in order to chelate the far C–H bond, in the second case the directing group can be considered as a real template.[35, 36, 37, 38, 39]

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[33] Boele, M. D. K.; Van Strijdonck, A. H. M.; De Vires, P. C. J.; Kramer, J. G.; De Vires, J. G.; Van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, 124, 1586-1587

[34] Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, 106, 5759-5760

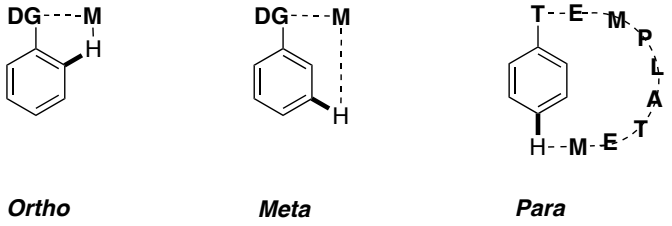
[35] Fang, L.; Saint-Denis, T. G.; Taylor, B. L. H.; Ahlquist, S.; Hong, K.; Liu, S.; Han, L.; Houk, K. N.; Yu, J-Q. *J. Am. Chem. Soc.* **2017**, 139, 10702-10714

[36] Chu, L.; Shang, M.; Tanaka, K.; Chen, Q.; Pissarnitski, N.; Streckfuss, E.; Yu, J-Q. *ACS Cent. Sci.* **2015**, 1, 463-463

[37] Wang, X-C.; Gong, W.; Fang, L-Z.; Zhu, R-Y.; Li, S.; Engle, K. M.; Yu, J-Q. *Nature* **2015**, 519, 334-338

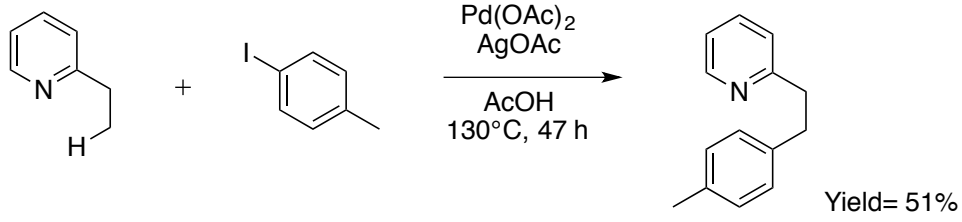
[38] Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, 312 ,1941-1943

[39] Breslow, R. *Acc. Chem. Res.* **1980**, 13, 170–177



Scheme 15 Modifications of directing group

Is clear wht these applications are still in widespread use compared to the simple one: is necessary to create the specific directing group, which should be related to the substrate. By contrast, in most cases, the same *ortho*-selective directing group can be applicable unalterated to different substrates. More fascinating is instead the case of the arylation of 2-ethilpiridine with 4-iodotoluene in the presence of palladium acetate and silver acetate (Scheme 15). [40]



Scheme 16 C-H activation with pyridine as directing group

The reaction seems to proceed through a catalysis of Pd(II)/Pd(IV) and is extremely slow even at 130 °C, but allows to obtain the product with moderate yield.

The yield is lower compared to the C(sp^2)–H examples showed before, but this case is one of the first C(sp^3)–H functionalization which is more difficult to be achieved because of the difference in reactivity of the two bonds. Despite the great developments in the C–H activation field, this activation remains not yet fully elucidated.

Recently, different research groups begin to use bidentate directing groups in order to facilitate the activation of C–H bonds; is possible not only for C(sp^2)–H bonds but also and especially for C(sp^3)–H bonds: this is why this methodology is particularly attractive.

With this kind of directing groups, chemists are able to exploit the potentiality of already used transition metals such as Ni, Pd, Ru, Cu for the common C(sp^2)–H functionalization.

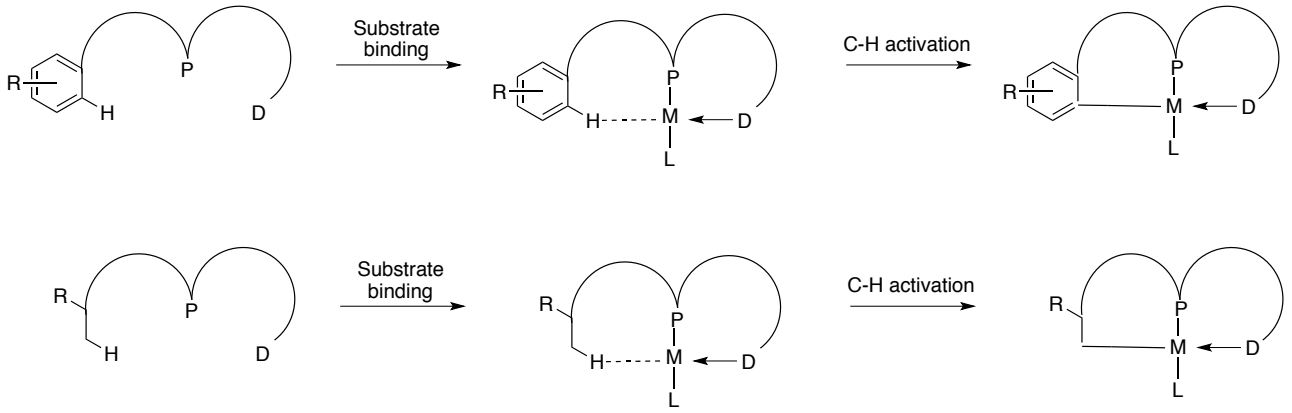
The aspect of novelty for these new directing groups is under spotlight in the work of Hao Tang in which also the reaction mechanism is investigated. [41]

[40] Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, 7, 3657-3659
[41] Tang, H.; Huang, X.; Yao, J.; Chen, H. *J. Org. Chem.* **2015**, 80, 4672-4682

As depicted in Scheme 17, the bidentate directing group has two donor group: the amido ligand wich is deprotonative at the proximal site of coordination (P) and a stronger ligand at the distal coordinating site (D).

The two directing groups bind the metal and help the C–H activation process.

At the end of the process, the metal complex generate before, present the ligand L that acts like a base in the deprotonation process.



Scheme 17 Bidentate directing group assisted C-H activation of C(sp^2)-H and C(sp^3)-H bonds

In literature are reported different of these directing groups, which encourage the research in the field of bidentate assisted C–H activation (Figure 9).

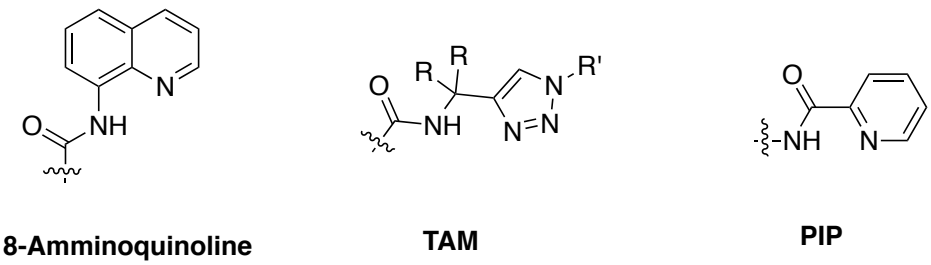


Figure 9 Examples of directing groups for C-H activation reactions

Particularly fascinating is the 1, 2, 3 triazole amide (TAM). [42, 43] With this kind of directing groups is possible to achieve the arylation but also the alkylation with different transition metals and both on C(sp^2)–H and C(sp^3)–H bonds.

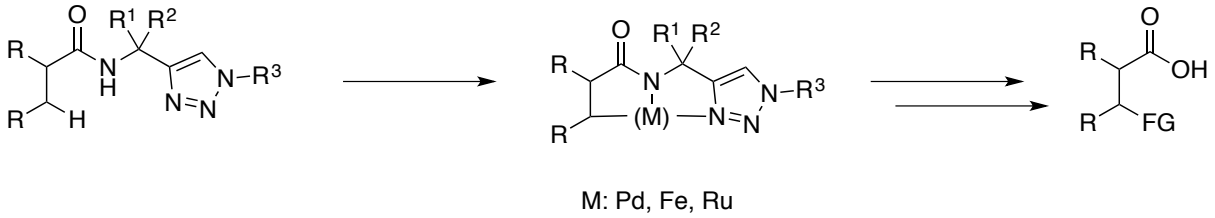
These directing groups have a lot of advantages: first, they should be easily accessible under mild condition; second, they form a more stable metal-complex rendering the functionalization more

[42] Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int.* Ed. **2014**, 53, 3868-3871

[43] Graczyk, K.; Haven, T.; Ackermann, L. *Chem. Eur. J.* **2015**, 21, 8812-8815

effective and third some of these should also be able to be obtained enantiomerically pure, in order to perform diastereoselective C(sp^3)–H activation.

In the Scheme here below, the TAM directing group, binds the metal through the formation of two five-membered cycles and once the complex is formed, the coupling partner (an Aryl-halide, an arylzinc or other halides) undergoes the functionalization of the desired C–H bond.



Scheme 18 TAM directing group

3.4 Regioselectivity and reaction conditions

In literature there are also a few examples of particular C–H activation reactions in which the regioselectivity is dependent on the reaction conditions: in these experiments, is possible to obtain different structural isomers starting from the same substrate by operating on several factors:

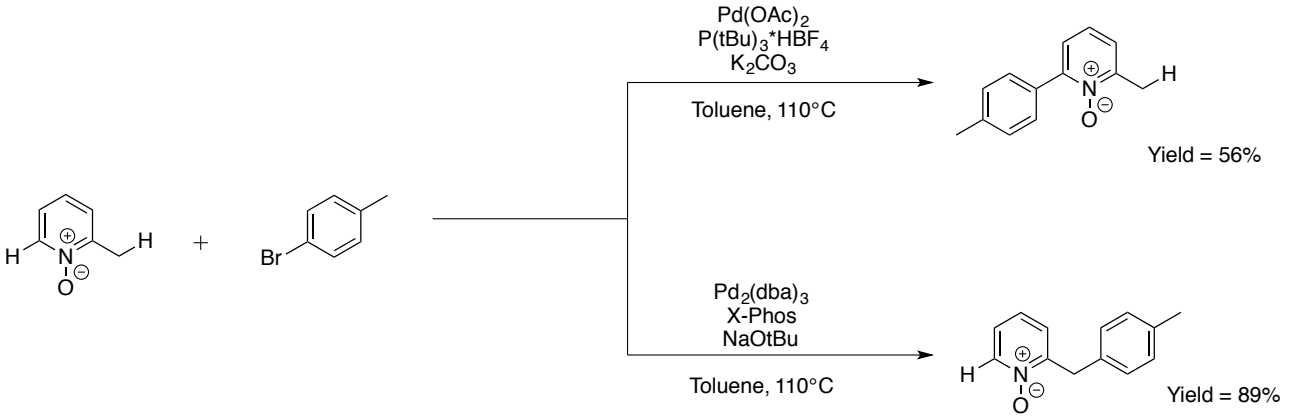
- Additives
- Solvents
- Ligands
- Palladium source
- Type of synthesis used

Fagnou and co-workers reported in 2008 an example of selective arylation of C(sp^2)–H and C(sp^3)–H of azines and diazines *N*-oxides and show how the reactivity can be modified by changing some of the above parameters [44].

It has been shown that the products synthesized in this way have a considerable importance in the field of medicinal chemistry and this new type of reactivity is a valid alternative to other synthetic approach for this class of compounds.

Interesting is the selectivity in the competition between activation of the C(sp^2)–H bond and the C(sp^3)-H bond that is strongly dependent on the nature of the base used (Scheme 19).

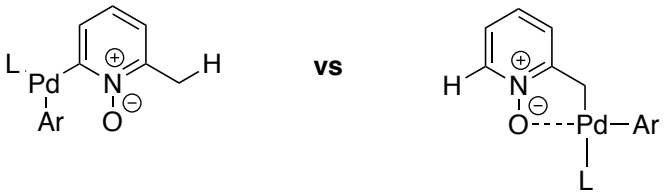
[44] Campeau, L.-C.; Schipper, D. J.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, 130, 3266-3267



Scheme 19 Selective arylations of N-oxide azines

With a strong base such as NaOtBu, the arylated product on C(sp^3) is obtained while using K_2CO_3 the other product is formed.

The explanation of the different selectivity is related to the formation of two intermediates of palladium in the course of the reaction.



Scheme 20 Proposed intermediates for arylation of N-oxides azines

In the case of sodium tert-butylate, the benzylic position is activated by N-oxide coordinating effect; in the case of carbonate, this type of support is not present and palladium chooses the C(sp^2)–H bond.[45]

Even if there are some examples in literature in which the regioselectivity can be modified by varying only the reaction conditions, it is usual to not consider this one of the strategies for the regioselective C–H activation.

[45] Kondo, Y.; Komine, T.; Sakamoto, T. *Org. Lett.* **2000**, 2, 3111-3113

4 Mechanisms in C–H activation

Different aspects of the C–H activation field have been observed and studied but some of the mechanistic aspects still remain not completely understood.

Over the years, several catalytic cycles and reaction's mechanism have been proposed, but is not possible to make a generalization that can explain all the cases present in literature.

Is possible, however, to divide the C–H activation reactions in two main different classes: the direct arylation (or in general functionalization) and the dehydrogenative coupling (Figure 10).

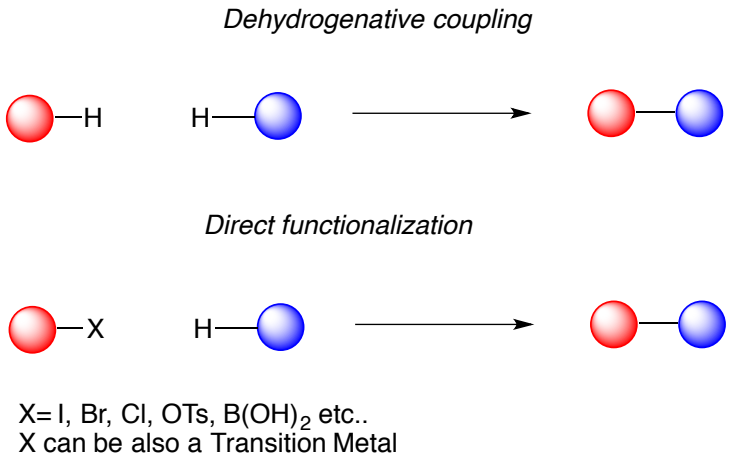


Figure 10 C-H activataion reactions

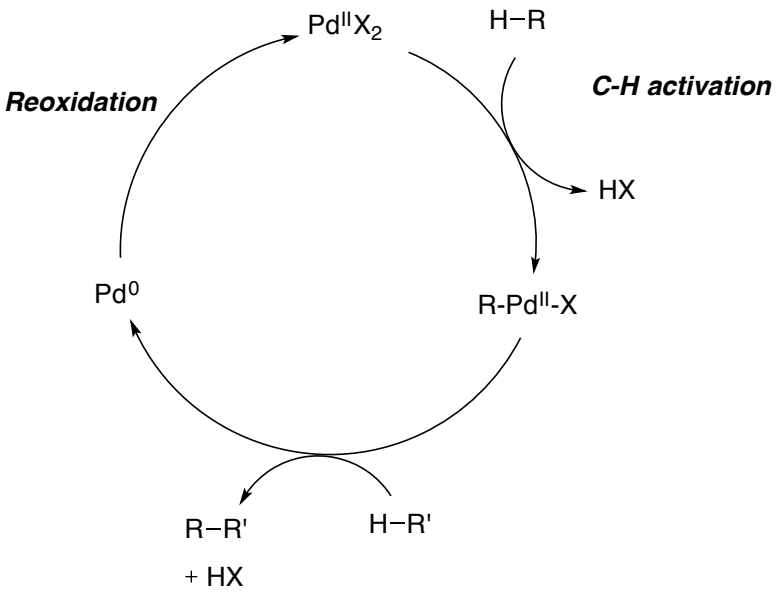
These two strategies are possible for C(sp^2)–H and C(sp^3)–H functionalization and is possible to use different type of catalyst; in this thesis we will discuss about palladium-catalyzed C–H activations because is the only metal used for all this work.

4.1 Dehydrogenative coupling

This kind of functionalization doesn't need preactivated coupling partner and the reaction takes place at two C–H bonds of the reactants.

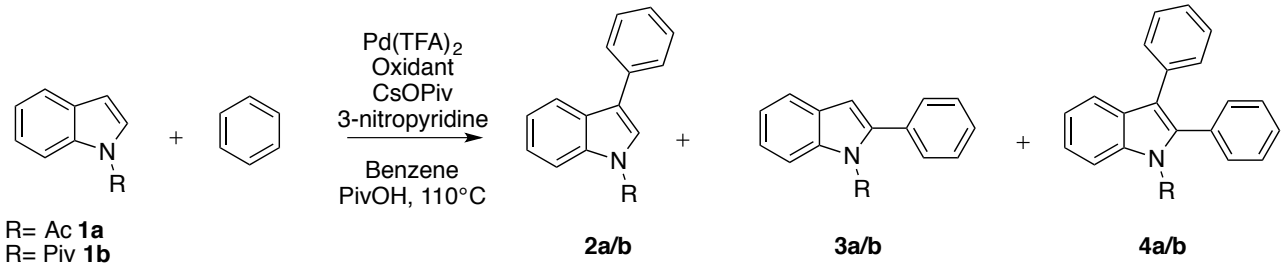
The substrate involved in this catalytic cycle reacts with Pd(II) catalyst in the metalation process which led to the new complex of Pd(II). Once obtained the product, after the reductive elimination, an oxidant is required in order to regenerate the catalytic active Pd(II) specie.

Is a Pd(II)/Pd(0) catalytic cycle and in the reaction are formed also two molecules of HX.



Scheme 21 Catalytic oxidative cross-coupling - Pd(0)/Pd(II) catalysis

One important example of this type of reaction is the work performed by Fagnou and co-workers on the arylation of indoles where they faced also a challenging regioselectivity problem (Scheme 22). [46]



Scheme 22 Arylations of indoles

In fact, as regarding the regioselectivity, the cross-dehydrogenative coupling constitutes the most challenging task. In particular, is not clear how the catalyst differentiates between the two C–H bond-containing components to achieve a chemoselective reaction, regardless of the regioselectivity issues of the reactants themselves.

Subsequently, Stuart and Fagnou developed a palladium-catalyzed oxidative cross-coupling of acetyl-protected indoles with simple arene following their hypothesis that coupling benzene with electronically different arenes could produce chemoselective coupling of arenes.

Palladium trifluoroacetate is the best Palladium source in combination with 3-nitropyridine, cesium pivalate and an oxidant.

[46] Stuart, D. R.; Fagnou, K. *Science* **2007**, 317, 1172-1175

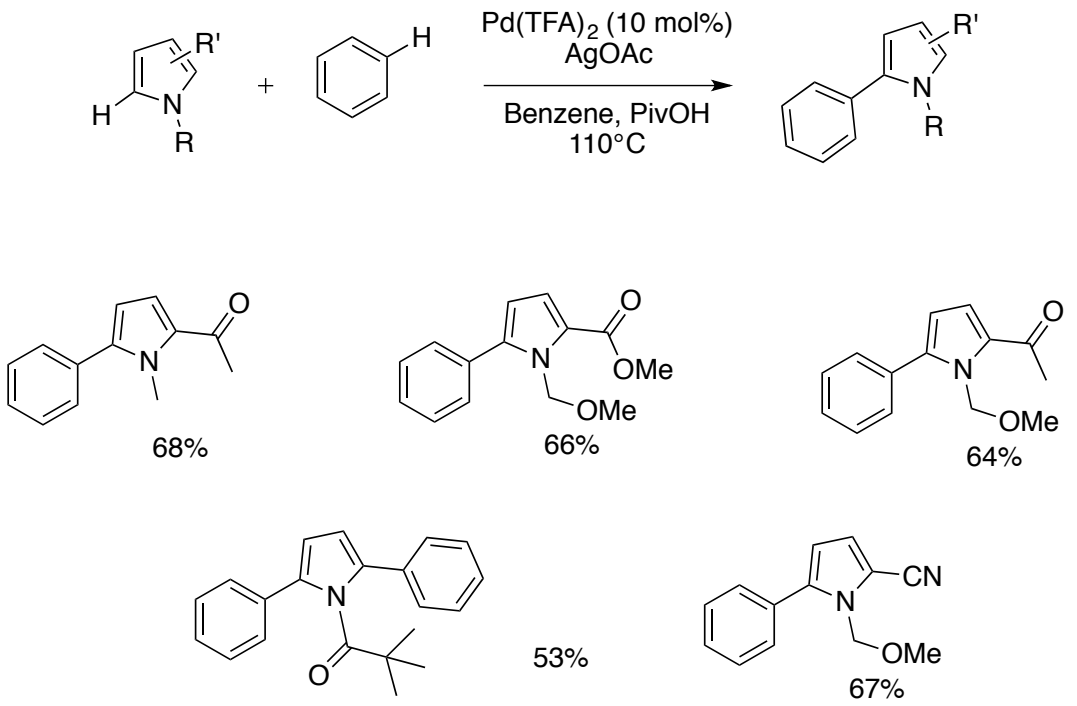
They showed how the oxidant, in cooperation with the R-group, can influence the regioselectivity: with $Cu(OAc)_2$ they obtained 9:1 of C-2/C-3 ratio instead AgOAc produced an inversion in selectivity favouring C-3 arylation (1:25 C-3/C-2 ratio).

The authors suggest that the addition of 3-Nitropyridine is necessary in order to avoid the precipitation of black palladium while the cesium pivalate, interacting with $Pd(TFA)_2$, generate the palladium pivalate early in the reaction.

Following their success with Pd-catalyzed indoles arylation, they demonstrated that also pyrroles can be successfully coupled using a Pd catalyst and a silver oxidant.[47]

In Scheme 23 is evident the preferred arylation on indole C-2 instead of C-3.

Further studies performed by the same group, indicate that the increased C-2 selectivity to the Pd catalyst is due to the acetate base and not to the metal counter-ion.



Scheme 23 Reactivity of pyrroles toward catalytic dehydrogenative coupling

These results led to new applications for the selectivity control in Pd-catalyzed dehydrogenative coupling reactions and may have broader impact also in Pd(II) catalysis.

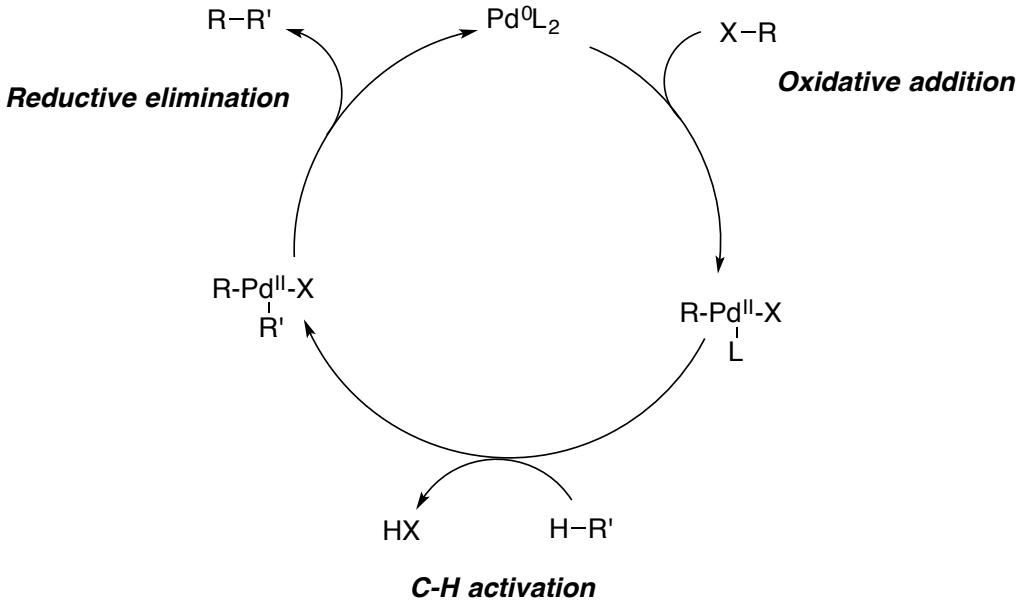
[47] Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, 129, 12072-12073

4.2 Direct Arylation Of Activated Coupling partners

In this type of reaction one of the reaction's partner must have a carbon-halogen (or a carbon-metal) bond in order to make possible the oxidative addition by Pd species.

The other reactant presents an available C–H bond which can be activated by one of the methods previously described and with one of the regioselective approaches.

The most common catalytic cycle is the one with Pd(0)/Pd(II) catalysis (Scheme 23).



Scheme 24 Direct functionalization with activated reagent – Pd(0)/Pd(II) catalysis

The first step is the oxidative addition of Pd(0) specie into the carbon-halogen bond which led to the Pd(II) complex, then in the C-H activation step a new Pd(II) complex is formed together with the release of a molecule of HX.

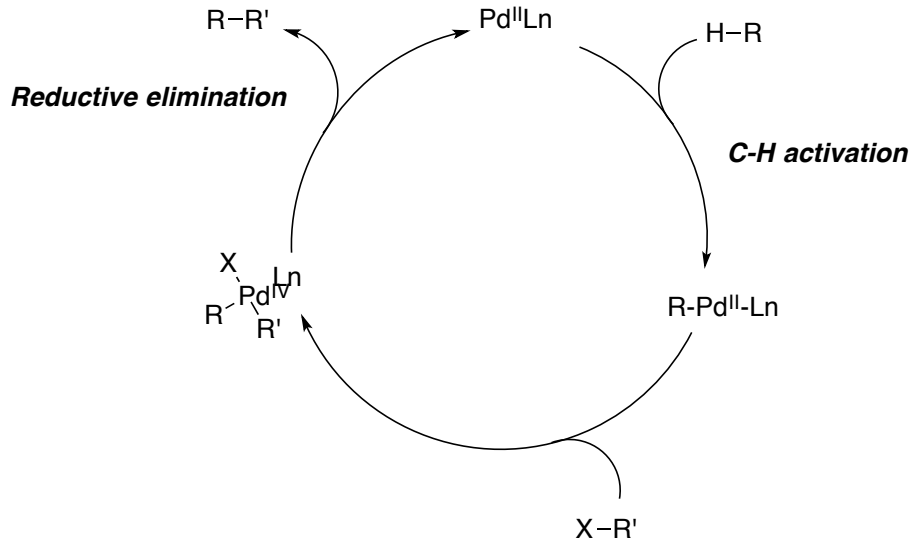
The reductive elimination gave the desired product and regenerates the Pd active specie.

Usually in this process a bidentate base is needed for the C-H activation step: the activation occurs with the base assisted metalation process (CMD) in which the base binds the metal and act as a proton shuttle to form the desired product (computational data support the hypothesis that the carboxylate anion lows the C–H bond's strength and helps the metalation process by Pd(II) species).[48]

This type of base assisted C–H activation is commonly used in C–H activation chemistry especially in previously described intermolecular and intramolecular reactions.

[48] Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 16496-16497

This type of C–H activation protocol can be used also with Pd(II)/Pd(IV) catalysis: the redox chemistry involving palladium (IV) has been studied for a long time and supported by X-ray crystallography, chemists determine this oxidation state of the metal.

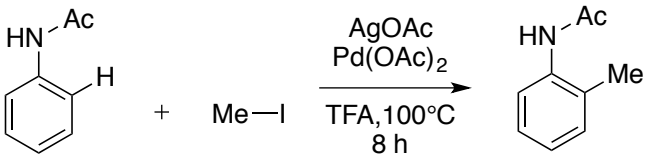


Scheme 25 Direct functionalization with activated reagent – Pd(II)/Pd(IV) catalysis

In this cycle, the oxidative addition of the activated coupling partner occurs after the C–H activation step and a Pd(IV) complex is formed.

Here is necessary to add an external oxidant to regenerate the Pd(II) needed for the catalysis.

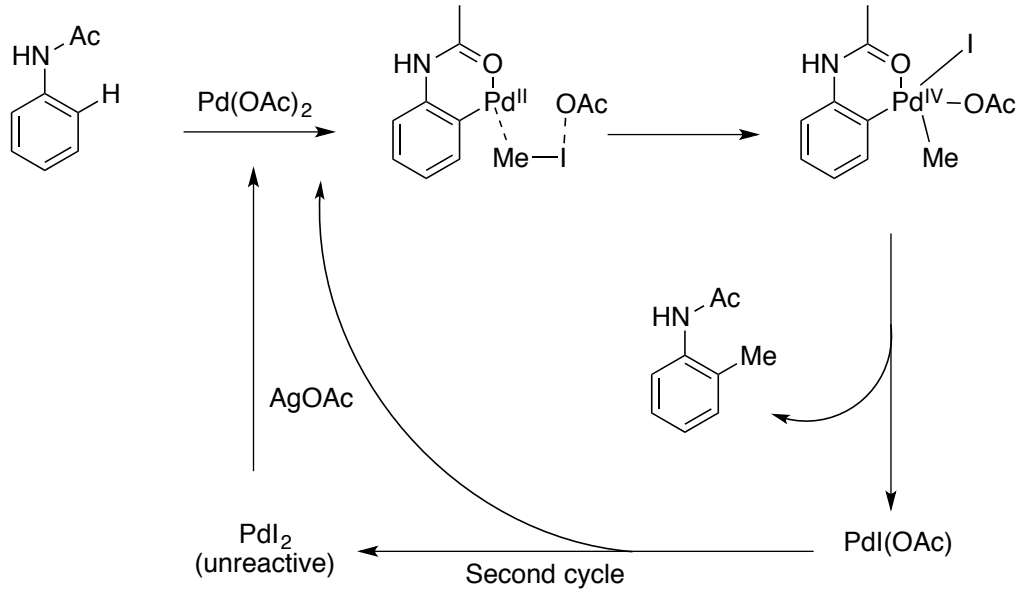
Tremont and Rahman reported what may be considered as the first example of regioselective methylation *ortho* to an acetanilide which proceed with the palladium catalysis described above (Scheme 26).[49,50]



Scheme 26 Ortho-metytatiom of acetanilides

The first step of the reaction involves the acetanilide metalation by the palladium which is followed by the oxidative addition of the Pd(II) in the carbon-halogen bond of methyl iodide and leads to the formation of a Pd(IV) intermediate (Scheme 27).

[49] Rostovtsev, V. V.; Henling, L. M.; Labinger, J. A.; Bercaw, J. E. *inorg. Chem.* **2002**, 41, 3608-3619
[50] Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, 106, 5759-5760



Scheme 27 Pd(II)/Pd(IV) catalyzed arylation of C-H bonds

The oxidation of palladium (II) to palladium (IV) mediated by MeI, was then supported by X-ray crystallography that allowed chemists to study this intermediate and thus determines the oxidation state of the metal.

After the completion of the catalytic cycle, the isolation of PdI_2 in quantitative manner, led further evidence in support of the chemistry of Pd (IV).

This and other examples of alkylation that proceed through a catalysis of Pd(II)/Pd(IV) have been exploited in the following years, to develop the catalytic arylation and olefination reactions.

This catalysis is often used to explain directing group assisted C–H activations.

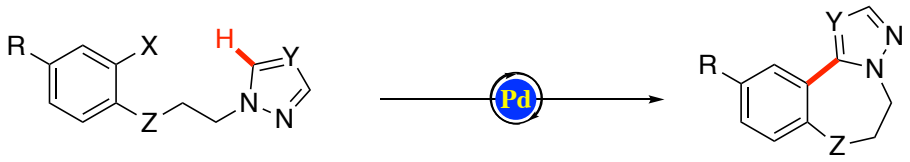
5 Aim of the thesis

This work, developed in collaboration with Prof. Dr. Lutz Ackermann of the University of Göttingen, has the purpose to find regioselective C–H activation strategies for the synthesis and the late-stage diversification of potentially biologically active molecules.

We tried different pathways and we approached several potential applications; palladium was chosen as transition metal for all the strategies we attempted and all the catalytic reactions were performed under inert atmosphere.

Intramolecular C-H activation

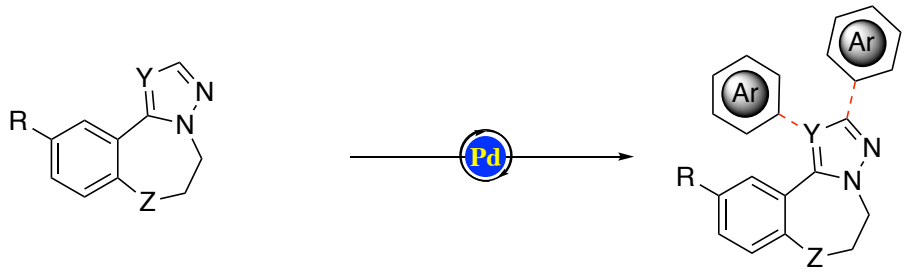
a)



X = Br, Cl
Y = N, CH
Z = CH_2, O, S, NR

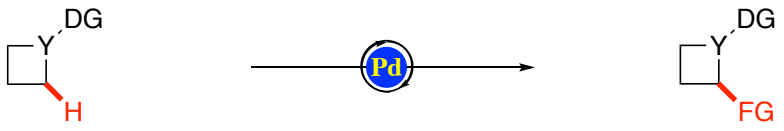
Intermolecular C-H activation

b)



Directing-group assisted C-H activation

c)



Y = CH, N

Figure 11 Regioselective adopted strategies

The thesis can be divided in three main parts: in the first we developed a protocol for the rapid access to 2-benzazepine derivatives via Palladium-catalyzed C–H activation (Figure 11a). The protocol is versatile, make use of a simple catalytic system and shows a good tolerance of functional group.

In the second part we tried some applications such as the derivatization of the cores obtained in the first part with an intermolecular C–H activation or the synthesis of well-known drugs. (Figure 11b). The principal goal is of course to obtain a library of molecules starting from the same substrate but also to extend the developed protocol for other purposes: in this part we proposed also the synthesis of one inihibitor of PDE10, known for its propreties related with the central nervous system which usually is prepared with tedious multi-step strategies.

In the last part, made also at the University of Göttingen, we focused our attention on the C(sp^3)–H functionalization of four-membered rings with directing group (Figure 11c).

This type of functionalization is well known to be very challenging compared to the previous two mentioned, and this is due to the high bond dissociation energy of the C(sp^3)–H bond; the choice of the correct directing group is crucial to exploit this purpose.

6 The C(Sp^2)–H Palladium catalyzed intramolecular C–H activation

Polyheterocyclic moieties represent key structural motifs of complex naturally occurring molecules, functional materials and pharmaceuticals in medicinal chemistry.

Thus, seven-membered benzo heterocycles such as 2-benzazepines and benzodiazepines, shown interesting biological and pharmacological feature such as inhibition PI3-kinase and hepatitis C Virus NS5B RNA polymerase, modulation of γ-secretase activity and potential HSP90 inhibitors (Figure 12).[51, 52, 53, 54, 55, 56, 57]

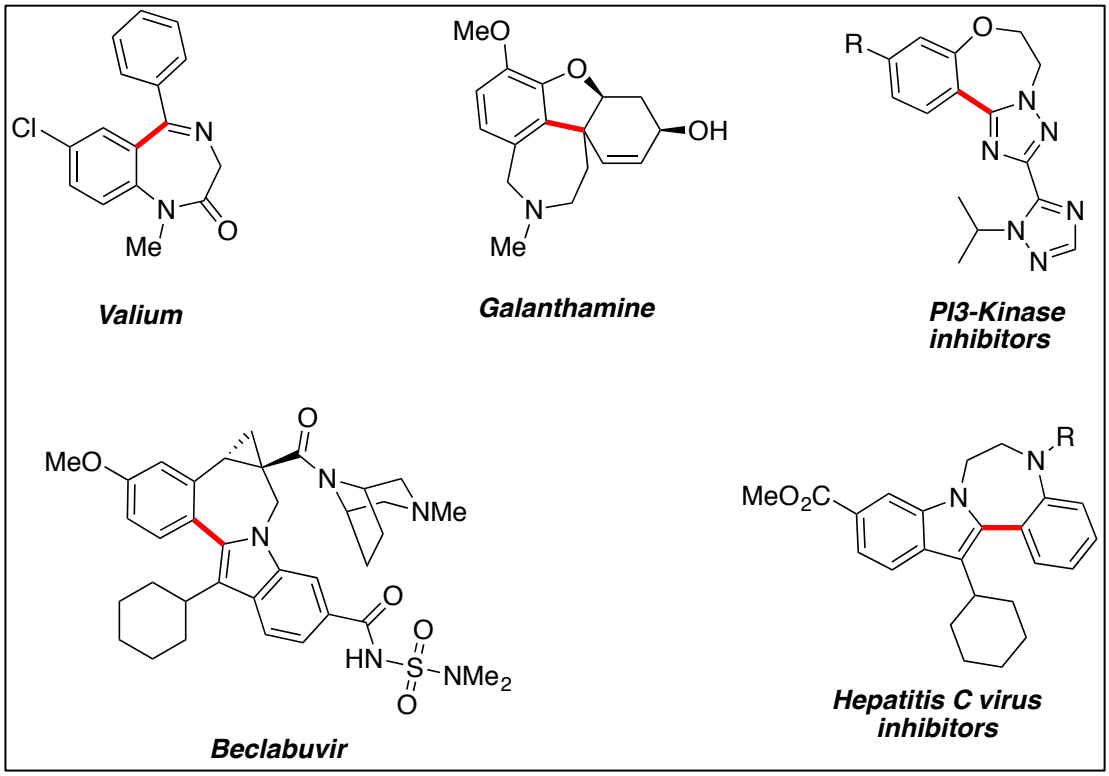


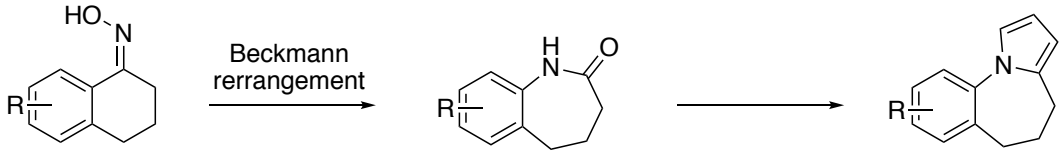
Figure 12 Biologically active benzazepines and benzodiazepines

The synthesis of these seven-membered scaffolds continues to be challenging for both pharmaceutical and synthetic research. Despite the significant advancements, the classical

[51] Ikegashira, K.; Oka, T.; Hirashima, S.; Noji, S.; Yamanaka, H.; Hara, Y.; Adachi, T.; Tsuruha, J-I.; Doi, S.; Hase, Y.; Noguchi, T.; Ando, I.; Ogura, N.; Ikeda, S.; Hashimoto, H. *Journal of Medicinal Chemistry*, **2006**, 49, 6950-6953.
[52] Zheng, B. Z.; D'Andrea, S.V.; Hanumegowda, U.; Knipe, J. O.; Mosure, K.; Zhuo, X.; Lemmc, J. A.; Liu, M.; Rigat , K. L.; Wangd, Y.-K.; Fang, H.; Poronsky, C.; Cutrone, J.; Wue, D. R.; Arunachalam, P. N.; Balapragalathan, T. J.; Arumugam, A.; Mathur, A.; Meanwell, N. A.; Gao, M.; Roberts, S. B.; Kadow, J. F. *Bioorganic & Medicinal Chemistry Letters* **2017**, 27, 3294–3300.
[53] Kornienko, A.; Evidente, A. *Chem. Rev.* **2008**, 108, 1982-2014
[54] Jin, Z. *Nat. Prod. Rep.* **2009**, 26, 363-381
[55] Staben, S. T. et al *Bioorganic & Medicinal Chemistry Letters* **2013**, 23, 2606–2613
[56] He, M.; Qu, C.; Gao, O.; Hu, X.; Hong, X. *RSC Adv.* **2015**, 5, 16562-16574
[57] Ghavre, M.; Froese, J.; Pour, M.; Hudlicky, T. *Angew. Chem. Int. Ed.* **2016**, 55, 5642-5691

approaches to access these benzo-fused heterocycles require tedious multi-step synthesis largely involving condensation type strategies.[58, 59]

For example, one possibility is to synthetize the fused benzazepine starting from the corresponding lactam, which can be obtained through a Beckmann rearrangement of tetralone oxime using polyphosphoric acid.



Scheme 28

The defect is that the process is not versatile and is not applicable to different types of heterocycles; besides the fact that another problem is the functionalization of the tetralone.

Metal catalysed coupling strategies have previously been used for the construction of N-fused heterocycles as an interesting alternative to the just mentioned pathways.

However, besides these fruitful accomplishments, these approaches have some drawbacks. Usually are required expensive catalysts, the scope was limited to only a few type of heterocycles, and for these reasons, a flexible strategy for the construction of chemical diverse heterocycles fused 2-benzazepine is still under investigation.[60, 61]

In this context, we became interested in exploring a simple and step economical protocol as an effective strategy for the synthesis of seven membered heterocycles.[62]

The key step of the process is the transition metal catalyzed intramolecular C(sp^2)–H activation of very simple substrates which can be easily obtained starting from the commercially available nitrogen heterocycle (Figure 13).

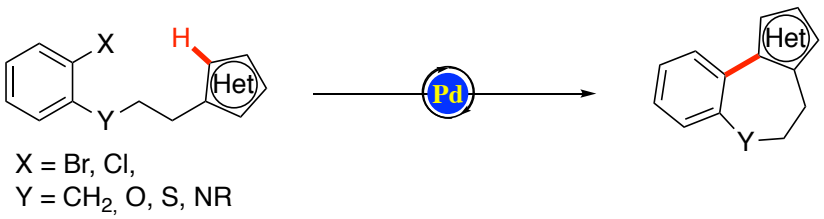


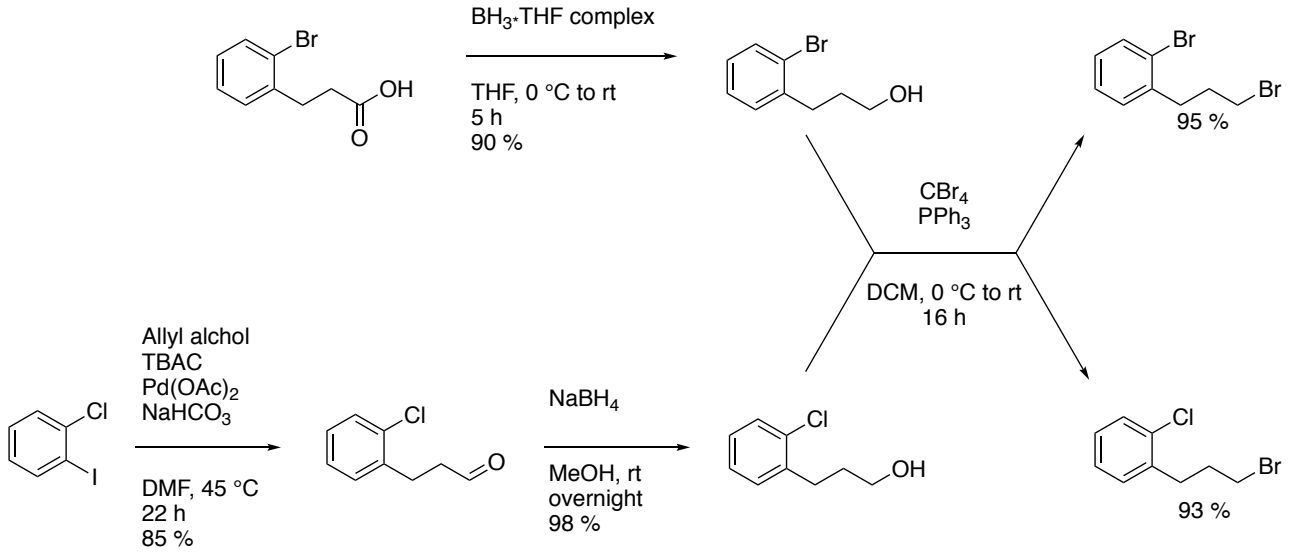
Figure 13 Proposed strategy

[58] Anderson, W. K.; Heider, A. R.; Raju, N.; Yucht, J. A. *J. Med. Chem.* **1988**, 31, 2097-2102
[59] Tsuda, Y.; Ohshima, T.; Hosoi, S.; Kaneuchi, S.; Kiuchi, F.; Toda, J.; Sano, T. *Chem. Pharm. Bull.* **1996**, 44, 3, 500-508
[60] Cahiez, G. R.; Moyeux, A.; *Chem. Rev.* **2010**, 110, 1435-1462
[61] Negishi, E.-I.; Anastasia, L.; *Chem. Rev.* **2003**, 103, 1979-2018
[62] Virelli, M.; Moroni, E.; Colombo, G.; Fiengo, L.; Porta, A.; Ackermann, L.; Zanoni, G. *Chem. Eur. J.* **2018**, 24, 16516-16520

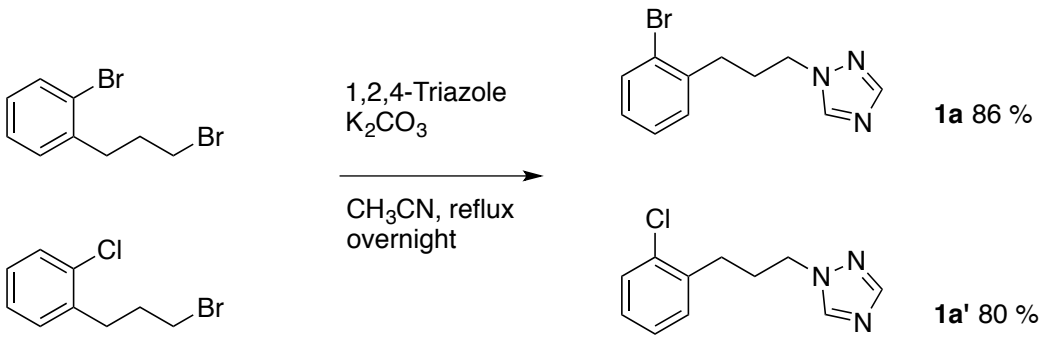
In this reaction the regioselectivity is mainly due to the intramolecular fashion of the process, but also the electronic effects of the nitrogen heterocycle play an important role.

In the case of more than one activable C–H bond, in principal, the reaction could form different compounds, but, due to a difference in reactivity, the reaction pathway led to only one, which is also the desired product. We decided to use palladium as the catalyst for our approach because is one of the most widely used metal in this type of reactions.

We commenced our studies with the C–H arylations of 1,2,4-triazoles **1a/a'** as the model substrates for the optimization that began with a screen of palladium catalyst. The desired starting materials for the cyclization reaction are easily prepared starting from the corresponding 2-bromo-propionic acid and from the 2-Iodo-chloro benzene.[63, 64, 65, 66] The yield of the whole process are very good.



Scheme 29 Synthesis of starting materials - part 1



Scheme 30 Synthesis of starting materials - part 2

[63] Patent WO 2010/045212 PCT/US2009/060473

[64] Tsuji, H.; Yamagata, K.-I.; Itoh, Y.; Endo, K.; Nakamura, M.; Nakamura, E. *Angew. Chem. Int. Ed.* **2007**, 46, 8060-8062

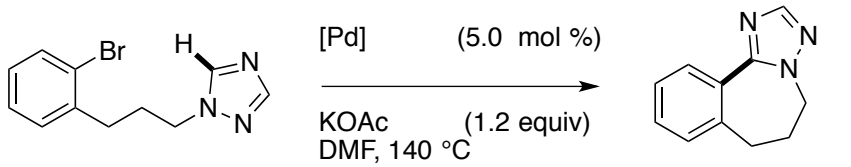
[65] Kuwabe, S.-I.; Torraca, K. E.; Buchwald, S. L.; *J. Am. Chem. Soc.* **2001**, 123, 49, 12202-12206

[66] Houghton, R. P.; Shervington, L. A. *J. Chem. Res. Miniprint*, **1989**, 1872

At this point, is important first of all to understand which is the active specie involved in the process. We know from literature that in the C–H activation reactions palladium mediated, the metal can act as a Pd^0 or as a Pd^{II}: the two catalytic cycles are profoundly different.[3]

We started with reaction's conditions found in the literature and we used different palladium sources, with the two possible oxidation states.

The solvent used was always DMF at 140°C for 20 hours. The catalyst loading is 5.0 mol% as starting point hoping it can be reduced. For these first experiments we used only the bromide as the substrate.



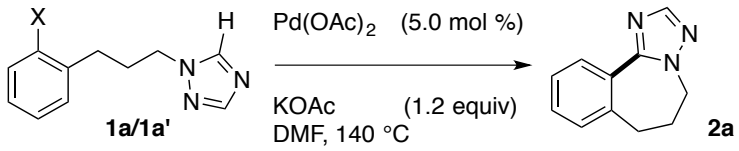
1a **2a**

Entry	[Pd]	Yield (%)
1	$Pd(OAc)_2$ (5 mol %)	25
2	$Pd(TFA)_2$ (5 mol %)	< 20
3	$Pd(PPh_3)_4$ (5 mol %)	75

Table 1

The reaction with palladium-tetrakis(triphenylphosphine) gave us the product in very good yield in comparison with the other palladium sources, which gave us the product only in a little amount. We supposed the Pd^0 as the active catalytic specie for our purpose.

At this point we were interested in finding the better leaving group present in our starting material so we tried for the cyclization reaction both chlorides and bromides in order to understand which could be the best choice. The reactions were performed with palladium tetrakis as the palladium source and potassium acetate as base.



Entry	Substrate	[Pd] cat.	Yield (%)
1	**1a**	$Pd(PPh_3)_4$ (5 mol %)	75
2	**1a'**	$Pd(PPh_3)_4$ (5 mol %)	58

Table 2

Encouraged by the positive outcome of the experiments, we decided to evaluate also the role of the base in order to understand better the mechanism of the reaction.

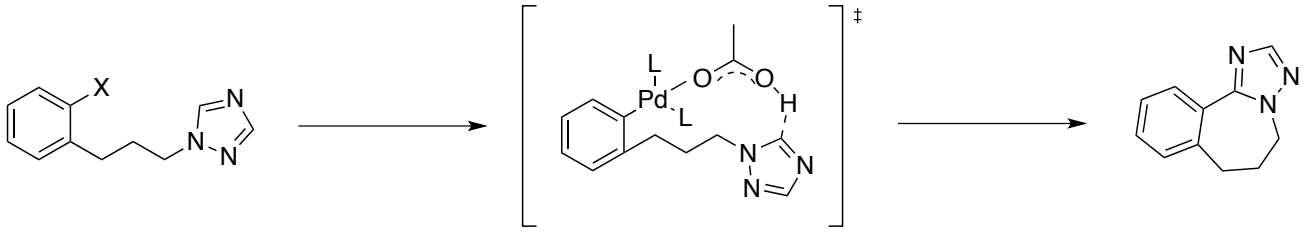
Entry	Base	Yield (%)
1	KOAc	75
2	AgOAc	28
3	K_2CO_3	38
4	KOtBu	< 20
5	Piv-OH + KOtBu	35
6	Piv-OH + K_2CO_3	50

Table 3

Supported by the literature and by the experimental datas, we proposed a C–H bond activation via a mechanism in which the metalation takes place via a concerted base-assisted deprotonation (CMCD).[4, 67, 68]

The base, a carboxylate or a pivalate, acts as a proton shuttle because from one side it helps the abstraction of the target proton and form the other side it helps the insertion of palladium in the desired bond.

[67] Balcells, D.; Clot, E.; Eisenstein, O. *Chem. Rev.* **2010**, 110, 749-823
[68] Lersch, M.; Tilset, M. *Chem. Rev.* **2005**, 105, 2471-2526

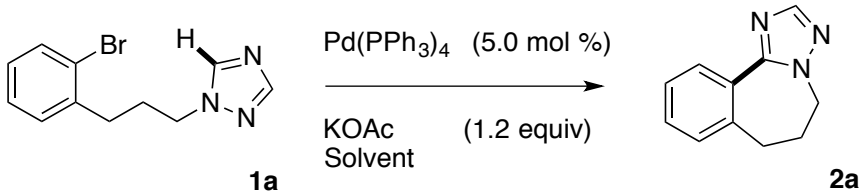


Proposed metalation step via base-assisted

Scheme 31 Proposed base assisted metalation-deprotonation process

In our case seems better to use directly the potassium acetate instead of generating it in situ from a monodentate base.

As the last two parameters of the optimization we tested the solvent and the temperature.



1a **2a**

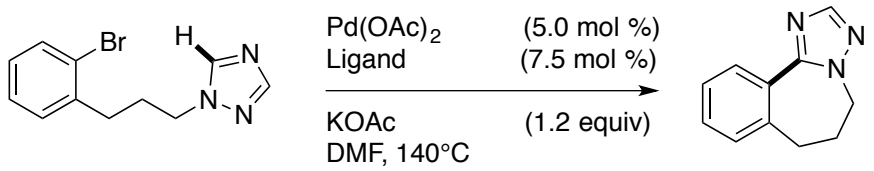
Entry	Solvent	Yield (%)
1	DMF	75
2	NMP	64
3	PhMe	37
4	DMA	71
5	DCE	54
6	1,4-Dioxane	52
7	DMF at 130 °C	63
8	DMF at 120 °C	60
9	DMF at 100 °C	49
10	DMF at 80 °C	44
11	DMF at 100 °C μw	57

Table 4

The palladium tetrakis used in all the optimization is very expensive and an easily oxidable salt so we decided to generate in situ the palladium specie we need for the reaction starting from a cheap palladium(II) source: the $Pd(OAc)_2$.

Any phosphine can be used as reducing agent for this purpose without "*de novo*" synthesis and isolation of Pd(0) species.

We started the screening of the most common phosphines with the best conditions obtained in the first part:



1a **2a**

Entry	Ligand	Yield (%)
1	PPh_3	64
2	PBu_3	89
3	Tri(o-tolyl)-phosphine	50
4	**PCy_{3*} HBF_4**	**95**
5	Diphenyl-methyl phosphine	62
6	p-Methoxyphenyl phosphine	68
7	Dppe	87
8	Dppb	70

Table 5

It seems that the aliphatic phosphines work better in comparison with the aromatic one and this is ascribable to the fact that they are more electron rich and so can facilitate the oxidative insertion step, which is supposed to be the rate determining step of the reaction.

Keeping the same electronic effects of the substituents on the Phosphine (eg dppe and diphenylmethyl) but changing the angle (P-Pd-P) that influences the electron density on Palladium due to an higher orbitals overlapping, we obtained different results (Table 5, entry 5 and 7). The dppe, which is a bidentate phosphine, works better, but we don't know if this is due to its nature (bidentate) or to the bite angle.

Using two bidentate ligands (dppe and dppb) we obtained two different results. With dppb, which has a larger bite angle, the yield is lower.

With the aromatic phosphines instead, the results are very close. We can see that the p-Methoxyphenyl, which is the more electron rich, the reaction works better; instead with the o-tolyl (the Me in ortho is little EDG) the steric factors work in order to gave the lower yield (bigger bite angle, less donation on the metal).

In our process there are both electronic and steric factors, remains unclear which of the two effects has the greatest impact on the reaction: from the experiments seems more important the electronic nature of phosphine and the phosphine seems to work as a monodentate ligand.

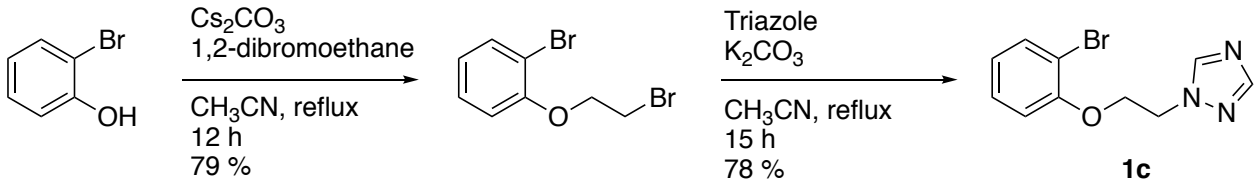
Encouraged by these satisfactory results, obtained the best condition for the palladium mediated C-H activation of $C(sp^2)$–H of triazole, we tried to reduce the catalyst loading.

Entry	$Pd(OAc)_2$	$PCy_3{*}HBF_4$	Yield (%)
1	5.0 mol %	7.5 mol %	95
2	2.5 mol %	3.75 mol %	92
3	1.0 mol %	1.5 mol %	90
4	0.5 mol %	0.75 mol %	60*

Table 6

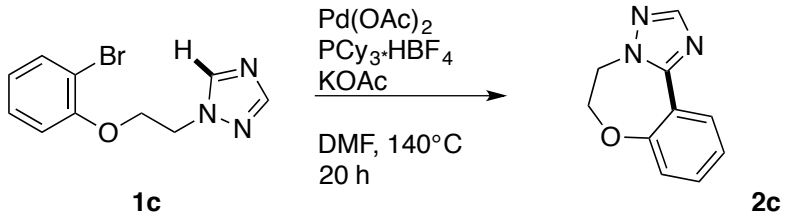
***Not fully conversion of the substrate after 24 hours of reaction**

The surprising result of entry 3 in Table 6 and all the other experiments showed above, inspired us to try the developed protocol for the synthesis of other type of azepines such as the benzoxazepine. The substrate is synthetized starting from the corresponding 2-halo-phenol and we decided to use only the bromide as the leaving group because of the experiments done in the first part.



Scheme 32

We achieved a short methodological study in order to confirm all the optimization reached:



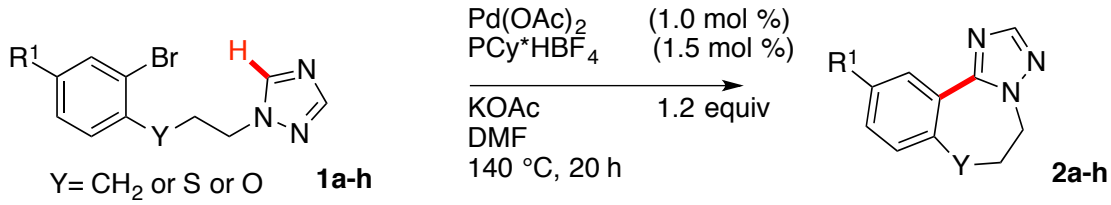
1c **2c**

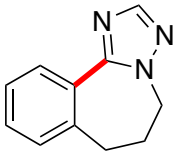
Entry	[Pd]	Phosphine	Base	Additives	Solvent	T(°C)	Yield (%)
1	$Pd(PPh_3)_4$ (1.0 mol%)	/	KOAc (1.2 eq)	/	DMF	140°C	77
2	$Pd(OAc)_2$ (1.0 mol %)	$HPCy_3\,BF_4$ (1.5 mol%)	KOAc (1.2 eq)	/	DMF	140°C	88
3	$Pd(OAc)_2$ (1.0 mol %)	PPh_3 (1.5 mol%)	KOAc (1.2 eq)	/	DMF	140°C	72
4	$Pd(OAc)_2$ (1.0 mol%)	dppe (1.5 mol%)	KOAc (1.2 eq)	/	DMF	140°C	83

Table 7

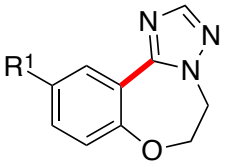
We tried only four different phosphines and the results are comparable with the other obtained for the benzazepine.

With these conditions in hands, we extended the scope of the reaction by varying the substituents on the aryl moiety and adding different heteroatoms in the spacer between the two reaction's partners.

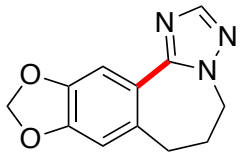




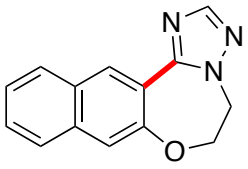
2a: 95 %



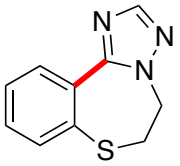
R^1 = H **2c**: 88 %
R^1 = Me **2d**: 85 %
R^1 = Et **2e**: 91 %
R^1 = Cl **2f**: 96 %
R^1 = NO_2 **2g**: 66 %



2b: 74 %



2h: 93 %



2i: 62 %

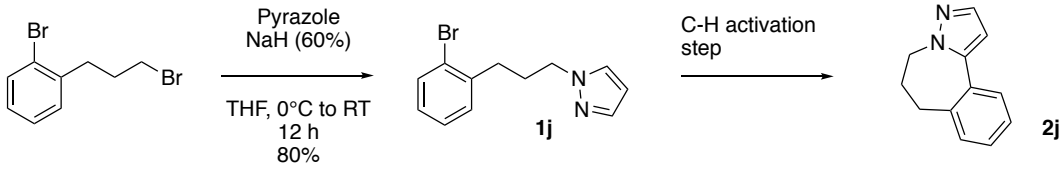
[a]Reactions conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (1.0 mol%), PCy_3*HBF_4 (1.5 mol%), KOAc (0.6 mmol, 1.2 equiv) in DMF (0.07 M, 7.1 mL) at 140 °C for 20 h.

Scheme 33 Substrate scope

A wide rande of spacers can be used for this reaction and in particular the chain containing the sulfur atom is fashinating because gives acces to different class of thiazepines in an innovating and new fashion.

Most importantly, the reaction operates very well with different substituents on the aryl moiety and can be used from simple functional group to more complex frameworks such as the acetal or the naphtalene moiety.

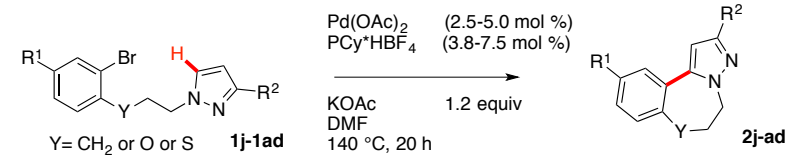
At this point, to improve the verstiliy of the protocol, we tested the reaction using the pyrazole as the nitrogen heterocycle.

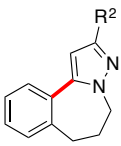


Entry	$Pd(OAc)_2$	$PCy_3{*}HBF_4$	Yield
1	5.0 mol%	7.5 mol%	76 %
2	2.5 mol%	3.75 mol%	76 %
3	1.0 mol%	1.5 mol%	30 %

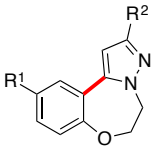
Table 8

The cyclization reaction with the pyrazole gave us lower yields respect to the results obtained with the triazole and we think that this is due to the nature of the nitrogen heterocycle (electronic effects). As regarding the catalyst loading, in that case was not possible to reduce it more than 2.5 mol%. The substrate scope of the reaction was investigated.

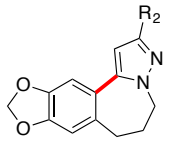




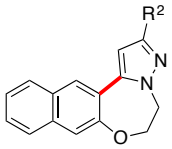
$R^2 = H$ **2j**: 76 %
$R^2 = Ph$ **2k**: 63 %
$R^2 = C_6H_3(OMe)_2$ **2l**: 59 %



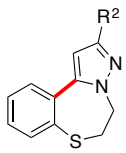
$R^1 = H$	$R^2 = H$	**2m**: 81 %[b]
$R^1 = Me$	$R^2 = H$	**2n**: 86 %[b]
$R^1 = Me$	$R^2 = Ph$	**2o**: 75 %
$R^1 = Et$	$R^2 = H$	**2p**: 86 %[b]
$R^1 = Et$	$R^2 = Ph$	**2q**: 76 %
$R^1 = Cl$	$R^2 = H$	**2r**: 77 %[b]
$R^1 = Cl$	$R^2 = Ph$	**2s**: 65 %
$R^1 = NO_2$	$R^2 = H$	**2t**: 88 %[b]
$R^1 = NO_2$	$R^2 = Ph$	**2w**: 63 %



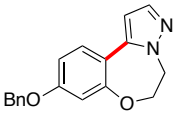
$R^2 = H$ **2x**: 67 %[b]
$R^2 = C_6H_3(OMe)_2$ **2y**: 77 %[b]



$R^2 = H$ **2z:** 65 %
$R^2 = Ph$ **2aa**: 64 %



$R^2 = H$ **2ab**: 54 %
$R^2 = Ph$ **2ac**: 51 %



2ad: 68 %

[a]Reactions conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (5.0 mol%), $PCy_3{\cdot}HBF_4$ (7.5 mol%), KOAc (0.6 mmol, 1.2 equiv) in DMF (0.07 M, 7.1 mL) at 140 °C for 20 h.[b] $Pd(OAc)_2$ (2.5 mol%) and $PCy_3{\cdot}HBF_4$ (3.8 mol%)

Scheme 34 Substrate scope

For the synthesis of the substrates, in the SN_2 reaction of the pyrazole with the bromide, sometimes is better to add the 1,3-dimetil-3,4,5,6-tetraidro-2(1H)-pirimidinone (DMPU) to the reaction mixture: it works as a cation scavenger and helps the formation of the desired product.

For the pyrazole already substituted at C-3 we used the cheaper reagents commercially available; with these two nitrogen heterocycles the steric hindrance of the phenyl group, especially the bis-methoxy phenyl, can influence the cyclization reaction and so the yield of the products.

We can say that the palladium mediated intramolecular C–H activation seems under the control of the entropic factors which led to the seven membered ring but also of the electronic effects of the heterocycle which can influence the reactivity of the different C–H bonds (see pyrazole against triazole).

As our delight, we tested also other heterocycles.

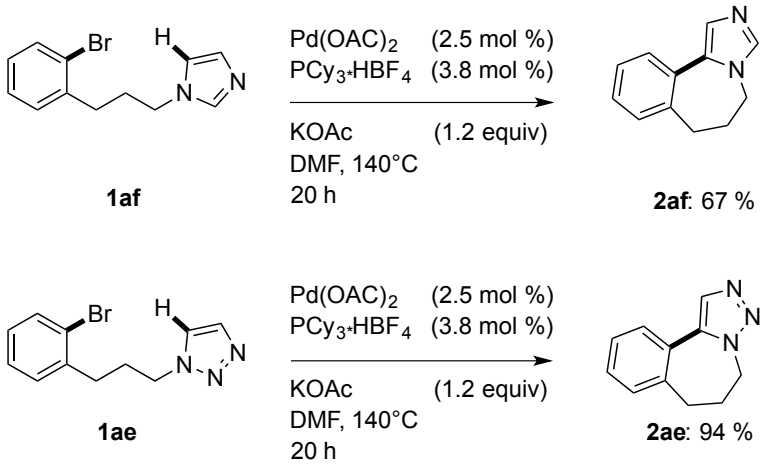


Figure 14

In particular, the regioselectivity of the process is well explained by the cyclization of the imidazole: here there are two C–H bonds that provide two different products (Figure 15).

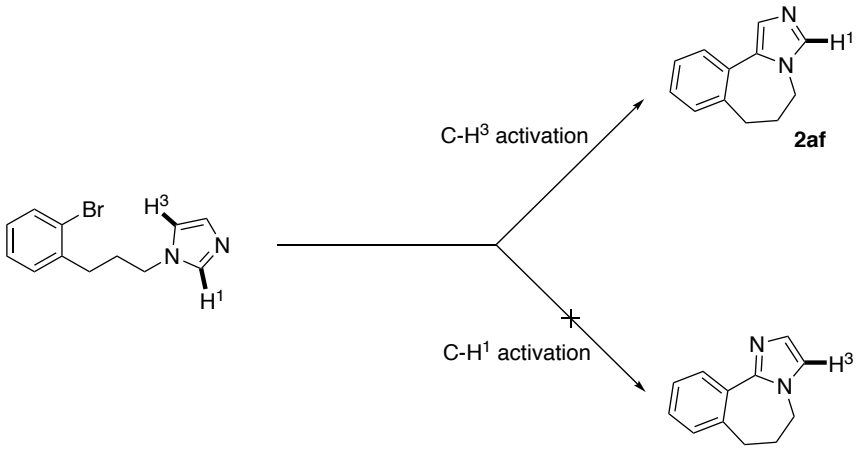
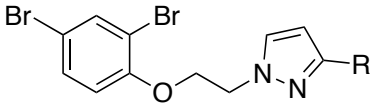


Figure 15

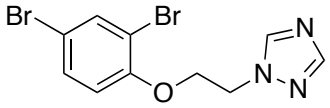
In our reaction conditions, only product **2af** was obtained and no traces of the C-H[1] activation were observed. This is mainly due to the electronic effects of the imidazole: the C-5 is the most nucleophilic position with respect to the position 2 and 4.

This is reasonable because of the inductive effect of the nitrogen in position 1 stabilizes the carbon-palladium bond on the C-5 and therefore the metalation to the C-5 appears to be favored by thermodynamic and kinetic factors. In contrast, the functionalization at the C-2 and at C-4 appears to be disfavored. In the presence of a strong base, however, the proton abstraction at C-2 position is very efficient and it is facilitated by the greater acidity of that position. (The inductive effect of the two nitrogen atoms makes the C-H bond in position 2 more electron-poor and more acidic).

Unfortunately, the substrates containing the Bromo as the substituent in the aromatic moiety didn't afford the desired products.



1ag R = H
1ah R = Ph

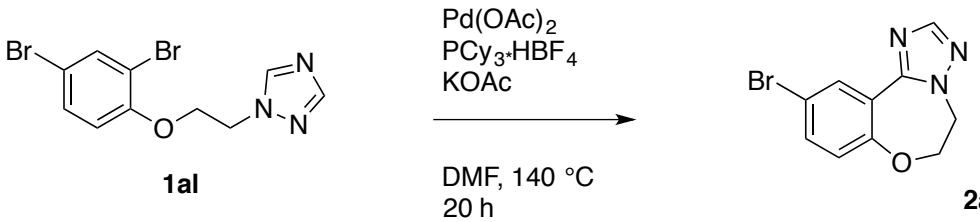


1al

Figure 16 Unsuccesfull substrates

Reasonably, this is due to the possibility for the palladium to insert in both the C-Br bonds: only one is effective for the cyclization reaction, the other pathway quenches the reactivity of the substrate. As a proof of the side reaction, was possible to observe in HPLC-MS one peak related to the loss of the bromine at the C-4 position, which happen after the reductive elimination.

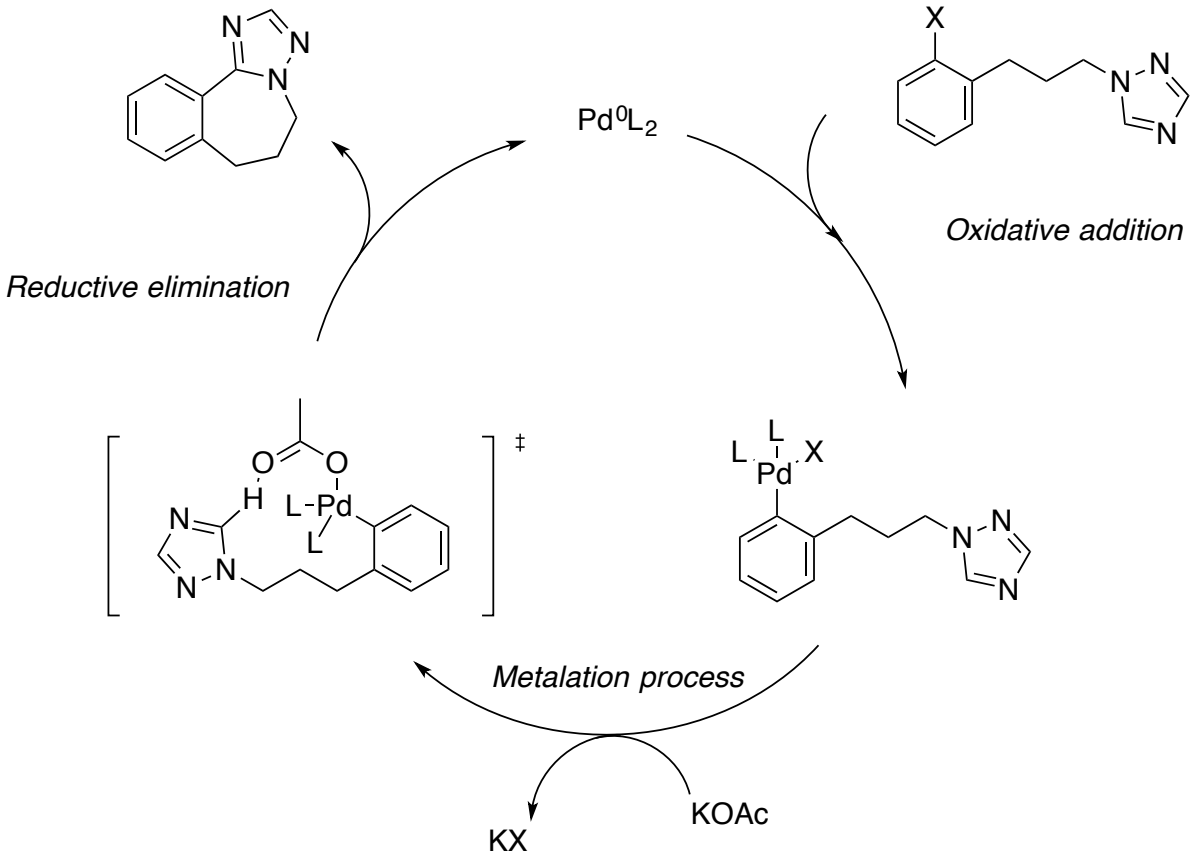
Increasing the amount of palladium to 20 mol% were observed some traces of product, but not in sufficient amount to isolate it.



Entry	$Pd(OAc)_2$	$PCy_3{*}HBF_4$	Yield
1	1.0 mol %	1.5 mol %	No Product
2	2.5 mol %	3.75 mol %	No Product
3	5.0 mol %	7.5 mol %	No Product
4	10 mol %	15 mol %	traces
5	20 mol %	30 mol %	traces

Table 9

In line with previous studies, a plausible mechanism for our C(sp^2)–H was proposed and is the one depicted in Scheme 35.



Scheme 35 Proposed reaction mechanism

The first step is an oxidative addition of the palladium in the carbon halogen bond that led to a complex, which undergoes the key step of the C–H activation. Trough the base-assisted metalation-deprotonation process, the acetate can activate the desired bond, which is the hydrogen at C-5 in the triazole moiety. After reductive elimination the proposed transition state led to the product and the palladium is ready to enter again in the catalytic cycle.

In the experiments showed above, bromide afforded the best result and we supposed that this is due to the much easier oxidative insertion step. The bromide is also a good compromise between the very expensive iodide and the cheaper but less reactive chloride; in this context we didn't try to use other leaving groups because their multi-step synthesis is losing value our simple and cheap synthetic approach.

At this point we were interested in changing the spacer between the two aromatic moieties with a more fascinating and more rigid functional group such as the amidic function: this led to a very important class of drugs (Figure 17). [69]

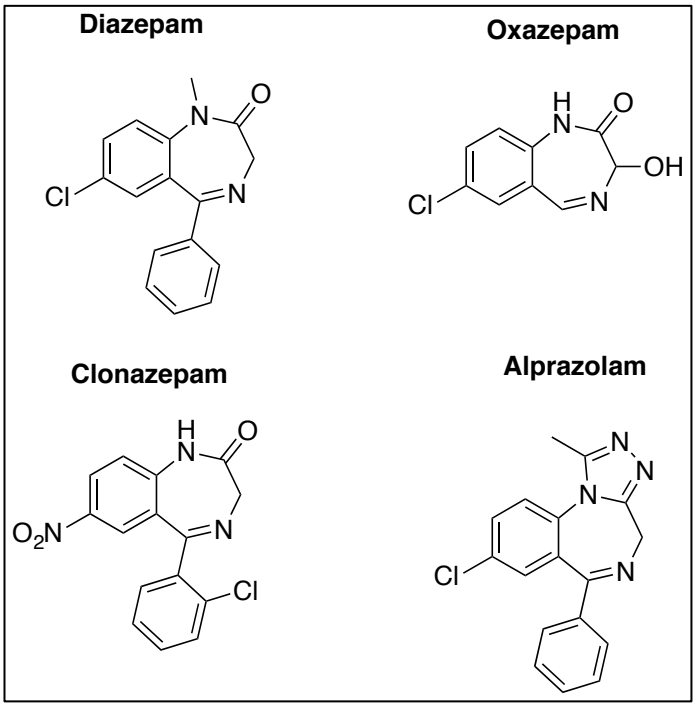
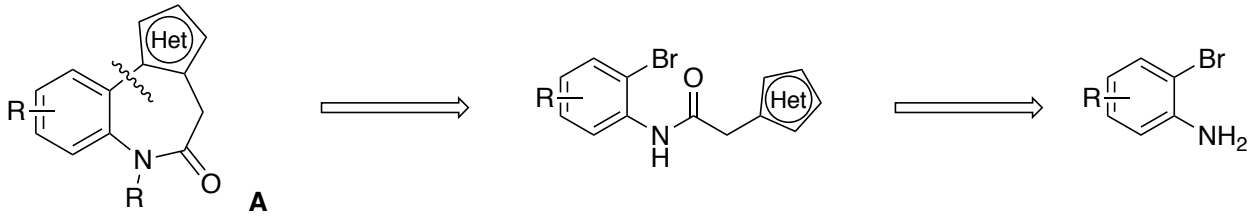


Figure 17

All the molecules in the figure belong to the class of the benzodiazepines, a very important class of compounds commonly used for their interaction with the nervous central system (CNS).

Their synthesis is not simple: are needed a lot of steps and usually high cost with regard to time and reagents.

With our protocol it is possible in principle to synthetize the benzodiazepine **A** and this new approach is meant to be an alternative to the classical chemistry with the purpose of showing the importance and usefulness of this new methodology (Scheme 36).



Scheme 36

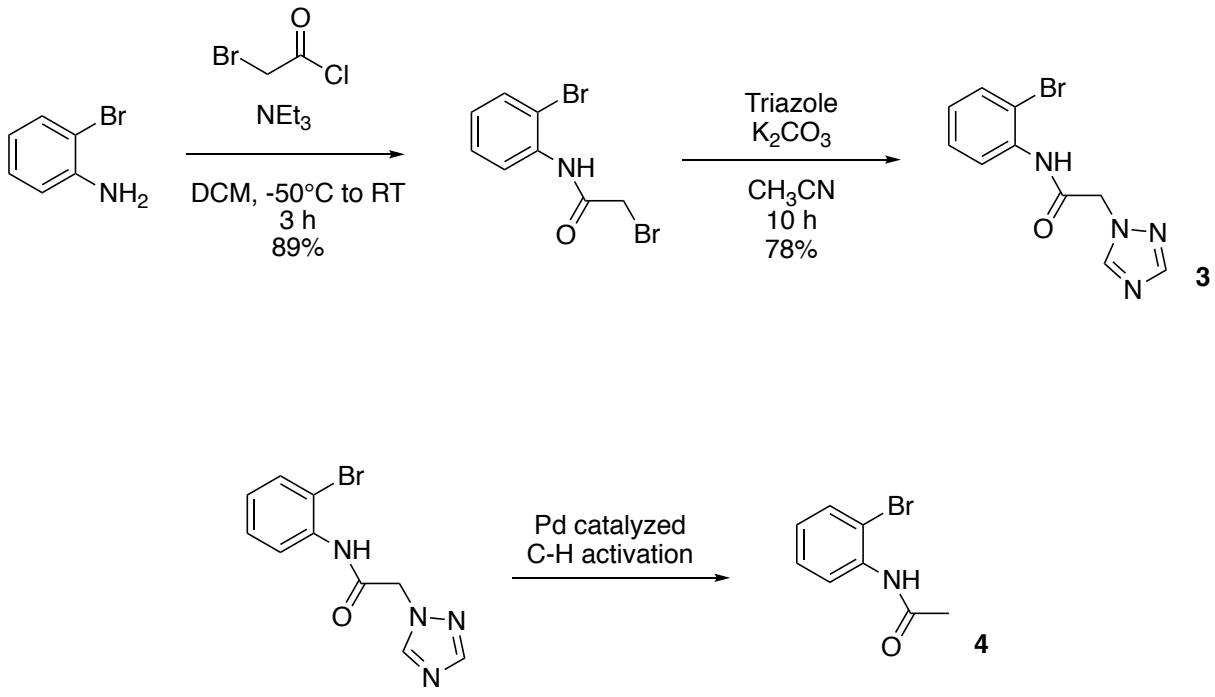
[69] Staben, S.T.; Ndubaku, C.; Blaquiere, N. *Bio. Med. Chem. Lett.* **2013**, 23, 2606-2613

As in all the reactions showed above, the starting material can be synthetized from the cheap and commercially available corresponding heteroatom-source, here the 2-bromo-aniline.

In this case the protection of the amine is necessary to afford the target product because the free NH is not compatible with the C–H activation conditions.

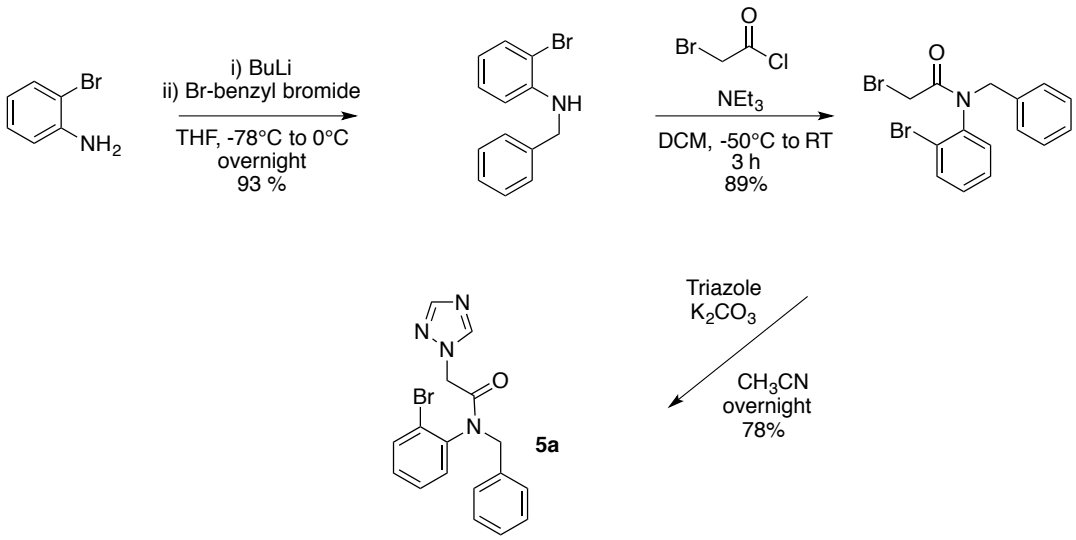
In fact, if we use directly the substrate **3** for the cyclization, we observed formal removal of the heterocycle, which led to the amide **4**.

The formation of this by-product is due to the insertion of the metal in the carbon-nitrogen bond: for our purpose this is a side product but unfortunately is also the only pathway of the reaction.



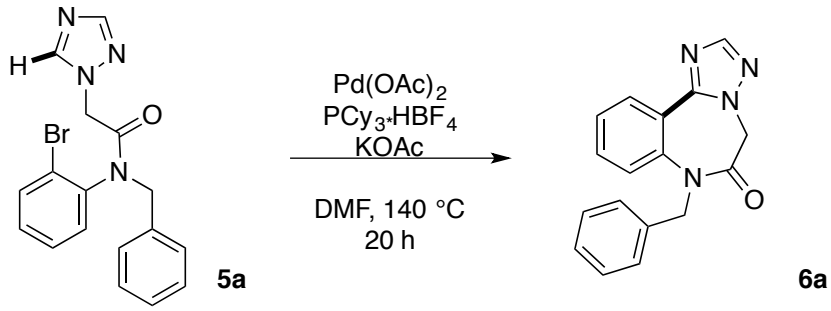
Scheme 37

The benzyl group was chosen as protecting group because is commonly used in classical chemistry for this purpose and can be deprotected with different methods and great tolerance of functional groups.The protection of the NH is realized in the first step of our strategy that includes also the formation of the amide in the second part; the last reaction is the classical alkylation of the triazole (Scheme 38).



Scheme 38

At this point is possible to try the cyclization reaction.



Entry	$Pd(OAc)_2$	PCy_3*HBF_4	KOAc	Yield (%)
1	1.0 mol %	1.5 mol %	1.2 equiv	22
2	2.5 mol %	3.75 mol %	1.2 equiv	34
3	5.0 mol %	7.5 mol %	1.2 equiv	42
4	10 mol %	15 mol %	1.2 equiv	56

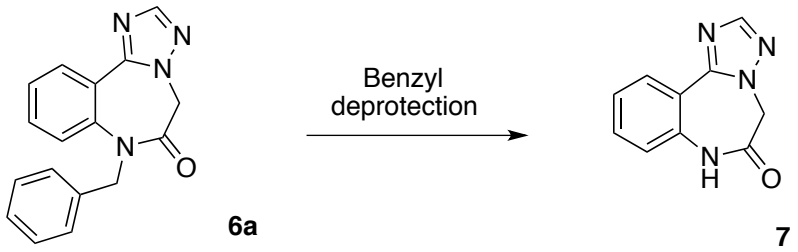
Table 10

In the table 10 are summarized all the experiments.

Once confirmed the structure of the product, we tried to modify the catalyst loading; in that case we started with the best result of 1 mol%. Unfortunately, under that conditions the product was recovered in a very low yield compared with the experiments done in the first part; the case of 10 mol % of palladium instead led to a yield higher than 50 %. We tried to use also more than 10 mol % (15% and 20%) but with these conditions we obtained a lot of side products making the purification more difficult. As the last experiment, the reaction was performed for 48 h instead of 20 h, but the result in entry 4 is still the best.

Maybe these results are related to the rigidity of the system: both the benzyl and the amide can forbid the rotation of the chain, making the C–H activation process less favoured.

To perform the deprotection of the benzyl group we tried different protocols and approaches, but finally we realized it.



6a **7**

Entry	Catalyst	Reagent	Solvent	Time	Yield (%)
1	Pd/C 10 wt	H_2 1 atm	MeOH	24 h	No reaction
2	Pd/C 10 wt	H_2 1 atm	MeOH/Acetic acid	36 h	No reaction
3	Pd/C 80 wt	H_2 1 atm	EtOH/Acetic acid	36 h	< 20*
4	/	/	TFA	24 h	No reaction
5	/	Triflic acid	TFA	24 h	75

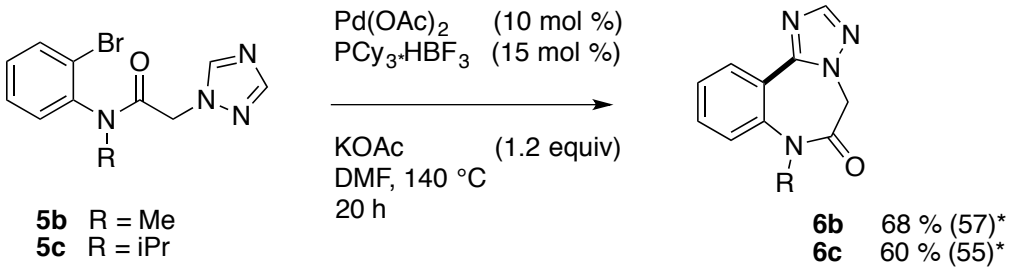
Table 11 ***Not fully conversion of the substrate**

Our function is not a simple benzyl group because is a benzyl-amide, but we tried first the most commonly used deprotection methods. Usually the benzyl group is deprotected with a heterogeneous hydrogenation on Pd/C (first three entries) but in our case, the reactions didn't work except in entry 3 but with a great amount of catalyst and a low yield of the product.

We tried in entry 4 the deprotection with TFA but unfortunately no reaction occurs and the substrate was recovered unreacted. In entry 5, with very harsh conditions, we obtained the target product in 75% yield after 24 h of reaction.

In conclusion we obtained the desired benzodiazepine in five steps starting from the 2-Bromo aniline. The strategy is very cheap and the whole process has the 31% of yield, not common for the synthesis of a benzodiazepine.

Not only the benzyl group can be used for the cyclization reaction (Scheme 39)



Scheme 39

***Reaction performed using 5 mol % of $Pd(OAc)_2$ and 7.5 mol % of $PCy_3{*}HBF_4$**

In the last part of the work we proposed also the synthesis of some analogues of the inhibitor of the hepatitis C virus, which present the indole as the nitrogen heterocycle.

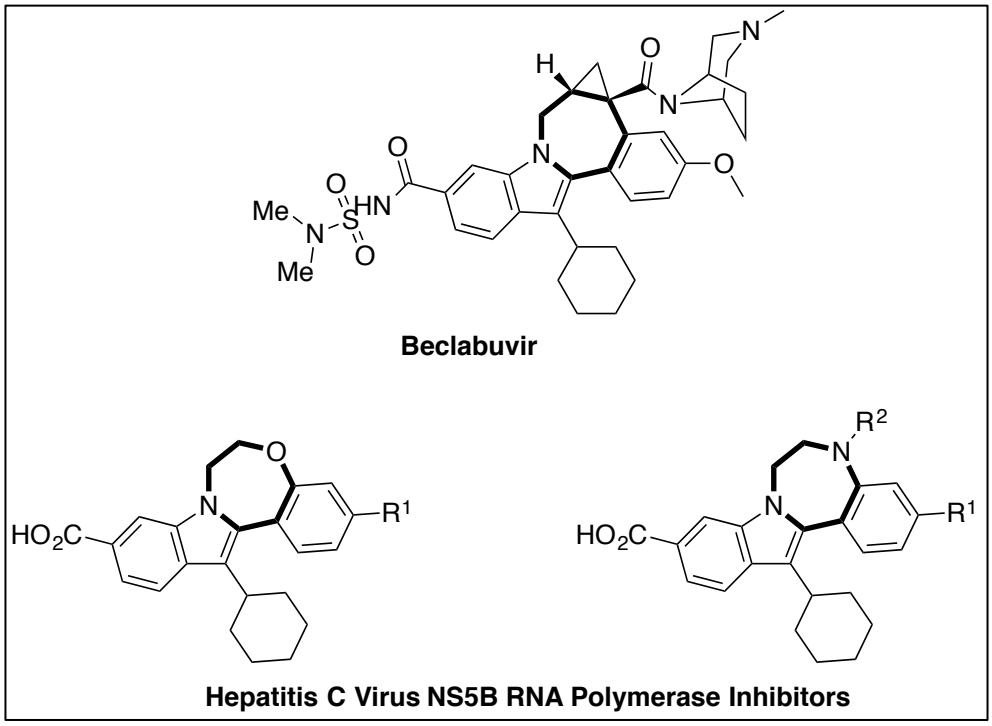
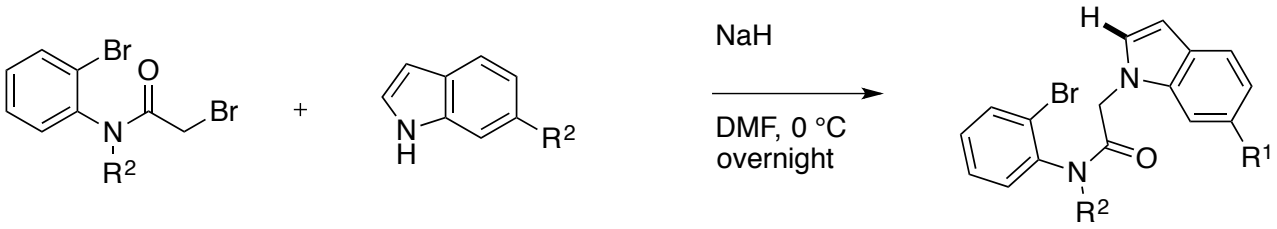
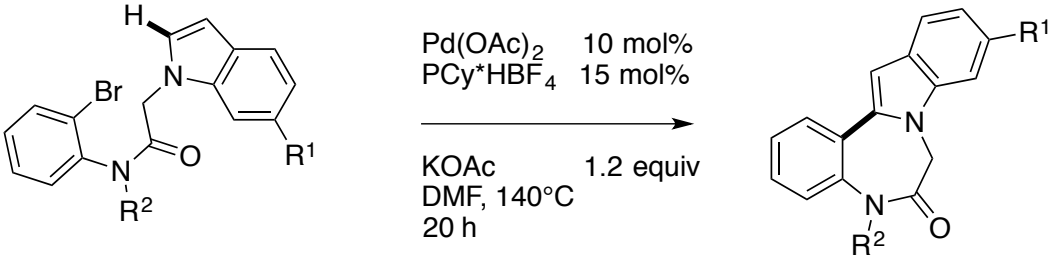


Figure 18 Examples of some inhibitor of the hepatitis C virus

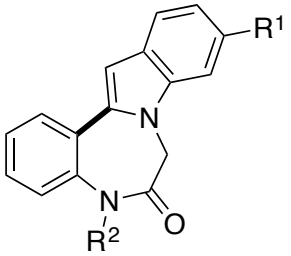
Substrates synthesis



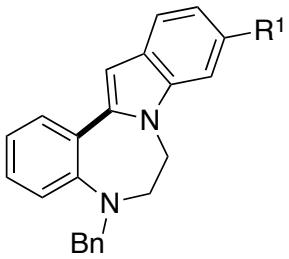
C-H activation reaction



8a-d $R^1 = CO_2Me$



9a R^2 = Bn 66 %
9b R^2 = Me 71 %
9c R^2 = iPr 54 %



9d 59 %

Scheme 40

At this point, in order to exploit the biological activity of these new benzazepines, some biological tests were carried out. First, due to chemical similarity, we tried the inhibition activity against the PI3-β kinase without any positive results.[42] On the other hand, our molecular modeling studies carried out on known available HSP90 inhibitors, showed that the benzofused azepines could be a interesting lead compounds.[70]

Compounds	kD (μM)	Compounds	kD (μM)
2k	**0.105 ± 0.012**	**2y**	20.9 ± 2.3
2n	5.71 ± 0.77	**2ad**	**0.63 ± 0.16**
2i	15 ± 0.2	**2d**	3.77 ± 1.40
9a	790 ± 5	**2g**	20.1 ± 2.3
9c	12.8 ± 0.2	**2a**	97.5 ± 6.2
2l	2390 ± 18	**2h**	3.59 ± 1.40
2s	34.8 ± 1.40	**2b**	4.48 ± 5.0
7	**0.005 ± 0.026**	**2aa**	51.6 ± 6.2
6a	15 ± 0.7	**2t**	677 ± 5
6b	13.2 ± 1.6	**2ae**	3.57 ± 1.40
2af	10.2 ± 2.3	**2w**	1.96 ± 2.1

Table 12 Pseudo-thermodynamic dissociation constants measured by SPR

Indeed, we were delighted to find that some compounds showed appreciable binding to recombinant human Hsp90α protein in a surface plasmon resonance (SPR) assay using 17-AAG as a positive control.[71, 72] Analysis of the SPR sensorgrams indicates that six compounds (**2k**, **2h**, **2o**, **2ad**, **2ae** and **7**) interacted with the protein in the range of μM (Table 12). Compounds **2k** and especially **7**, were shown to have a high affinity towards the chaperon, as inferred by the measured KD values falling in the nM range. 5H-Benzo-triazolodiazepinone **7** shows an activity even higher than NVP-AUY922, one of the most active reference compounds (Table 13).

Heatshock protein Hsp90 is a ubiquitous ATP-dependent molecular chaperone which promotes the correct folding and stability of proteins together with other co-chaperones.[73, 74, 75, 76]

[70] Matteo Virelli, Master Thesis, **2014/2015** "Studio di metodologie di attivazione C-H per la sintesi di nuovi inibitori dell'HSP90"

[71] Dal Piaz, F.; Vassallo, A.; Temraz, A.; Cotugno, R.; Belisario, M.A.; Bifulco, G.; Chini, M.G.; Pisano, C.; De Tommasi, N.; Braca, A. *J. Med. Chem.* **2013**, 56, 1585-1595

[72] Guo, W. C.; Reigan, P.; Siegel, D.; Zirrolli, J.; Gustafson, D.; Ross, D. *Cancer Res.* **2005**, *65*, 10006-10015

[73] Wang, H.; Lu, M.; Yao, M.; Zhu, W. *Mol. Clin. Oncol.* **2016**, 5, 326-334

[74] Buchner, J. et al. *J. Bio. Chem.* **2017**, 292, 17073-17083

[75] Zhao, Q-S. et al. *J. Med. Chem*. **2017**, 60, 9053-9066

[76] Forsberg, L. K.; Liu, W.; Holzbeierlein, J.; Blagg, B. S. J. *Bioorganic & Med. Chem.* **2017**, 27, 4514-4519

Hsp90 is commonly expressed in eukaryotes, but is also over-expressed at 2-10 fold higher levels in tumor cells compared to normal cells, suggesting that it may be extremely important for the survival and growth of cancer cells.

Targeting Hsp90 by designed low-molecular weight compounds, constitutes an exciting therapeutic approach and, at the same time, provides access to possible targets, such as specific Hsp90 co-chaperones.

To better rationalize the distinct activities of the various compounds and better understand the outcome of the biological tests, helped by Professor Giorgio Colombo (University of Pavia) and Dr. Elisabetta Moroni (IRCCS MultiMedica), we envishioned a complete docking analysis.

The crystal structures of the receptor were obtained from the RCSB Protein Data Bank (PDB), PDB code 2CCS (resolution 1.79 Å), where the N-terminal domain of Hsp90 has been co-crystalized with the piperazine-containing compound **A**:

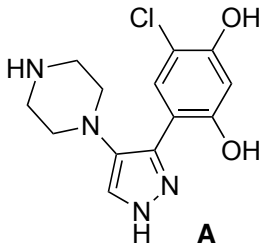


Figure 19 Piperazine-containing compound

With his procedure was possible to reproduce the binding pose of the crystal structure 2CCS, with a RMSD between the crystal pose and the docking calculation of the two ligands of 0.57 Å. Figure 19 reports on the overlay of the crystal structure (green) and the binding pose of compound **A** (pink).

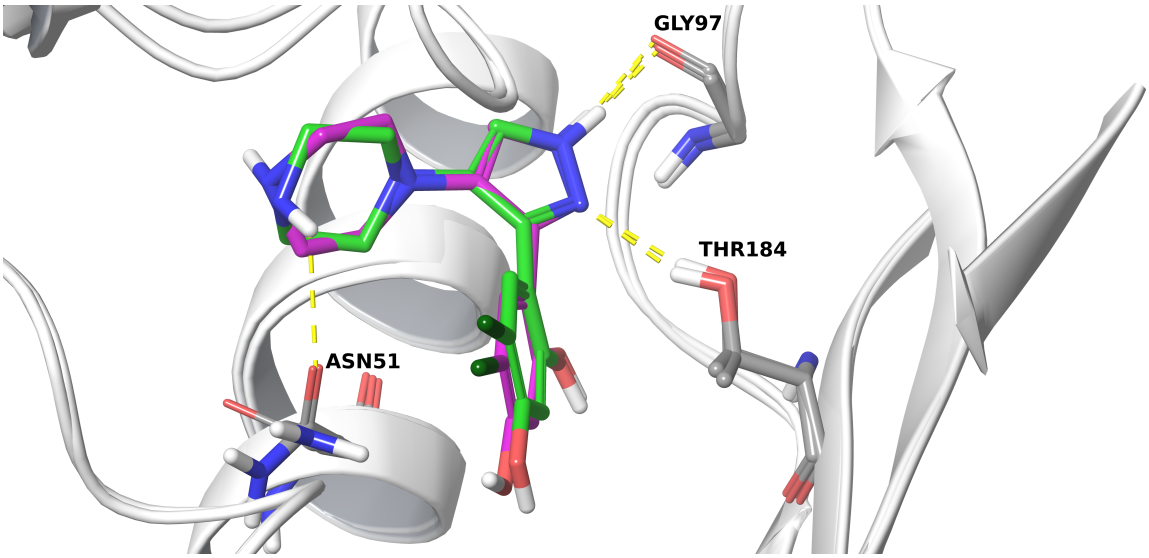


Figure 20 Superposition of the crystal structure 2CCS of compound A (pink) in complex with the NTD of Hsp90 and the best binding pose obtained from docking calculations (green). Yellow dashed lines represent H-bond interactions.

Figure 19 shows that compound **A** in the crystal structure 2CCS establishes HydrogenBond (HB) interaction with residues THR184, ASN51, and GLY97.

It is worth reminding the interactions established by ATP in the N terminal domain of Hsp90 (Figure 20): the N6 atom of the adenine group forms a direct hydrogen bond with the carboxyl group of ASP93, which is know to be critical for recognition of the nucleotide, while the N1 atom of the adenine ring forms a HB bond with residues THR184. A magnesium ion is coordinated with oxygen atoms of the α-, β-, and γ-phosphate groups, the side chain of ASN51 and two water molecules.

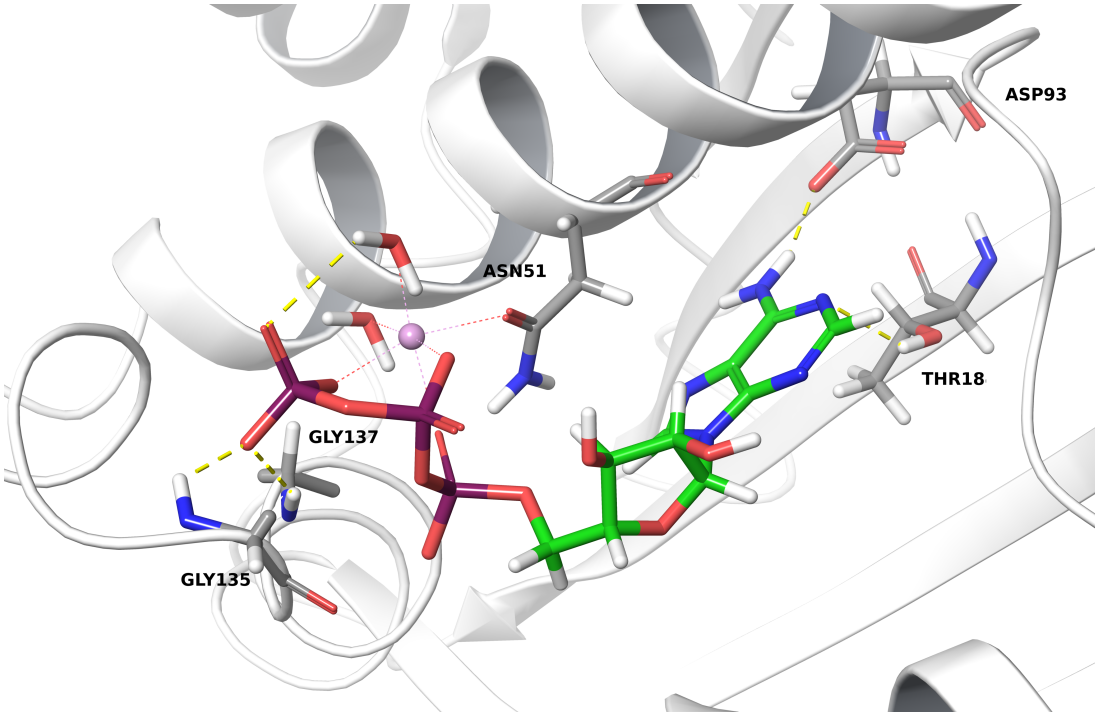


Figure 21 Crystal structure of **ATP** (green) in complex with the NTD of Hsp90 (pdb code **3t0z**). The pink sphere represents a magnesium ion. Yellow dashed lines represent H-bond interactions.

The most active compound **7** showed five possible binding poses within 3 Kcal/mol from the lowest energy one. The lowest energy binding pose is also the most represented among the 20 poses that

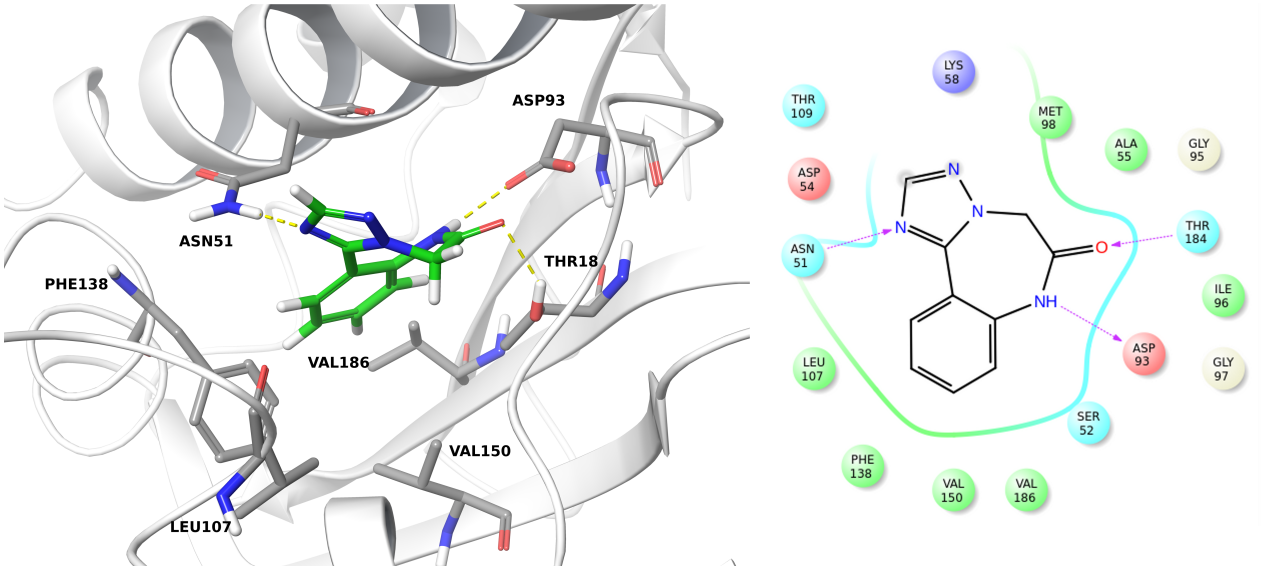


Figure 22 3D and 2D best binding pose of compound **7** (green) in complex with NTD of Hsp90. In the 2D representation, amino acids are colored according to hydrophobicity, charge, and polarity (Gray- GLY, dark green- hydrophobic, cyan- polar uncharged, blue – positives, red – negatives). Yellow dashed lines represent H-bond interactions.

have been retained at the end of the docking run. Docking calculations of the stage 4 were performed using two different methodologies, SP and XP. XP does more extensive sampling than SP and it uses a more sophisticated scoring function, with stricter requirements for ligand-receptor shape complementarity. The XP run confirmed that the most represented binding pose corresponds to the most represented one observed in SP run. In this binding pose compound **7** establishes a network of HB interactions with the critical residue ASP93 and residues ASN51 and THR184 (Figure 21) and accommodates its benzene ring in a hydrophobic pocket made by LEU107, PHE138, VAL150, VAL186 (pocket A). In the most represented binding pose, compound **2i** overlaps almost perfectly with compound **7**. The N2 and N4 atoms of the triazole ring are able to establish HB interactions with LYS58 and ASN51, and the benzene ring accommodates in hydrophobic pocket A as observed for compound **7**, however compound **2i** lacks of the possibility of establishing any interactions with ASP93 and THR184 (Figure 22).

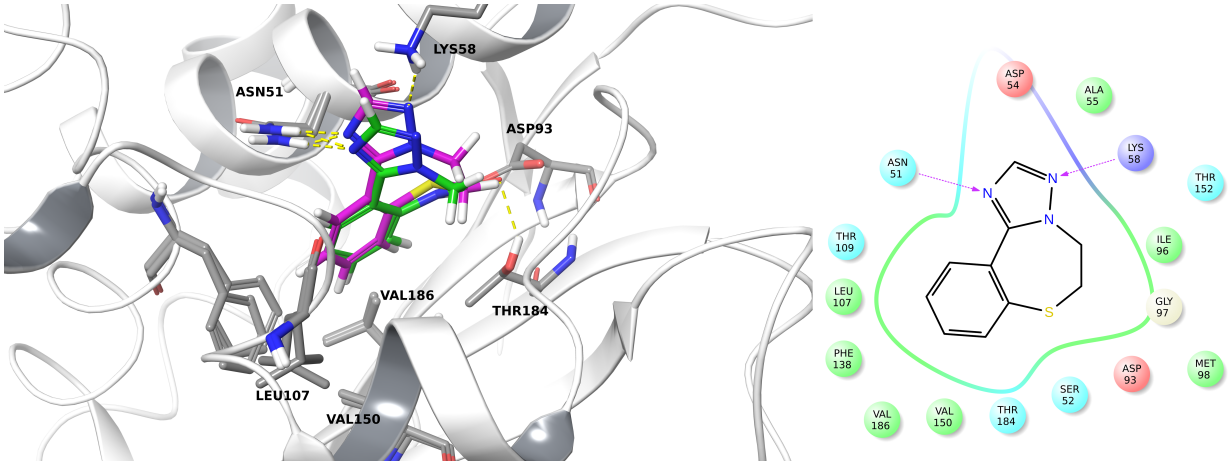


Figure 23 Docking pose of compound **2i** in the NTD of Hsp90. 3D representation shows the superposition of the best binding poses of compounds **2i** (pink) and **7** (green). In the 2D representation of the best binding pose of **2i**, amino acids are colored according to hydrophobicity, charge, and polarity (Gray- GLY, dark green- hydrophobic, cyan- polar uncharged, blue – positives, red – negatives). Yellow dashed lines represent H-bond interactions.

The binding pose of compound **6a** is slightly different compared to the binding mode of compound **7**. In particular, compound **6a** is rotated in the binding site so that the carboxyl group in the azepine ring still engages in HB to THR184, but the benzyl group accommodates more deeply in the hydrophobic pocket compared to the benzene ring of compound **7**. The N2 and N4 atoms of the triazole ring can establish HB interactions with LYS58 and GLY97 (Figure 23).

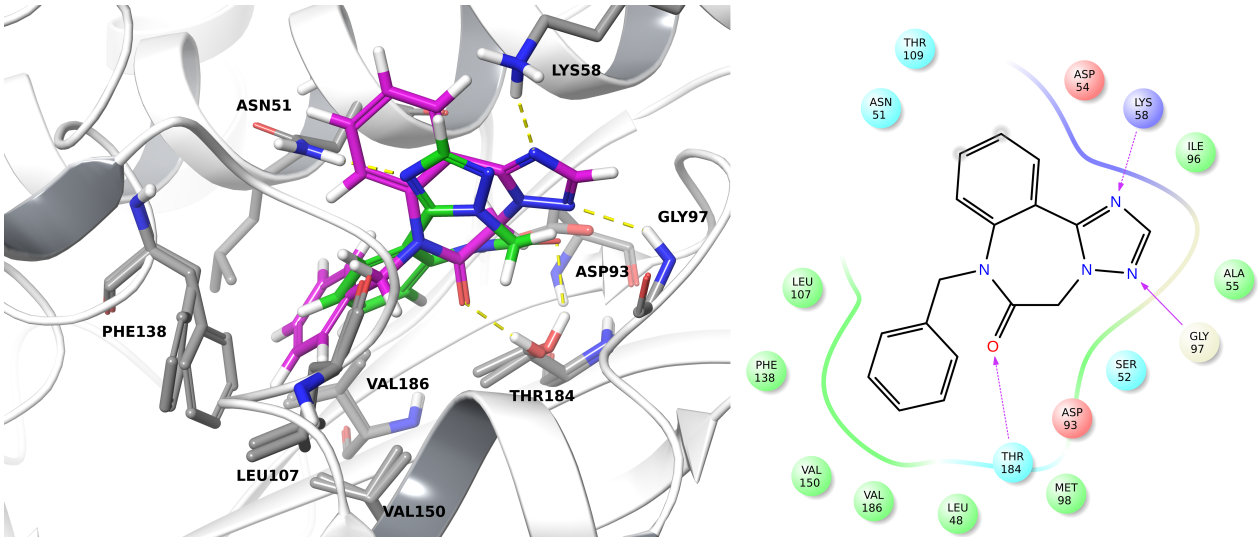


Figure 24. Docking pose of compound **6a** in the NTD of Hsp90. 3D representation of the ligand-protein interaction shows the superposition of the best binding poses of compounds **6a** (pink) and **7** (green). In the 2D representation, amino acids are colored according to hydrophobicity, charge, and polarity (Gray- GLY, dark green- hydrophobic, cyan- polar uncharged, blue – positives, red – negatives). Yellow dashed lines represent H-bond interactions.

Compound **6b** has a very similar binding mode to compound **6a**. The N2 atom of the triazole ring can establish a HB interaction with LYS58, while the carbonyl group of the azepine ring can bind residue THR184. The entire scaffold is slightly shifted in respect to compound **6a**, and this shift

orients the methyl group in the azepine ring towards the hydrophobic pocket A. However, this group cannot accommodate inside pocket A, unlike the long benzyl group of compound **6a** (Figure 24).

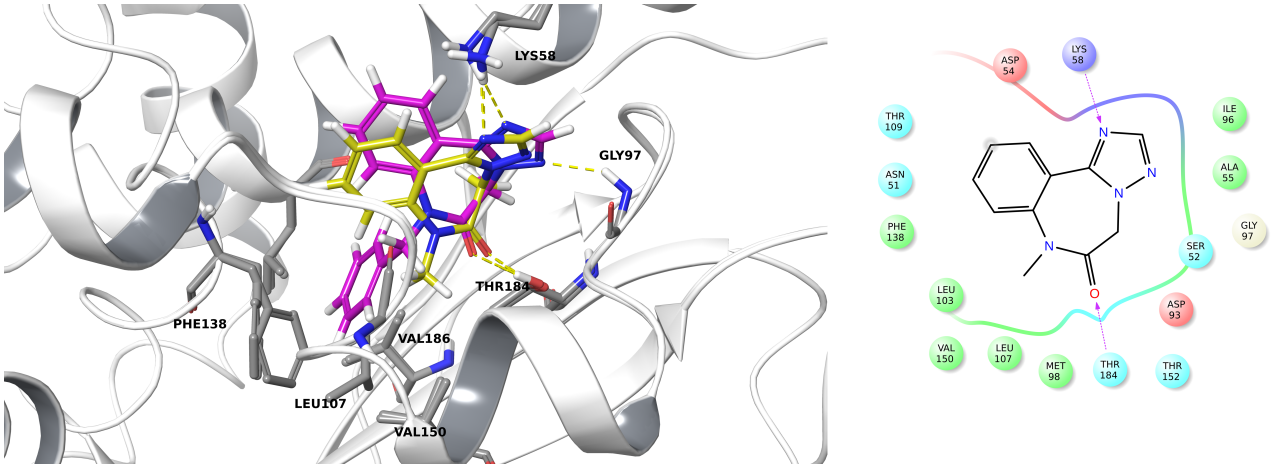


Figure 25 Docking pose of compound **6b** in the NTD of Hsp90. 3D representation shows the superposition of the best binding poses of compounds **6a** (pink) and **7** (yellow). In the 2D representation of the best binding pose of **7**, amino acids are colored according to hydrophobicity, charge, and polarity (Gray- GLY, dark green- hydrophobic, cyan- polar uncharged, blue – positives, red – negatives). Yellow dashed lines represent H-bond interactions.

From this analysis the interactions that seem to favour the binding are the H bonds with ASP93 and THR184 (see compound the comparison between **2i** and **2b**), while some improvements could be obtained optimizing the interaction with the hydrophobic pocket A (see for example the Bn group of compound 6**a** compared to the metyl group of copound **2c**).

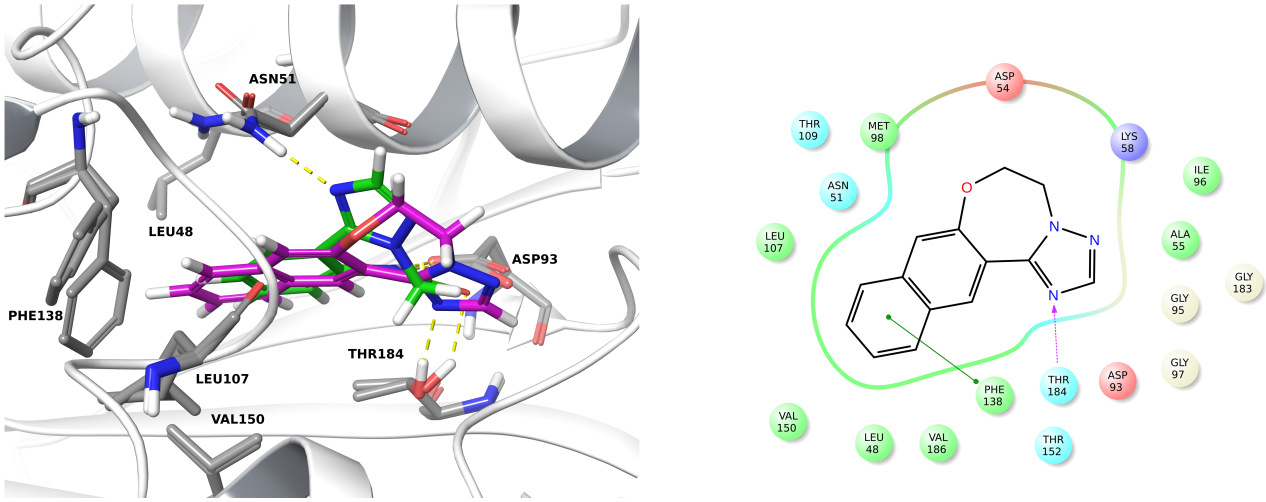


Figure 26 3D and 2D docking pose showing interaction for compound **2h** in the binding site of the NTD of Hsp90. Best poses of compounds **2h** (pink) and **3b** (green) have been superimposed in the 3D representation. In the 2D representation of the best binding pose of **2h**, amino acids are colored according to hydrophobicity, charge, and polarity (Gray- GLY, dark green- hydrophobic, cyan- polar uncharged, blue – positives, red – negatives). Yellow dashed lines represent H-bond interactions.

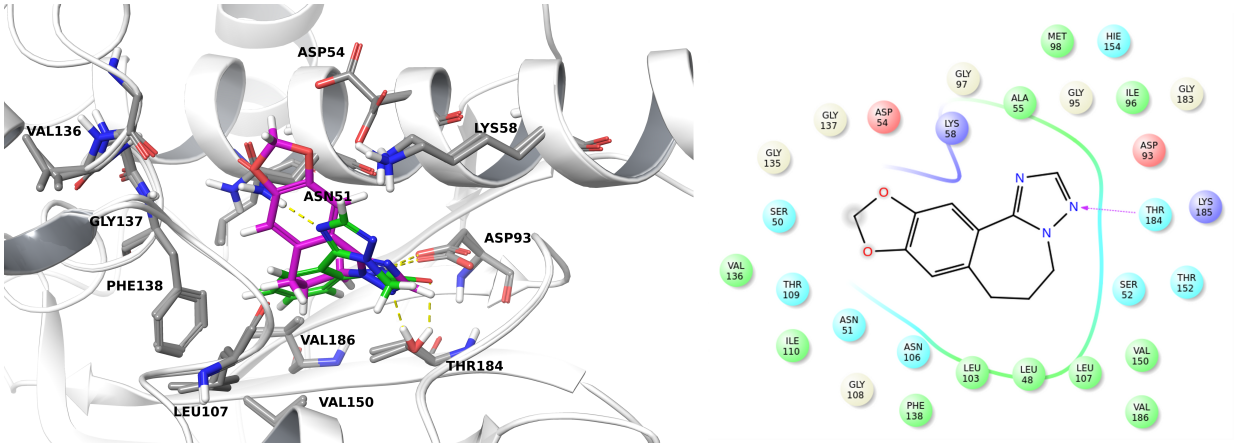
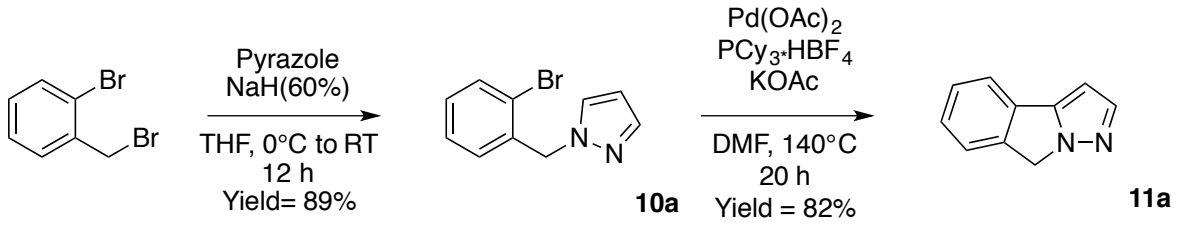


Figure 27 3D and 2D docking pose showing interaction for compound **2b** in the binding site of the NTD of Hsp90. The 3D representation shows the best poses of compounds **2b** (pink) and **7** (green). In the 2D representation of the best binding pose of **2b**, amino acids are colored according to hydrophobicity, charge, and polarity (Gray- GLY, dark green- hydrophobic, cyan- polar uncharged, blue – positives, red – negatives). Yellow dashed lines represent H-bond interactions.

As our delight, we found that with this protocol is possible to obtain not only benzazepines but also polycyclic structures containing a five membered ring between the two aromatic moieties (Scheme 40).



Scheme 41

The protocol, in that case, gave us a good yield for the target product **11a**, which is the only product obtained and there is no evidence of the unstable product of the pyrazole C-4 functionalization.

The protocol led us also to pyrazole already substituted at C-3 (Figure 18).

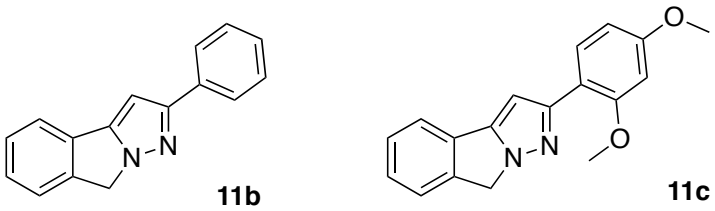


Figure 28 Other possible targets

We can conclude that in this first part, we proposed the palladium catalyzed C–H activation as an effective strategy for the step-economical synthesis of benzo-fused seven-membered heterocycles. The protocol is simple, is characterized by low catalyst loading, mild bases and ample substrate scope to various azepines, benzoxazepines, thiazepines, and even benzodiazepines. In contrast to

cross-coupling-based strategies, our approach involves the direct activation of otherwise inert C–H bonds without the need for tedious prefunctionalizations.

The approach shows a wide versatility as regards both the aromatic heterocycle and the spacer, which can present different functional groups or heteroatoms. In the case of the amidic function, the lower yield of process is due to the more rigid spacer that can influence the intramolecular fashion of the reaction; here is also necessary to protect the free N-H bond before the C–H activation step.

The reaction consists of a Pd^{0}-Pd^{II} catalytic cycle in which the key step is the metalation process due to a bidentate base; like a lot of C–H activation reactions, also in our approach, are needed high temperatures and is not possible to define it a mild functionalization.

It should be pointed out as a positive outcome of the biological tests, let us say that some of the compounds synthesized present a high biological acitivty: these identified structures are low molecular weight inhibitors of HSP90 with a relatively new scaffold.

Besides, the computational study allows us to rationalize better the distinc activities of our molecules giving an idea of their position in the pocket task of the protein; structural modifications potentially able to improve their inhibitory activity are put forward.

Furthermore, these structures open the way to a subsequent functionalization on the heterocycle moiety with a C–H activation strategy but in this case in an intermolecular fashion; this type of functionalization is commonly called *late stage diversification* and is very useful in pharmaceutical chemistry because is possible to obtain a library of compounds directly from the same precursor and in a short time.

We will discuss the intermolecular C–H activation in the next chapter.

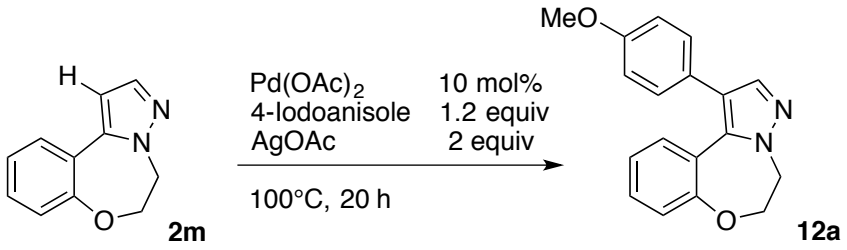
7 The C(Sp^2)–H palladium catalyzed intermolecular C–H activation

This part of the work consists in the functionalization of some of the benzazepines obtained in the previous part.

The intermolecular C–H activation is a useful method to achieve a library of molecules starting from the same substrate and give access to a good functional groups diversification in only one step. As regards the substrates we had two class of possible candidates: the one with the pyrazole moiety and the other with the 1, 2, 4 triazole. The first class is more fascinating because in this nitrogen heterocycle we have two free C–H bonds and so a clear regioselectivity problem; the second one instead has only one free C–H bond and so there is only one reaction's pathway.

For this *late-stage* diversification we supposed the Pd^{II}-Pd^{IV} catalysis as the effective catalysis for the purpose. The first step is the insertion of the metal in the carbon-hydrogen bond and the subsequent oxidative insertion led to the formation of the Pd^{IV} complex. This intermediate afford the desired product after the reductive elimination and release a Pd^0; here is necessary an internal oxidant to re-generate the active palladium(II) specie.

Starting with compound **2m** in our hands, was performed a methodological study with the 4-iodoanisole as the coupling partner in order to find the best conditions for this reaction.



Entry	Solvent	Conversion (%)	Yield (%)
1	PhMe	30	10
2	DMF	50	20
3	DMA	40	18
4	1,4-dioxane	/	/
5	*o*–Xylene	< 10	< 10
6	HFIP	/	/

Table 13 Solvent screening

The C–H activation is regioselective and only the C-4 of the pyrazole can be activated with this palladium catalysis; the reaction is driven by electronic factors and the C-4, the most nucleophilic position, reacts preferentially compared to the C-3, which is very difficult to functionalize also when all the other positions are substituted.

The best solvent seems to be the DMF (entry 2), which led to the functionalized product **12a** in 20 % yield; comparable result was obtained using the DMA (entry 3) instead no reaction occurs with 1,4-dioxane (entry 4).

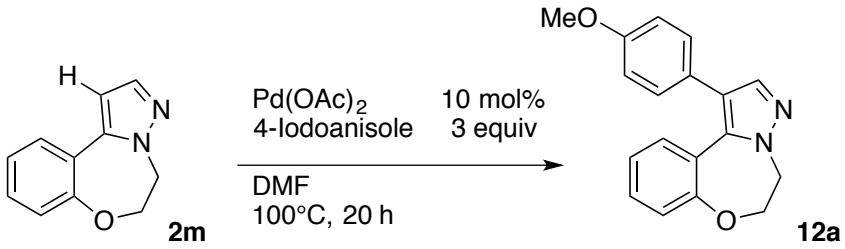
We tried also the HFIP as solvent because is known to be a good solvent for this class of reactions because it can modify the steric hindrance of the substrate, the coordination properties of the metal and in some cases also the mechanism of the reaction. Unfortunately, in this experiment (entry 6) the reagent was recovered unreacted.

Once found the best solvent, we tested the coupling partner; in particular, we focused our attention on the bromo and iodo-derivatives because the corresponding chloro one should be less reactive.

Entry	Coupling Partner	Yield (%)
1	4-idoanisole 1,2 equiv	20
2	4-idoanisole 1,5 equiv	23
3	4-idoanisole 2,2 equiv	26
4	4-idoanisole 3 equiv	30
5	4-bromoanisole 1,2 equiv	/
6	4-bromoanisole 1,5 equiv	/
7	4-bromoanisole 3 equiv	Traces

Table 14 Coupling partner screening

From 1.2 to 3 equivalent of the iodo-anisole was observed an increasing in the final yield (Table 14, entry 1 and 4) compared to the bromide in which no product was afforded also with 3 equivalents of the coupling partner (entry 7). Unfortunately, the conversion in all the experiments performed was not higher than 50 %.

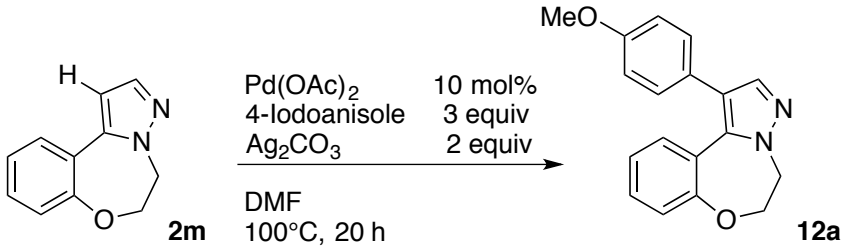


Entry	Base	Yield (%)
1	AgOAc 1,2 equiv	13
2	AgOAc 2 equiv	33
3	CsF 2 equiv	/
4	KOAc 2 equiv	< 10
5	Ag_2CO_3 2 equiv	42
6	K_2CO_3 2 equiv	30

Table 15 Base screening

In this part of the work was possible to observe as the silver salts gave us the best results and in particular the silver carbonate afforded compound **12a** in 42 % yield (entry 5).
Comparable yield was found with 2 equivalents of silver acetate (entry 2) and 2 equivalents of potassium carbonate (entry 6).

Another parameter we were really interested in was the possibility of using some additives, which could improve the yield of the whole process; we did some experiments in order to achieve this goal.



Entry	Additive 20 mol%	Yield (%)
1	Dppe	21
2	PPh_3	13
3	2,6-lutidine	/
4	Piv-OH	/
5	1,10-phenantroline	22
6	P(n-Bu)Ad_2	< 10

Table 16 Additive screening

The presence of additives in the reaction mixture seems to affect the reaction, but not in the positive manner: in all the experiments was obtained a lower yield compared to the one showed above.

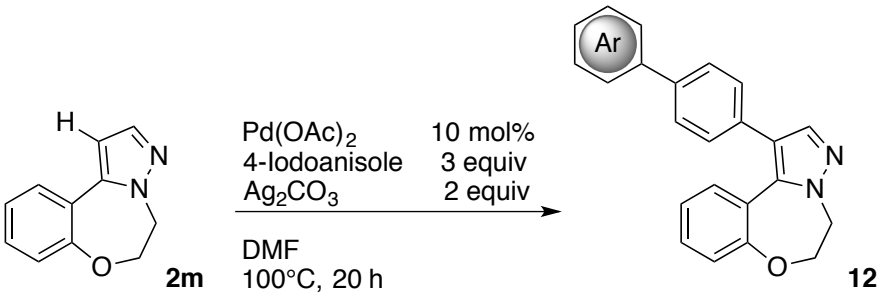
In particular, the 2,6-lutidine and the 1,10-phenantroline (entry 3 and 5) have a nitrogen atom which can competes with the metal for the coordination of the palladium atom and so can poison the catalyst.

To our delight, we tested also some other palladium sources.

Entry	[Pd] 10mol %	Yield (%)
1	$Pd(TFA)_2$	35
2	$PdCl_2(PhCN)$	Traces
3	$PdCl_2(PhMe)$	Traces
4	$Pd(OAc)_2$	42

Table 17 Palladium source screening

With the best conditions for the intermolecular palladium catalyzed C(sp^2)–H activation in our hands we extended the scope of the reaction in order to obtain a small library of benzoxazepines.



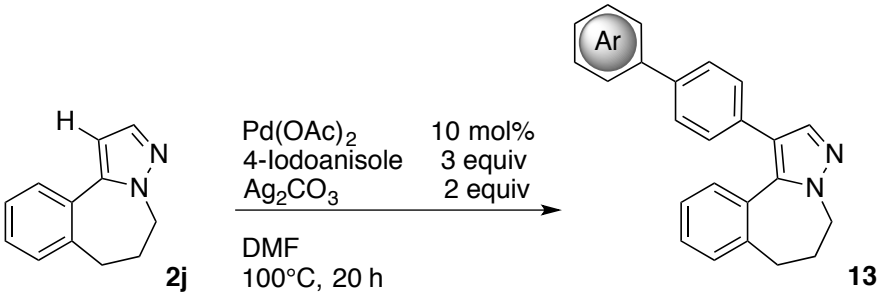
Entry	Iodo arene	Yield (%)
1	4-Iodoanisole	42
2	Methyl-4-Iodobenzoate	37
3	Ethyl-4-Iodobenzoate	33
4	4-Iodopyridine	< 10

Table 18 Substrate scope

Unfortunately, because of the low yields, we were not able to create a larger library; the 4-iodoanisole seems to be the best coupling partner for this reaction (entry 1) compared with the benzoates which led the product in 37 % and 33 % yield respectively (entry 2 and 3).

The reaction with the 4-Iodopyridine affords the product only in a small amount, not enough for a fully characterization (entry 4).

The same reaction was performed using the benzazepine **2j** as starting material and testing different coupling partners.



Entry	Iodo arene	Conversion (%)	Yield (%)
1	4-iodoanisole	/	/
2	Methyl-4-bromobenzoate	50	34
3	4-Iodopyridine	20	Traces

Table 19 Substrate scope for 10a

Unfortunately, the reaction didn't afford satisfactory yields, furthermore in some cases was not even possible to isolate the product (entry 1 and 3); the low yield was also the consequence of the not fully conversion of the starting material which was not higher than 50 % in the best case. Importantly, this is the the first example of one-pot functionalization of azepines and therefore an unexplored field.

This approach, the intermolecular C–H activation, can be a useful tool for the diversification of the same cores by varying only the reaction's partner, but the reaction is strongly dependent on the starting material. Specifically, the pyrazole moiety present in our benzazepines, can be regioselectively functionalized at the C-4, but with low yields: our library is so composed by only a few compounds.

Changing the catalysis from a Pd^{II}-Pd^{IV} cycle to a Pd^{0}-Pd^{II} similar to the one used in the cyclization reaction showed in the previous chapters didn't afford any advantages.

We do not think is a steric hindrance the reason of the poor reactivity, but at most the presence of this aryl system can influence the electronic factors of the pyrazole moiety and so the capacity of the C–H bonds to react. Certainly, further studies will be performed in order to use this process productively as in many examples regarding the late stage diversification present in literature.

8 PDE10 inhibitor synthesis

In literature there are different benzazepines structures expressing biological activity. Our purpose, in this part of the work, was to try the protocol showed in chapter 6 for the synthesis of well-known compounds used or studied to treat different diseases.

We focused our attention on the PDE10 inhibitor, an important compound well note in the scientific community for its role in the treatment of CNS disorders.

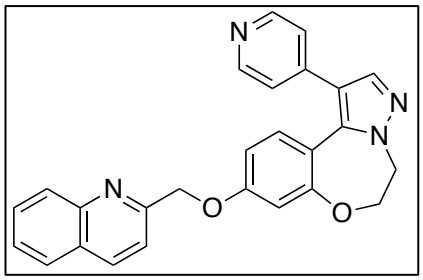


Figure 29 Target compound

The PDE are a class of enzymes able to degrade the phosphodiester bond in two second messenger molecules, the cyclic adenosine monophosphate (cAMP) and the cyclic guanosine monophosphate (cGMP). [77]

There are 11 different families of PDEs (PDE1-11), which differ for the target substrate, for the cinetic properties, the regulation mode and the location in the body. Therefore, it is clear that PDEs, given the broad range of subtypes and their varied tissue- and region-specific distributions, provide a range of possibilities as drug targets in various neurologic diseases.

In particular, the most important of the PDE10, the PDE10A, is located in the brain and for this reason is useful for the treatment of schizophrenia and of the Huntington disease. [78]

Because of the direct known relationship between dopamine and cAMP in dopaminergic signalling in the nigrostriatal system, there are certain studies that claim phosphodiesterase inhibitors also as possible anti-Parkinson's disease drugs.

As regarding our target compound, the *de novo* synthesis is not easy and involve the use of fine chemicals and multi-step process.[79]

The aim of this chapter is to emphasize the usefulness of the C–H activation as the key step of the new synthetic approach. Our plan is made of three different steps: the first which is the synthesis of the benzoxazepine core with the intramolecular palladium catalyzed C(sp^2)–H activation (see

[77] Nthenge-Ngumbau D. M.; Mohanakumar K. P. *Mol. Neurobiol* **2018**, 55, 822-834
[78] Blokland A.; Menniti F. S.; Prickaerts J. *Expert Opin. Ther. Patents* **2012**, 4, 349-354
[79] Patent WO 2008/001182 PCT/IB2007/001696

Chapter 6); the second which is the synthesis of the side chain and the last one which is the late stage diversification of the molecule with an intermolecular C–H activation (Figure 29).

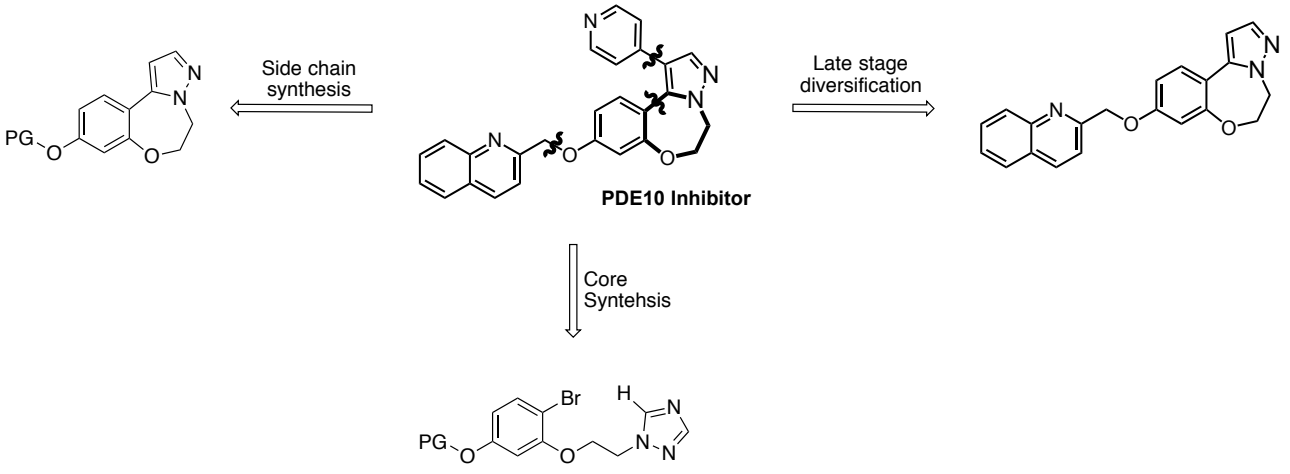
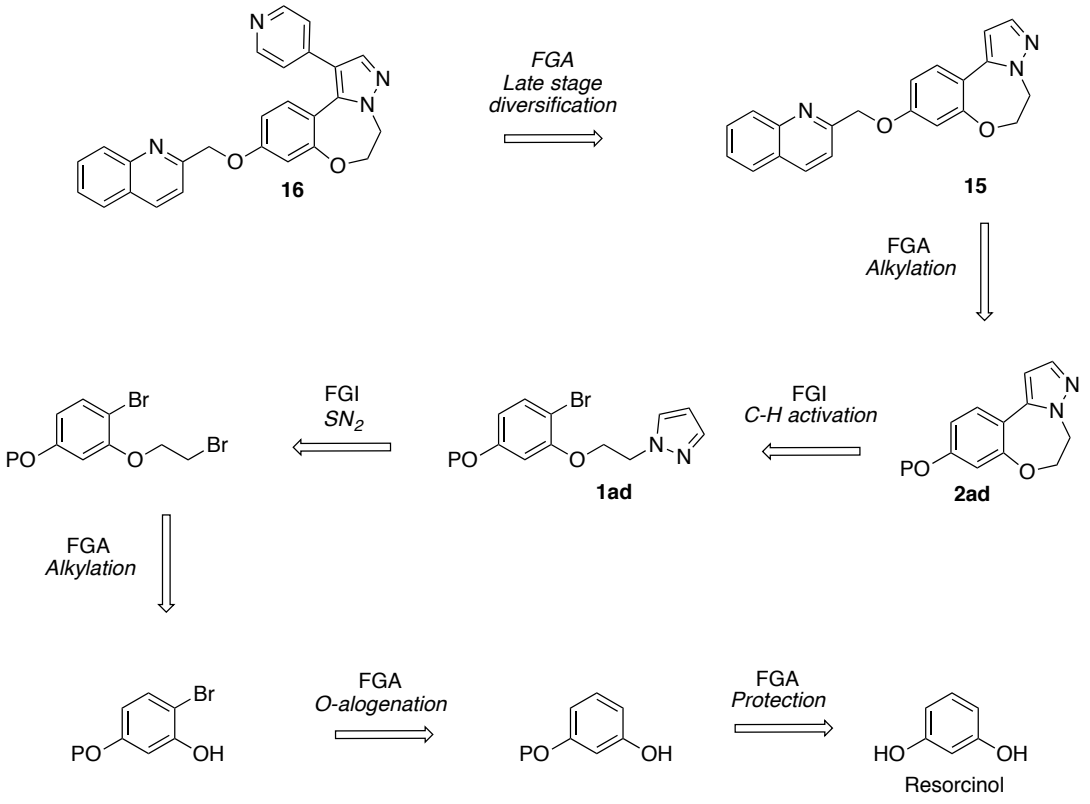


Figure 30

The retro-synthetic plan proposed for the PDE 10 inhibitor is shown in scheme 42: the starting material is a very cheap and commercially available reagent such as the resorcinol and due to its nature, is important to insert the protecting group of the free hydroxy already before the cyclization reaction.



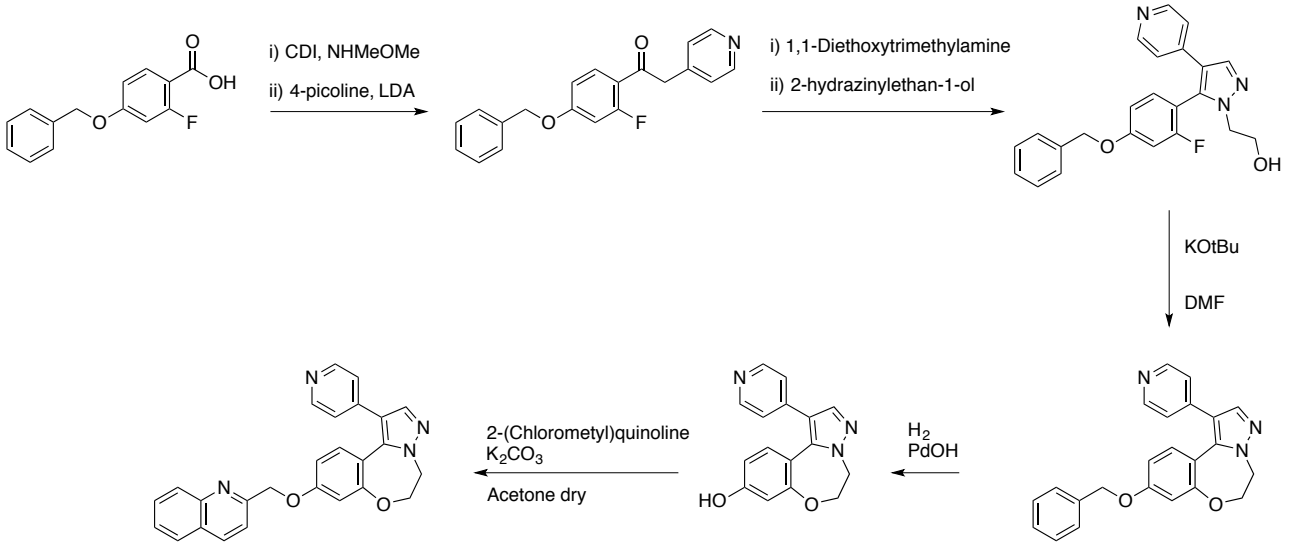
Scheme 42 Retroshyntetic strategy

The substrate **2ad** was used as model for the first part of the synthesis.

This new strategy paves the way to important developments in the pharmacological field because starting from the compound **15** you can get not only the desired inhibitor **16** but also a library of potentially biologically active molecules by changing the substituent on the pyrazole moiety. This means that with a diversification in the final step is not necessary to start again the synthesis, which is the main problem of the classical approach.

In fact, with the already used approach (Scheme 43) is not possible to have chemical differentiation on the pyrazole moiety because is already formed before the benzoxazepine core; for the synthesis of different compounds is necessary to change the reagent or to add new intermediate steps.

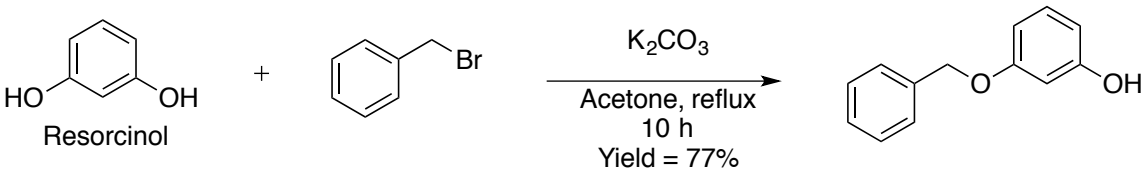
Another important aspect is that the SNA_r reaction, performed for the core's synthesis, is not so simple to perform: it cannot tolerate all the functional groups, needs a good leaving group and usually require harsh conditions.



Scheme 43 Classical approach

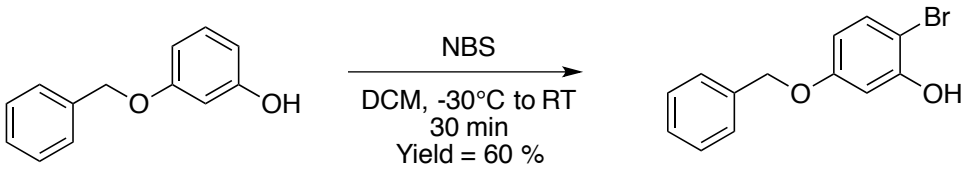
For the synthesis of the benzoxazepine core (see chapter 6), briefly we can see the several steps.

The protection of the hydroxyl group was performed with a classical SN_2 reaction toward the resorcinol, which gave us the desired mono-benzylated product in a very good yield.



Scheme 44 Monoprotection of resorcinol

The following reaction is an aromatic bromination with NBS in dichloromethane.[80, 81]

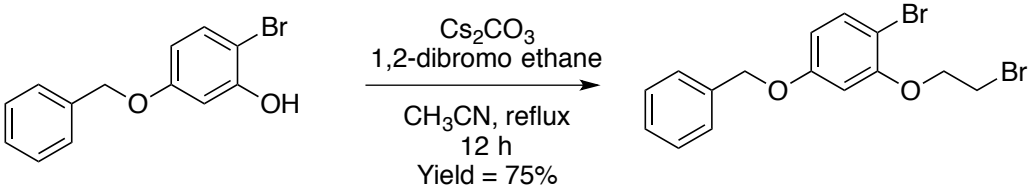


Scheme 45 Bromination reaction

In the compound there are two possible positions that can be functionalized, the C-4 and the C-6, the reaction is completely regioselective and led to the desired compound in a good yield.

The regiochemistry of the product was investigated through a NOESY experiment by irradiating the two benzylic protons; we observed NOE effect on the expected C-2 and C-6 protons (See experimental section).

The subsequent O-alkylation involve a SN_2 reaction between the phenol group and the 1,2 dibromoethane through Cs_2CO_3 as a base and CH_3CN as solvent.

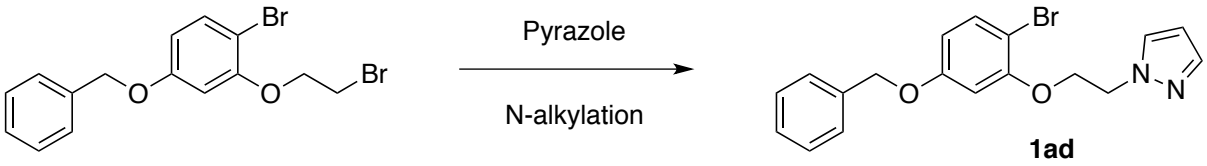


Scheme 46 O-alkylation reaction

[80] Pingali, S. R. K.; Madhav, M.; Jursic, B. S. *Tetrahedron letters* **2010**, 51, 1383-1385

[81] Sivakamasundri, S.; Ganesan, R. *Int. J. Chem. Kinet.* **1980**, 12, 837-850

Once prepared the alkylating agent, the next reaction was the synthesis of the substrate necessary for the intramolecular C-H activation.



Scheme 47 Pyrazole alkylation reaction

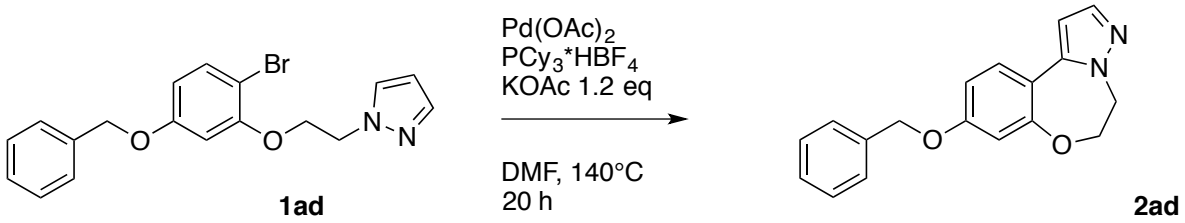
We tried different conditions for this reaction:

Entry	Base	Solvent	Additive	T(°C)	Yield
1	Cs_2CO_3	CH_3CN	/	reflux	50 %
2	NaH	THF	/	RT	40 %
3	NaH	THF	DMPU	RT	89 %

Table 20 Effectiveness of the DMPU additive

As mentioned in chapter 6, in some cases we didn't found a satisfactory yield using the classical condition for the alkylation of pyrazole (entry 2, Table 20). By adding DMPU as a cation scavenger, the product was obtained in very good yield (entry 3, Table 20).

At this point, we tried the cyclization reaction with the best conditions developed in the previous part.



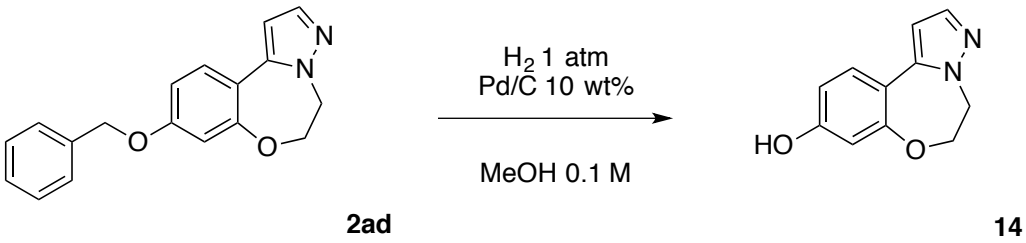
Entry	$Pd(OAc)_2$	$PCy_3{*}HBF_4$	Yield (%)
1	1.0 mol%	1.5 mol%	43
2	2.5 mol %	3.8 mol%	55
3	5 mol %	7.5 mol %	68

Table 21

Were tested different catalyst loading for detecting that the best result can be achieved using 5 mol % of palladium (entry 3, Table 21). The difficulties found in the cyclization of **1ad** are probably due to the substrate, which is more complex in terms of steric hindrance than the others mentioned in the first part.

The subsequent step is the formation of the side chain.

First of all, compound **2ad** was involved in the benzyl-deprotection by catalytic hydrogenation on palladium supported on carbon. This reaction is a classical heterogeneous hydrogenolysis with H_2 gas in protic solvent.

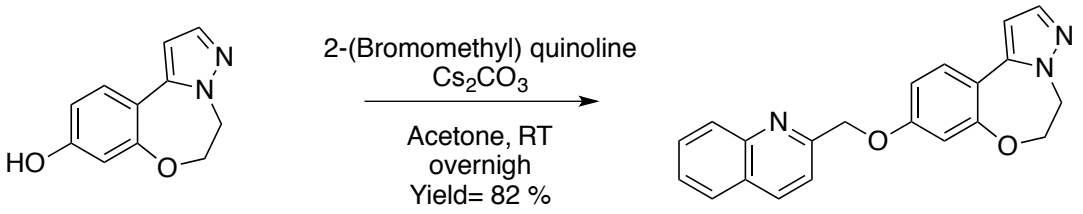


2ad **14**

Scheme 48 Deprotection reaction

Unfortunately, for us was impossible to change the pressure in the reaction and we worked with 1 atm of hydrogen. We started with methanol as solvent (Yield = 75%), but the best result was obtained with MeOH and 2% of CH_3COOH (Yield = 90 %).

The last reaction before the *late stage diversification* is a classical SN_2 of the phenolic group of compound **14** with the 2-(bromomethyl) quinoline.

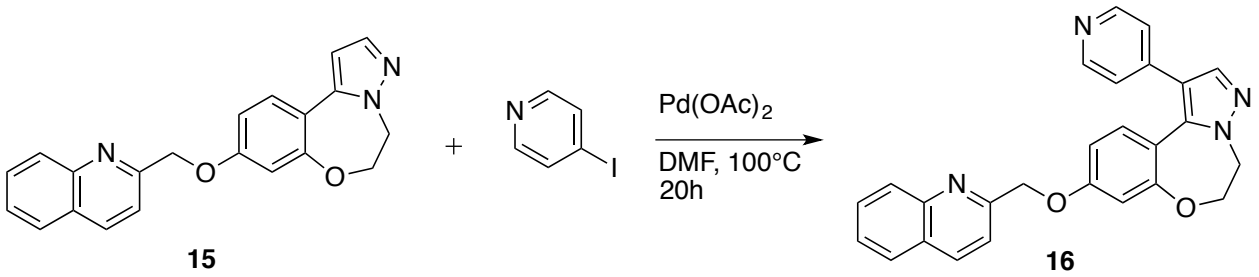


14 **15**

Scheme 49 Synthesis of the side-chain

The overall yield of the whole process for the synthesis of **15** (7 steps) is 15 %, a very good result because led to a polycyclic structure difficult to be achieved with a classical chemistry and starting from a very cheap reagent.

At this point we were able to try the C–H activation for the functionalization of the pyrazole moiety.



15 **16**

Scheme 50 Intermolecular C-H activation

Unfortunately, the study done for the intermolecular reaction (see Chapter 7), showed us how difficult this reaction is and in fact, also in this case, we faced some problems.

Entry	Base	Conversion (%)	Yield (%)
1	AgOAc 2 equiv	< 10	< 10
2	KOAc 2 equiv	< 10	< 10
3	Ag_2CO_3 2 equiv	< 10	< 10
4	K_2CO_3 2 equiv	< 10	< 10

Table 22

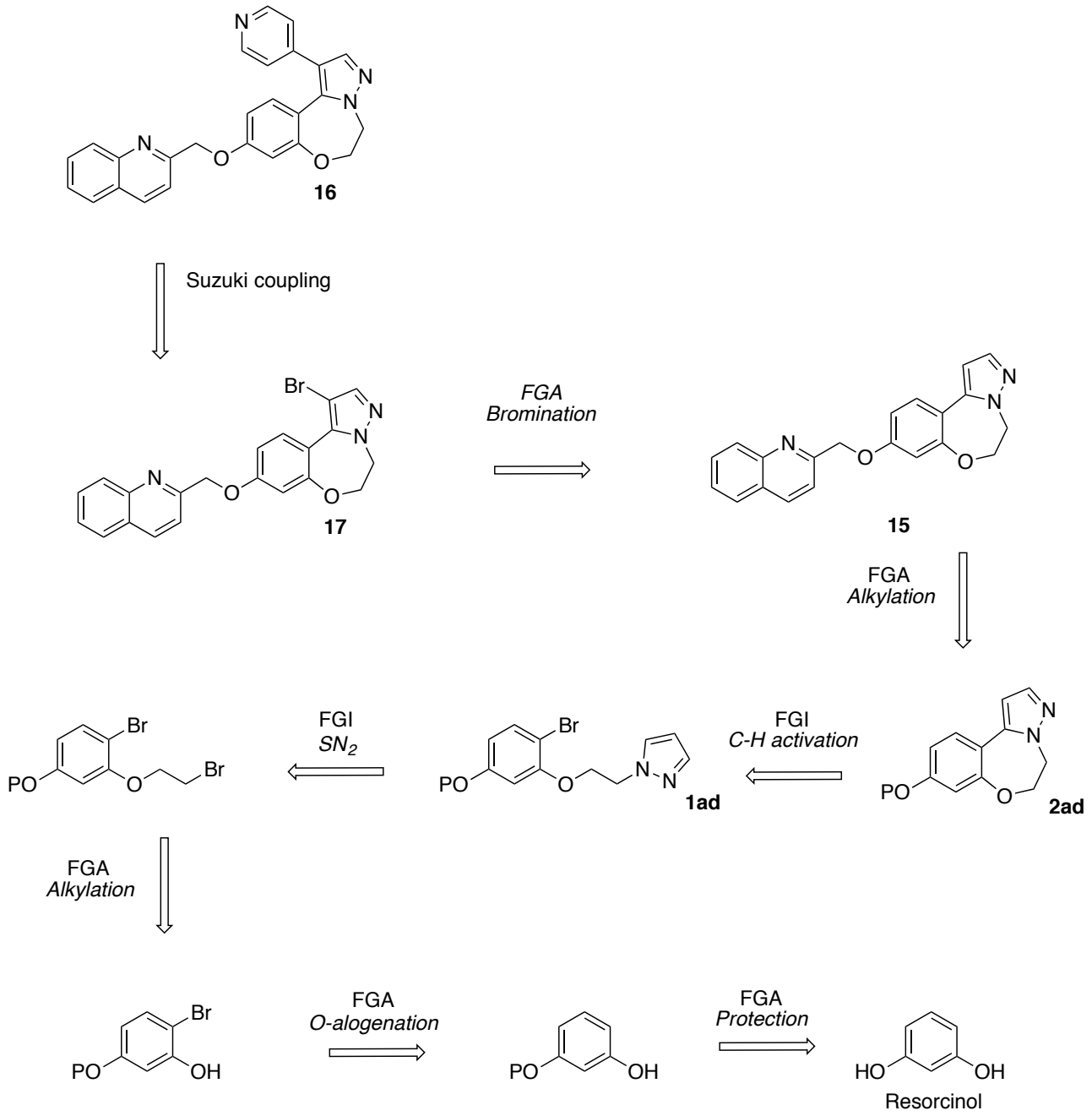
First of all, the product **16** was not isolated in a good yield for a fully characterization but was observed only with an HPLC-MS analysis; the other problem was that in all the experiments tried, most of the reagent was recovered, maybe due to a poisoning of the catalyst.

Furthermore, we think that all the nitrogen present in the core can compete with the C–H bond that we want to react.

For this reason, we decided to modify our strategy: the Suzuki coupling with the pyridin-4-ylboronic acid was chosen for the last step of the process instead of the C-H activation.

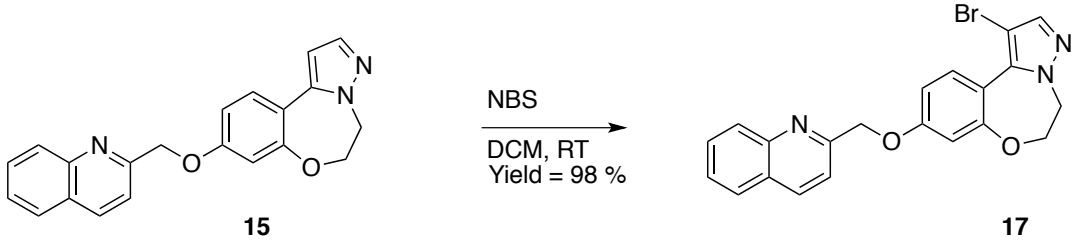
Using this coupling is still present the possibility to obtain a library of molecules starting from the core **15** by changing only the boronic acid.

The new strategy has one more step, which is the formation of the bromide of the benzoxazepine core that is regioselective at the C-4 of the pyrazole.



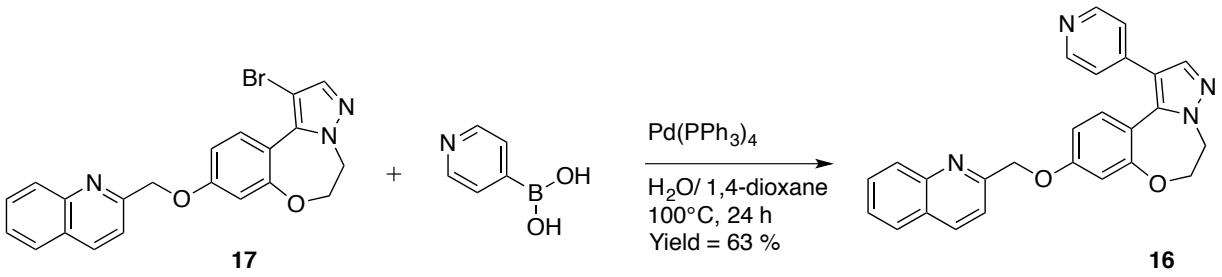
Scheme 51 New retrosynthetic strategy

The reaction nrequired a lot of time compared to the classical bromination: the reaction was performed in dry CH_2Cl_2 protected from light for 36 h leading the corresponding bromide **17** in 98 % yield.



Scheme 52 Bromination reaction

The last step was the Suzuki-coupling with the pyridin-4-ylboronic acid previously prepared.[82]



Scheme 53 Suzuki coupling

As all the other couplings, the first step is the oxidative addition of the palladium specie in the carbon-halogen bond that led to the stable palladium complex after a ligand exchange.

The boronic acid enters in the catalytic cycle and with the transmetalation step the pyridine moiety is transferred to the palladium centre. The final reductive elimination led to the desired product and regenerates the palladium catalyst. With this coupling we were finally able to synthetize our final target.

In conclusion, in this section, we proposed a new strategy for the PDE10 inhibitor synthesis: the new strategy is similar in term of steps compared to the classical one, but our starting material is cheaper and most important, is commercially and readily available.

Is important to underline also that with this alternative methodology we give access to a library of potentially PDE10 inhibitors only by changing the partner of the Suzuki coupling: maybe in the library there is one molecule that enhances the inhibition properties.

It would have been better to use a C–H activation approach instead of a cross-coupling for the final step, but unfortunately, as observed in the previous chapter, this reaction has a loto of problems in term of conversion and low yields.

It is clear that the C–H activation methodology has become an important tool not only to discover new reactions or functionalization, but also for the development of new synthetic strategies for the preparation of known molecules with complex scaffolds.

[82] Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, 67, 5394-5397

9 Four-membered rings Palladium catalyzed C–(sp^3)H activation

In the last ten years, despite undisputable progress, the fundamental challenge of chemists in the transition metal catalysis field is the functionalization of alkyl C(sp^3)–H, the most ubiquitous chemical bond in nature.[83,84]

The poor reactivity of this bond is mainly due to its high bond energy (typically 90-100 kcal/mol) but also the low acidity (pK_a= 45-60) can play an important role: despite the low reactivity, it is not completely inert. The use of transition metal-catalyzed C–H activation reactions can be, in this field, an important tool for the solution of this problem.

Examples of palladium-catalyzed C(sp^3)–H activation have been reported, using specific auxiliaries, such as 8-aminoquinoline or picolinamide based bidentate directing groups (Figure 30a), as well as rather expensive fluorine-containing directing groups (Figure 30b-c).[85, 86, 87]

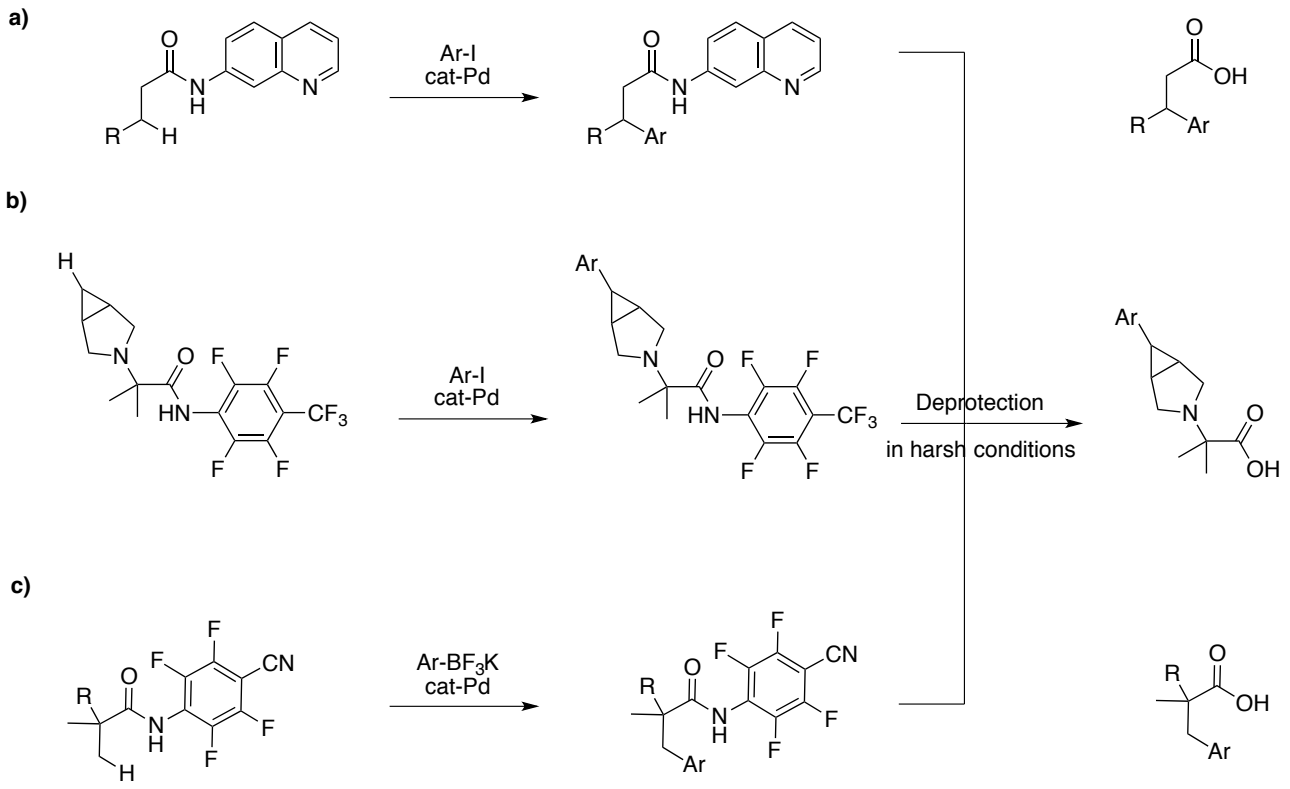


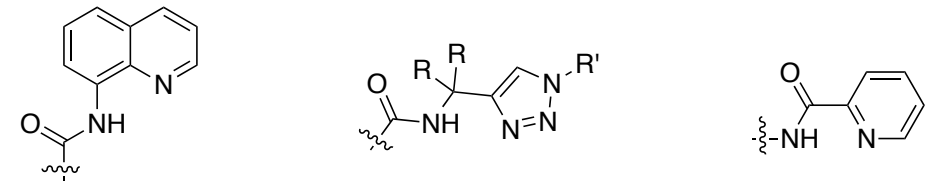
Figure 31 Palladium catalyzed C(sp^3)-H activation using elaborated directing groups

[83] Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, 28, 154-162
[84] Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, 97, 2879-2932
[85] Daugulis, O.; Roane, J.; Tran, L.D. *Acc. Chem. Res.* **2015**, 48, 1053–1064
[86] Rouquet, G.; Chatani, N. *Angew. Chem. Int. Ed.* **2013**, 52, 11726-11743
[87] Xiao, K.-J.: Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, 136, 8138–8142

These pre-installed functional groups can chelate the transition metal catalyst and cleave selectively the desired C–H bond: traditionally are used strong σ-donor and/or π-acceptor such as nitrogen-, sulfur- or phosphorus-containing moieties (e.g. pyridine, oxazoline, thioamide).

Despite the advances, the above-mentioned groups continue to face major drawbacks. Thus, structural modifications of fluorine-containing auxiliaries remain challenging, and harsh reaction conditions are required for their removal, strongly limiting their applications to the synthesis of complex functionalized organic molecules.

We propose in this chapter the C(sp^3)–H activation palladium catalyzed using nitrogen containing bidentate directing groups.



8-Amminoquinoline **TAM** **PIP**

Figure 31 Common directing groups for the C(sp^3)-H functionalization

The key strategy for achieving high reactivity in Pd-catalyzed C(sp^3)–H activation, involves the use of these directing groups, which are known to form a five-membered or six-membered palladacycle intermediates, thus lowering the activation energy during the C(sp^3)–H cleavage step.

We decided to apply this methodology for the functionalization and diversification of specific substrates such as cyclobutane derivatives and azetidine derivatives (Figure 32), which are omnipresent in numerous natural product and drug scaffolds.[88]

In spite of the great importance of these scaffolds in drugs and bioactive compounds, unfortunately, to date, there is a lack of strategies for the late stage diversification of these cores.

Figure 33 Target substrates

[88] Dembitsky, V. M. *J. Nat. Med. Chem*. **2008**, 62, 1–33

9.1 Azetidine C−H activation

Four-membered aza-heterocycles are well important in literature but also in the common life: there are a lot of bioactive compounds and biologically active molecules commonly use to treat a wide range of diseases.

The greatest interest was obviously gathered by azetidine-2-ones (β-lactams structures) for their key role in antibacterial activity, but still the main object of study was the synthesis of bicyclic fused compounds for their relationship with natural antibacterial agents.[89, 90]

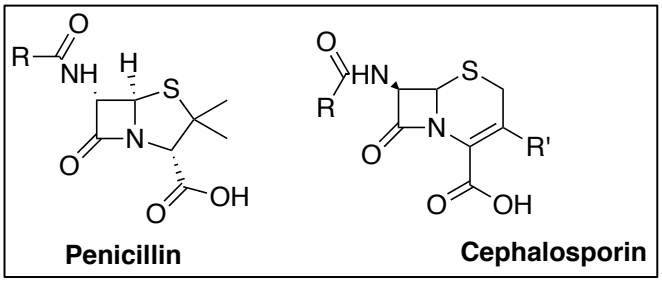


Figure 34 Some β -lactam antibiotics

The lower general interest in azetidines is probably due to their difficult synthesis and their particular reactivity because of their strained nature.

In the last years numerous biologically active azetidines were discovered and some of them are currently used as drugs.[91, 92]

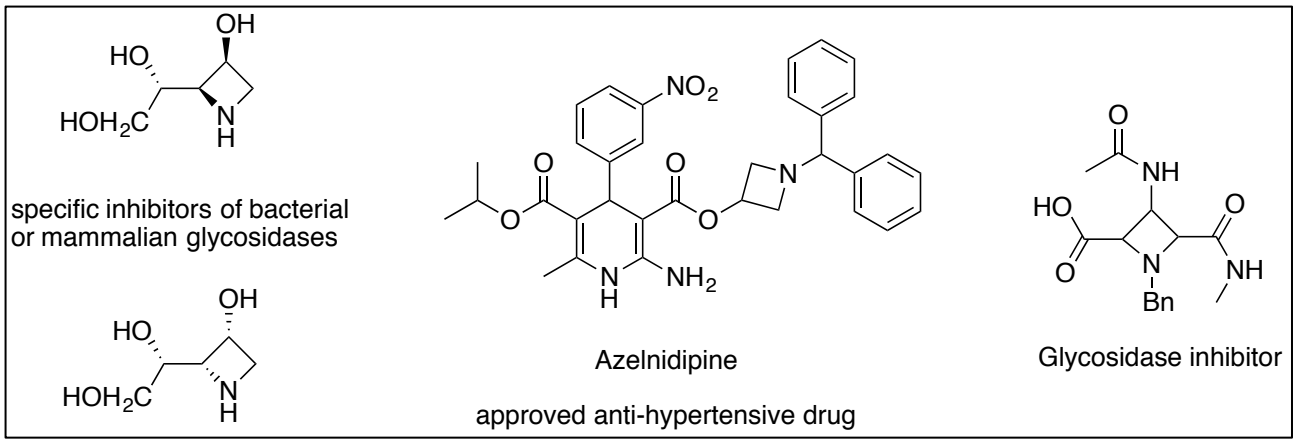


Figure 35 Bioactive azetidines

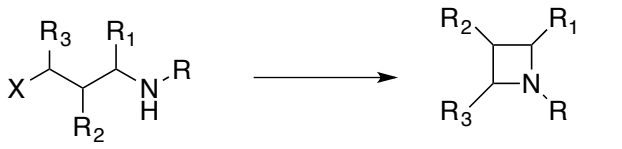
[89] Fleming, A. *Rev. Infect. Dis.* **1980**, 2, 129-139
[90] Ross Pitts, C.; Lectka, T. *Chem. Rev.* **2014**, 114, 7930-7953
[91] Liu, Z. et al. *Tetrahedron: Asymmetry* **2016**, 27, 872-881
[92] Lenagh-snow, G. M.; Araujo, N.; Jenkinson, S. F.; Rutherford, C.; Nakagawa, S.; Kato, A.; Yu, C.-Y.; Weymouth-Wilson, A. C.; Fleet, G. W. *J. Org. Lett.* **2011**, 13, 5834-5837

As regarding the synthesis of this structural motif there are some common strategies used: the nucleophilic substitution of amine nucleophiles (Figure 35a) and the reduction of β-lactams (Figure 35b) are two of the most used methods for their synthesis. [93,94]

In the first strategy the major drawback of the reaction is the formation of one molecule of HX which can competes with the synthesis of the ring itself; in the second approach the reduced molecule can be obtained with different reducing agents such as Ni-Raney, $LiAlH_4$, borane complexes or as the example in the figure with the chloroalane.

The azetidine can also be obtained with a cycloaddition reaction, but in this case, it is used for the synthesis of the azetidin-one which needs a subsequent reduction.

a



b

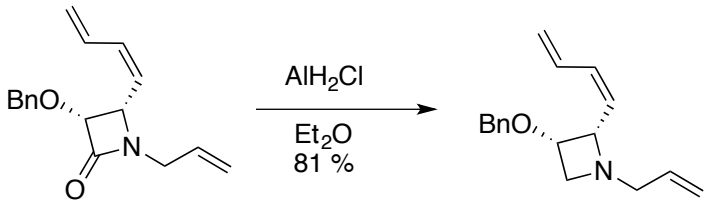


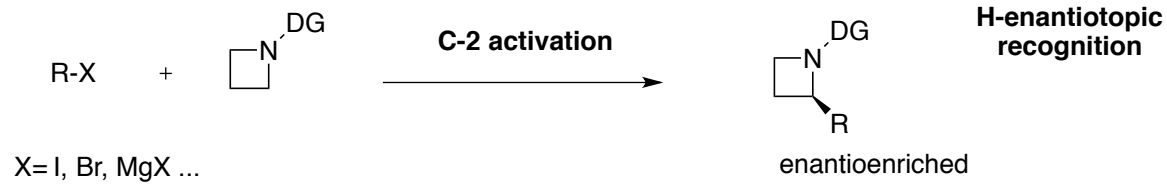
Figure 36 a) Nucleophilic substitution of amine nucleophiles and b) reduction of azetidin-2-ones

These two methods, but also others not showed here, have a great limitation: in order to afford substituted azetidine is necessary to have the functional groups you want in the target molecule already in the starting material, before the formation of the four-membered ring.

It is therefore necessary and useful to find new strategies that can functionalize and derivatize the azetidine starting directly from the commercially available amine: we proposed the C–H activation to achieve this goal (Scheme 54).

[93] Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Azetidines, Azetines And Azetes: Monocyclic*. In Comprehensive Heterocyclic Chemistry III; Stevens, C. V., Ed.; Elsevier: Oxford, U.K., **2008**; Vol. 2

[94] Nadir, U. K; Arora, A. *Indian J. Chem., Sect. B* **1998**, 37b, 163

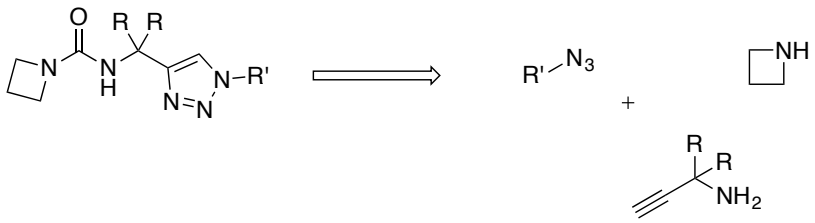


Scheme 54 Proposed strategy

Of course, it is essential the use of the proper directing group for the C-2 functionalization even if the α position should be the easiest to activate; in principle is possible also the C-3 functionalization with a directing group which can activate a far C–H bond, but is not part of this work.

In collaboration with the Professor Lutz Ackermann, we decided to use the 1, 2, 3-Triazole Amine (TAM) directing group for our functionalization and the Palladium as the metal. Triazole amine was identified as an effective directing group in promoting C–H alkynylation and arylation; is also possible to obtain it in an enantiomerically pure form, in order to perform diastereoselective C(sp-3)–H activation.[95, 96]

TAM as directing group can be easily accessed under mild reaction conditions in a highly modular fashion via 1,3-dipolar Huisgens cycloaddition reaction (Scheme 55).



Scheme 55 Retrosynthetic strategy to access TAM-azetidine

In this way is possible to prepare different TAM just by changing the R groups in the propargyl amine and so modulate the functionalization.

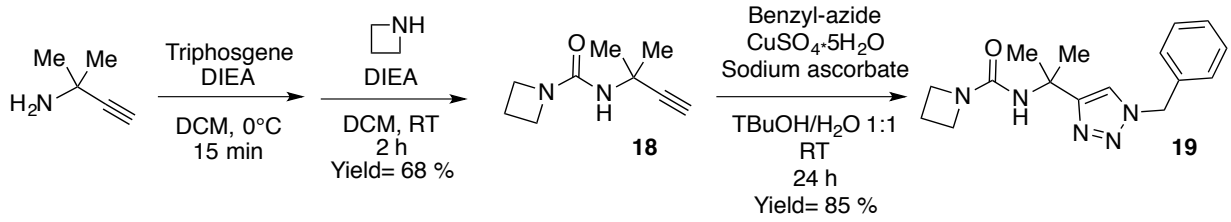
The mild removal of the bidentate auxiliaries is one of the principal required obstacles: as described in literature, the treatment of TAM products by aqueous HCl at reflux or $NOBF_4$ in MeCN at 50 °C will provide the corresponding amine and the recovery of the TAM moiety.

We decided to start our strategy with the dimethyl-TAM (R = Me) because with the Thorpe-Ingold effect we think that we can enhance the stability of the metal complex.

The starting material for our study can be easily prepared starting from the two corresponding amines: the first step is the formation of the disubstituted urea with triphosgene which can

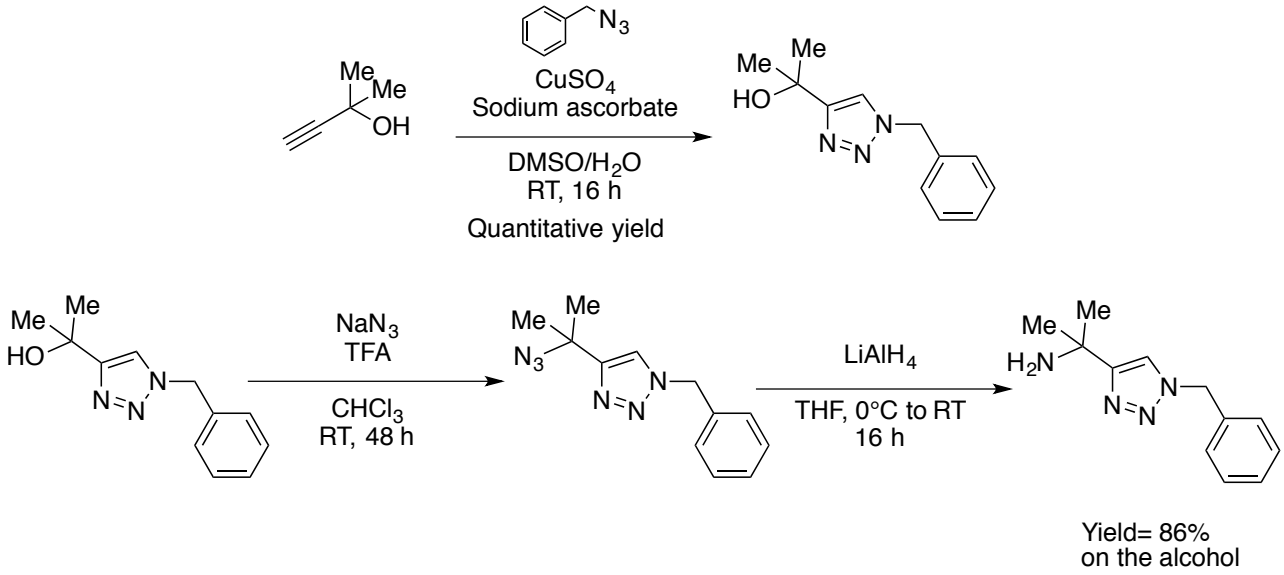
[95] Ye, X.; Xu, C.; Wojtas, L.; Novruz, G. A.; Chen, H.; Shi, X. *Org. Lett.* **2016**, 18, 12, 2970-2973
[96] Graczyk, K.; Haven, T.; Ackermann, L. *Chem. Eur. J.* **2015**, 21, 8812-8815

undergoes a click chemistry copper-catalyzed to afford the target azetidine. The disubstituted urea is not sufficiently pure for the subsequent reaction and is needed a purification on silica gel to afford the pure product. The overall yield of the process is very good.

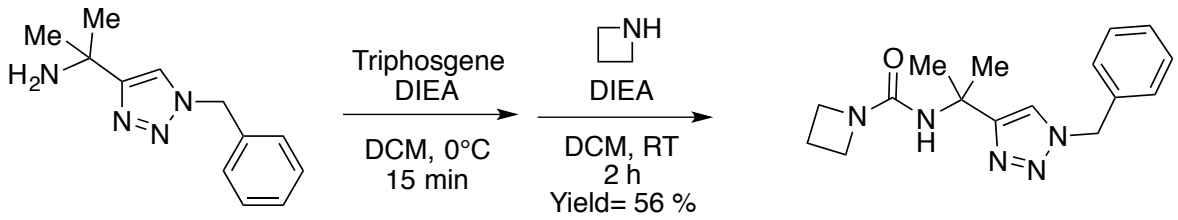


Scheme 56 First synthetic approach

Is possible also to synthetize the disubstituted urea with the coupling between the azetidine and the NH_2-TAM obtained directly from the corresponding propargyl alchol (Scheme 57).



Scheme 57 Second synthetic approach part 1



Scheme 58 Second synthetci approach part 2

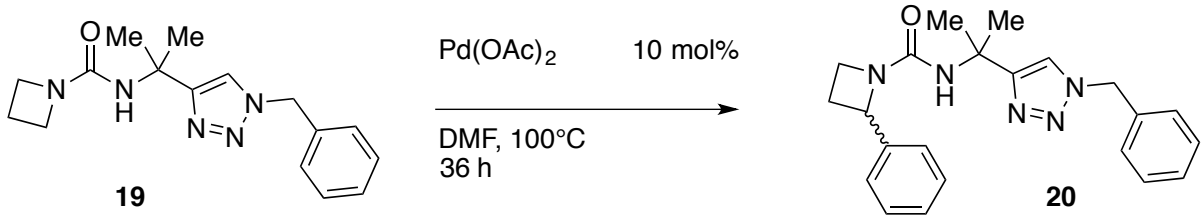
This process consist in two more steps and the yield is a little bit lower, but the propargyl alchol is cheaper than the corresponding amine.

The synthesis of these directing group is simple and the protocol applicable to different substrates.

9.1.1 Arylation reaction

Once obtained the starting material, we decided to explore the behavior of our substrate in the palladium catalyzed C–H arylation conditions.

The first experiments were performed at 100°C in DMF and using 10 mol % of $Pd(OAc)_2$ as catalyst.

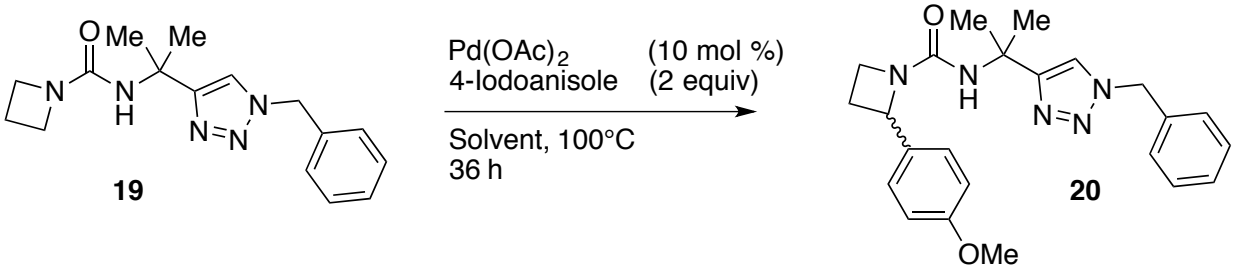


Entry	Base	Ar-X	Reagent
1	AgOAc 2 equiv	Br-benzene 1.5 equiv	Not recovered
2	KOAc 2 equiv	Br-benzene 1.5 equiv	Recovered
3	AgOAc 2 equiv	I-benzene 1.5 equiv	Not recovered
4	KOAc 2 equiv	I-benzene 1.5 equiv	Recovered

Table 23

In all these experiments we were not able to isolate the desired product but we observed how the use of silver salt as base led to the disappereance of the reagent (entry 1 and 3), while the potassium acetate has given back the starting material unreacted (entry 2 and 4).

A very complex mixture was obtained in all the experiments with AgOAc but further experiments were attempted to detect the presence of the desired product.



Scheme 59

We started to screen some solvents using the 4-iodo anisole as the coupling partner, high temperatures (100°C) and 36 hours of reaction.

Entry	[Pd]	Base	4-I-anisole	Solvent	Yield (%)
1	$Pd(OAc)_2$ 5 mol%	AgOAc 2 equiv	1.5 equiv	DMF	<10*
2	$Pd(OAc)_2$ 5 mol%	AgOAc 2 equiv	1.5 equiv	DMA	traces*
3	$Pd(OAc)_2$ 5 mol%	AgOAc 2 equiv	1.5 equiv	m-xylene	<10*
4	$Pd(OAc)_2$ 5 mol%	AgOAc 2 equiv	1.5 equiv	o-xylene	<10*
5	$Pd(OAc)_2$ 5 mol%	AgOAc 2 equiv	1.5 equiv	1,4-dioxane	traces*
6	$Pd(OAc)_2$ 5 mol%	AgOAc 2 equiv	1.5 equiv	Toluene	14*
7	$Pd(OAc)_2$ 5 mol%	AgOAc 2 equiv	1.2 equiv	Toluene	15*
8	$Pd(OAc)_2$ 10 mol%	AgOAc 2 equiv	1.2 equiv	Toluene	18 *
9	$Pd(OAc)_2$ 10 mol%	AgOAc 1.2 equiv	1.2 equiv	Toluene	20 *

Table 24. Reactions conditions: 19 (0.3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (1.2-2 equiv), 4-iodoanisole (1.2-1.5 equiv) at 100 °C for 36 h.

Unfortunately, in any of the experiments above we were able to recover the target product **20** but the yield of the table 24 is referred to the only isolated product, which presents the TAM moiety in the structure and for this reason we supposed is releated also to the presence of the azetidine core. The mass analysis on the product showed that it has the molecular weight of 511 that matches with a di-arylation of the azetidine and we proposed as the product the molecules in Figure 36.

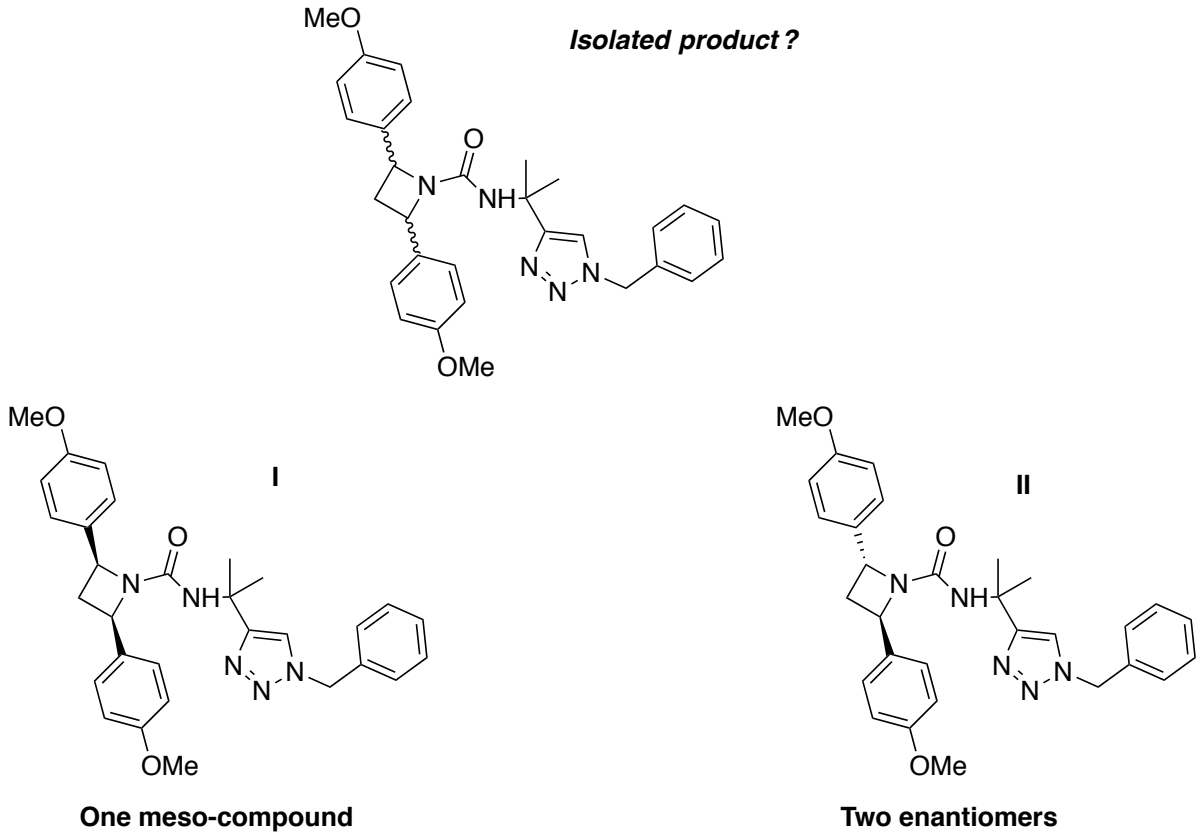


Figure 37

This compound should exist as a mixture of isomers, but in our case was isolated only one of these and so we proposed the meso-compound **I** (Figure 37).

Further analysis showed that the real structure of our product is the one in Figure 37 (compound **21**) and so a bis-aryl-allyl urea due to the ring opening; all the subsequent analysis proved this structure: in H-NMR is easy to identify the vinylic proton which presents a triplet at 5.90 ppm with a J constant of 6.8 Hertz.

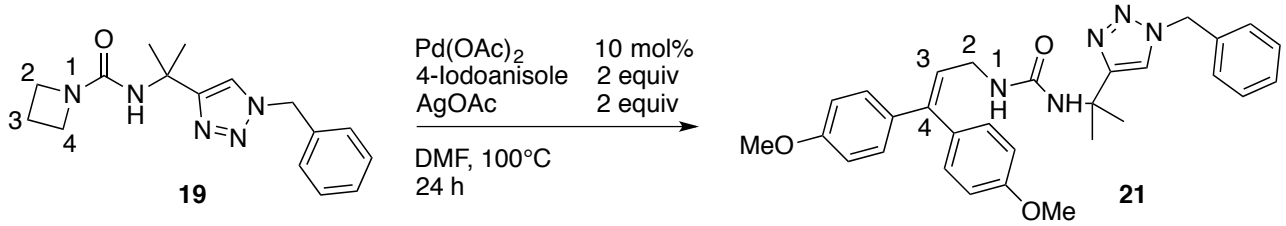
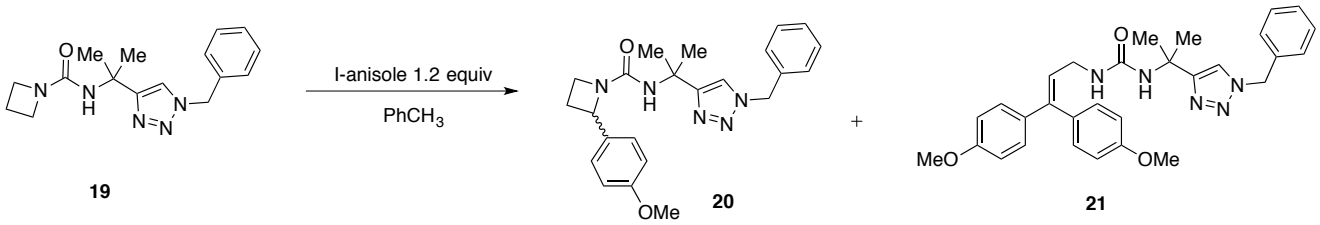


Figure 38

The opened product could be obtained as a consequence of the high reaction temperature, which can open the four-membered ring before the functionalization reaction.

To exclude this parameter as the reason for the opening, we tried to reduce the temperature using toluene as the solvent for all the new experiments.



19 20 21

Scheme 60

Entry	Palladium source	Base	Temperature	Time	21 Yield (%)
1	$Pd(OAc)_2$ 5.0 mol %	AgOAc 1.2 equiv	100 °C	36 h	<10
2	$Pd(OAc)_2$ 10 mol %	AgOAc 1.2 equiv	100 °C	24 h	20
3	$Pd(OAc)_2$ 10 mol %	AgOAc 1.2 equiv	80 °C	24 h	15
4	$Pd(OAc)_2$ 10 mol %	AgOAc 2 equiv	65 °C	24 h	19
5	$Pd(OAc)_2$ 10 mol %	AgOAc 1.2 equiv	50 °C	24 h	38
6	$Pd(OAc)_2$ 10 mol %	AgOAc 2 equiv	50 °C	24 h	28

Table 25

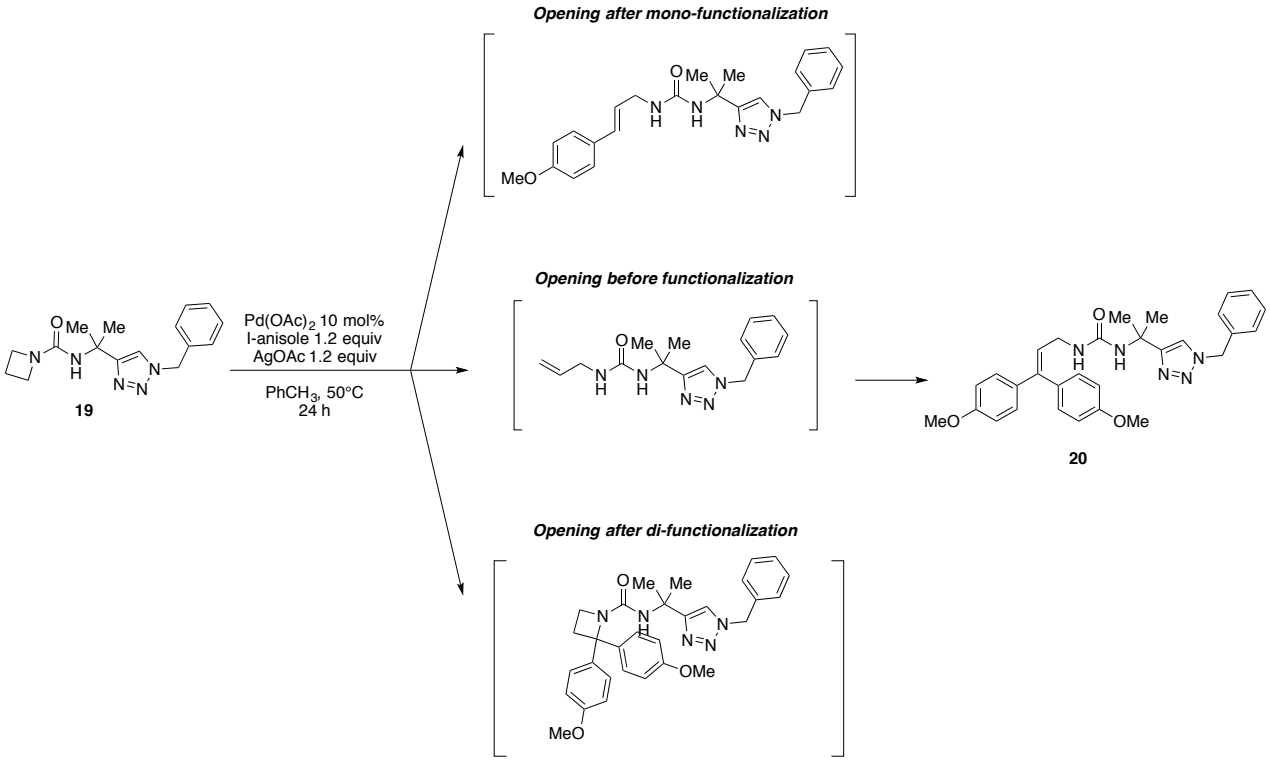
Surprisingly, in all the experiments we were not able to recover the product **20** in a good amount (Table 25 entry 1, 2 and 3) but we obtained a very good result in entry 5 by using only 1.2 equivalent of AgOAc and 1.2 equivalent of I-anisole at 50 °C.

The product is still the opened one, but was obtained in 38 % yield compare to the 20 % at 100 °C. The temperature could not be the problem, but something else influences the reaction's pathway.

In this context is important to better understand which could be the mechanism of the reaction and at which level happens the ring opening.

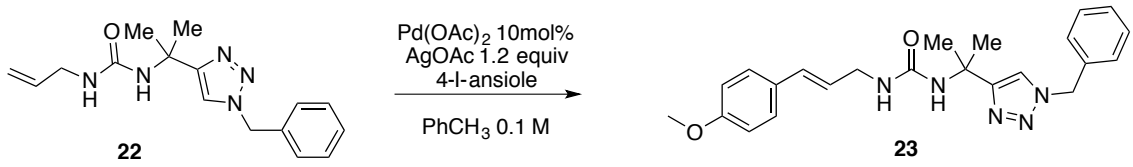
We put forward three hypotheses: the first in which the opening happens after the first arylation and a subsequent functionalization takes place; the second where the functionalization takes place after the formation of the terminal double-bond and the last pathway, the least likely, in which the opening is due to a di-arylation reaction on the same carbon atom which form a too strained structure (Scheme 61).

After some studies of literature, we proposed the first as the more plausible.



Scheme 61

In order to prove our proposal, we synthetized the disubstitued urea **22** and perform the reaction with the same conditions using the 4-iodo anisole as coupling partner; the molecule **23** was obtained with the same protocol showed in the previous part with a 44 % yield and a small amount of reagent was recovered.

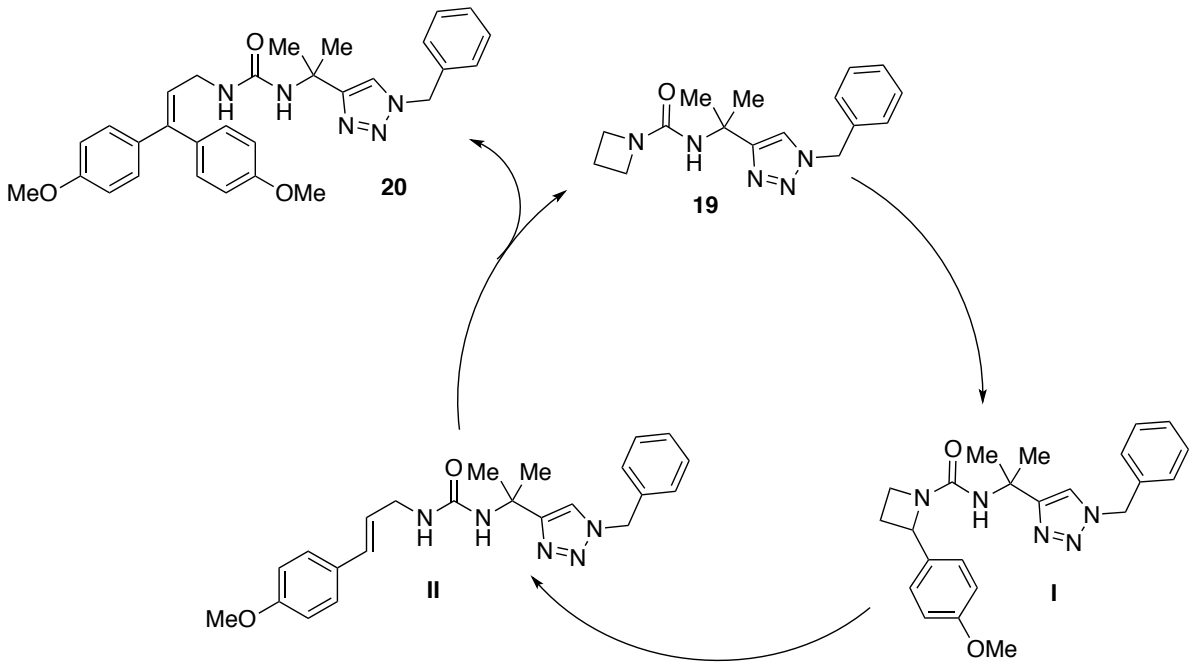


Entry	Temperature	23 Yield (%)	Reagent recovered (%)
1	50° C	40	23
2	80° C	50	10

Table 26

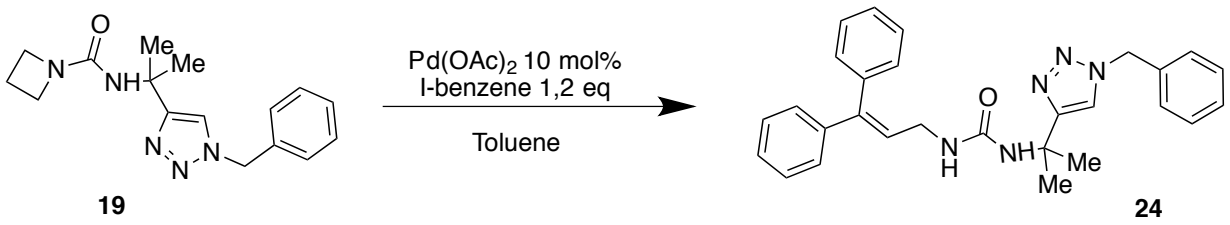
The desired di-arylated product was not observed at 50 and neither at 80 °C, but only the mono arylated one formed due to an Heck-like reaction.

We supposed that after the first arylation happens the ring opening and the subsequent functionalization takes place on the double-bond; is still not completely understood the reason for the formation of the compound **II** and if is really this intermediate which led to our opened structure (Scheme 62).



Scheme 62

The same behaviour was observed also by changing the coupling partner and so by using 1.2 equivalent of Iodo-benzene in the reaction.



19 **24**

Entry	Base	Temperature	Yield (%)
1	AgOAc 1.2 eq	50°C	35
2	AgOAc 2 eq	50°C	20
3	AgOAc 1.2 eq	100°C	< 10
4	AgOAc 2 eq	100°C	< 10

Table 27

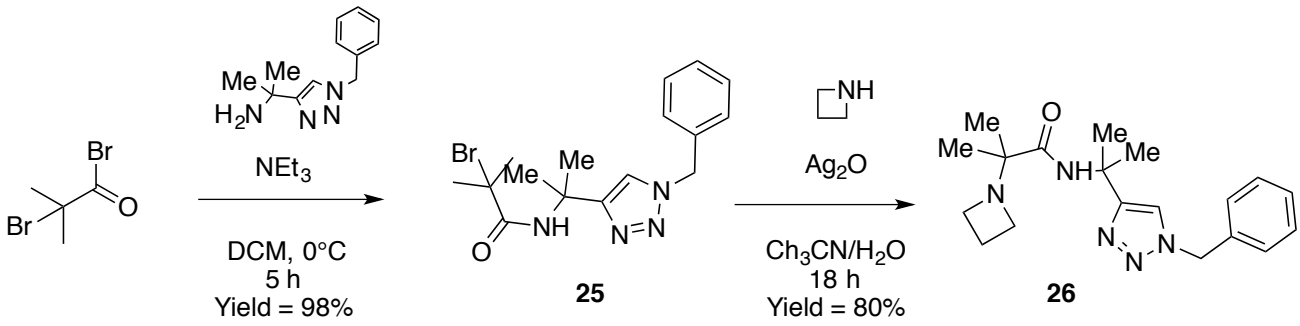
As another proof of the reaction's mechanism, we tried to modify the substrate and to re-establish the basicity of the nitrogen atom in the azetinic ring: we decided to add one more carbon atom between the carbonyl moiety and the azetidinic ring.

We prepared the substrate in two steps starting from the α-bromoisobutyryl bromide by using, in the key step, silver oxide in stoichiometric amount.[97]

In this reaction, the presence of water in the reaction media is thought to be the reason for the rate acceleration and increased selectivity for the desired product over undesired by-products such as the elimination one.

Alternatively, another explanation for the rate acceleration could be the increased concentration of the free hydroxide anion in the reaction mixture due to the elevated solubility of silver oxide.

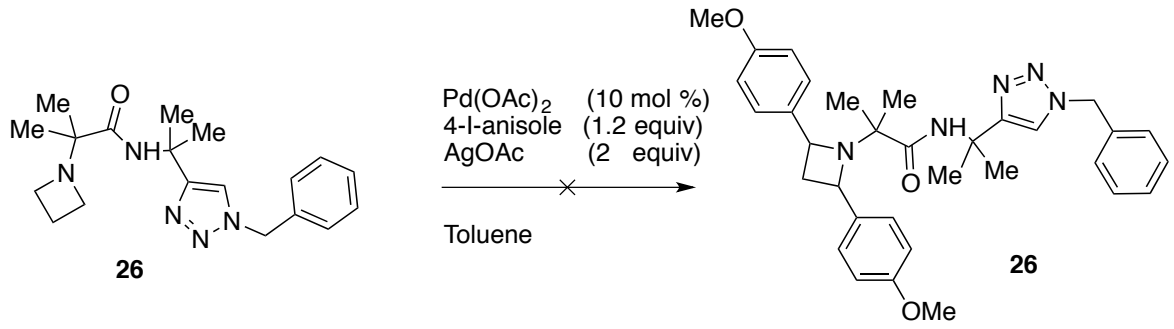
[97] Vachal, P.; Fletcher, J. M.; Hagmann, W. K. *Tetrahedron Lett.* **2007**, 48, 33, 5761-5765



Scheme 63 Synthesis of the modified TAM-azetidine

The 1, 2, 3-Triazole amine, needed for the first reaction, is easily prepared with a click-chemistry starting from the corresponding butyl-amine.

In the reaction with the modified substrate we did not obtain the desired product, only unreacted reagent was recovered:



Entry	Base	Temperature	Product
1	AgOAc 1,2 equiv	50°C	NR
2	AgOAc 2 equiv	50°C	NR
3	AgOAc 2 equiv	80°C	NR
4	AgOAc 2 equiv	90°C	NR
5	AgOAc 2 equiv	100°C	NR

Table 28. Reactions conditions: 26 (0.3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (2.0 equiv), 4-iodoanisole (1.2 equiv) at different temperatures for 20 h.

This behaviour explains our hypothesis about the activation's mechanism for the C–H arylation and proves that the opening of the four-membered ring is not due to the temperature or to the base used.

As regarding the palladacycle, with this modified substrate, is not possible to obtain two five membered rings in the complex: the first ring should be a six membered ring and is impossible to activate the desired C-H bond, which is too far from the metal (Figure 38).

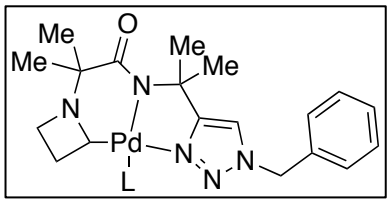
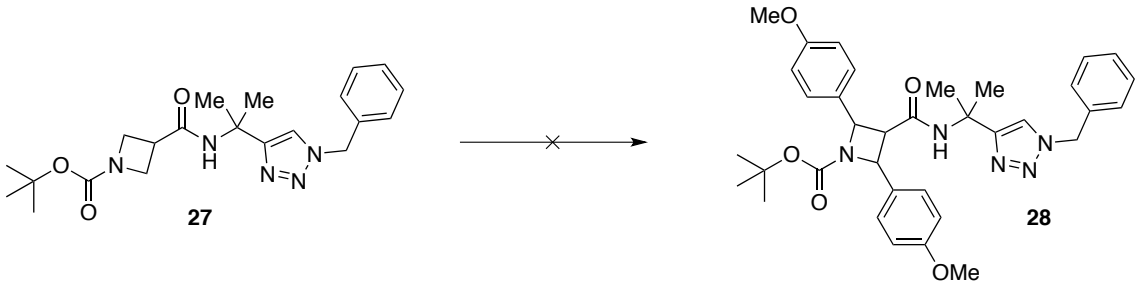


Figure 39 Proposed Palladium complex

The last resort, obtained modifying the under frame of the azetidine by protecting the NH with a protecting group such as the BOC and making the directing group on the other side of the molecule, didn't afford any significant improvement.



Scheme 64 Another modified TAM-azetidine

The reagent was not recovered completely, the reaction led to a complex mixture in which there was not a main product.

Entry	Base	Temperature	Product
1	AgOAc 1,2 equiv	50 °C	NR
2	AgOAc 2 equiv	50 °C	NR
3	AgOAc 2 equiv	80 °C	NR
4	AgOAc 2 equiv	90 °C	NR
5	AgOAc 2 equiv	100 °C	NR

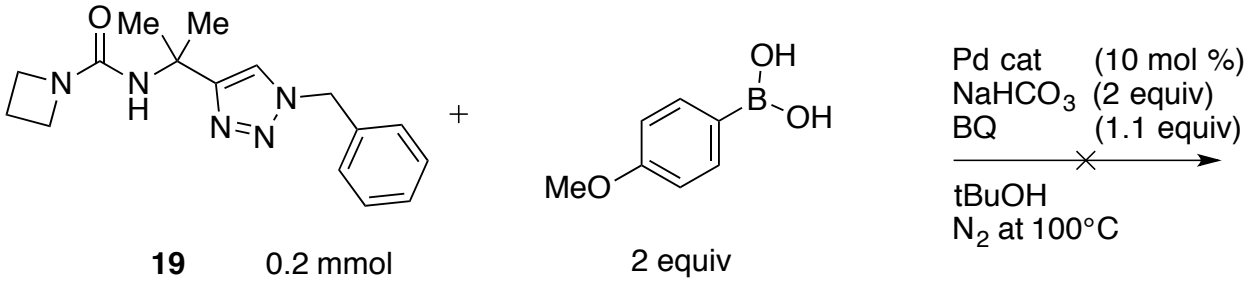
Table 29. Reactions conditions: 27 (0.3 mmol), $Pd(OAc)_2$ (10 mol%), AgOAc (1.2-2.0 equiv), 4-iodoanisole (1.2 equiv) at different temperatures for 20 h.

Influenced by recent works on the C(sp^3)–H arylation palladium catalyzed with boron derivatives, we decided to try the electrophilic C–H activation on our substrate.[98, 99]

Compared to the traditional Suzuki–Miyaura coupling, which requires aryl halides, direct arylation of arenes with boronic acids is possible directly on the activable C-H bond .[100, 101]

The reaction seems proceed with a first electrophilic attack of Pd^{II} on the arene, with subsequent trans-metalation and reductive elimination to produce the desired product; is possible to use not only boronic acids but also different types of boron derivatives.

The first experiments were performed using the boronic acid as the coupling partner instead, in the others, the boronate pinacol ester was used together with some N-protected amino acids as ligand.



19 0.2 mmol 2 equiv

Entry	Pd catalyst	Yield
1	$Pd(OAc)_2$	NR
2	$Pd(TFA)_2$	NR

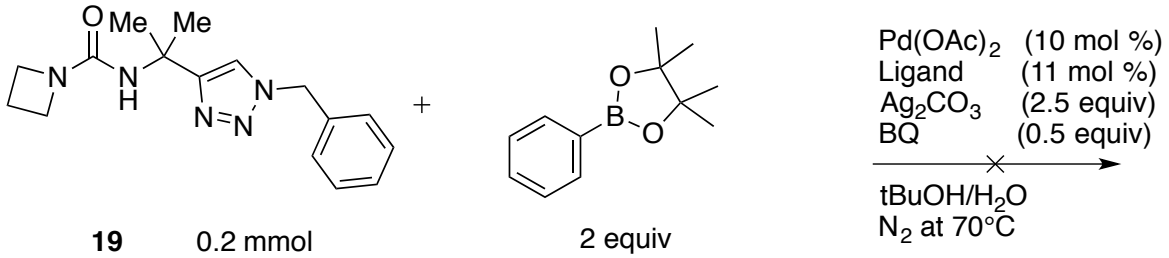
Table 30

[98] Xiao, K-J.; Lin, D. W.; Miura, M.; Zhu, R-Y.; Gong, W.; Wasa, M.; Yu, J-Q. *J. Am. Chem. Soc.* **2014**, 136, 8138-8142

[99] Jain, P.; Verma, P.; Xia, G.; Yu, J-Q. *Nature Chemistry* **2017**, 9, 140-144

[100] "Synthesis of biaryls via the cross-coupling reaction of arylboronic acids": N. Miyaura in Advances in Metal-Organic Chemistry, Vol. 6 (Ed.: L. S. Liebeskind), JAI, Stamford, **1998**, p. 187

[101] Yang, S-D.; Sun, C-L.; Fang, Z.; Li, B-J.; Li, Y-Z.; Shi, Z-J. *Angew. Chem.* **2008**, 120, 1495-1498



19 0.2 mmol 2 equiv

Entry	Ligand	Base	Yield
1	Boc-Leu-OH	K_2CO_3 2.5 equiv	NR
2	Boc-Leu-NhOMe	K_2CO_3 2.5 equiv	NR
3	Boc-Leu-OH	Na_2CO_3 2.5 equiv	NR
4	Boc-Leu-NhOMe	Na_2CO_3 2.5 equiv	NR

Table 31

In all the experiments showed above we were not able to isolate any type of product, but our starting material was recovered unreacted.

As showed before, the mechanisms of these two types of functionalization and the first one in the previous part are so different and is not possible to do a comparison; we can say that the new reaction's conditions seem too mild for the functionalization: our substrate is more stable than what we supposed at the beginning.

The changing of the base, the ligand or the catalyst doesn't affect the final result of each experiment.

In onclusion, we can say that the C–H arylation of the azetidine is a very fascinating challenge, which could open a broad range of new applications; the particular reactivity of this ring is due of course to its great strain but also to the different functional groups present in our starting material.

In all the reactions performed, we were not able to detect any type of C-2 arylated product keeping the ring intact, but in particular conditions, is possible to isolate an interesting di-functionalized product containing the TAM moiety and the four atoms of the ring.

The opened structure recovered from this reaction contains a disubstituted allylic amine motif that is commonly seen in drug molecules and other bioactive compounds (Figure 39a). [102, 103, 104]

[102] Barbui, C.; Hotopf, M. *Br. J. Psychiatry* **2001**, 178, 129-144

[103] Prochazka, A. V.; Weaver, M. J.; Keller, R. T.; Fryer, G. E.; Licari, P. A.; Lofaso, D. *Arch. Intern. Med.* **1998**, 158, 2035-2039

[104] Fulton-Kehoe, D.; Rossing, M. A.; Rutter, C.; Mandelson, M. T.; Weiss, N. S. *Br. J. Cancer* **2006**, 94, 1071-1078

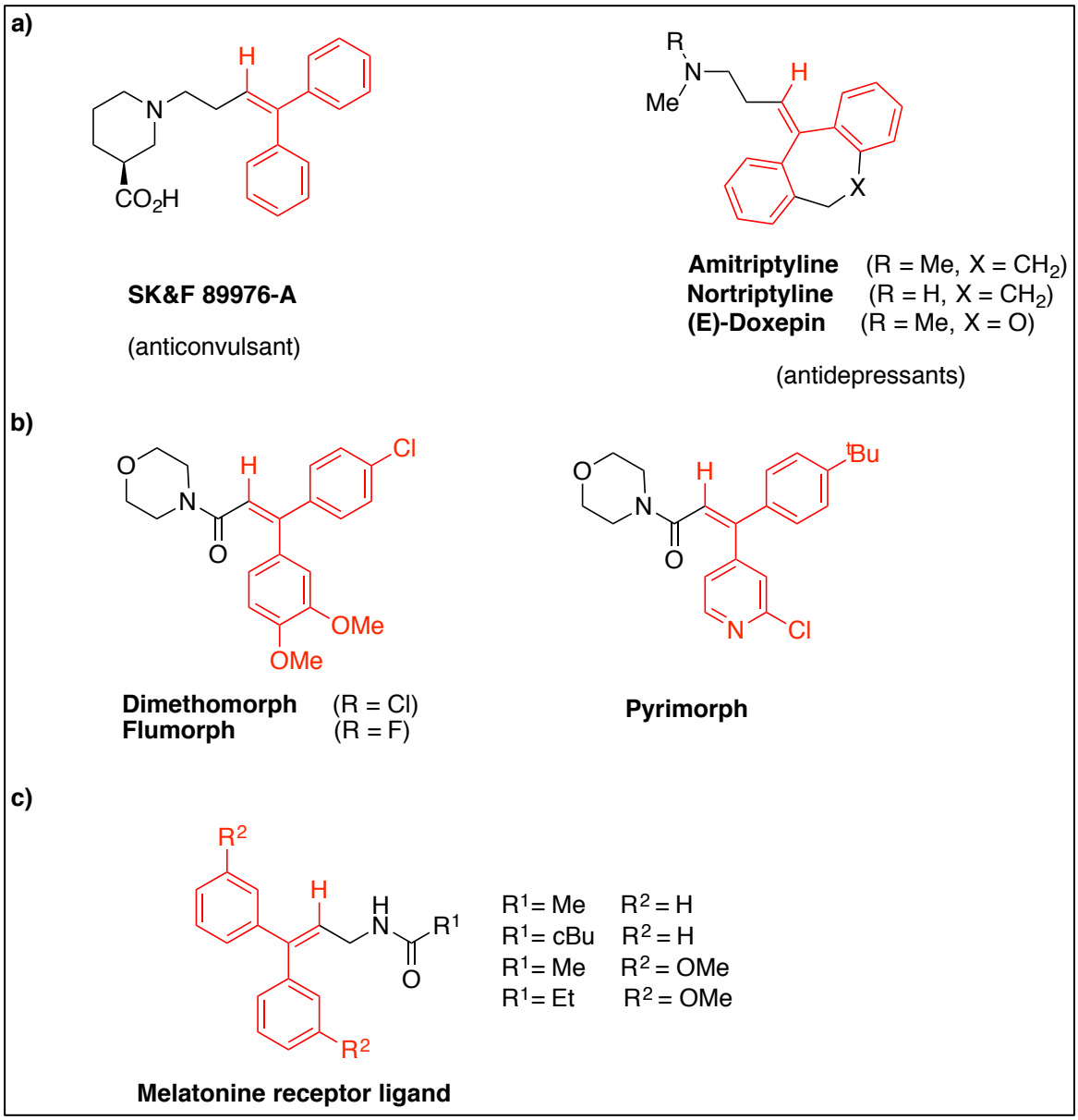


Figure 40 biologically active bis-aryl allyl motifs

A similar structural motif is present also in some cinnamamide derivatives, an important class of agrochemicals, which exhibit herbicidal and fungicidal activities, as well as different biological activities, such as antituberculosis, anticonvulsant, analgesic, antiestrogenic agents, and function as mPTP inhibitors (Scheme 39b). [105, 106, 107, 108]

Recently, the same motif, was discovered in a novel class of high-affinity MT2-selective melatonin receptor ligands obtained by the opening of cyclic scaffolds of known classes of high affinity

[105] Yan, X.; Qin, W.; Sun, L.; Qi, S.; Yang, D.; Qin, Z.; Yuan, H. *J. Agric. Food Chem.* **2010**, 58, 2720-2725
[106] Luo, Y.; Zhu, Y.; Ran, K.; Liu, Z.; Wang, N.; Feng, Q.; Zeng, J.; Zhang, L.; He, B.; Ye, T.; Zhu, S.; Qiu, X.; Yu, L. *Med. Chem. Comm.* **2015**, 6, 1036-1042
[107] Fancelli, D.; Abate, A.; Amici, R.; Bernardi, P.; Ballarini, M.; Cappa, A.; Carenzi, G.; Colombo, A.; Contursi, C.; Di Lisa, F.; Dondio, G.; Gagliardi, S.; Milanesi, E.; Minucci, S.; Pain, G.; Pelicci, P. G.; Saccani, A.; Storto, M.; Thaler, F.; Varasi, M.; Villa, M.; Plyte, S. *J. Med. Chem.* **2014**, 57, 5333 and references cited therein.
[108] Wu, Y.-J.; He, Y.-J.; Sun, L.-Q.; L'Heureux, A.; Chen, J.; Dextraze, P.; Starrett, J. E. Jr.; Boissard, C. G.; Gribkoff, V. K.; Natale, J.; Dworetzky, S. I. *J. Med. Chem.* **2004**, 47, 2887 and references cited therein

melatonin receptor antagonists (Scheme 39c). [109]

The bis-aryl allyl system is difficult to be achieved with the classical functionalization of the terminal double bond; moreover, in no case has ever been performed one-pot.

In the paste years, both Ackermann and Babu reported several examples of metal catalyzed C–H arylation of unsubstituted acrylamide, which either gave moderate yield or poor selectivity (Figure 40a).[110, 111]

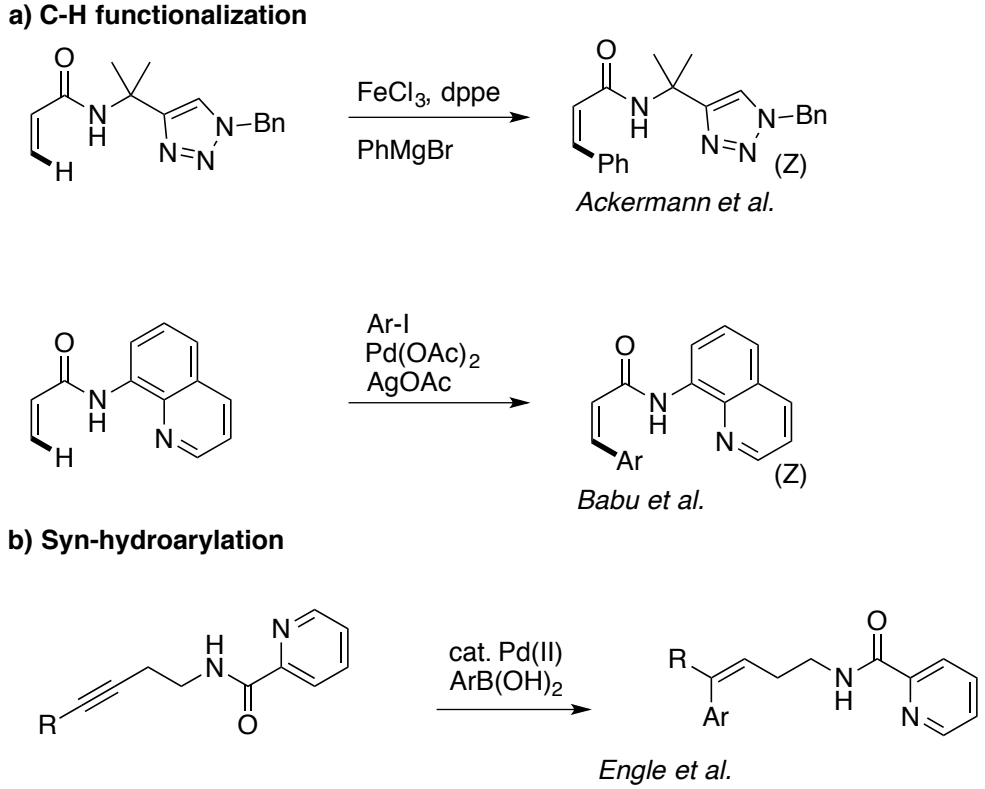


Figure 41

A regioselective syn-hydroarylation of nonsymmetrical disubstituted alkyne substrates using a removable picolinamide directing group is also possible (Figure 40b).[112]

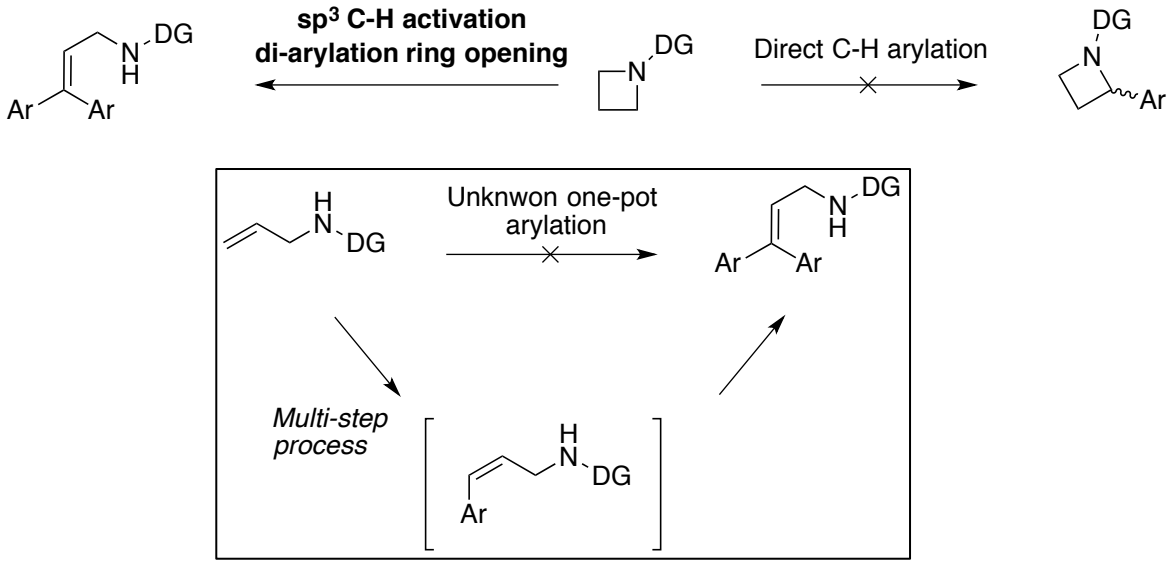
All these approaches mentioned have drawbacks: first, the harsh reaction conditions, but also the selectivity of the reaction, not to mention the tolerance of functional groups; in this conext, it is also worth mentioning that this functionalization is possible one-pot using an C(sp^3)–H activation di-arylation ring opening starting from the commercially available four-membered ring (Scheme 65).

[109] Bedini, A.; Spadoni, G.; Gatti, G.; Lucarini, S.; Tarzia, G.; Rivara, S.; Lorenzi, S.; Lodola, A.; Mor, M.; Lucini, V.; Pannacci, M.; Scaglione, F. *J. Med. Chem.* **2006**, 49, 7393-7403

[110] Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem. Int. Ed.* **2014,** 53, 3868

[111] Ramarao Parella, R.; Babu, S. A. *J. Org. Chem.* **2015**, 80, 12379−12396

[112] Liu, Z.; Drosa, J.; Engle, K. M. *J. Am. Chem. Soc.* **2016**, 138, 13076−13081



Scheme 65 Unprecedent transformation

Despite this compound is not our initial target, with this strategy is possible to acces bis-allyl-aryl ureas with moderate yields.

The determination of the ring's opening will be one of the principal goal of further studies together with a substrate scope and the the extension of the protocol to other DGs.

9.1.2 Alkenylation reaction

In the last years, the oxidative Heck-type reaction, has emerged as a powerful method for the coupling of arenes and olefines.[113, 114, 115]

The introduction of an alkene into the C–H bond is not easy and often requires a large excess of arene (sometimes is also the solvent of the reaction) in addition to the common problem of the regioselectivity.

To overcome these problems, recently, were adopted different directing groups and palladium was the transition metal commonly used in these reactions.[116, 117]

[113] Moritani, I.; Fujiwara, Y. *Tetrahedron Lett.* **1967**, 8 ,1119-1122
[114] Jia, C.; Piao, D.; Oyamada, J.; Lu, W.; Kitamura, T.; Fujiwara, Y. *Science* **2000**, 287, 1992-1995
[115] Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, 34, 633-639
[116] Wang, D-H.; Engle, K. M.; Shi, B-F.; Yu, J-Q. *Science* **2010**, 327, 315-319
[117] Boele, M. D. K.; Van Strijdonck, G. P. F.; De Vries, A. H. M.; Kamer, M. P. C. J.; De Vries, J. G.; Van Leeuwen, P. W. N. M. *J. Am.Chem. Soc.* **2002**, 124, 1586-1587

Despite the enormous advances achieved in this topic, little has been done on the alkenylation of C(sp^3)–H.

As the directing group, also in this case, the TAM should work as a bidentate directing group by forming two five-membered cycles and our hypothesis is the successive coordination of the activated olefin (acrylates) which after the reductive elmination led to the desired product.[118]

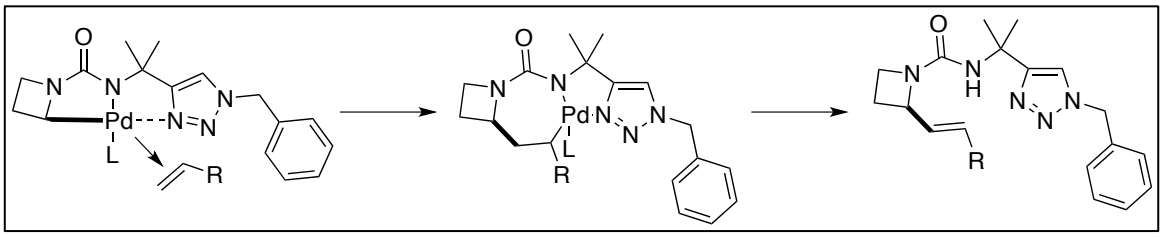
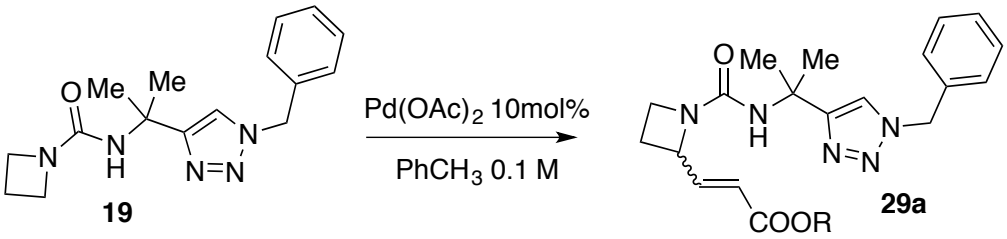


Figure 42 Olefin coordination

Following the arylation experiments on the azetidine we thought that another type of functionalization could keep the ring closed: the α-olefinated azetidine should show less strain than the arylated one.



19 **29a**

Entry	Me-acrylate	AgOAc	Temperature	Product	Reagent
1	1.1 equiv	1.1 equiv	50 °C	Not detected	Recovered
2	1.5 equiv	1.5 equiv	50 °C	Not detected	Recovered
3	1.5 equiv	1.5 equiv	75 °C	Not detected	Recovered
4	1.5 equiv	1.5 equiv	90 °C	Not detected	Recovered
5	1.5 equiv	2.5 equiv	100 °C	Not detected	Recovered

Table 32

[118] Deb, A.; Hazra, A.; Peng, Q.; Paton, R. S.; Maiti, D. *J. Am.Chem. Soc.* **2017**, 139, 763-775

Supported by all the experiments done in the first part we started our screening by using low temperatures (Entry 1 and 2, Table 32) and only 1-1.5 equivalent of the acrylate in order to achieve only the mono-functionalization.

Unfortunately, in these two reactions we were not able to observe any type of product but the starting material was recovered unreacted. Increasing the temperature and using the same equivalents of Me-acrylate (Entry 3, 4 and 5) didn't afford any improvement.

At this point, because of the no reactivity of our substrate, we decided to use more harsh condition: we increase not only the temperature but also the equivalent of the coupling partner.

19 **29b**

Entry	Solvent	Temperature	Product	Reagent
1	$PhCH_3$ 0.1 M	75 °C	Not detected	Recovered
2	$PhCH_3$ 0.1 M	90 °C	Not detected	Recovered
3	$PhCH_3$ 0.1 M	100 °C	Not detected	Recovered
4	$PhCH_3$ 0.1 M	110 °C	Traces of MW = 445	Recovered 50%
5	HFIP 0.1 M	110 °C	Yield = 15 % MW = 445	traces
6	$PhCH_3$ 0.1 M + 5 equiv HFIP	110 °C	Yield = 44 % MW= 445	traces

Table 33

The reagent was recovered at temperature below 100 °C, but some reactivity was observed in entry 4, 5 and 6 especially by adding some HFIP to the reaction mixture.

The role of 1,1,1,3,3,3-Hexafluoroisopropanol (HFIP) is not completely understood, but is used in this topic because it seems to overcome modification of steric hindrance, to modify the coordinating

properties of the directing groups and in some case can influence and change the C-H activation mechanism (especially the cleavage).[119]

Surprised by the reactivity, we isolated the main product formed during the reaction (MW= 445).

We did the all the necessaries analysis and we were able to characterize the structure **30** (Figure 42).

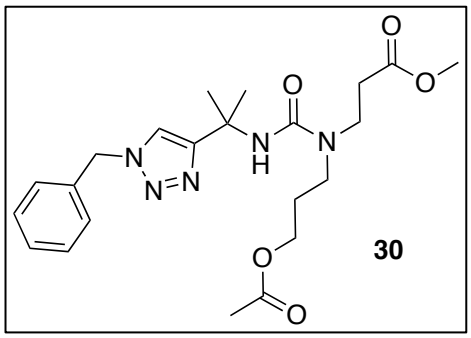


Figure 43 Isolated product

Of course, this is not the desired product of the reaction but is the major one and the only which present the TAM moiety in the structure; the compound presents also an acetate in the molecule and so we were interested in better understand why is incorporate in the structure.

We assumed that this was due to the base used and we performed the screening of the oxidant by using different reagent and particularly another acetate source as the copper acetate.

Entry	Catalyst	Solvent	Me-acrylate	Oxidant	Temperature	Product	Reagent
1	$Pd(OAc)_2$ 10 mol%	$PhCH_3$ 0.1M + 5 equiv HFIP	3 equiv	1,4-BQ 2.2 equiv	110 °C	Complex mixture	Recovered 50%
2	$Pd(OAc)_2$ 10 mol%	$PhCH_3$ 0.1M + 5 equiv HFIP	3 equiv	Ag_2CO_3 2.2 equiv	110 °C	Complex mixture	Recovered 50%
3	$Pd(OAc)_2$ 10 mol%	$PhCH_3$ 0.1M + 5 equiv HFIP	3 equiv	$Cu(OAc)_2$ 2.2 equiv	110 °C	traces	Recovered 20%

Table 34

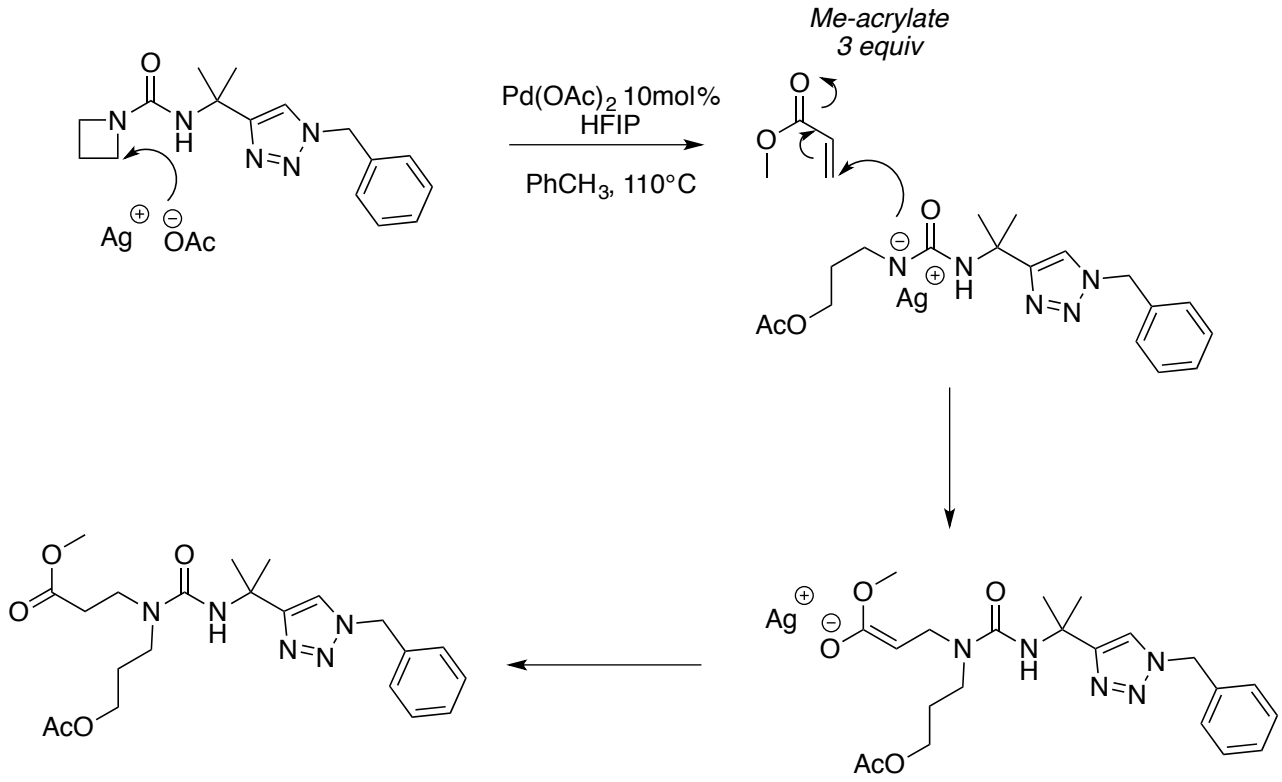
[119] Dherbassy, Q.; Schwertz, G.; Chessé, M.; Hazra, C. K.; Wencel-Delord, J.; Colobert, F. *Chemistry* **2016**, 22, 5, 1735-1743

As expected we were not able to recover the opened product in entry 1 and 2 (Table 34); the reaction led to a very complex mixture in which was recovered only the 50 % of the reagent but was not possible to isolate any type of by-product.

In entry 3, by using $Cu(OAc)_2$ as the oxidant, the staring material was almost disappeared completely and some traces of the opened structure were isolated.

This behaviour led us to think about the mechanism of the ring-opening which is different from what we observed in the arylation reaction.

We proposed a mechanism in which the opening of the azetidine, due to the acetate at high temperature, forms the intermediate free amine, which can react in a Michael-addition with the α, β-unsaturated carbonyl compound.



Scheme 66

It is not completely understood why this reaction is favoured by adding 5 equivalents of HFIP, but maybe the fluorinated compound can influence the reaction mechanism by changing the stability of the starting material; is clear that in the normal condition (low temperature and 1.5 equivalent of acrylate) the substrate is stable.

In conclusion the arylation of the azetidine didn't give us the expected results, as well as the alkenylation reaction.

In the first one, we were able to recover, as the main product, one interesting compound in which unfortunately the ring was not retained, but which present a bis-aryl-ally motif; in the second

reaction at higher temperature than the 50 °C and expecially by adding HFIP to the reaction medium, a tertiary amine was recovered in which the acetate is incorporated in the structure.
This product is a consequence of the ring opening that happens in a different way compared to the one in the previous section (Chapter 9, section 9.1.1) and is supposed to be due to the base in the mixture; unluckily this is a simple tertiary amine and this scaffold is not of particular interest.

9.2 Cyclobutane C-H activation

Cyclobutane as a structural motif of bioactive compounds is present in numerous natural products, which show a wide variety of biological activities.
For example, the piperaborenines (B and D), the dictazole A and the anthocertotonic acid
are only a few of these molecules and differ not only for the substituent in the ring but also for their stereochemistry (Figure 43).[120, 121, 122]

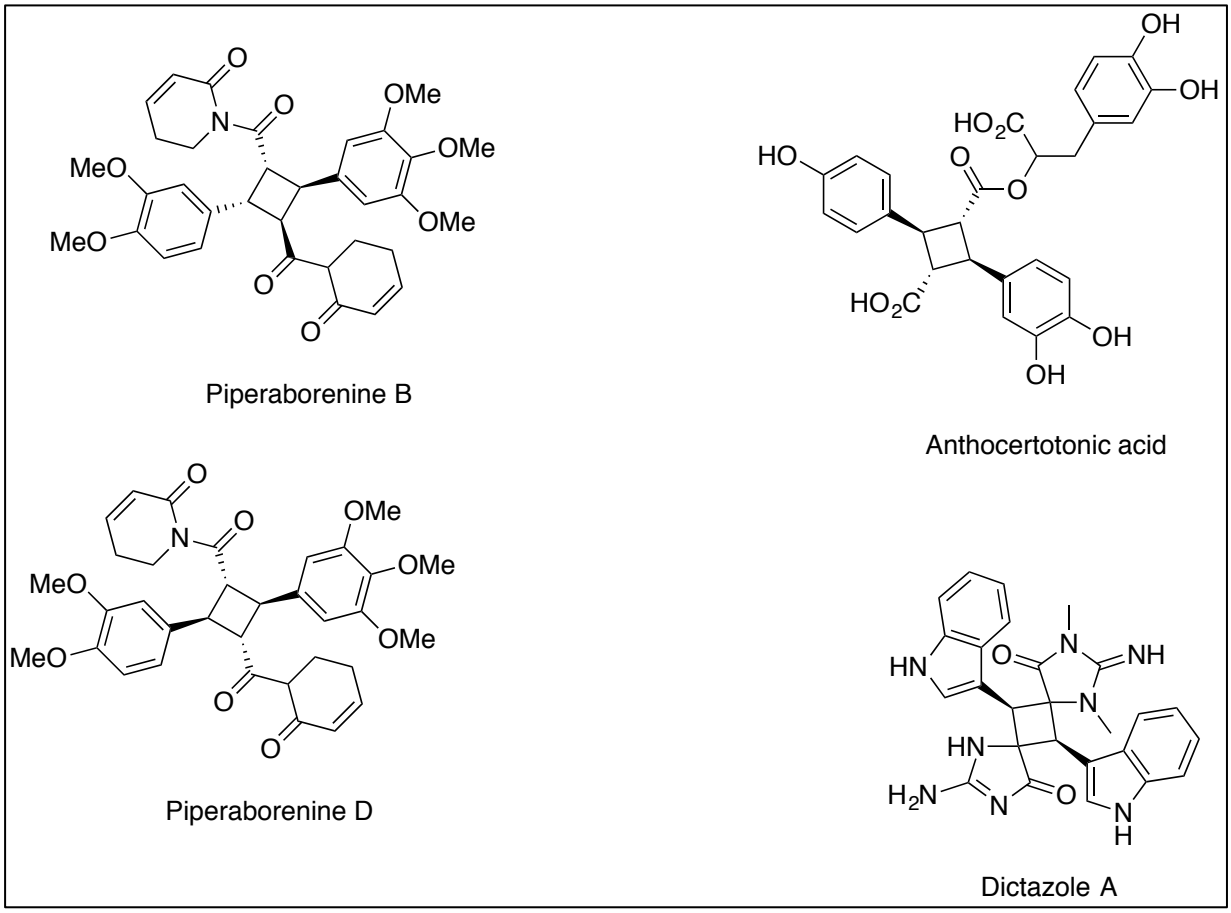


Figure 44 Biologically avtice cyclobutanes

[120] Dai, J.; Jim_enez, J. I.; Kelly, M.; Williams, P. G. *J. Org. Chem.* **2010**, 75, 2399–2402
[121] Lee, F.-P.; Chen, Y.-C.; Chen, J.-J.; Tsai, I.-L.; Chen, I.-S. *Helv. Chim. Acta* **2004**, 87, 463–468
[122] Tsai, I.-L.; Lee, F.-P.; Wu, C.-C.; Duh, C.-Y.; Ishikawa, T.; Chen, J.-J.; Chen, Y.-C.; Seki, H.; Chen, I.-S. *Planta Med.* **2005**, 71, 535–542

It is assumed that the synthesis of these molecules, in nature, takes place through the [2+2] photocycloaddition of monomeric olefins.

The [2+2] photocycloaddition is infact, the method still most widely used in organic chemistry for the synthesis of substituted cyclobutanes.

Unfortunately, this approach is quite problematic for several reasons, including homodimerization, heterodimerization, orientation (head-to-head vs head-to-tail), and E/Z isomerization, leading to a variety of possible structural and stereochemical outcomes (Figure 4). [123]

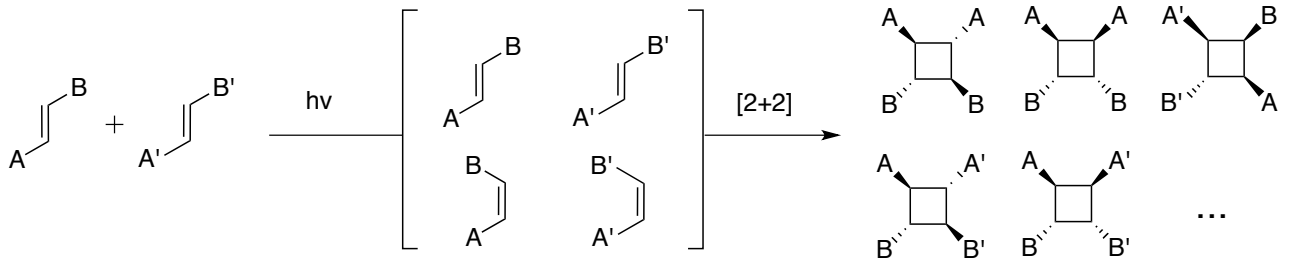


Figure 45 [2+2] Photocycloaddition

In 1964, Schmidt discovered the possibility to irradiate in the solid state two different polymorphs of the cinnamic-acid to afford two products with complete stereocontrol of the reaction (Scheme 37).[124]

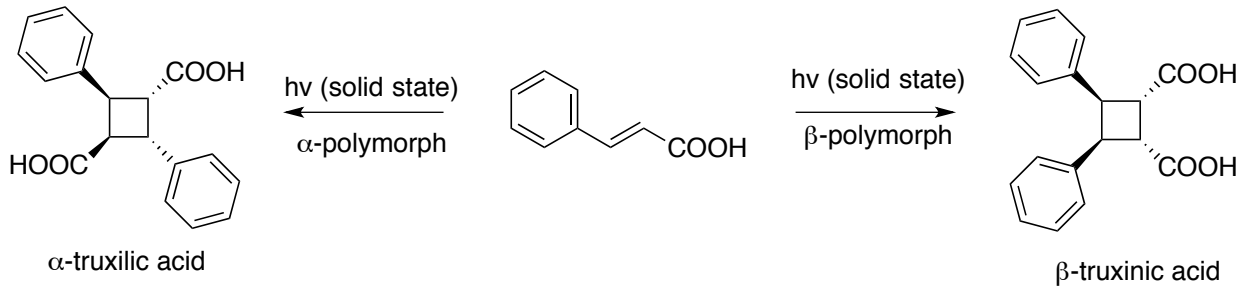


Figure 46 Schmidt's experiment

The solid-state photochemistry could be a good alternative to the classical [2+2] strategy but this approach is limited in scope and not applicable to access all the cyclobutanes.

As in the case of the azetidine, is useful to find some alternatives to the classical chemistry in order to obtain substituted cyclobutanes with fixed stereochemistry.

In this context, the C–H activation was used for this purpose and some bidentate groups were tested in the past years to achieve substituted cyclobutanes.[125, 126, 127]

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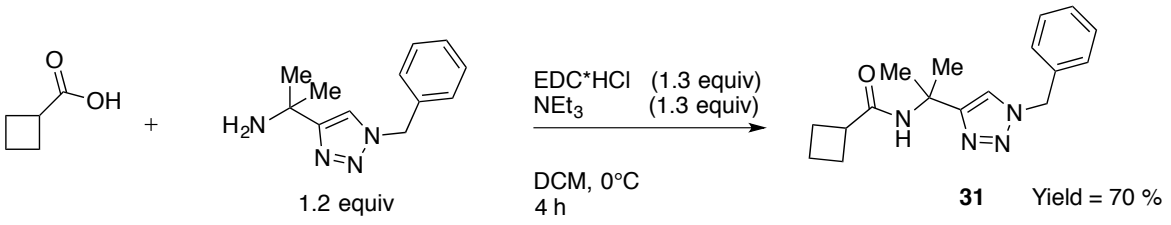
[123] Lewis, F. D.; Quillen, S. L.; Hale, P. D.; Oxman, J. D. *J. Am. Chem. Soc.* **1988**, 110, 1261-1267
[124] Cohen, M. D.; Schmidt, G. M. J. *J. Chem. Soc.* **1964**, 1996-2000
[125] Gutekunst, W. R.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, 133, 19076-19079
[126] Gutekunst, W. R.; Gianatassio, R.; Baran, P.S. *Angew. Chem. Int. Ed*. **2012**, 51, 7507-7510
[127] Parella, R.; Gopalakrishnan, B.; Babu, S.A. *J. Org. Chem.* **2013**, 78, 11911-11934

Here we report the first example of palladium C(sp^3)–H functionalization of cyclobutanes using the TAM as the bidentate directing group.

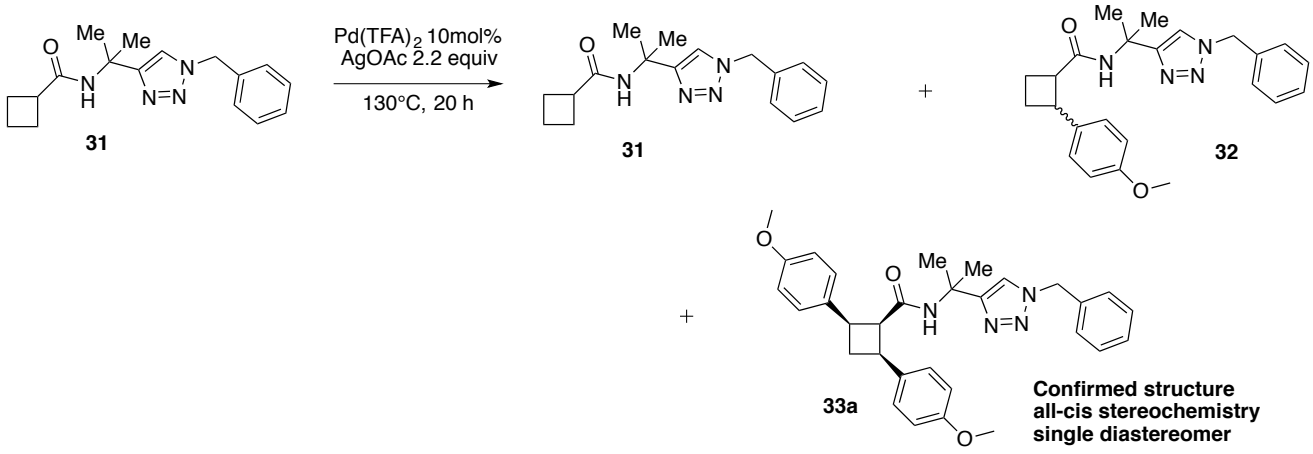
9.2.1 Arylation reaction

The starting material is easily accessible by using the EDC as coupling agent for the formation of the amide bond with the cyclobutane carboxylic acid. The TAM amine is prepared accorded to the procedure showed in the previous chapter (see section 9.1.1).

With the starting material in our hands, we performed the methodological study by screening some solvent using Iodo-anisole as the coupling partner and the silver acetate as the base.



Scheme 67 Synthesis of TAM-cyclobutane



Entry	I-anisole	Solvent	32 yield (%)	33a yield (%)	31 yield (%)
1	3 equiv	*o*-xylene	traces	81	/
2	3 equiv	$PhCH_3$	traces	73	/
3	3 equiv	1,4-dioxane	traces	68	/
4	3 equiv	tBuOH	11	61	/
5	3 equiv	tBuOH+HFIP	13	68	/
6	3 equiv	DCE	15	55	/

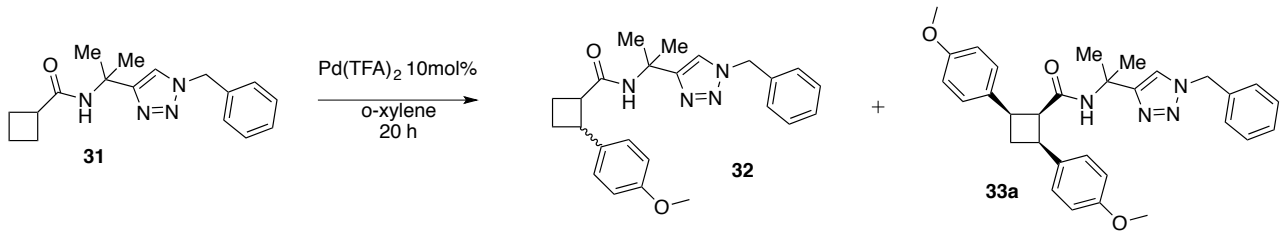
Table 35

In all the cases, the major product obtained was the di-arylated one as the only diastereomer in which all the substituents are in cis.

The best result was achieved using the *o*-xylene as solvent (Table 35, entry 1) and the mono arylated product was observed only in small amount. Also with toluene and 1,4-dioxane (entry 2 and 3) the reagent was completely consumed but the yield was lower.

In entry 4, 5 and 6, we obtained as products not only the compound **33a** in lower yield, but also from 11 to 15% of the mono arylated one.

O-xylene was found to be the best solvent for our reaction, but in all the case the di-arylated product was the major one; the control of the mono-arylated compound seems difficult to achieve so first of all we continued our study in order to find the best conditions for the di-arylation.



Entry	I-anisole	Oxidant	Temperature	32 yield (%)	33a yield (%)	Reagent recovered
1	3 equiv	AgOAc 2.2 equiv	110 °C	10	73	/
2	4 equiv	AgOAc 2.2 equiv	110 °C	traces	76	/
3	3 equiv	AgOAc 2.2 equiv	110 °C μW	10	37	/
4	3 equiv	$Cu(OAc)_2$ 2.2 equiv	130 °C	10	/	40
5	3 equiv	Ag_2CO_3 2.2 equiv	130 °C	20	50	20
6	3 equiv	1,4-BQ 2.2 equiv	130 °C	/	/	100

Table 36

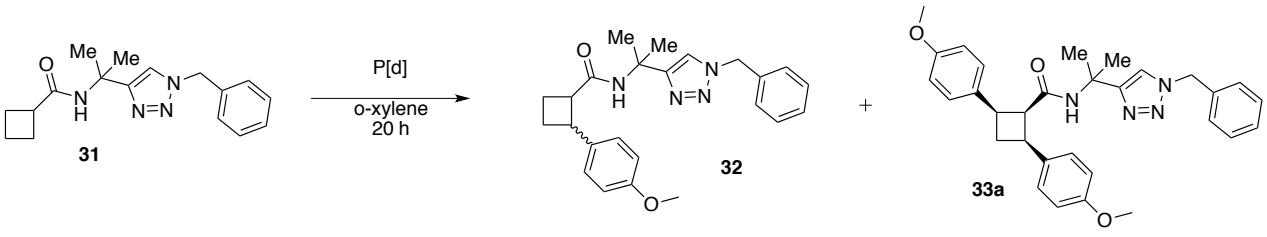
Keeping the *o*-xylene as the solvent we screened different bases and we tried also to reduce the temperature in order to achieve a milder functionalization.

Unfortunately, no significant increase in the mono-arylated product by reducing the temperature to 110 °C (entry 1, 2); in entry 3, with the microwave heating also a significant drop in yield of **33a** maybe due to the decomposition of the product.

When we tried other oxidant, not fully conversion of the reagent (entry 5 and 6) and in one case no reaction at all (entry 6).

We supposed that the silver acetate is necessary as iodide scavenger for the reaction to proceed.

Then we decided to try different palladium(II) catalyst.



Entry	Catalyst	I-anisole	Oxidant	32 yield (%)	33a yield (%)	31 yield (%)
1	$Pd(TFA)_2$ 10 mol %	4 equiv	AgOAc 2.2 equiv	/	83	/
2	$PdCl_2(PhCN)_2$ 10 mol %	4 equiv	AgOAc 2.2 equiv	20	59	/
3	$Pd(OAc)_2$ 10 mol %	4 equiv	AgOAc 2.2 equiv	10	81	/
4	$PdCl_2(MeCN)_2$ 10 mol %	4 equiv	AgOAc 2.2 equiv	10	55	/

Table 37

Palladium trifluoroacetate is still the best catalyst for our reaction (entry 1); similar result was obtained by using $Pd(OAc)_2$ (entry 3) but significant decrease in yield was obtained with other palladium salts (entry 2 and 4).

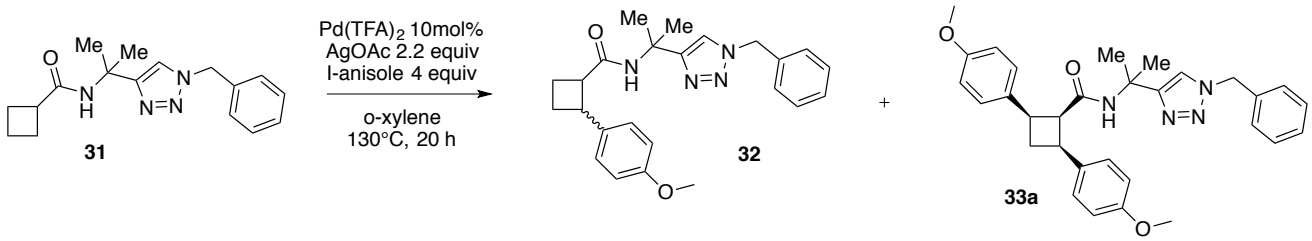
Using $Pd(TFA)_2$ and $Pd(OAc)_2$ as catalyst we tried some experiments reducing the equivalents of the iodide in order to achieve the mono-arylated product.

Entry	Catalyst	I-anisole	Oxidant	32 yield (%)	33a yield (%)	31 yield (%)
1	$Pd(TFA)_2$ 10 mol %	2.2 equiv	AgOAc 2.2 equiv	10	60	/
2	$Pd(TFA)_2$ 10 mol %	1.1 equiv	AgOAc 1.1 equiv	35	20	10
3	$Pd(OAc)_2$ 10 mol %	2.2 equiv	AgOAc 2.2 equiv	16	65	traces
4	$Pd(OAc)_2$ 10 mol %	1.1 equiv	AgOAc 1.1 equiv	23	36	12

Table 38

The rection did not led to the expected result. By reducing the iodide to 1.1 equivalent we observed an increase in yield of the mono-arylated product, but also a complex mixture containing the recovered reagent (entry 2 and 4); using 2.2 equivalent not better results but fully conversion of starting material (entry 1 and 3).

At this point we decide to focus our attention on the di-arylated product as our target molecule and we finished some experiments before the scope of the reaction.

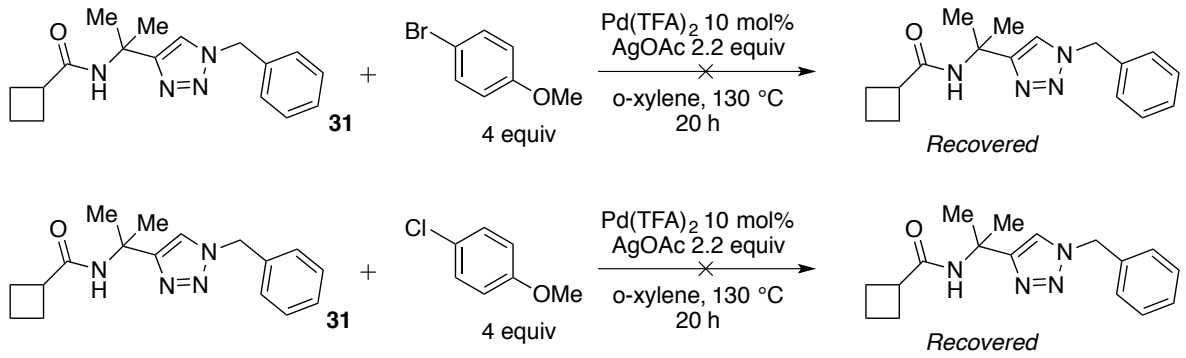


Entry	Concentration	32 yield (%)	33a yield (%)	31 yield (%)
1	0.1 M	/	83	/
2*	0.1 M	/	81	/
3	0.05 M	/	74	/
4	0.2 M	/	80	/

Table 39

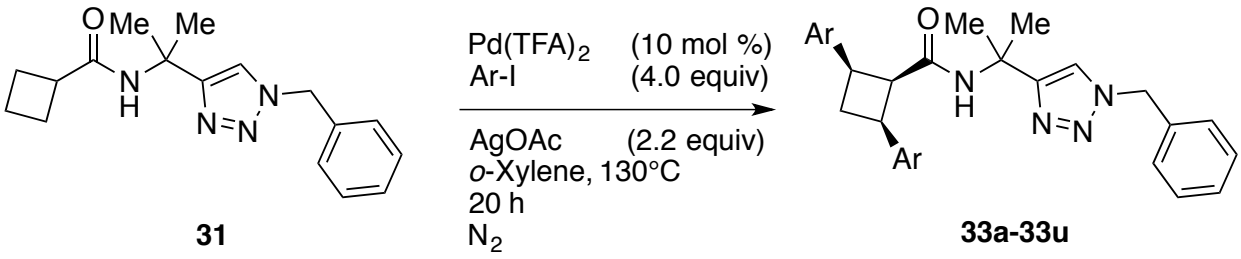
*using $Pd(OAc)_2$ instead of $Pd(TFA)_2$

We tried some different concentrations for the reaction but the 0.1 M is still the best (entry 1); comparable yield was obtained using $Pd(OAc)_2$ instead of the palladium trifluoroacetate (entry 2).
As the last experiment, other halo-derivatives were tested, but both bromide and chloride didn't afford the desired product: only starting material was recovered (Scheme 68).

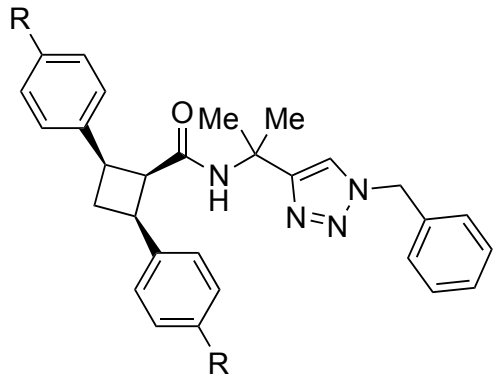


Scheme 68 Experiments with different halides

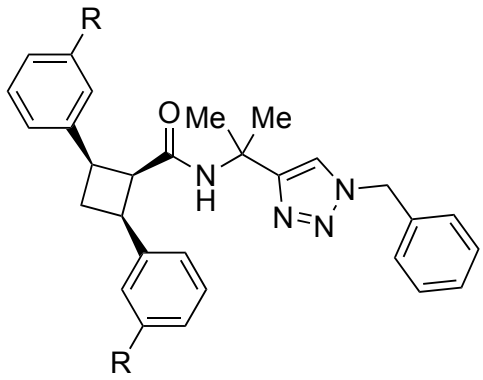
Once obtained the best conditions, we extended the scope of the reaction.



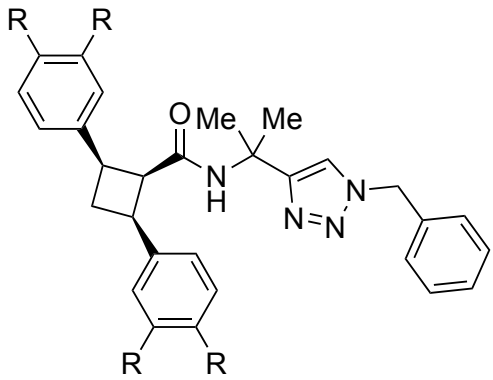
31 **33a-33u**



R = OMe	**33a**: 83 %
R = Et	**33c**: 98 %
R = Me	**33b**: 73 % (71 %)*
R = Ph	**33d**: 70 %
R = CO_2Me	**33e**: 74 %
R = CO_2Et	**33f**: 72 %
R = CF_3	**33g**: 78 %
R = NO_2	**33h**: 58 %
R = I	**33i**: 50 %
R = Br	**33j**: 71 %
R =Cl	**33k**: 64 %
R = F	**33l**: 57 %
R = NHAc	**33m**: 73 %



R = Me	**33n**: 65 %
R = OMe	**33o**: 80 %
R = CF_3	**33p**: 72 %
R = I	**33q**: 44 %
R = Cl	**33r**: 60 %
R = F	**33s**: 66 %



R = OMe	**33t**: 65 %
R = Cl	**33u**: 59 %

[a]Reaction conditions: **31** (0.15 mmol), $Pd(TFA)_2$ (10mol%), AgOAc (2.2 equiv), Ar-I (4.0 equiv), *o*-Xylene (1.5 mL), N_2, 130 °C, 20 h.*Reaction performed on 4 mmol scale.

Scheme 69 Substrate scope

The reaction showed a good tolerance of functional group and from moderate to very good yield.
The usefulness of this method was further demonstrated by the 4 mmol scale reaction, which provide the corresponding product **33b** in comparable yield (71 %).
The *para*-iodo-derivatives work better than the *meta* ones, but not all these derivatives afforded the desired di-arylated product: this behaviour is clearly emphasized with phenol and aniline, but also with some bis-aryl structures (indole and naphthalene, Figure 46).

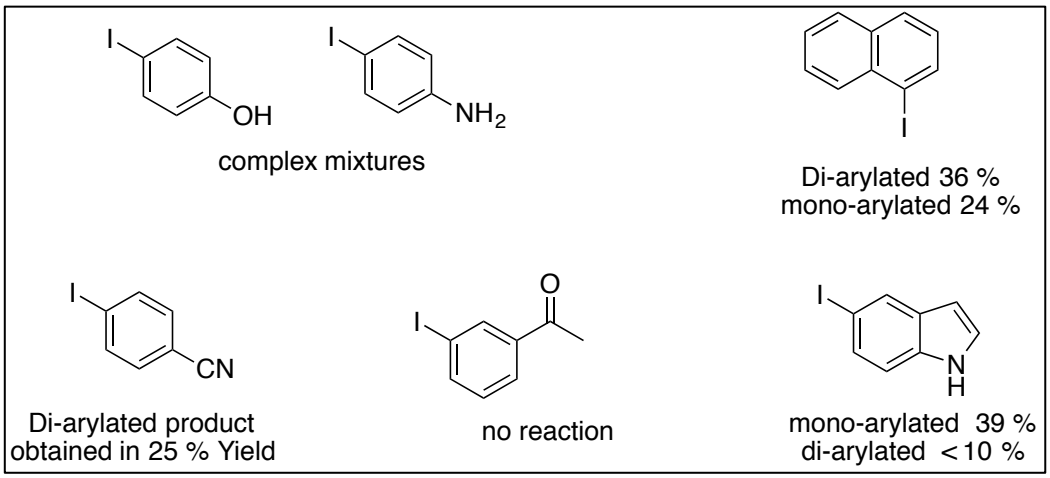
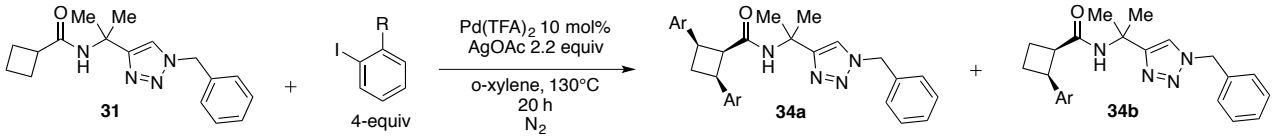


Figure 47 Unsuccessfull iodide

Particularly interesting were the experiments performed with the hindered *ortho*-substituted (Scheme 69).



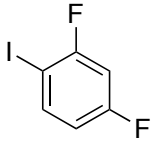
Entry	Ar-I	34a Yield (%)	34b Yield (%)
1	R = Me	7	29
2	R = NO_2	37	26
3		/	44

Table 40

As can be seen from the table we observed a shift in the selectivity of the product formed because in these new experiments, except for entry 2, the mono-arylated product is the major one. In the case of the 2,4-difluoro-iodobenzene (entry 3) no di-arylated product was observed.

Surprisingly the reaction works also with peptides containing aryl-iodo moiety (Figure 47).

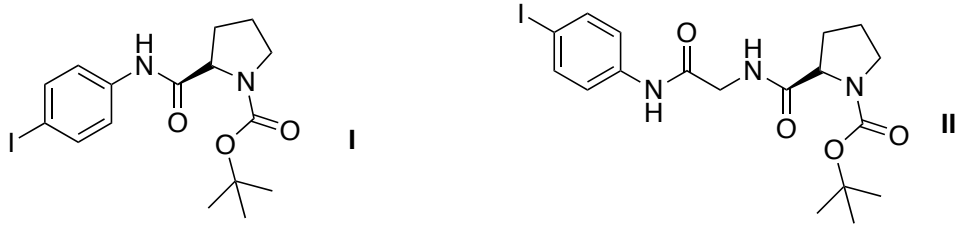
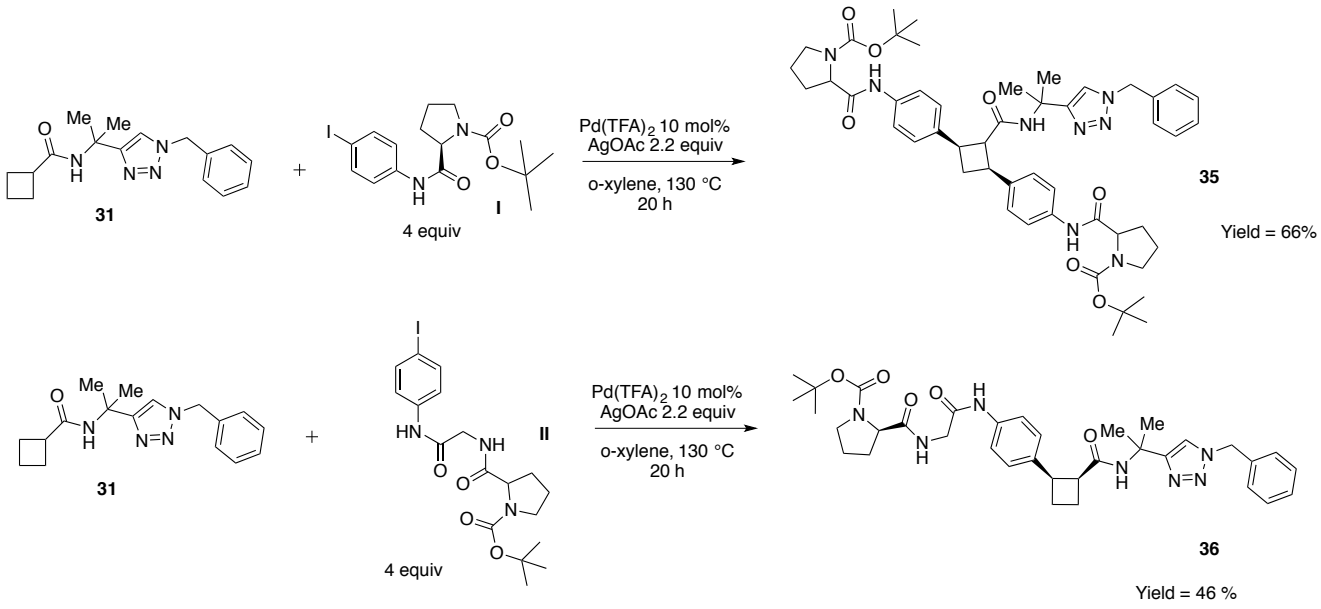


Figure 48

In particular, with **I** as the iodide, the di-arylated product was recovered in 66 % Yield; with **II** as the coupling partner no di-arylated was observed, but only the mono-one in 46 % Yield (Scheme 70).



Scheme 70

In line with the pioneering studies carried out by Daugulis and other, a plausible mechanism for our C(sp^3)–H is proposed and is the one in Scheme 71.[128]

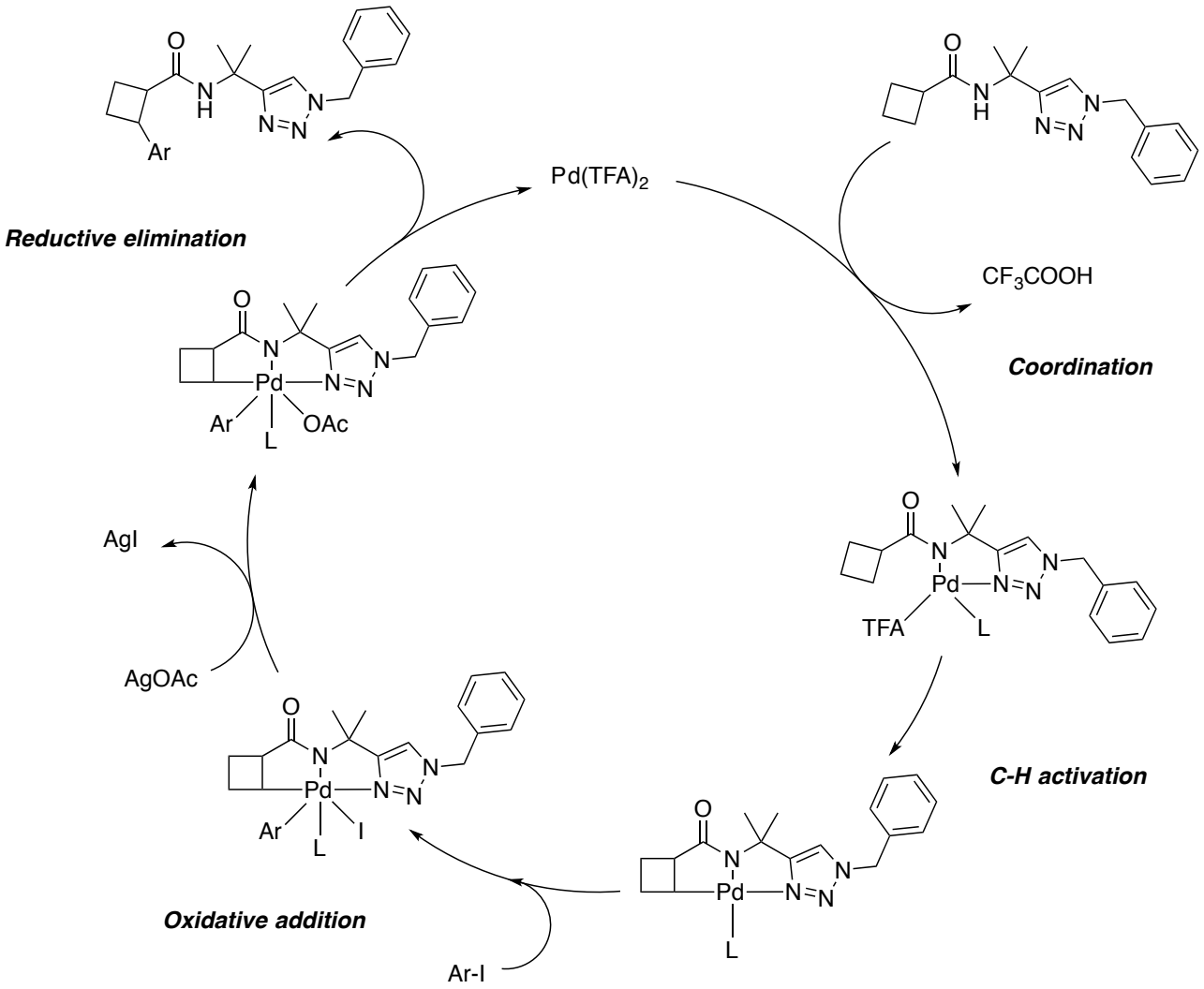
The reaction seems to start with the coordination of the palladium to the bidentate group which undergoes the key-step of C–H activation.

The Pd(II)-complex already formed, after the oxidative addition of the aryl-iodide access a new Pd(IV)-complex.

[128] Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, 132, 3965-3972

In the next step the AgOAc works as iodide-scavenger promoting the last intermediate of the reaction before the reductive elimination which afford the arylated product.

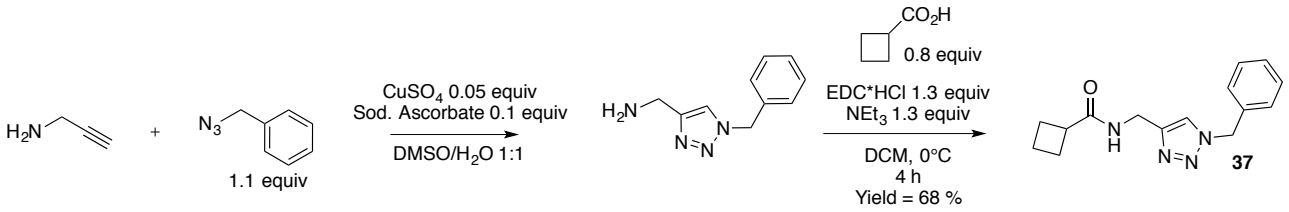
After the catalytic cycle, the Pd(II) is regenerated and ready for the subsequent functionalization.



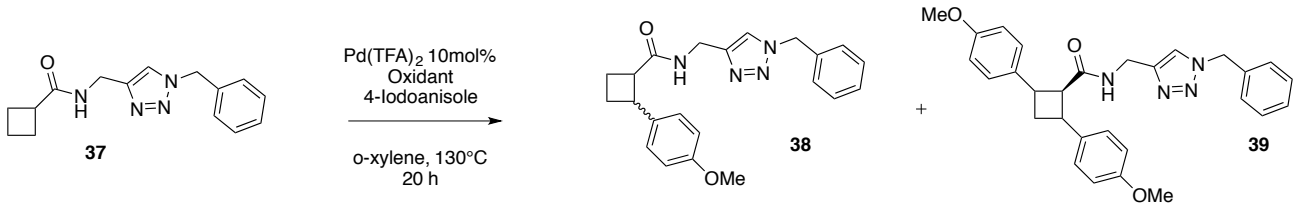
Scheme 71

At this point we were interested in test different TAMs in order to see if was possible to modulate the selectivity of the mono on the diarylated product by modifying the directing group.

Our first idea was to use the simplest-one (**37**) obtained starting from the propargyl-amine.



Once obtained the starting material, we tried some arylation reactions with some of the conditions used before for the other substrate.



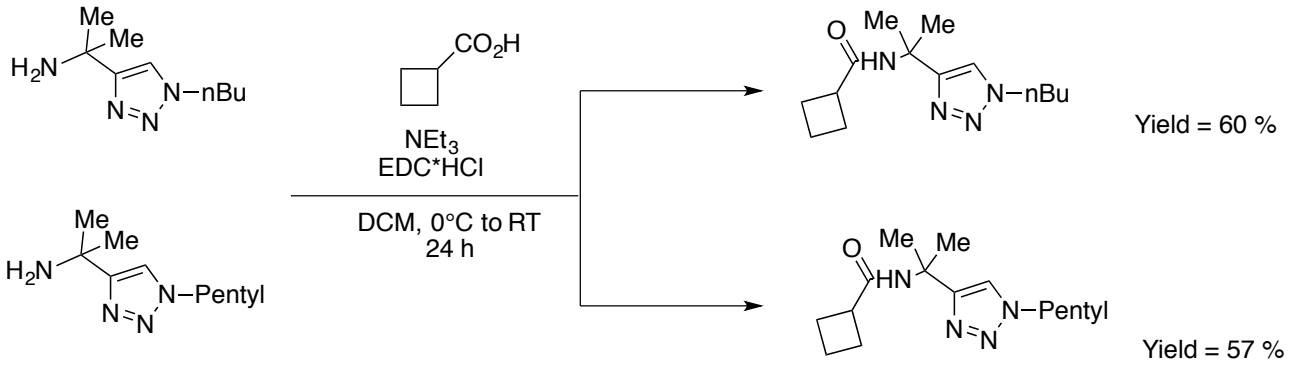
Entry	Oxidant	4-I-Anisole	Additive	38 Yield (%)	39 Yield (%)	Recovered SM (%)
1	AgOAc 2.2 equiv	4 equiv		24	/	50
2	Ag_2CO_3 2.2 equiv	4 equiv		15	/	57
3	$Cu(OAc)_2$ 2.2 equiv	4 equiv		traces	/	65
4	AgOAc 2.2 equiv	4 equiv	1-Ad-COOH 30 mol %	traces	/	65
5	AgOAc 2.2 equiv	4 equiv	Piv-OH 30 mol %	traces	/	63

Table 41

In all the experiments, using 4 equivalents of the aryl-iodide, was not observed the fully conversion of the strating material; the best result was obtained by using the conditions developed for the previous TAM (entry 1) but the mono-arylated product was isolated only in 24% yield.

The addition of acids as additives (entry 4 and 5) did not improve the reaction; indeed the conversion was also lower.

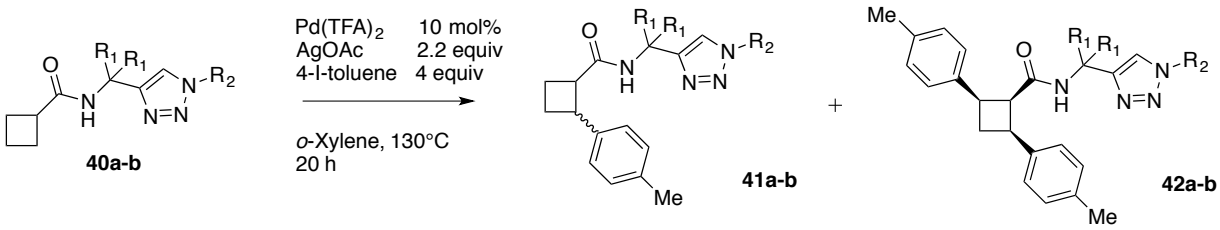
Our second idea was to change the triazole moiety striating from a different azide (Scheme 72). The two amines were prepared according to the strategy showed in the previous part (see 9.1.1).



Scheme 72

For the arylation reaction we were interested first of all to try the diarylation protocol and later the mono one.

We used the 4-Iodo-toluene as the coupling partner.



Entry	R_1	R_2	42 yield (%)[b]	41 yield (%)[b]
1	Me	Bn	73	--
2	Me	nBu	74	--
3	Me	nPentyl	70 (64)[c]	--
4[d]	Me	nBu	68	< 5
5[d]	Me	nPentyl	66	< 5
6	H	Bn	--	24
7[d]	H	Bn	7	29
8[e]	H	Bn	--	15
9[f]	H	Bn	--	traces
10[g]	H	Bn	--	traces

Table 42

[a] Reaction conditions: **40** (0.15 mmol), AgOAc (2.2 equiv), $Pd(TFA)_2$ (10 mol%), 4-I-toluene (4 equiv), *o*-Xylene (1.5 mL), N_2, 130 °C, 20 h. [b] Isolated yield. [c]Gram scale reaction. [d]Reaction performed adding 30 mol% of Piv-OH and 2 equiv of $KHCO_3$. [e]Reaction performed using Ag_2CO_3 instead of AgOAc. [f]Reaction performed usign $Cu(OAc)_2$ instead of AgOAc.[g]Reaction performed adding 30mol% of 1-Ad-COOH.

We can conclude that the presence of two methyl groups in the TAM is essential for the stability of the palladium complex and so to achieve the C–H activation; while the type of triazole in the structure can not influence the reactivity of the ring maybe because the reactive center is too far from it.

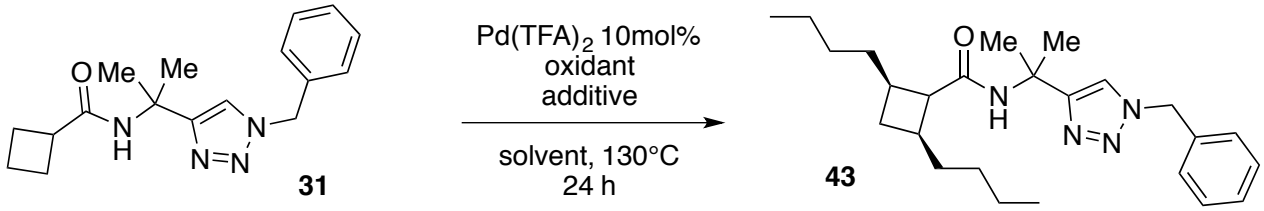
The cyclobutane, in comparison with the azetidine, is reactive towards the palladium catalyzed arylation and can be functionalized keeping the ring intact; the reaction can be selective for the di-arylated product with a good functional group tolerance and from good to excellent yield.

The direct double C–H activation led to the installation of two aryl groups on cyclobutanecarboxamide and a facile synthesis of several novel 1,2-cis, 1,3-cis and 2,3-cis trisubstituted cyclobutanecarboxamide frameworks having three contiguous stereocenters, which are relatively difficult to prepare via the existing, popular direct [2+2] photocycloaddition method with a high degree of regio- and stereocontrol.

Is very difficult to achieve only the mono-functionalization, but this product can be obtained as the minor one by changing different parameters; further studies will be focused on this aspect.

9.2.2 Alkylation and alkenylation reactions

In order to reveal the synthetic potentiality of this protocol, we were interested in other types of functionalization and in particular the alkylation and alkenylation.

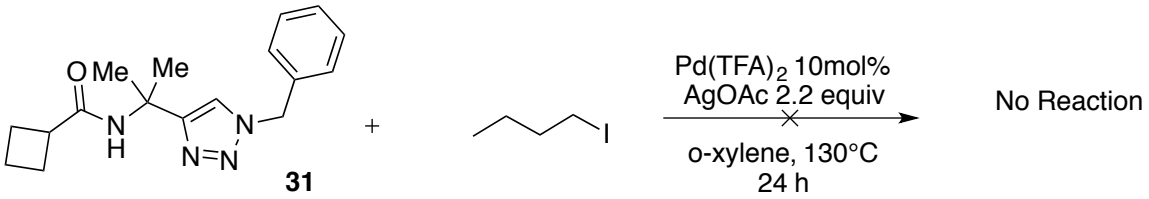


Entry	Oxidant	Additive	Solvent	40 Yield (%)
1	AgOAc 2.2 equiv	/	o-xylene	Traces of mono-alkylated
2	AgOAc 2.2 equiv	/	toluene	/
3	AgOAc 2.2 equiv	/	tBuOH	/
4	Ag_2CO_3 2.2 equiv	/	o-xylene	/
5	Ag_2CO_3 2.2 equiv	/	toluene	/
6	AgOAc 2.2 equiv	Piv-OH 1 equiv	o-xylene	/
7	AgOAc 2.2 equiv	1-Ad-CO_2H 1 equiv	o-xylene	/

Table 43

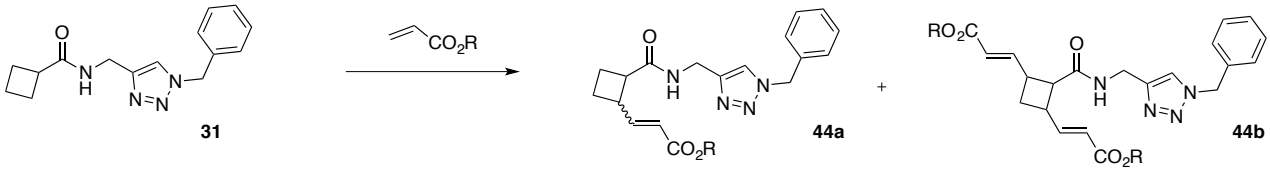
Unfortunately, all our attempts failed to give the bis- or mono-alkylated product; only in one case (entry 1) we were able to observe the formation of the mono-functionalized cyclobutane, but only in traces. In all the other cases the starting material was recovered unreacted.

The same behaviour was observed by changing the alkyl iodide and using iodo-butane instead of iodo-propane (Scheme 73).



Scheme 73

When we tried to switch to the alkenylation reaction, we had to face the same results.



Entry	Catalyst	Oxidant	Additive	Acrylate	Solvent	Mono	Di
1	$Pd(TFA)_2$ 10 mol%	AgOAc 2.2 equiv	/	Me-acrylate 4 equiv	*o*-xylene 130 °C	/	/
2	$Pd(OAc)_2$ 10 mol%	AgOAc 2.2 equiv	/	Me-acrylate 4 equiv	*o*-xylene 130 °C	/	/
3	$Pd(OAc)_2$ 10 mol%	AgOAc 2.2 equiv	BOC-Gly-OH 20 mol%	Me-acrylate 4 equiv	HFIP 130 °C	/	/
4	$Pd(OAc)_2$ 10 mol%	AgOAc 2.2 equiv	Piv-OH 20 mol%	Me-acrylate 4 equiv	HFIP 130 °C	/	/
5	$Pd(OAc)_2$ 10 mol%	AgOAc 2.2 equiv	BOC-Gly-OH 20 mol%	Me-acrylate 4 equiv	DMF 130 °C	/	/
6	$Pd(OAc)_2$ 10 mol%	AgOAc 2.2 equiv	Piv-OH 20 mol%	Me-acrylate 4 equiv	DMF 130 °C	/	/

Table 44

In all the experiments no conversion at all; the starting material was recovered unreacted.

Changing the catalyst and also by testing some additives such as aminoacids or pivalic acid, no significant improvements were observed.

With these two different reactions (alkylation and alkenylation) we proved how the C–H activation depends not only on the substrate and its reactivity (as demonstrated in Chapter 7) but also on the type of functionalization; if the arylation is a good approach for the functionalization of cyclobutane scaffolds, the same reaction is not possible with activated alkenes and alkanes.

10 Experimental section

10.1 General remarks

All solvents were of commercial quality and were purified by distillation over the drying agents indicated: THF and Et_2O (Na/benzophenone), CH_2Cl_2 and hexane (CaH_2), toluene (Na). All other solvents and reagents were purchased from Aldrich, Alfa Aesar, TCI, and Fluorochem and used as received. All Reactions palladium catalyzed were carried out under a Argon atmosphere. All moisture-sensitive reactions were carried out under a positive static atmosphere of Ar using standard Schlenk techniques. Syringes, needles and the other glassware were dried at 140 °C for at least one night and allowed to cool in a desiccator over P_2O_5 before use. Routine monitoring of reactions was performed using silica gel 60 mesh (0.25 mm) aluminium-supported TLC plates (purchased from Merck). Yields refer to isolated compounds, estimated to be >95% pure as determined by ^1H NMR; conversion based on the recovered starting material by column chromatography. Flash chromatography: Merck silica gel 60 (40-63 μm). Compounds were visualized by UV irradiation at a wavelength of 254 nm or stained by exposure to a 0.5% solution of vanillin in H_2SO_4/EtOH, followed by charring. Flash column chromatography (FCC) was performed on silica gel (40−63 μm). ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in the solvents indicated; chemical shifts (δ) are given in ppm relative to TMS, and coupling constants (J) are in hertz (Hz). The solvent signals were used as references, and the chemical shifts were converted to the TMS scale ($CDCl_3$: δ-C 77.00; residual $CHCl_3$ in $CDCl_3$: δ-H 7.26; CD_2Cl_2: δ-C 53.8; residual CH_2Cl_2 in CD_2Cl_2: δ-H 5.32 ppm). COSY, DEPT, and NOESY spectra were recorded using a standard pulse program library. The number of H-atoms attached to each C-atom (C_q= 0H, CH = 1H, CH_2 = 2H, CH_3 = 3H) was determined by DEPT experiments. Mass spectrometry was performed by THERMO LTQ-XL using electrospray ionization (ESI) mode [$M+H^+$ or $M+Na^+$ adducts for positive mode and $M-H^+$ for the negative mode]. High Resolution Mass Spectra were recorded on a Thermo Q-Exactive Plus mass spectrometer. IR spectra (in cm^{-1}) were recorded either on NaCl film (for solids) or neat (for liquids) on an Alpha Bruker FTIR spectrometer.

List of common abbreviations in the text

THF: tetrahydrofuran

CH_3CN: acetonitrile

DMA: N, N-dimethylacetamide

DMF: dimethylformamide

DCM: dichloromethane

HFIP: 1,1,1,3,3,3-Hexafluoro-2-propanol

NMP: 1-methyl-2-pyrrolidinone

EtOAc: Ethyl acetate

$PhCH_3$: toluene

iPrOH: 2-propanol

Et_2O: Diethyl ether

TFA: trifluoroacetic acid

PivOH: Pivalic acid

$NaBH_4$: sodium borohydride

PPh_3: Triphenylphosphine

PBu_3: Tributyl phosphine

Dppb: 1,4-Bis(diphenylphosphino)butane

P(n-Bu)Ad_2: Di(1-adamantyl)-n-butylphosphine or cataCXium® A

$PCy_3{*}HBF_4$: tricyclohexylphosphine tetrafluoroborate salt

$Pd(OAc)_2$: Palladium acetate

$Pd(TFA)_2$: Palladium trifluoroacetate

NCS: *N*-chlorosuccinimide

NBS: *N*-bromosuccinimide

CBr_4: tetrabromometano

AgOAc: silvera acetate

Ag_2CO_3: silver carbonate

CsF: cesium fluoride

K_2CO_3: potassium carbonate

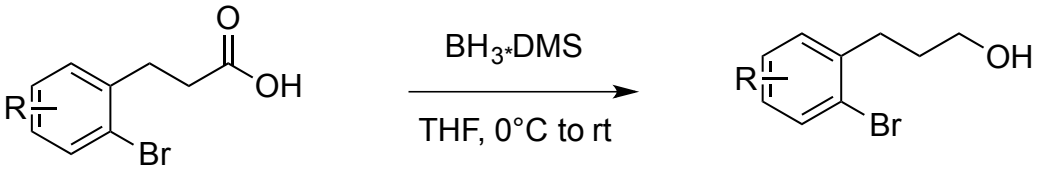
Cs_2CO_3: cesium carbonate

$Cu(OAc)_2$: copper acetate

NaH: sodium hydride

10.2 Representative procedures for the intramolecular C-H activation

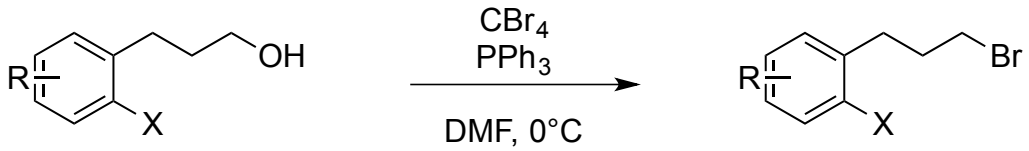
Reduction of carboxylic acid (General procedure A)



To a 0 °C solution of carboxylic acid (23 mmol, 1 equiv) in dry THF (125 mL, 0.18 M) under Argon was added the BH_3*DMS complex (2 M solution in THF, 1.4 equiv) dropwise *via* dropping funnel over 30 min. The reaction mixture was stirred at rt for 1 h and then heated to reflux for 2 h. After cooling to rt, distilled water (10 mL) was added to the reaction mixture and the solvent was removed under reduced pression. The crude was portioned between Et_2O (100 mL) and H_2O (100 mL) and the aqueous phase was extracted with Et_2O (3 x 50 mL).

The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford a colourless oil. Tue crude was used directly for the next step without further purification.

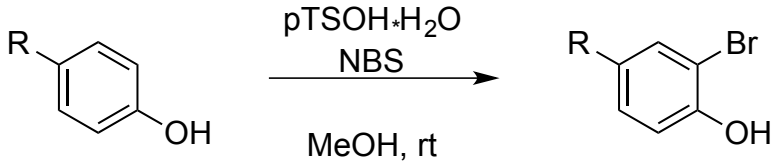
The synthesis of bromides with Mitsunobu-like reaction (General procedure B)



To a 0 °C solution of alcohol (4.65 mmol, 1 equiv) in dry DMF (31 mL, 0.15 M) under Argon were added in one portion the CBr_4 (5.58 mmol, 1.2 equiv) and the PPh_3 (6.52 mmol, 1.4 equiv). After being stirred at rt overnight, the mixture was quenched with H_2O (30 mL).

The water phase was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford the desired product.

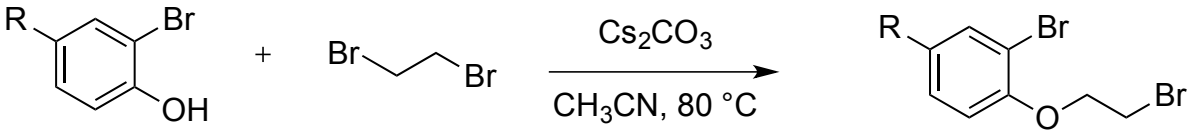
Bromination of phenols (General procedure C)



R = Me, Et, Cl, NO_2,

To a stirred solution of phenol (1 equiv) and pTSOH∗H_2O (10 mol %) in MeOH (1 M) was added a solution of NBS (1 equiv) in MeOH (0.1 M) dropwise via dropping funnel over 20 min. The reaction mixture was stirred at rt for 10 min and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography to afford the desired product.

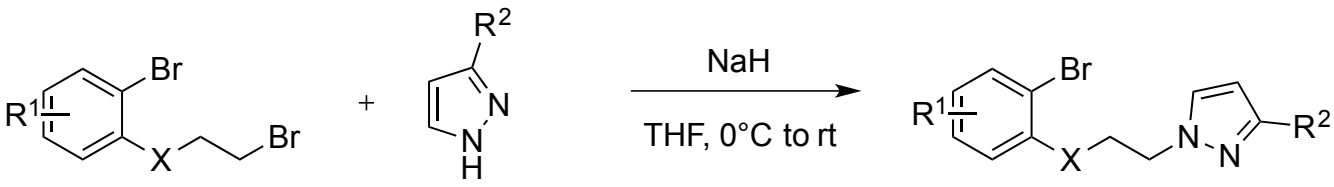
The synthesis of bromides with Williamson etherification (General procedure D)



R = Me, Et, Cl, NO_2, Napthyl

To a solution of Cs_2CO_3 (2 equiv) and dibromoethane (8 equiv) in CH_3CN (5 mL) was added the corresponding bromo-phenol (1 equiv) dissolved in CH_3CN. After being stirred at 80°C overnight, the mixture was quenched with H_2O (10 mL) and the CH_3CN removed. The water phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to afford the desired product.

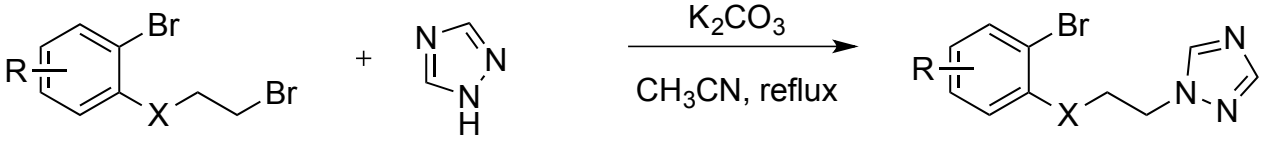
Alkylation of pyrazoles (General procedure E)



To a solution of pyrazole (1.2 mmol, 1.2 equiv) in dry THF (1.5 mL) was added NaH (61 mg, 1.5 mmol) portion-wise. The suspension was stirred at room temperature for 1 h and a solution of bromide (1.0 mmol) in dry THF was added followed by DMPU (5 equiv). After being stirred at

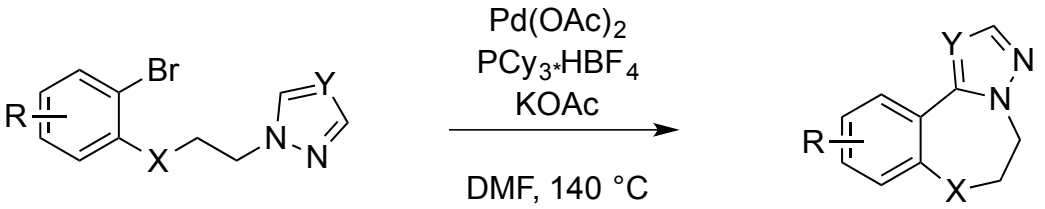
40 °C for 10 h, the mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to afford the desired product.

Alkylation of triazoles (General procedure F)



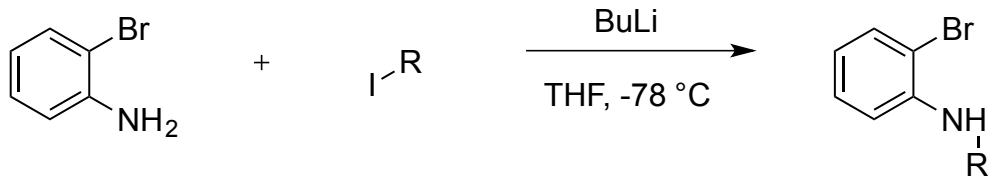
To a solution of K_2CO_3 (2 mmol, 2 equiv) and triazole (103 mg, 1.2 mmol, 1.2 equiv) in dry CH_3CN (12 mL) was added the bromide (1 mmol, 1 equiv) dissolved in CH_3CN. After being stirred at reflux overnight, the mixture was quenched with H_2O (20 mL) and the CH_3CN removed.
The water phase was extracted with DCM (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford the desired product.

The Preparation of Intramolecular C(sp^2)-H activation (General Procedure G)



A solution of nitrogen heterocylce N-alkylated 1 (0.5 mmol), $Pd(OAc)_2$ (0.005 mmol, 1 mol %), $PCy_3{*}HBF_4$ (0.0075 mmol, 1.5 mol%), KOAc (0.6 mmol, 1.2 equiv) in anhydrous DMF (6.4 mL) was heated at 140 °C for 20 h. The reaction mixture was then diluted with EtOAc (10 mL) and concentrated in vacuum and the resulting mixture was purified by column furnishing the corresponding benzoazepine structure.

Alkylation of aniline (General procedure H)

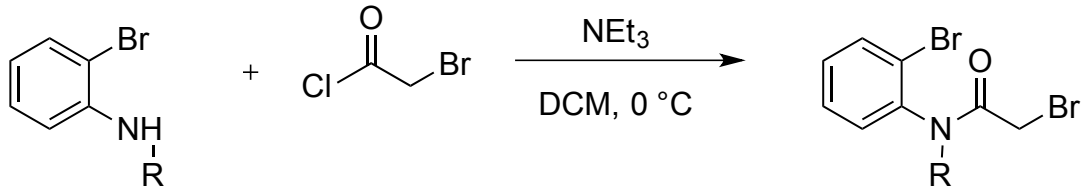


R = Bn, Me, iPr

To a solution at -78°C of 2-bromo aniline (1 mmol) in THF (2 mL, 0.05 M) was added dropwise BuLi 1.6 M in Hexane (0.31 mL, 0.5 mmol) and the reaction was stirred at the same temperature for 15 min. Then the benzyl bromide (1.1 mmol, 1,1 equiv) was added dropwise.

The reaction was stirred at room temperature for 10 h. The mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford a colourless oil. The crude oil was purified by column chromatography on silica gel.

Synthesis of 2-Bromo-N-(2-bromophenyl) acetamides (General procedure I)

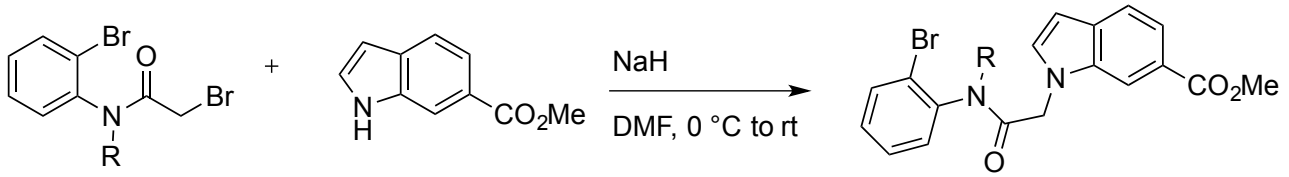


R = Bn, Me, iPr

To a solution at 0°C of N-benzyl-2-bromoaniline (1 mmol) in DCM (4 mL, 0.25 M) and NEt_3 (0.17 mL, 1.2 mmol), bromoacetyl chloride (0.10 mL, 1.2 mmol) was added. The reaction was stirred at the same temperature for 15 min. Then the benzyl bromide (1.1 mmol, 1,1 equiv) was added dropwise.

The reaction was stirred at room temperature for 10 h. The mixture was quenched with NH_4Cl and extracted with EtOAc (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated.

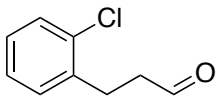
Alkylation of methyl 1H-indole-6-carboxylate (General procedure L)



R = Bn, Me, iPr

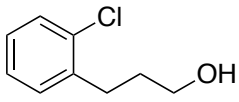
To a 0 °C solution of methyl 1H-indole-6-carboxylate (1.2 mmol, 1.2 equiv) in dry DMF (5.0 mL) was added NaH (61 mg, 1.5 mmol) portion-wise. The suspension was stirred at the same temperature for 2 h and a solution of bromide (1.0 mmol) in dry DMF was added. After being stirred at room temperature for 10 h, the mixture was quenched with H_2O (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography to afford the desired product.

3-(2-Chlorophenyl)-propanal. (The literature procedure was adapted for this substrate.)[1]



An oven-dried 100 mL Schlenk tube with stirbar was charged with tetrabutylammonium chloride (4 mmol, 1 equiv), sodium bicarbonate (10 mmol, 2.5 equiv), and palladium acetate (135 mg, 0.60 mmol). The flask was evacuated and back-filled with argon. Dry DMF (5 mL, 0.75 M) was added followed by 2-iodochlorobenzene (0.5 mL, 4 mmol), allyl alcohol (6 mmol, 1.5 equiv) and additional DMF. The reaction mixture was heated to 45 °C for 22 h, and after cooling to room temperature, distilled water (10 mL) was added to the cooled reaction mixture. The product was extracted with Et_2O (5 x 10 mL), filtered through a plug of silica gel and concentrated to give a yellow oil. The crude oil was purified by chromatography on silica gel eluting with 9:1 Hex/EtOAc to yield 571 mg (85%) of a yellow oil. The spectral data were in agreement with those reported in the literature.[2]

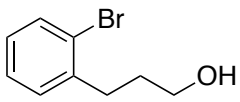
3-(2-Chlorophenyl)-propanol. (The literature procedure was adapted for this substrate.)[1]



A round bottom flask with stirring bar was charged with 3-(2- chlorophenyl)-propanal (500 mg, 3 mmol) and MeOH (3 mL). Sodium borohydride (4.5 mmol, 1.5 equiv) was added in small portions with constant stirring. The solution was stirred at room temperature overnight. The reaction was quenched with acetone (5 mL) and the crude mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated to afford a yellow oil. Tue crude oil was purified by chromatography

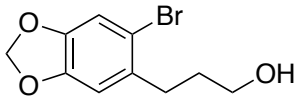
on silica gel eluting with 9:1 Hex/EtOAc to yield 500 mg (98%) of a colourless oil. The spectral data were in agreement with those reported in the literature.[3]

3-(2-Bromophenyl)propan-1-ol.



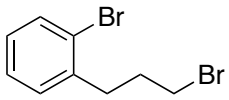
The general procedure **A** was followed using 3-(2-bromophenyl)propionic acid (5 g, 23 mmol). After 2 h, the product was obtained in high purity affording the alcohol (4.69 g, 95 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[4]

3-(6-bromobenzo[d-1,3]dioxol-5-yl)propan-1-ol



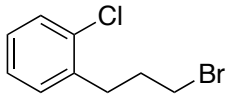
The general procedure **A** was followed using 3-(2-bromo-4,5-methylenedioxyphenyl)propionic acid (2 g, 7.3 mmol) After 2 h, the product was obtained in high purity (1.74 g, 92 %) as a white solid. The spectral data were in agreement with those reported in the literature.[5]

1-bromo-2-(3-bromopropyl)benzene



The general procedure **B** was followed using 3-(2-Bromophenyl)propan-1-ol (1 g, 4.65 mmol). After 10 h, purification by column chromatography (pure Hexane) affording the bromide (1.23 g, 95 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[4]

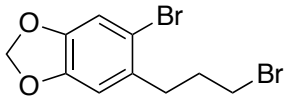
1-(3-bromopropyl)-2-chlorobenzene



The general procedure **B** was followed using 3-(2-Chlorophenyl)-propanol (1 g, 5.9 mmol). After 10 h, purification by column chromatography (pure Hexane) afforded the bromide (1.28 g, 93 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38 (dd, J = 7.0, 2.0 Hz, 1H), 7.30-7.20 (m, 3H), 3.45 (t, J = 6.6 Hz, 2H), 2.93 (t, J = 7.2 Hz, 2H), 2.22 (q, J = 6.6 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) 138.08 (C_q), 133.88 (C_q), 130.57 (CH), 129.54 (CH), 127.63 (CH), 126.76 (CH), 32.93 (CH_2), 32.25 (CH_2), 31.90 (CH_2). **IR (υ max in CH_2Cl_2):** 2960, 2359, 1473, 1239, 1051, 750 cm^{-1}. **MS (ESI)** m/z (relative intensity): 232.97

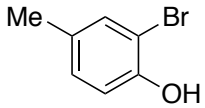
(100) $[M+H]^+$, 234.97 (90) $[M+H]^+$, 254.95 (30) $[M+Na]^+$, 256.95 (20) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_9H_{11}BrCl$ $[M+H]^+$ 232.9727 found 232.9724.

5-bromo-6-(3-bromopropyl)benzo[d-1,3]dioxole



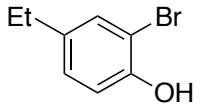
The general procedure **B** was followed using 3-(6-bromobenzo[d-1,3]dioxol-5-yl)propan-1-ol (1.5 g, 5.81 mmol). After 10 h, purification by column chromatography (pure Hexane) afforded the bromide (1.01 g, 82 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.00 (s, 1H), 6.76 (s, 1H), 5.97 (s, 2H), 3.44 (t, J =6.5 Hz, 2H), 2.82 (t, J =7.1 Hz, 2H), 2.15 (q, J = 7.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) 147.26 (C_q), 147.79 (C_q), 132.74 (C_q), 114.24 (C_q), 112.72 (CH), 110.04 (CH), 101.54 (CH_2), 34.27 (CH_2), 32.83 (CH_2), 32.58 (CH_2). **IR (υ max in CH_2Cl_2):** 2896, 2360, 1476, 1232, 1038, 934, 862 cm^{-1}. **MS (ESI)** m/z (relative intensity): 322.91 (100) $[M+H]^+$, 344.89 (40) $[M+Na]^+$, 666.79 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{11}Br_2O_2$ $[M+H]^+$ 320.9120 found 320.9124. **mp** 24-28 °C.

2-bromo-4-methylphenol



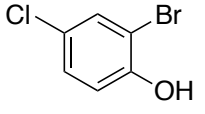
The general procedure **C** was followed using p-cresol (500 mg, 4.6 mmol). After 30 min, purification by column chromatography (pure DCM) afforded the phenol (705 mg, 82 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[6]

2-bromo-4-ethylphenol



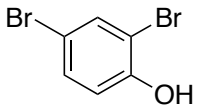
The general procedure **C** was followed using 4-ethylphenol (2 g, 16.4 mmol). After 30 min, purification by column chromatography (pure DCM) afforded the phenol (2.6 g, 79 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[6]

2-bromo-4-chlorophenol



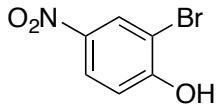
The general procedure **C** was followed using 4-chlorophenol (2 g, 15.6 mmol). After 30 min, purification by column chromatography (Hex/DCM 1:1) afforded the phenol (2.3 g, 72 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[6]

2,4-dibromophenol



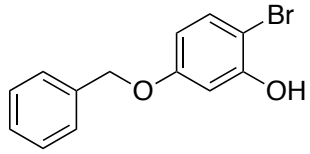
The general procedure **C** was followed using 4-bromophenol (2.5 g, 14.5 mmol). After 30 min, purification by column chromatography (Hex/EtOAc 8:2) affordedthe phenol (2.0 g, 70 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[6]

2-bromo-4-nitrophenol



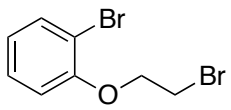
The general procedure **C** was followed using 4-nitrophenol (2 g, 14.4 mmol). After 30 min, purification by column chromatography (Hex/EtOAc 1:1) afforded the phenol (2.2 g, 71 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[6]

5-(benzyloxy)-2-bromophenol (The general procedure **C** was adapted for this substrate)



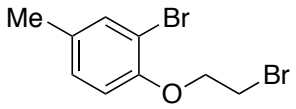
To a -30°C solution 3-(benzyloxy)phenol (1 g, 5 mmol) in dry DCM (15 mL, 0.33 M) was added in two portions the NBS (0.88 mg, 5 mmol) and the suspension obtained was stirred at the same temperature for 10 min. After being stirred at rt for 30 min the mixture was concentrated in vacuo and the residue was purified by silica gel column chromatography to afford the desired product. Purification by column chromatography (Hex/DCM 1:1) affording the phenol (837 mg, 60 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64-7.29 (m, 6H), 6.70 (d, J = 2.8 Hz, 1 H), 6.51 (dd, J = 8.8, 2.8 Hz, 1H), 5.49 (s, 1H), 5.05 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.87 (C_q), 136.35 (C_q), 131.86 (CH), 128.52 (CH), 128.00 (CH), 127.33 (CH), 126.89 (C_q), 109.56 (CH), 102.56 (CH), 101.08 (C_q), 70.16 (CH_2). **IR (υ max in CH_2Cl_2)**: 3700, 3200, 1629, 1517, 1293, 1203, 1021, 653 cm^{-1}. **MS (ESI)** m/z (relative intensity): 279.00 (100) $[M+H]^+$, 280.99 (90) $[M+H]^+$, 300.98 (50) $[M+Na]^+$, 302.98 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{13}H_{12}BrO_2$ $[M+H]^+$ 279.0015 found 279.0018.

1-bromo-2-(2-bromoethoxy)benzene



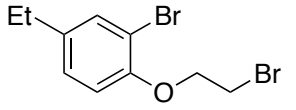
The general procedure **D** was followed using 2-bromophenol (500 mg, 2.9 mmol) After 11 h, purification by column chromatography (Hex/EtOAc 1:1) afforded the bromide (1.84 g, 88 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[7]

2-bromo-1-(2-bromoethoxy)-4-methylbenzene



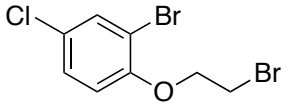
The general procedure **D** was followed using 2-bromo-4-methylphenol (1.4 g, 7.5 mmol) After 11 h, purification by column chromatography (Hex/EtOAc 9:1) afforded the bromide (1.84 g, 84 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[7]

2-bromo-1-(2-bromoethoxy)-4-ethylbenzene



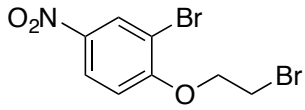
The general procedure **D** was followed using 2-bromo-4-ethylphenol (1.6 g, 8 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 9:1) afforded the bromide (2.2 g, 89 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 6.86 (d, J = 8.3 Hz, 1H), 4.33 (t, J = 6.7 Hz, 2H), 3.68 (t, J = 6.5 Hz, 2H), 2.6 (q, J = 7.6 Hz, 2H), 1.23 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.48 (C_q), 139.08 (C_q), 132.76 (CH), 127.66 (CH), 114.41 (CH), 112.49 (C_q), 69.40 (CH_2), 28.58 (CH_2), 27.63 (CH_2), 15.49 (CH_3). **IR (υ max in CH_2Cl_2)**: 2964, 2930, 1603, 1496, 1251, 1046, 811 cm^{-1}. **MS (ESI**) m/z (relative intensity): 308.93 (100) $[M+H]^+$, 330.91 (30) $[M+Na]^+$, 638.84 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{13}Br_2O$ $[M+H]^+$ 306.9328 found 306.9331.

2-bromo-1-(2-bromoethoxy)-4-chlorobenzene



The general procedure **D** was followed using 2-bromo-4-chlorophenol (1.9 g, 9.5 mmol) After 11 h, purification by column chromatography (Hex/EtOAc 9:1) afforded the bromide (2.5 g, 84 %) as a white solid. The spectral data were in agreement with those reported in the literature.[7]

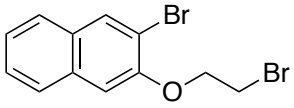
2-bromo-1-(2-bromoethoxy)-4-nitrobenzene



The general procedure **D** was followed using 2-bromo-4-nitrophenol (1 g, 4.6 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 9:1) affordec the bromide (1.4 g, 94 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 (d, J = 2.4 Hz, 1H), 8.20 (dd, J = 8.7, 2.3 Hz, 1H), 6.96 (d, J = 9.0 Hz, 1H), 4.47 (t, J = 6.2 Hz, 2H), 3.75 (t, J = 6.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.43 (C_q), 141.81 (C_q), 129.17 (CH), 124.53 (CH), 112.24 (C_q), 111.78 (CH), 69.31 (CH_2), 27.66 (CH_2).

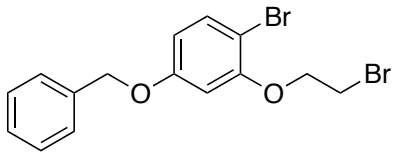
IR (υ max in CH_2Cl_2): 3097, 2921, 1583, 1342, 897, 823 cm^{-1}. **MS (ESI)** m/z (relative intensity): 325.89 (100) $[M+H]^+$, 347.86 (50) $[M+Na]^+$, 672.90 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_8H_8Br_2NO_3$ $[M+H]^+$ 323.8865 found 323.8869. **mp** 67-70 °C

2-bromo-3-(2-bromoethoxy)naphthalene



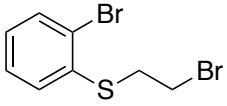
The general procedure **D** was followed using 3-bromonaphthalen-2-ol (1 g, 4.5 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 95:5) afforded the bromide (1.6 g, quantitative yield) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.75-7.71 (m, 2H), 7.52-7.38 (m, 2H), 7.17 (s, 1H), 4.46 (t, J = 6.6 Hz, 2H), 3.78 (t, J = 6.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.00 (C_q), 133.20 (C_q), 132.44 (CH), 129.66 (C_q), 126.71 (CH), 126.64 (CH), 126.54 (CH), 124.77 (CH), 113.48 (C_q), 108.23 (CH), 68.80 (CH_2), 28.27 (CH_2). **IR (υ max in CH_2Cl_2)**: 3055, 2918, 1588, 1452, 1250, 1216, 1018 cm^{-1}. **MS (ESI)** m/z (relative intensity): 330.91 (100) $[M+H]^+$, 352.90 (50) $[M+Na]^+$, 682.80 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{11}Br_2O$ $[M+H]^+$ 328.9171 found 328.9174. **mp** 58-60 °C

4-(benzyloxy)-1-bromo-2-(2-bromoethoxy)benzene



The general procedure **D** was followed using 5-(benzyloxy)-2-bromophenol (300 mg, 1.1 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 95:5) afforded the bromide (311 mg, 75 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.45-7.38 (m, 6H), 6.58 (d, J = 2.7 Hz, 1H), 6.54 (dd, J = 8.6, 2.7 Hz, 1H), 5.10 (s, 2H), 4.31 (t, J = 6.7 Hz, 2H), 3.67 (t, J = 6.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.10 (C_q), 155.07 (C_q), 136.27 (C_q), 133.34 (CH), 128.57 (CH), 128.09 (CH), 127.39 (CH), 108.07 (CH), 103.47 (C_q), 102.56 (CH), 70.33 (CH_2), 68.96 (CH_2), 28.22 (CH_2). **IR (υ max in CH_2Cl_2)**: 3203, 1638, 1516, 1309, 1222, 1027, 674 cm^{-1}. **MS (ESI)** m/z (relative intensity): 386.94 (100) $[M+H]^+$, 408.92 (30) $[M+Na]^+$, 794.85 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{15}H_{15}Br_2O_2$ $[M+H]^+$ 384.9433 found 384.9436.

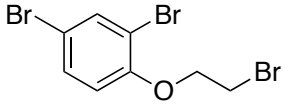
(2-bromoethyl)(2-bromophenyl)sulfane (The general procedure **D** was adapted for this substrate)



A solution of 2-bromobenzenethiol (500 mg, 2.65 mmol), 1,2-dibromoethane (5.3 mmol, 2 equiv), K_2CO_3 (4 mmol, 1.5 equiv), KI (2 mol%, 0.05 mmol) in

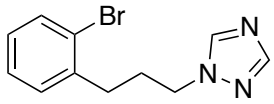
acetone (13 mL, 0.2 M) was stirred at rt for 20 h. The reaction mixture was diluted with EtOAc (5 mL) and concentrated in vacuum. Purification by column chromatography (Hex/MTBE 98:2) afforded the bromide (494 mg, 63 %) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.61 (dd, J = 8.0, 1.2 Hz, 1H), 7.40-7.32 (m, 2H), 7.13 (dt, J = 7.3, 6.0 Hz, 1H), 3.52 (dt, J = 7.7, 1.5 Hz, 2H), 3.37 (dt, J = 7.9, 1.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.39 (C_q), 133.39 (CH), 129.83 (CH), 127.91 (CH), 127.87 (CH), 125.25 (C_q), 35.10 (CH_2), 29.03 (CH_2). **IR (υ max in CH_2Cl_2)**: 3058, 2968, 1574, 1192, 1020, 744 cm^{-1}. **MS (ESI**) m/z (relative intensity): 296.87 (100) $[M+H]^+$, 318.86 (50) $[M+Na]^+$, 614.73 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_8H_9Br_2S$ $[M+H]^+$ 294.8786 found 294.8790.

2,4-dibromo-1-(2-bromoethoxy)benzene



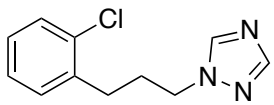
The general procedure **D** was followed using 2,4-dibromophenol (2.0 g, 8 mmol) After 11 h, purification by column chromatography (Hex/EtOAc 9:1) afforded the bromide (2.1 g, 73 %) as a white solid. The spectral data were in agreement with those reported in the literature.[7]

1-[3-(2-bromophenyl)propyl]-1*H*-1,2,4-triazole (1a):



The general procedure **F** was followed using 1-bromo-2-(3-bromopropyl)benzene (300 mg, 1.1 mmol). After 10 h, purification by column chromatography (pure EtOAc) yielded **1a** (229 mg, 86 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.94 (s, 1H), 7.51 (dd, J = 8.0, 1.0 Hz, 1H), 7.21-7.14 (m, 2H), 7.05 (dt, J = 7.9, 2.0 Hz, 1H), 4.19 (t, J = 7.1 Hz, 2H), 2.73 (t, J = 6.3 Hz, 2H), 2.21 (p, J = 7.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.40 (CH), 142.42 (CH), 139.07 (C_q), 132.45 (CH), 129.84 (CH), 127.58 (CH), 127.10 (CH), 123.79 (C_q), 48.37 (CH_2), 32.39 (CH_2), 29.20 (CH_2) **IR (υ max in CH_2Cl_2)**: 2942, 2359, 1507, 1274, 1140, 1021, 752 cm^{-1}. **MS (ESI**) m/z (relative intensity): 266.03 (100) $[M+H]^+$, 268.03 (90) $[M+H]^+$, 288.01 (35) $[M+Na]^+$, 290.01 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{13}BrN_3$ $[M+H]^+$ 266.0287 found 266.0290.

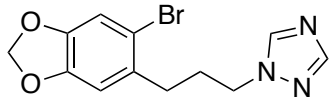
1-[3-(2-chlorophenyl)propyl]-1H-1,2,4-triazole (1a'):



The general procedure **F** was followed using 1-(3-bromopropyl)-2-chlorobenzene (580 mg, 2.5 mmol). After 10 h, purification by column chromatography (pure EtOAc) yielded **1a'** (442 mg, 80 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.89 (s, 1H), 7.27 (dd, J = 6.6, 0.5 Hz, 1H), 7.11-7.07 (m, 3H), 4.13 (t, J =

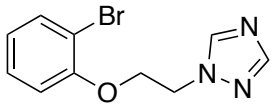
7.0 Hz, 2H), 2.69 (t, J = 7.0 Hz, 2H), 2.16 (p, J = 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.78 (CH), 142.83 (CH), 137.76 (C_q), 133.69 (C_q), 130.26 (CH), 129.50 (CH), 127.72 (CH), 126.83 (CH), 48.74 (CH_2), 30.21 (CH_2), 29.40 (CH_2). **IR (υ max in CH_2Cl_2)**: 2951, 2347, 1501, 1282, 1133, 750 cm^{-1}. **MS (ESI)** m/z (relative intensity): 222.08 (100) $[M+H]^+$, 244.06 (40) $[M+Na]^+$, 465.13 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{13}ClN_3$ $[M+H]^+$ 222.0793 found 222.0796.

1-[3-(6-bromobenzo[d-1,3]dioxol-5-yl)propyl]-1H-1,2,4-triazole (1b)



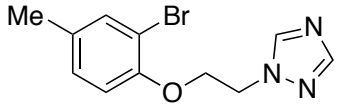
The general procedure **F** was followed using 5-bromo-6-(3-bromopropyl)benzo[d-1,3]dioxole (400 mg, 1.2 mmol). After 10 h, purification by column chromatography (pure EtOAc) yielded **1b** (326 mg, 88 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.92 (s, 1H), 6.93 (s, 1H), 6.63 (s, 1H), 5.91 (s, 2H), 4.16 (t, J = 7.0 Hz, 2H), 2.63 (t, J = 7.1 Hz, 2H), 2.13 (p, J = 7.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.81 (CH), 147.35 (C_q), 146.71 (C_q), 142.82 (CH), 132.43 (C_q), 114.11 (C_q), 112.66 (CH), 109.69 (CH), 101.56 (CH_2), 48.68 (CH_2), 32.67 (CH_2), 29.88 (CH_2). **IR (υ max in CH_2Cl_2)**: 2940, 1537, 1460, 1222, 1030, 754 cm^{-1}. **MS (ESI)** m/z (relative intensity): 310.02 (100) $[M+H]^+$, 312.02 (90) $[M+H]^+$, 332.00 (30) $[M+Na]^+$, 334.00 (15) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{13}BrN_3O_2$ $[M+H]^+$ 310.0186 found 310.0190.

1-[3-(2-chlorophenyl)propyl]-1H-1,2,4-triazole (1c):



The general procedure **F** was followed using 1-bromo-2-(2-bromoethoxy)benzene (250 mg, 0.9 mmol). After 10 h, purification by column chromatography (pure EtOAc) yielded **1c** (182 mg, 78 %) as a colourless oil. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 8.40 (s, 1H), 7.93 (s, 1H), 7.56 (dd, J = 8.4, 1.7 Hz, 1H), 7.30 (dt, J = 8.1, 1.6 Hz, 1H), 6.93-6.88 (m, 2H), 4.67 (t, J = 4.7 Hz, 2H), 4.38 (t, J = 4.7 Hz, 2H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ 155.14 (C_q), 152.55 (CH), 145.29 (CH), 134.13 (CH), 129.37 (CH), 123.36 (CH), 113.94 (CH), 112.66 (C_q), 67.57 (CH_2), 49.90 (CH_2). **IR (υ max in CH_2Cl_2)**: 3095, 1510, 1263, 1044, 783 cm-1. **MS (ESI)** m/z (relative intensity): 268.00 (100) $[M+H]^+$, 270.00 (90) $[M+H]^+$, 289.99 (40) $[M+Na]^+$, 291.99 (25) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{11}BrN_3O$ $[M+H]^+$ 268.0080 found 268.0084.

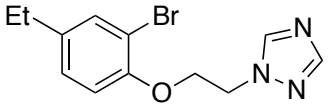
1-[2-(2-bromo-4-methylphenoxy)ethyl]-1H-1,2,4-triazole (1d):



The general procedure **F** was followed using 2-bromo-1-(2-bromoethoxy)-4-methylbenzene (500 mg, 1.7 mmol). After 10 h,

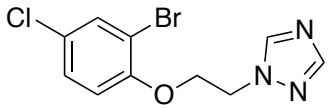
purification by column chromatography (EtOAc/Hex 9:1) yielded **1d** (340 mg, 72 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.97 (s, 1H), 7.36 (d, J = 2.0 Hz, 1H), 7.03 (dd, J = 8.2, 2.1 Hz, 1H), 6.71 (d, J = 8.3 Hz, 1H), 4.64 (t, J = 4.9 Hz, 2H), 4.32 (t, J = 4.9 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.07 (C_q), 151.86 (CH), 144.50 (CH), 133.82 (CH), 132.61 (C_q), 128.83 (CH), 113.24 (CH), 111.88 (C_q), 66.93 (CH_2), 49.22 (CH_2), 20.09 (CH_3). **IR (υ max in CH_2Cl_2)**: 2918, 2355, 1491, 1242, 1090, 740 cm^{-1}. **MS (ESI**) m/z (relative intensity): 282.02 (100) $[M+H]^+$, 284.02 (90) $[M+H]^+$, 304.00 (30) $[M+Na]^+$, 306.00 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{13}BrN_3O$ $[M+H]^+$ 282.0237 found 282.0240.

1-[2-(2-bromo-4-ethylphenoxy)ethyl]-1H-1,2,4-triazole (1e):



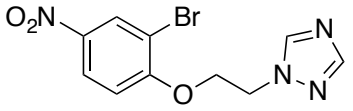
The general procedure **F** was followed using 2-bromo-1-(2-bromoethoxy)-4-ethylbenzene (600 mg, 2 mmol). After 10 h, purification by column chromatography (EtOAc/Hex 9:1) yielded **1e** (382 mg, 66 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.44 (s, 1H), 7.97 (s, 1H), 7.38 (d, J = 2.0 Hz, 1H), 7.06 (dd, J = 8.3, 2.1 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 4.64 (t, J = 4.8 Hz, 2H), 4.32 (t, J = 4.9 Hz, 2H), 2.57 (q, J = 7.6 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.17 (C_q), 151.77 (CH), 144.47 (CH), 139.07 (Cq), 132.71 (CH), 127.65 (CH), 113.28 (CH), 111.96 (Cq), 66.90 (CH2), 49.23 (CH2), 27.58 (CH2), 15.45 (CH3). **IR (υ max in CH_2Cl_2)**: 2973, 1592, 1511, 1290, 1048, 904, 744 cm^{-1}. **MS (ESI**) m/z (relative intensity): 296.04 (100) $[M+H]^+$, 298.04 (85) $[M+H]^+$, 318.02 (40) $[M+Na]^+$, (35) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{15}BrN_3O$ $[M+H]^+$ 296.0393 found 296.0367.

1-[2-(2-bromo-4-chlorophenoxy)ethyl]-1H-1,2,4-triazole (1f):



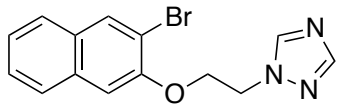
The general procedure **F** was followed using 2-bromo-1-(2-bromoethoxy)-4-chlorobenzene (500 mg, 1.6 mmol). After 10 h, purification by column chromatography (EtOAc/Hex 9:1) yielded **1f** (300 mg, 62 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 7.97 (s, 1H), 7.53 (d, J = 2.5 Hz, 1H), 7.22 (dd, J = 8.8, 2.5 Hz, 1H), 6.75 (d, J = 8.8 Hz, 1H), 4.65 (t, J = 4.9 Hz, 2H), 4.33 (t, J = 4.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.03 (C_q), 152.02 (CH), 144.48 (CH), 132.94 (CH), 128.26 (CH), 127.05 (C_q), 113.72 (CH), 112.63 (C_q), 67.00 (CH_2), 49.00 (CH_2). **IR (υ max in CH_2Cl_2)**: 3047, 1487, 1284, 1051, 902 cm^{-1}. **MS (ESI**) m/z (relative intensity): 301.96 (100) $[M+H]^+$, 303.96 (95) $[M+H]^+$, 323.95 (10) $[M+Na]^+$, 325.95 (10) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{10}BrClN_3O$ $[M+H]^+$ 301.9690 found 301.9693. **mp** 87-91 °C.

1-[2-(2-bromo-4-nitrophenoxy)ethyl]-1H-1,2,4-triazole (1g):



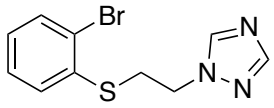
The general procedure **F** was followed using 2-bromo-1-(2-bromoethoxy)-4-nitrobenzene (400 mg, 1.2 mmol). After 10 h, purification by column chromatography (EtOAc/Hex 9:1) yielded **1g** (209 mg, 66 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.40 (d, J = 2.3 Hz, 1H), 8.39 (s, 1H), 8.15 (dd, J = 9.0, 2.3 Hz, 1H), 7.95 (s, 1H), 6.90 (d, J = 9.0 Hz, 1H), 4.70 (t, J = 4.3 Hz, 2H), 4.47 (t, J = 4.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.04 (C_q), 152.24 (CH), 144.58 (C_q), 141.93 (CH), 129.06 (CH), 124.55 (CH), 112.03 (C_q), 111.54 (CH), 67.25 (CH_2), 48.65 (CH_2). **IR (υ max in CH_2Cl_2)**: 2982, 1563, 1321, 1250, 741 cm^{-1}. **MS (ESI)** m/z (relative intensity): 311.99 (100) $[M+H]^+$, 314.99 (85) $[M+H]^+$, 334.98 (30) $[M+Na]^+$, 336.97 (20) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{10}BrN_4O_3$ $[M+H]^+$ 312.9931 found 312.9935. **mp** 64-68 °C.

1-{2-[(3-bromonaphthalen-2-yl)oxy]ethyl}-1H-1,2,4-triazole (1h):



The general procedure **F** was followed using 2-bromo-3-(2-bromoethoxy)naphthalene (330 mg, 1 mmol). After 10 h, purification by column chromatography (EtOAc/Hex 9:1) yielded **1h** (162 mg, 51 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.01 (d, J = 9.2 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.42 (dt, J = 15.0, 7.2 Hz, 2H), 7.06 (s, 1H), 4.70 (t, J = 4.6 Hz, 2H), 4.41 (t, J = 4.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.94 (CH), 151.62 (C_q), 144.63 (CH), 133.06 (C_q), 132.,37 (CH), 129.59 (C_q), 126.81 (CH), 126.64 (CH), 126.51 (CH), 124.84 (CH), 112.99 (C_q), 107.58 (CH), 66.49 (CH_2), 49.02 (CH_2). **IR (υ max in CH_2Cl_2)**: 3053, 1506, 1251, 1218, 1053, 745 cm^{-1}. **MS (ESI)** m/z (relative intensity): 318.02 (100) $[M+H]^+$, 320.02 (90) $[M+H]^+$, 340.00 (45) $[M+Na]^+$, 342.00 (35) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{14}H_{13}BrN_3O$ $[M+H]^+$ 318.0237 found 318.0240. **mp** 113-116 °C.

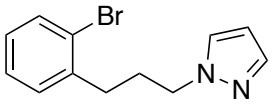
1-{2-[(2-bromophenyl)thio]ethyl}-1H-1,2,4-triazole (1i):



The general procedure **F** was followed using 2-bromo-3-(2-bromoethoxy)naphthalene (382 mg, 1.3 mmol). After 12 h, purification by column chromatography (EtOAc/Hex 9:1) yielded **1i** (110 mg, 41 %) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.89 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.27-7.21 (m, 2H), 7.04 (dt, J = 8.3, 2.0 Hz, 1H), 4.34 (t, J = 6.6 Hz, 2H), 3.36 (t, J = 6.6 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.25 (CH), 169.5 (C_q), 135.14 (CH), 133.35 (CH), 129.71 (CH), 127.94 (CH), 127.90 (CH),

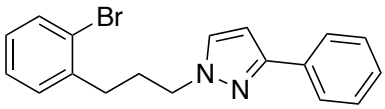
125.03 (C_q), 48.45 (CH_2), 32.85 (CH_2). **IR (υ max in CH_2Cl_2)**: 3083, 1557, 1484, 1315, 1169, 1021, 768 cm^{-1}. **MS (ESI)** m/z (relative intensity) 283.99 (100) $[M+H]^+$, 285.99 (80) $[M+H]^+$, 305.97 (30) $[M+Na]^+$, 307.97 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{11}BrN_3S$ $[M+H]^+$ 283.9852 found 283.9855.

1-[3-(2-bromophenyl)propyl]-1H-pyrazole (1j):



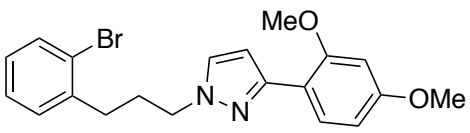
The general procedure **E** was followed using 1-bromo-2-(3-bromopropyl)benzene (277 mg, 1 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 1:1) yielded **1j** (177 mg, 80 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.55-7.53 (m, 2H), 7.42 (d, J = 2.0 Hz, 1H), 7.27-7.19 (m, 2H), 7.07 (dt, J = 7.8, 2.5 Hz, 1H), 6.27 (d, J = 2.0 Hz, 1H), 4.20 (t, J = 7.0 Hz, 2H), 2.75 (t, J = 8.3 Hz, 2H), 2.21 (p, J = 7.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.08 (C_q), 138.81 (CH), 132.80 (CH), 130.34 (CH), 129.07 (CH), 127.80 (CH), 127.45 (CH), 124.28 (C_q), 105.37 (CH), 51.30 (CH_2), 33.01 (CH_2), 30.30 (CH_2). **IR (υ max in CH_2Cl_2)**: 3130, 3074, 1511, 1444, 1026, 761 cm^{-1}. **MS (ESI)** m/z (relative intensity): 265.03 (100) $[M+H]^+$, 267.03 (90) $[M+H]^+$, 287.01 (60) $[M+Na]^+$, 289.01 (50) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{14}BrN_2$ $[M+H]^+$ 265.0335 found 265.0339.

1-[3-(2-bromophenyl)propyl]-3-phenyl-1H-pyrazole (1k):



The general procedure **E** was followed using 1-bromo-2-(3-bromopropyl)benzene (277 mg, 1 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **1k** (317 mg, 93 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86-7.83 (m, 2H), 7.56 (d, J = 8.4 Hz, 1H), 7.46-7.40 (m, 3H), 7.34-7.25 (m, 3H), 7.10 (dt, J = 9.0, 4.9 Hz, 1H), 6.58 (d, J = 2.3 Hz, 1H), 4.24 (t, J = 7.0 Hz, 2H), 2.82 (t, J = 8.1 Hz, 2H), 2.28 (p, J = 7.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.31 (C_q), 140.21 (C_q), 133.58 (C_q), 132.81 (CH), 130.38 (CH), 130.27 (CH), 128.47 (CH), 127.77 (CH), 127.42 (CH), 127.38 (CH), 125.49 (CH), 124.32 (C_q), 102.55 (CH), 51.54 (CH_2), 33.10 (CH_2), 30.35 (CH_2). **IR (υ max in CH_2Cl_2)**: 3061, 1547, 1255, 1027, 760 cm^{-1}. **MS (ESI)** m/z (relative intensity): 341.06 (100) $[M+H]^+$, 343.06 (95) $[M+H]^+$, 363.05 (50) $[2M+Na]^+$, 365.05 (50) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{18}BrN_2$ $[M+H]^+$ 341.0648 found 341.0652.

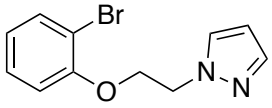
1-[3-(2-bromophenyl)propyl]-3-(2,4-dimethoxyphenyl)-1H-pyrazole (1l):



The general procedure **E** was followed using 1-bromo-2-(3-bromopropyl)benzene (277 mg, 1 mmol). After 11 h,

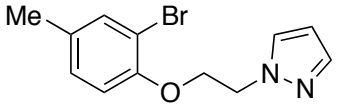
purification by column chromatography (Hex/EtOAc 7:3) yielded **1l** (365 mg, 91 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 (d, J = 8.3 Hz, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.44 (d, J = 1.9 Hz, 1H), 7.28-7.25 (m, 2H), 7.09 (q, J = 4.5 Hz, 1H), 6.73 (d, J = 2.2 Hz, 1H), 6.60 (d, J = 2.4 Hz, 1H), 6.57 (dd, J = 3.2, 2.2 Hz, 1H), 4.24 (t, J = 7.0 Hz, 2H), 3.90 (s, 3H), 3.86 (s, 3H), 2.82 (t, J = 8.2 Hz, 2H), 2.27 (p, J = 7.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.25 (C_q), 157.69 (C_q), 148.04 (C_q), 140.32 (C_q), 132.78 (CH), 130.40 (CH), 129.32 (CH), 129.29 (CH), 127.74 (CH), 127.41 (CH), 124.33 (C_q), 115.59 (C_q), 105.94 (CH), 104.72 (CH), 98.71 (CH), 55.38 (CH_3), 55.29 (CH_3), 51.39 (CH_2), 33.13 (CH_2), 30.40 (CH_2). **IR (υ max in CH_2Cl_2)**: 3028, 1661, 1550, 1343, 1241, 1110, 768 cm^{-1}. **MS (ESI**) m/z (relative intensity): 401.09 (100) $[M+H]^+$, 403.08 (90) $[M+H]^+$, 423.07 (50) $[M+Na]^+$, 425.07 (40) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{20}H_{22}BrN_2O_2$ $[M+H]^+$ 401.0859 found 401.0862.

1-[2-(2-bromophenoxy)ethyl]-1H-pyrazole (1m):



The general procedure **E** was followed using 1-bromo-2-(2-bromoethoxy)benzene (279 mg, 1 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **1m** (187 mg, 70 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.73 (d, J = 1.8 Hz, 1H), 7.54 (dd, J = 1.8, 1.3 Hz, 1H), 7.51 (d, J = 1.4 Hz, 1H), 7.21 (dt, J = 8.1, 1.5 Hz, 1H), 6.86-6.77 (m, 2H), 6.28 (d, J = 2.1 Hz, 1H), 4.59 (t, J = 5.2 Hz, 2H), 4.32 (t, J = 5.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.52 (C_q), 139.54 (CH), 133.29 (CH), 130.78 (CH), 128.44 (CH), 122.31 (CH), 113.04 (CH), 112.00 (C_q), 105.62 (CH), 67.72 (CH_2), 51.36 (CH_2). **IR (υ max in CH_2Cl_2)**: 3090, 1510, 1263, 1040, 764 cm^{-1}. **MS (ESI**) m/z (relative intensity): 267.01 (100) $[M+H]^+$, 269.01 (100) $[M+H]^+$, 288.99 (20) $[M+Na]^+$, 290.99 (10) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{12}BrN_2O$ $[M+H]^+$ 267.0128 found 267.0132.

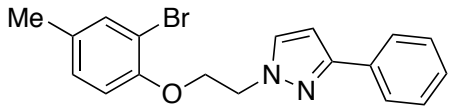
1-[2-(2-bromo-4-methylphenoxy)ethyl]-1H-pyrazole (1n):



The general procedure **E** was followed using 2-bromo-1-(2-bromoethoxy)-4-methylbenzene (500 mg, 1.7 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 1:1) yielded **1n** (350 mg, 74 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, J = 2.2 Hz, 1H), 7.56 (d, J = 1.5 Hz, 1H), 7.36 (d, J = 1.5 Hz, 1H), 7.03 (dd, J = 8.3, 1.4Hz, 1H), 6.70 (d, J = 8.3 Hz, 1H), 6.29 (t, J = 2.1 Hz, 1H), 4.60 (t, J = 5.0 Hz, 2H), 4.33 (t, J = 5.1 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.44 (C_q), 139.45 (CH), 133.68 (CH), 132.12 (CH), 130.76 (CH), 128.79 (C_q), 113.17 (CH), 111.77 (C_q), 105.59 (CH), 67.99 (CH_2), 51.44 (CH_2), 20.06 (CH_3). **IR (υ max in**

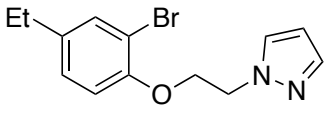
CH_2Cl_2): 2917, 2360, 1497, 1285, 1256, 741 cm^{-1}. **MS (ESI**) m/z (relative intensity): 281.03 (100) $[M+H]^+$, 283.03 (95) $[M+H]^+$, 303.01 (40) $[M+Na]^+$, 305.01 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{14}BrN_2O$ $[M+H]^+$ 281.0284 found 281.0288. **mp** 80-83 °C

1-[2-(2-bromo-4-methylphenoxy)ethyl]-3-phenyl-1H-pyrazole (1o):



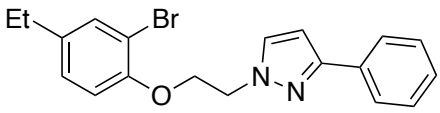
The general procedure **E** was followed using 2-bromo-1-(2-bromoethoxy)-4-methylbenzene (500 mg, 1.7 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **1o** (400 mg, 64 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (dd, J = 8.3, 1.1 Hz, 2H), 7.76 (d, J = 2.2 Hz, 1H), 7.44-7.28 (m, 4H), 7.03 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.58 (d, J = 2.3 Hz, 1H), 4.63 (t, J = 4.8 Hz, 2H), 4.38 (t, J = 5.2 Hz, 2H), 2.27 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.46 (C_q), 151.68 (C_q), 133.69 (CH), 133.37 (C_q), 132.27 (CH), 132.12 (Cq), 128.80 (CH), 128.49 (CH), 127.50 (CH), 125.54 (CH), 113.17 (CH), 111.76 (C_q), 102.94 (CH), 68.07 (CH_2), 51.70 (CH_2), 20.06 (CH_3). **IR (υ max in CH_2Cl_2)**: 2932, 2251, 1488, 1236, 1290, 767 cm^{-1}. **MS (ESI**) m/z (relative intensity): 357.06 (100) $[M+H]^+$, 359.06 (90) $[M+H]^+$, 379.04 (30) $[M+Na]^+$, 381.04 (20) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{18}BrN_2O$ $[M+H]^+$ 357.0597 found 357.0601.

1-[2-(2-bromo-4-ethylphenoxy)ethyl]-1H-pyrazole (1p):



The general procedure **E** was followed using 2-bromo-1-(2-bromoethoxy)-4-ethylbenzene (500 mg, 1.6 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 1:1) yielded **1p** (345 mg, 73 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, J = 1.9 Hz, 1H), 7.55 (s, 1H), 7.38 (d, J = 1.6 Hz, 1H), 7.38 (dd, J = 8.3, 1.5 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.28 (d, J = 1.7 Hz, 1H), 4.59 (t, J = 5.0 Hz, 2H), 4.32 (t, J = 5.0 Hz, 2H), 2.57 (q, J = 7.6 Hz, 2H), 1.2 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.55 (C_q), 139.48 (CH), 138.57 (C_q), 132.57 (CH), 130.76 (CH), 127.64 (CH), 113.17 (CH), 111.83 (C_q), 105.59 (CH), 67.97 (CH_2), 51.44 (CH_2), 27.59 (CH_2), 15.54 (CH_3). **IR (υ max in CH_2Cl_2)**: 2961, 1606, 1497, 1282, 1063, 916, 748 cm^{-1}. **MS (ESI**) m/z (relative intensity): 295.04 (100) $[M+H]^+$, 295.04 (90) $[M+H]^+$, 317.02 (45) $[M+Na]^+$, 319.02 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{13}H_{16}BrN_2O$ $[M+H]^+$ 295.0441 found 295.0445.

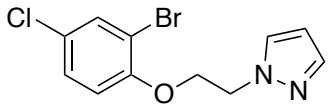
1-[2-(2-bromo-4-ethylphenoxy)ethyl]-3-phenyl-1H-pyrazole (1q):



The general procedure **E** was followed using 2-bromo-1-(2-bromoethoxy)-4-ethylbenzene (500 mg, 1.6 mmol). After 11 h,

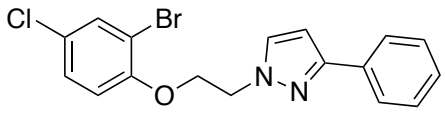
purification by column chromatography (Hex/EtOAc 7:3) yielded **1q** (317 mg, 53 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2 H), 7.78 (d, J = 1.5 Hz, 1H), 7.47-7.42 (m, 3 H), 7.35 (d, J = 7.6 Hz, 1H), 7.06 (d, J = 8.3 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 1.5 Hz, 1H), 4.62 (t, J = 4.8 Hz, 2H), 4.36 (t, J = 4.8 Hz, 2H), 2.58 (q, J = 7.6 Hz, 2H), 1.22 (t, J = 7.5 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.60 (C_q), 151.69 (C_q), 138.58 (C_q), 133.49 (CH), 132.61 (CH), 132.32 (C_q), 128.55 (CH), 127.69 (CH), 127.53 (CH), 125.56 (CH), 113.19 (CH), 111.85 (C_q), 102.97 (CH), 68.05 (CH_2), 51.72 (CH_2), 27.64 (CH_2), 15.59 (CH_3). **IR (υ max in CH_2Cl_2)**: 2977, 1652, 1521, 1247, 1052, 840, 733 cm^{-1}. **MS (ESI)** m/z (relative intensity): 371.08 (100) $[M+H]^+$, 373.07 (90) $[M+H]^+$, 393.06 (50) $[M+Na]^+$, 395.06 (40) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{19}H_{20}BrN_2O$ $[M+H]^+$ 371.0754 found 371.0758. **mp** 94-98 °C.

1-[2-(2-bromo-4-chlorophenoxy)ethyl]-1H-pyrazole (1r):



The general procedure **E** was followed using 2-bromo-1-(2-bromoethoxy)-4-chlorobenzene (500 mg, 1.5 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1r** (352 mg, 78 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.70 (d, J = 2.1 Hz, 1H), 7.55 (dd, J = 8.3, 2.5 Hz, 2H), 7.21 (dd, J = 8.8, 2.5 Hz, 1H), 6.72 (d, J = 8.8 Hz, 1H), 6.29 (d, J = 2.1 Hz, 1H), 4.61 (t, J = 4.9 Hz, 2H), 4.34 (t, J = 5.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.44 (C_q), 139.64 (CH), 132.80 (CH), 130.77 (CH), 128.22 (CH), 126.60 (C_q), 113.71 (CH), 112.54 (C_q), 105.70 (CH), 68.12 (CH_2), 51.29 (CH_2). **IR (υ max in CH_2Cl_2)**: 3098, 1645, 1509, 1316, 1199, 1060, 750 cm-1. **MS (ESI)** m/z (relative intensity): 300.97 (100) $[M+H]^+$, 302.97 (95) $[M+H]^+$, 322.96 (40) $[M+Na]^+$, 324.95 (35) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{11}BrClN_2O$ $[M+H]^+$ 300.9738 found 300.9734. **mp** 65-68 °C.

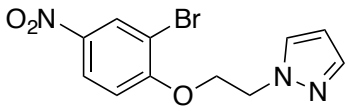
1-[2-(2-bromo-4-chlorophenoxy)ethyl]-3-phenyl-1H-pyrazole (1s):



The general procedure **E** was followed using 2-bromo-1-(2-bromoethoxy)-4-chlorobenzene (500 mg, 1.5 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1s** (361 mg, 63 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.84-7.81 (m, 2H), 7.72 (d, J = 2.3 Hz, 1H), 7.54 (d, J = 2.5 Hz, 1H), 7.45-7.40 (m, 2H), 7.35-7.33 (m, 1H), 7.20 (dd, J = 8.8, 2.5 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 6.59 (d, J = 2.3 Hz, 1H), 4.63 (t, J = 4.9 Hz, 2H), 4.38 (t, J = 5.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.47 (C_q), 151.89 (C_q), 133.29 (C_q), 132.79 (CH), 132.24 (CH), 128.52 (CH), 128.22 (CH), 127.59 (CH), 126.58 (C_q), 125.53 (CH), 113.74 (CH), 112.55 (C_q), 103.00 (CH), 68.20 (CH_2), 51.54 (CH_2). **IR (υ max in CH_2Cl_2)**: 3066, 2949, 1501, 1287, 1074, 753 cm^{-1}. **MS (ESI)** m/z (relative intensity): 377.01 (100) $[M+H]^+$, 379.00 (95)

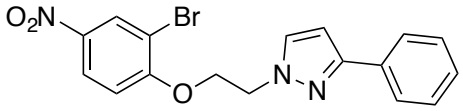
$[M+H]^+$, 398.99 (45) $[M+Na]^+$, 400.99 (45) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{15}BrClN_2O$ $[M+H]^+$ 377.0051 found 377.0048. **mp** 49-51 °C.

1-[2-(2-bromo-4-nitrophenoxy)ethyl]-1H-pyrazole (1t):



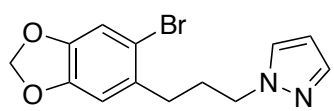
The general procedure **E** was followed using 2-bromo-1-(2-bromoethoxy)-4-nitrobenzene (325 mg, 1 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1t** (146 mg, 47 %) as a pale yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.42 (d, J = 2.6 Hz, 1H), 8.15 (dd, J = 9.1, 2.6 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 7.55 (s, 1H), 6.86 (d, J = 9.1 Hz, 1H), 6.28 (d, J = 1.7 Hz, 1H), 4.64 (t, J = 4.8 Hz, 2H), 4.48 (t, J = 4.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.50 (C_q), 147.70 (CH), 140.00 (C_q), 130.74 (CH), 128.98 (CH), 124.54 (CH), 111.95 (C_q), 111.51 (CH), 105.83 (CH), 68.41 (CH_2), 50.99 (CH_2). **IR (υ max in CH_2Cl_2)**: 2977, 1584, 1343, 1278, 745 cm^{-1}. **MS (ESI**) m/z (relative intensity): 311.99 (100) $[M+H]^+$, 313.99 (90) $[M+H]^+$, 333.98 (40) $[M+Na]^+$. 335.98 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{11}BrN_3O_3$ $[M+H]^+$ 311.9978 found 311.9982. **mp** 96-99 °C.

1-[2-(2-bromo-4-nitrophenoxy)ethyl]-3-phenyl-1H-pyrazole (1w):



The general procedure **E** was followed using 2-bromo-1-(2-bromoethoxy)-4-nitrobenzene (325 mg, 1 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1w** (117 mg, 30 %) as a pale yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.43 (d, J = 2.6 Hz, 1H), 8.11 (dd, J = 9.1, 2.6 Hz, 1H), 7.82-7.77 (m, 3H), 7.70 (d, J = 2.3 Hz, 1H), 7.45-7.42 (m, 2H), 6.83 (d, J = 9.1 Hz, 1H), 6.59 (d, J = 2.3 Hz, 1H), 4.66 (t, J = 4.8 Hz, 2H), 4.48 (t, J = 4.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.46 (C_q), 152.17 (C_q), 141.61 (C_q), 133.15 (C_q), 132.38 (CH), 128.94 (CH), 128.60 (CH), 127.75 (CH), 125.51 (CH), 124.58 (CH), 111.88 (C_q), 111.49 (CH), 103.13 (CH), 68.42 (CH_2), 51.22 (CH_2). **IR (υ max in CH_2Cl_2)**: 2956, 1602, 1519, 1341, 1275, 756 cm^{-1}. **MS (ESI**) m/z (relative intensity): 388.03 (100) $[M+H]^+$, 390.03 (90) $[M+H]^+$, 410.01 (30) $[M+Na]^+$, 412.01 (20) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{15}BrN_3O_3$ $[M+H]^+$ 388.0291 found 388.0294. **mp** 74-77 °C.

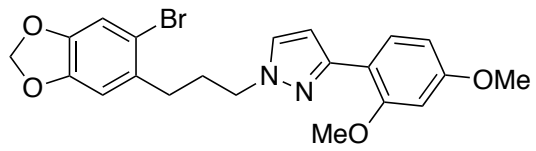
1-[3-(6-bromobenzo[d-1,3]dioxol-5-yl)propyl]-1H-pyrazole (1x):



The general procedure **E** was followed using 6-(3-bromopropyl)benzo[d-1,3]dioxole (400 mg, 1.2 mmol). After 11 h,

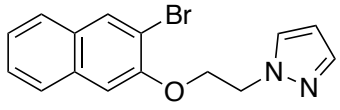
purification by column chromatography (Hex/EtOAc 7:3) yielded **1x** (280 mg, 75 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.52 (d, J = 1.9 Hz, 1H), 7.40 (d, J = 2.2 Hz, 1H), 6.97 (s, 1H), 6.67 (s, 1H), 6.25 (t, J = 2.0 Hz, 1H), 5.90 (s, 2H), 4.16 (t, J = 7.0 Hz, 2H), 2.63 (t, J = 7.4 Hz, 2H), 2.14 (p, J = 7.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.27 (C_q), 146.70 (C_q), 139.07 (CH), 133.15 (C_q), 128.80 (CH), 114.14 (C_q), 112.61 (CH), 109.82 (CH), 105.23 (CH), 101.59 (CH_2), 51.16 (CH_2), 32.91 (CH_2), 30.55 (CH_2). **IR (υ max in CH_2Cl_2)**: 2937, 2897, 1503, 1478, 1232, 1037, 752 cm^{-1}. **MS (ESI**) m/z (relative intensity): 309.02 (100) $[M+H]^+$, 311.02 (95) $[M+H]^+$, 331.00 (50) $[M+Na]^+$, 333.00 (40) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{13}H_{14}BrN_2O_2$ $[M+H]^+$ 309.0233 found 309.0235. **mp** 42-35 °C.

1-[3-(6-bromobenzo[d-1,3]dioxol-5-yl)propyl]-3-(2,4-dimethoxyphenyl)-1H-pyrazole (1y):



The general procedure **E** was followed using 5-bromo-6-(3-bromopropyl)benzo[d-1,3]dioxole (400 mg, 1.2 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1y** (356 mg, 67 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (d, J = 8.3 Hz, 1H), 7.51 (d, J = 2.2 Hz, 1H), 6.99 (s, 1H), 6.74 (s, 1H), 6.73 (s, 1H), 6.60 (d, J = 2.3 Hz, 1H), 6.57 (dd, J = 4.4, 2.3 Hz, 1H), 5.93 (s, 2H), 4.19 (t, J = 7.1 Hz, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 2.70 (t, J = 7.3 Hz, 2H), 2.19 (p, J = 7.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.21 (C_q), 157.67 (C_q), 148.03 (C_q), 147.27 (C_q), 146.68 (C_q), 133.31 (C_q), 129.27 (CH), 129.22 (CH), 115.69 (C_q), 114.18 (C_q), 112.60 (CH), 109.95 (CH), 105.95 (CH), 104.71 (CH), 101.52 (CH), 98.68 (CH_2), 55.36 (CH_3), 55.28 (CH_3), 51.26 (CH_2), 33.00 (CH_2), 30.63 (CH_2). **IR (υ max in CH_2Cl_2)**: 3005, 2986, 1451, 1225, 1187, 1007, 783 cm-1. **MS (ESI**) m/z (relative intensity): 445.08 (100) $[M+H]^+$, 447.07 (90) $[M+H]^+$, 467.06 (30) $[M+Na]^+$, 469.06 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{21}H_{22}BrN_2O_4$ $[M+H]^+$ 445.0757 found 445.0760. **mp** 30-33 °C.

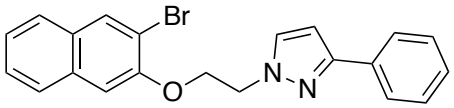
1-{2-[(3-bromonaphthalen-2-yl)oxy]ethyl}-1H-pyrazole (1z):



The general procedure **E** was followed using 2-bromo-3-(2-bromoethoxy)naphthalene (330 mg, 1 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1z** (317 mg, 72 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.78 (d, J= 1.8 Hz, 1H), 7.66 (d, J = 8.3 Hz, 2H), 7.59 (s, 1H), 7.45 (dt, J = 15.0, 6.9 Hz, 1H), 7.41 (dt, J = 15.1, 6.9 Hz, 1H), 7.03 (s, 1H), 6.31 (d, J = 2.0 Hz, 1H), 4.66 (t, J = 4.9 Hz, 2H), 4.42 (t, J = 4.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.03 (C_q), 139.61 (CH), 133.20 (C_q), 132.23 (CH), 130.80 (CH), 129.47 (C_q), 126.68

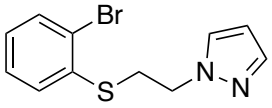
(CH), 126.58 (CH), 126.54 (CH), 113.21 (C_q), 107.55 (CH), 105.71 (CH), 67.68 (CH_2), 51.31 (CH_2). **IR (υ max in CH_2Cl_2)**: 2928, 1660, 1257, 1050 cm^{-1}. **MS (ESI**) m/z (relative intensity): 317.03 (100) $[M+H]^+$, 319.03 (95) $[M+H]^+$, 339.01 (50) $[M+Na]^+$, 341.09 (45) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{15}H_{14}BrN_2O$ $[M+H]^+$ 317.0284 found 317.0288. **mp** 85-89 °C.

1-{2-[(3-bromonaphthalen-2-yl)oxy]ethyl}-3-phenyl-1H-pyrazole (1aa):



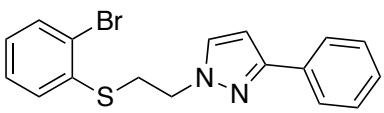
The general procedure **E** was followed using 2-bromo-3-(2-bromoethoxy)naphthalene (330 mg, 1 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **1aa** (259 mg, 66 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.85 (d, J = 7.4 Hz, 2H), 7.80 (d, J = 2.2 Hz, 1H), 7.68 (t, J = 7.0 Hz, 2H), 7.48-7.33 (m, 5H), 7.08 (s, 1H), 6.60 (d, J = 2.3 Hz, 1H), 4.70 (t, J = 4.9 Hz, 2H), 4.50 (t, J = 5.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.10 (C_q), 151.83 (C_q), 133.45 (C_q), 133.24 (C_q), 132.25 (CH), 129.52 (C_q), 128.51 (CH), 127.52 (CH), 126.66 (CH), 126.58 (CH), 126.56 (CH), 125.56 (CH), 124.64 (CH), 113.26 (C_q), 107.69 (CH), 103.02 (CH), 67.82 (CH_2), 51.59 (CH_2). **IR (υ max in CH_2Cl_2)**: 2931, 2360, 1668, 1243, 1389, 1256, 1096 cm^{-1}. **MS (ESI**) m/z (relative intensity): 393.06 (100) $[M+H]^+$, 395.06 (90) $[M+H]^+$, 415.04 (40) $[M+Na]^+$, 417.04 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{21}H_{18}BrN_2O$ $[M+H]^+$ 393.0597 found 393.0600. **mp** 62-67 °C.

1-{2-[(2-bromophenyl)thio]ethyl}-1H-pyrazole (1ab):



The general procedure **E** was followed using (2-bromoethyl)(2-bromophenyl)sulfane (472 mg, 1.6 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **1ab** (90 mg, 46 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.57 (s, 1H), 7.54 (s, 1H), 7.42 (d, J = 2.0 Hz, 1H), 7.31-7.24 (m, 2H), 7.05 (dt, J = 6.4, 2.5 Hz, 1H), 6.23 (t, J = 1.9 Hz, 1H), 4.36 (t, J = 6.8 Hz, 2H), 3.41 (t, J = 7.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.85 (CH), 136.05 (C_q), 133.16 (CH), 129.64 (CH), 128.82 (CH), 127.89 (CH), 127.29 (CH), 124.30 (C_q), 105.51 (CH), 50.81 (CH_2), 33.13 (CH_2). **IR (υ max in CH_2Cl_2)**: 2934, 1513, 1449, 1020, 746 cm^{-1}. **MS (ESI**) m/z (relative intensity): 282.99 (100) $[M+H]^+$, 284.99 (95) $[M+H]^+$, 304.97 (50) $[M+Na]^+$, 306.97 (40) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{12}BrN_2S$ $[M+H]^+$ 282.9899 found 282.9902.

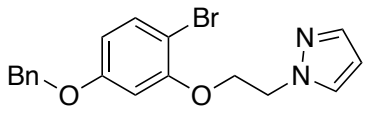
1-{2-[(2-bromophenyl)thio]ethyl}-3-phenyl-1H-pyrazole (1ac):



The general procedure **E** was followed using (2-bromoethyl)(2-bromophenyl)sulfane (296 mg, 1 mmol). After 11 h, purification by

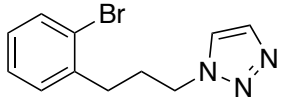
column chromatography (Hex/EtOAc 8:2) yielded **1ac** (147 mg, 41 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.82 (d, J = 7.2 Hz, 2H), 7.59 (d, J = 7.9 Hz, 1H), 7.46-7.26 (m, 6H), 7.07 (dt, J = 7.9, 1.4 Hz, 1H), 6.52 (d, J = 2.2 Hz, 1H), 4.42 (t, J = 6.7 Hz, 2H), 3.49 (t, J = 6.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.06 (C_q), 136.07 (C_q), 133.32 (C_q), 133.15 (CH), 131.12 (CH), 129.00 (CH), 128.50 (CH), 127.83 (CH), 127.58 (CH), 127.27 (CH), 125.55 (CH), 124.37 (C_q), 102.78 (CH), 51.24 (CH_2), 33.30 (CH_2). **IR (υ max in CH_2Cl_2)**: 2922, 1471, 1397, 1123, 1055, 780 cm^{-1}. **MS (ESI**) m/z (relative intensity): 359.02 (100) $[M+H]^+$, 361.02 (95) $[M+H]^+$, 381.00 (30) $[M+Na]^+$, 383.00 (20) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{16}BrN_2S$ $[M+H]^+$ 359.0212 found 359.0215.

1-{2-[5-(benzyloxy)-2-bromophenoxy]ethyl}-1H-pyrazole (1ad):



The general procedure **E** was followed using 4-(benzyloxy)-1-bromo-2-(2-bromoethoxy)benzene (386 mg, 1 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1ad** (332 mg, 89 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74 (d, J = 1.8 Hz, 1H), 7.55 (d, J = 1.8 Hz, 1H), 7.42-7.37 (m, 6H), 6.51-6.48 (m, 2H), 6.29 (dd, J = 3.4, 1.5 Hz, 1H), 5.02 (s, 2H), 4.60 (t, J = 5.0 Hz, 2H), 4.31 (t, J = 5.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.12 (C_q), 155.19 (C_q), 139.56 (CH), 136.28 (C_q), 133.13 (CH), 130.78 (CH), 128.56 (CH), 128.07 (CH), 127.35 (CH), 107.75 (CH), 105.63 (CH), 102.96 (C_q), 101.64 (CH), 70.26 (CH_2), 67.75 (CH_2), 51.33 (CH_2). **IR (υ max in CH_2Cl_2)**: 3080, 1645, 1509, 1316, 1199, 1060 cm^{-1}. **MS (ESI**) m/z (relative intensity): 373.05 (100) $[M+H]^+$, 375.05 (95) $[M+H]^+$, 395.04 (40) $[M+Na]^+$, 397.04 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{18}BrN_2O_2$ $[M+H]^+$ 373.0546 found 373.0549.

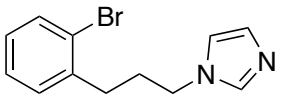
1-[3-(2-bromophenyl)propyl]-1H-1,2,3-triazole (1ae):



The general procedure **E** was adapted using 1-bromo-2-(3-bromopropyl)benzene (277 mg, 1 mmol) and 1,2,3-triazole (1.2 mmol, 1.2 equiv). After 11 h, purification by column chromatography (EtOAc/Hex 9:1) yielded **1ae** (168 mg, 63 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.59 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.21-7.16 (m, 2H), 7.05 (dt, J = 8.1, 2.3 Hz, 1H), 4.41 (t, J = 7.1 Hz, 2H), 2.74 (t, J = 7.3 Hz, 2H), 2.22 (p, J = 7.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.45 (C_q), 133.70 (CH), 132.84 (CH), 130.40 (CH), 128.03 (CH), 127.56 (CH), 124.17 (C_q), 123.28 (CH), 46.26 (CH_2), 33.02 (CH_2), 30.84 (CH_2). **IR (υ max in CH_2Cl_2)**: 3128, 2954, 1472, 1440, 1216, 1020, 755 cm^{-1}. **MS (ESI**) m/z (relative intensity): 266.03 (100) $[M+H]^+$, 268.03 (95)

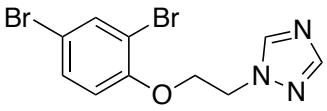
$[M+H]^+$, 288.01 (40) $[M+Na]^+$, 290.01 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{13}BrN_3$ $[M+H]^+$ 266.0287 found 266.0290.

1-[3-(2-bromophenyl)propyl]-1H-imidazole (1af):



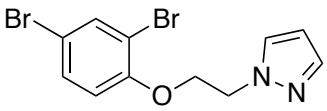
The general procedure **E** was adapted using 1-bromo-2-(3-bromopropyl)benzene (277 mg, 1 mmol) and imidazole (1.2 mmol, 1.2 equiv). After 11 h, purification by column chromatography (EtOAc/Hex 9:1) yielded **1af** (204 mg, 77 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53-7.48 (m, 2H), 7.22 (d, J = 7.4 Hz, 1H), 7.15-7.04 (m, 3H), 6.93 (s, 1H), 3.97 (t, J = 7.01 Hz, 2H), 2.72 (t, J = 7.2 Hz, 2H), 2.10 (p, J = 7.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 139.67 (C_q), 136.99 (CH), 132.89 (CH), 130.18 (CH), 129.47 (CH), 127.98 (CH), 127.53 (CH), 124.20 (C_q), 118.61 (CH), 46.26 (CH_2), 33.02 (CH_2), 30.84 (CH_2). **IR (υ max in CH_2Cl_2)**: 3067, 1548, 1268, 1103, 1026, 774 cm^{-1}. **MS (ESI)** m/z (relative intensity): 265.03 (100) $[M+H]^+$, 267.03 (95) $[M+H]^+$, 287.01 (40) $[M+Na]^+$, 289.01 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{14}BrN_2$ $[M+H]^+$ 265.0335 found 265.0339.

1-[2-(2,4-dibromophenoxy)ethyl]-1H-1,2,4-triazole



The general procedure **F** was followed using 2-bromo-1-(2-bromoethoxy)-4-chlorobenzene (500 mg, 1.6 mmol). After 10 h, purification by column chromatography (EtOAc/Hex 9:1) yielded **1al** (300 mg, 62 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.96 (s, 1H), 7.64 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 8.7, 2.2 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 4.64 (t, J = 4.7 Hz, 2H), 4.31 (t, J = 4.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.48 (C_q), 152.00 (CH), 144.49 (CH), 135.58 (CH), 131.20 (CH), 114.20 (CH), 113.98 (C_q), 112.99 (C_q), 66.90 (CH_2), 48.96 (CH_2). **IR (υ max in CH_2Cl_2)**: 3007, 2362, 1474, 1282, 1057, 750 cm^{-1}. **MS (ESI)** m/z (relative intensity): 347.92 (100) $[M+H]^+$, 369.89 (40) $[M+Na]^+$, 716.81 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{10}Br_2N_3O$ $[M+H]^+$ 345.9185 found 345.9181. **mp** 133-137 °C.

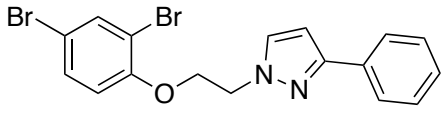
1-[2-(2,4-dibromophenoxy)ethyl]-1H-pyrazole



The general procedure **E** was followed using 2,4-dibromo-1-(2-bromoethoxy)benzene (500 mg, 1.4 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1ag** (339 mg, 70 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.69 (d, J = 2.3 Hz, 1H), 7.67 (d, J = 2.4 Hz, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.34 (dd, J = 8.7, 2.4 Hz, 1H), 6.68 (d, J = 8.7 Hz, 1H), 6.29 (d, J = 1.9 Hz, 1H), 4.61 (d, J = 5.0 Hz, 2H), 4.35 (d, J = 4.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.94 (C_q),

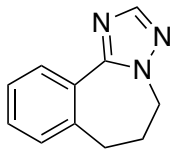
139.63 (CH), 135.48 (CH), 131.16 (CH), 130.71 (CH), 114.32 (CH), 113.59 (C_q), 112.99 (C_q), 105.68 (CH), 68.09 (CH_2), 51.26 (CH_2). **IR (υ max in CH_2Cl_2)**: 3061, 2359, 1579, 1477, 1283, 1055, 745 cm^{-1}. **MS (ESI)** m/z (relative intensity): 346.92 (100) $[M+H]^+$, 368.90 (40) $[M+Na]^+$, 714.82 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{11}Br_2N_2O$ $[M+H]^+$ 344.9233 found 344.9229. **mp** 110-113 °C.

1-[2-(2,4-dibromophenoxy)ethyl]-3-phenyl-1H-pyrazole



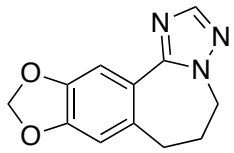
The general procedure **E** was followed using 2,4-dibromo-1-(2-bromoethoxy)benzene (500 mg, 1.4 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **1ah** (378 mg, 64 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.83 (dd, J = 8.6, 1.5 Hz, 2H), 7.69 (dd, J = 8.5, 2.3 Hz, 2H), 7.45-7-40 (m, 2H), 7.35-7.30 (m, 2H), 6.67 (d, J = 8.8 Hz, 1H), 6.58 (d, J = 2.3 Hz, 1H), 4.61 (t, J = 5.0 Hz, 2H), 4.36 (d, J = 4.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.95 (C_q), 151.90 (C_q), 135.46 (CH), 133.35 (C_q), 132.18 (CH), 131.17 (CH), 128.52 (CH), 127.57 (CH), 125.53 (CH), 114.31 (CH), 113.55 (C_q), 112.98 (C_q), 102.99 (CH), 68.15 (CH_2), 51.51 (CH_2). **IR (υ max in CH_2Cl_2)**: 3073, 2372, 1589, 1472, 1286, 1059, 753 cm^{-1}. **MS (ESI)** m/z (relative intensity): 422.95 (100) $[M+H]^+$, 444.93 (50) $[M+Na]^+$, 866.88 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{15}Br_2N_2O$ $[M+H]^+$ 420.9546 found 420.9543. **mp** 65-67 °C.

6,7-dihydro-5H-benzo[c][1,2,4]triazolo[1,5-a]azepine (2a):



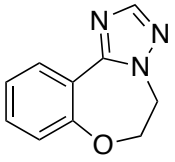
The general procedure **G** was followed using 1-[3-(2-bromophenyl)propyl]-1H-1,2,4-triazole (133 mg, 0.5 mmol). After 20 h, purification by column chromatography (EtOAc/Hex 1:1) yielded **2a** (88 mg, 95 %) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06-8.03 (m, 1H), 7.97 (s, 1H), 7.41-7-36 (m, 2H), 7.30-7.26 (m, 1H), 4.35 (t, J = 6.7 Hz, 2H), 2.89 (t, J = 6.5 Hz, 2H), 2.41 (p, J = 6.7 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.27 (C_q), 152.40 (CH), 141.14 (C_q), 132.07 (CH), 131.40 (CH), 131.17 (CH), 129.16 (C_q), 128.92 (CH), 51.07 (CH_2), 33.82 (CH_2), 30.67 (CH_2). **IR (υ max in CH_2Cl_2)**: 2939, 2361, 1476, 1291, 1107, 821, 736 cm^{-1}. **MS (ESI)** m/z (relative intensity) 186.10 (100) $[M+H]^+$, 208.08 (40) $[M+Na]^+$, 393.18 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{12}N_3$ $[M+H]^+$ 186.1026 found 186.1030.

6,7-dihydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2-c][1,2,4]triazolo[1,5-a]azepine (2b):



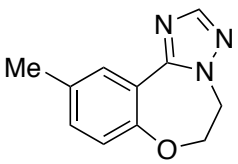
The general procedure **G** was followed using 1-[3-(6-bromobenzo[d][1,3]dioxol-5-yl)propyl]-1H-1,2,4-triazole (155 mg, 0.5 mmol). After 20 h, purification by column chromatography (EtOAc/Hex 7:3) yielded **2b** (85 mg, 74 %) as white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.45 (s, 1H), 6.74 (s, 1H), 6.01 (s, 2H), 4.29 (t, J = 6.8 Hz, 2H), 2.76 (t, J = 6.9 Hz, 2H), 2.37 (p, J = 6.5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.39 (C_q), 150.43 (CH), 149.06 (C_q), 146.68 (C_q), 134.20 (C_q), 120.91 (C_q), 109.70 (CH), 109.14 (CH), 101.46 (CH_2), 48.78 (CH_2), 31.65 (CH_2), 29.40 (CH_2). **IR (υ max in CH_2Cl_2)**: 2975, 2361, 1499, 1223, 1143, 815 cm^{-1}. **MS (ESI**) m/z (relative intensity) 230.09 (100) $[M+H]^+$, 252.07 (40) $[M+Na]^+$, 481.16 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{12}N_3O_2$ $[M+H]^+$ 230.0924 found 230.0927. **mp** 110-112 °C.

5,6-dihydrobenzo[f][1,2,4]triazolo[1,5-d][1,4]oxazepine (2c):



The general procedure **G** was followed using 1-[2-(2-bromophenoxy)ethyl]-1H-1,2,4-triazole (134 mg, 0.5 mmol). After 20 h, purification by column chromatography (EtOAc/Hex 8:2) yielded **2c** (82 mg, 88 %) as a white foam. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.51 (dd, J = 8.1, 1.7 Hz, 1H), 8.00 (s, 1H), 7.40 (dt, J = 7.3, 1.4 Hz, 1H), 7.20 (dt, J = 7.3, 1.2 Hz, 1H), 7.11 (dd, J = 8.2, 1.1 Hz, 1H), 4.70 (dd, J = 4.2, 2.7 Hz, 2H), 4.52 (dd, J = 4.4, 2.8 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) 157.16 (C_q), 151.66 (C_q), 150.68 (CH), 131.84 (CH), 130.61 (CH), 123.21 (CH), 120.62 (CH), 115.31 (C_q), 67.21 (CH_2), 52.89 (CH_2). **IR (υ max in CH_2Cl_2):** 2939, 1632, 1525, 1058, 911, 750 cm^{-1}. **MS (ESI)** m/z (relative intensity) 188.08 (100) $[M+H]^+$, 210.06 (50) $[M+Na]^+$, 397.14 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{10}N_3O$ $[M+H]^+$ 188.0818 found 188.0821.

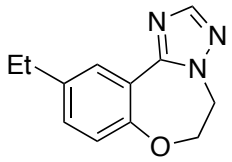
10-methyl-5,6-dihydrobenzo[f][1,2,4]triazolo[1,5-d][1,4]oxazepine (2d):



The general procedure **G** was followed using 1-[2-(2-bromo-4-methylphenoxy)ethyl]-1H-1,2,4-triazole (70 mg, 0.25 mmol). After 20 h, purification by column chromatography (Hex/MTBE 6:4) yielded **2d** (43 mg, 85 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.26 (d, J = 1.2 Hz, 1H), 7.93 (s, 1H), 7.16 (dd, J = 8.3, 2.1 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 4.64 (dd, J = 6.4, 4.2 Hz, 2H), 4.45 (dd, J = 6.0, 4.4 Hz, 2H), 2.36 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) 155.11 (C_q), 151.84 (C_q), 150.85 (CH), 132.60 (C_q), 132.48 (CH), 130.35 (CH), 120.34 (CH), 115.15 (C_q), 67.18 (CH_2), 52.87 (CH_2), 20.34 (CH_3). **IR (υ max in CH_2Cl_2):** 2941, 1513, 1209, 1132, 818 cm^{-1}. **MS (ESI)**

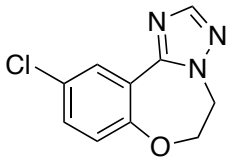
m/z (relative intensity) 202.10 (100) $[M+H]^+$, 224.08 (40) $[M+Na]^+$, 425.17 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{12}N_3O$ $[M+H]^+$ 202.0975 found 202.0978. **mp** 114-116 °C

10-ethyl-5,6-dihydrobenzo[f][1,2,4]triazolo[1,5-d][1,4]oxazepine (2e):



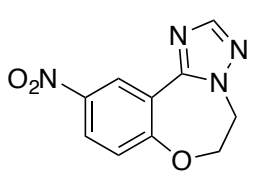
The general procedure **G** was followed using 1-[2-(2-bromo-4-ethylphenoxy)ethyl]-1H-1,2,4-triazole (89 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/MTBE 1:1) yielded **2e** (51 mg, 91 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.28 (d, J = 1.9 Hz, 1H), 7.93 (s, 1H), 7.18 (dd, J = 8.3, 1.9 Hz, 1H), 6.98 (d, J = 8.3 Hz, 1H), 4.63 (dd, J = 6.4, 4.1 Hz, 2H), 4.44 (dd, J = 5.7, 4.0 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.24 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) 155.22 (C_q), 151.90 (C_q), 150.85 (CH), 139.01 (C_q), 131.33 (CH), 129.30 (CH), 120.44 (CH), 115.21 (C_q), 67.15 (CH_2), 52.87 (CH_2), 27.87 (CH_2), 15.52 (CH_3). **IR (υ max in CH_2Cl_2):** 2955, 1498, 1220, 1126, 821 cm^{-1}. **MS (ESI)** m/z (relative intensity) 216.11 (100) $[M+H]^+$, 238.10 (40) $[M+Na]^+$, 453.20 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{14}N_3O$ $[M+H]^+$ 216.1131 found 216.1135. **mp** 104-106 °C.

10-chloro-5,6-dihydrobenzo[f][1,2,4]triazolo[1,5-d][1,4] (2f):



The general procedure **G** was followed using 1-[2-(2-bromo-4-chlorophenoxy)ethyl]-1H-1,2,4-triazole (76 mg, 0.25 mmol). After 20 h, purification by column chromatography (EtOAc/Hex 7:3) yielded **2f** (53 mg, 96 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.46 (d, J = 2.6 Hz, 1H), 7.94 (s, 1H), 7.29 (dd, J = 8.7, 2.6 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 4.66 (dd, J = 6.1, 4.1 Hz, 2H), 4.49 (dd, J = 6.1, 4.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.56 (C_q), 151.05 (CH), 150.63 (C_q), 131.39 (CH), 129.78 (CH), 128.30 (C_q), 122.08 (CH), 116.88 (C_q), 67.39 (CH_2), 52.74 (CH_2). **IR (υ max in CH_2Cl_2)**: 3095, 2950, 1512, 1215, 1044, 834 cm^{-1}. **MS (ESI)** m/z (relative intensity) 222.04 (100) $[M+H]^+$, 244.02 (40) $[M+Na]^+$, 465.06 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_9ClN_3O$ $[M+H]^+$ 222.0429 found 222.0432. **mp** 172-175 °C.

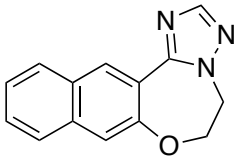
10-nitro-5,6-dihydrobenzo[f][1,2,4]triazolo[1,5-d][1,4]oxazepine (2g):



The general procedure **G** was followed using 1-[2-(2-bromo-4-nitrophenoxy)ethyl]-1H-1,2,4-triazole (156 mg, 0.5 mmol). After 20 h, purification by column chromatography (EtOAc/Hex 1:1) yielded **2g** (77 mg, 66 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.43 (d, J = 2.3 Hz, 1H), 8.23 (dd, J = 9.0, 2.5 Hz, 1H), 8.02 (s, 1H), 7.23 (d, J = 9.0 Hz, 1H), 4.76 (d, J = 3.5 Hz, 2H),

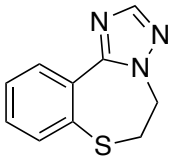
4.64 (d, J = 3.6 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.94 (C_q), 151.38 (CH), 149.98 (C_q), 143.12 (C_q), 127.06 (CH), 126.22 (CH), 121.86 (CH), 115.74 (C_q), 67.90 (CH_2), 52.33 (CH_2). **IR (υ max in CH_2Cl_2)**: 3095, 2360, 1491, 1346, 1106, 746 cm^{-1}. **MS (ESI)** m/z (relative intensity) 233.07 (100) $[M+H]^+$, 255.05 (40) $[M+Na]^+$, 487.11 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_9N_4O_3$ $[M+H]^+$ 233.0669 found 233.0666. The product decomposes at 210 °C.

5,6-dihydronaphtho[2,3-f][1,2,4]triazolo[1,5-d][1,4]oxazepine (2h):



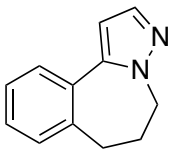
The general procedure **G** was followed using 1-{2-[(3-bromonaphthalen-2-yl)oxy]ethyl}-1H-1,2,4-triazole (96 mg, 0.3 mmol). After 20 h, purification by column chromatography (DCM/EtOAc 98:2) yielded **2h** (73 mg, 93 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.02 (s, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.52-7.39 (m, 3H), 4.69 (dd, J = 6.3, 4.3 Hz, 2H), 4.52 (dd, J = 6.4, 4.6 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.18 (C_q), 151.89 (C_q), 151.19 (CH), 134.83 (C_q), 131.43 (CH), 129.64 (C_q), 128.65 (CH), 127.92 (CH), 126.41 (CH), 125.26 (CH), 117.25 (C_q), 116.37 (CH), 67.64 (CH_2), 53.02 (CH_2). **IR (υ max in CH_2Cl_2)**: 3050, 2360, 1499, 1282, 1169, 748 cm^{-1}. **MS (ESI)** m/z (relative intensity) 238.10 (100) $[M+H]^+$, 260.08 (40) $[M+Na]^+$, 497.17 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{14}H_{12}N_3O$ $[M+H]^+$ 238.0975 found 238.0978. **mp** 166-170 °C.

5,6-dihydrobenzo[f][1,2,4]triazolo[1,5-d][1,4]thiazepine (2i):



The general procedure **G** was followed using 1-{2-[(2-bromophenyl)thio]ethyl}-1H-1,2,4-triazole (71 mg, 0.25 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 6:4) yielded **2i** (32 mg, 62 %) as a pale yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.08 (dd, J = 7.6, 1.7 Hz, 1H), 8.02 (s, 1H), 7.6 (dd, J = 7.5, 1.4 Hz, 1H), 7.48-7.37 (m, 2H), 4.62 (t, J = 6.1 Hz, 2H), 3.51 (t, J = 6.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.86 (C_q), 150.80 (CH), 133.85 (C_q), 133.14 (CH), 131.20 (CH), 131.14 (C_q), 130.34 (CH), 128.30 (CH), 50.42 (CH_2), 35.87 (CH_2). **IR (υ max in CH_2Cl_2)**: 2975, 2360, 1509, 1482, 1296, 1008, 736 cm^{-1}. **MS (ESI)** m/z (relative intensity) 204.06 (100) $[M+H]^+$, 226.04 (40) $[M+Na]^+$, 429.09 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_{10}N_3S$ $[M+H]^+$ 204.0590 found 204.0593. **mp** 87-90 °C.

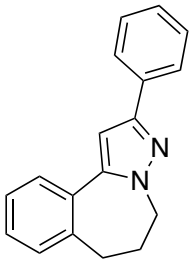
6,7-dihydro-5H-benzo[c]pyrazolo[1,5-a]azepine (2j):



The general procedure **G** was adapted using 1-[3-(2-bromophenyl)propyl]-1H-pyrazole (106 mg, 0.4 mmol). After 20 h, purification by column chromatography

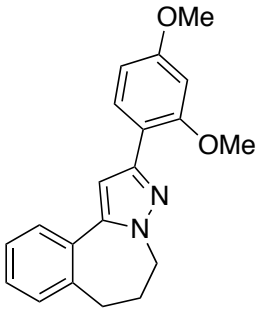
(Hex/EtOAc 6:4) yielded **2j** (56 mg, 76 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54 (d, J = 1.9 Hz, 1H), 7.54-7.43 (m, 1H), 7.36-7.31 (m, 3H), 6.40 (d, J = 1.8 Hz, 1H), 4.21 (t, J = 6.9 Hz, 2H), 2.71 (t, J = 7.0 Hz, 2H), 2.4 (p, J = 7.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 143.07 (C_q), 138.38 (C_q), 138.10 (CH), 130.83 (C_q), 129.43 (CH), 128.59 (CH), 128.03 (CH), 126.87 (CH), 104.26 (CH), 47.85 (CH_2), 31.68 (CH_2), 30.80 (CH_2). **IR (υ max in CH_2Cl_2)**: 2942, 1449, 1367, 947, 760 cm^{-1}. **MS (ESI)** m/z (relative intensity) 185.11 (100) $[M+H]^+$, 207.09 (55) $[M+Na]^+$, 391.19 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{13}N_2$ $[M+H]^+$ 185.1073 found 185.1076.

2-phenyl-6,7-dihydro-5H-benzo[c]pyrazolo[1,5-a]azepine (2k):



The general procedure **G** was adapted using 1-[3-(2-bromophenyl)propyl]-3-phenyl-1H-pyrazole (136 mg, 0.4 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **2k** (66 mg, 63 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.4, 1.3 Hz, 2H), 7.53-7.48 (m, 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.38-7.34 (m, 5H), 6.58 (d, J = 2.3 Hz, 1H), 4.26 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 7.0 Hz, 2H), 2.45 (p, J = 7.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.17 (C_q), 144.60 (C_q), 138.48 (C_q), 133.44 (C_q), 130.77 (C_q), 129.50 (CH), 128.73 (CH), 128.54 (CH), 128.00 (CH), 127.44 (CH), 126.93 (CH), 125.39 (CH), 101.43 (CH), 48.05 (CH_2), 31.66 (CH_2), 30.84 (CH_2). **IR (υ max in CH_2Cl_2)**: 2942, 1468, 1453, 1348, 962, 759 cm^{-1}. **MS (ESI)** m/z (relative intensity) 261.14 (100) $[M+H]^+$, 283.12 (40) $[M+Na]^+$, 543.25 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{17}N_2$ $[M+H]^+$ 261.1386 found 261.1390.

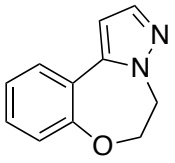
2-(2,4-dimethoxyphenyl)-6,7-dihydro-5H-benzo[c]pyrazolo[1,5-a]azepine (2l):



The general procedure **G** was adapted using 1-[3-(2-bromophenyl)propyl)]-3-(2,4-dimethoxyphenyl)-1H-pyrazole (201 mg, 0.5 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **2l** (94 mg, 59 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 (d, J = 8.2 Hz, 1H), 7.56-7.53 (m, 1H), 7.38-7.28 (m, 3H), 6.90 (s, 1H), 6.63 (d, J = 2.4 Hz, 1H), 6.59 (d, J = 2.6 Hz, 1H), 4.25 (t, J = 6.9 Hz, 2H), 3.93 (s, 3H), 3.87 (s, 3H), 2.78 (t, J = 7.1 Hz, 2H), 2.43 (p, J = 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.16 (C_q), 157.58 (C_q), 146.82 (C_q), 143.51 (C_q), 138.40 (C_q), 131.01 (C_q), 129.35 (CH), 128.97 (CH), 128.35 (CH), 127.94 (CH), 126.73 (CH), 115.32 (C_q), 104.81 (CH), 104.64 (CH), 98.62 (CH), 55.32 (CH_3), 55.21 (CH_3), 47.82 (CH_2), 31.60 (CH_2), 30.81 (CH_2). **IR (υ max in CH_2Cl_2)**: 2949, 1452, 1336, 950, 748 cm^{-1}. **MS (ESI)** m/z (relative intensity) 321.16 (100) $[M+H]^+$, 343.14 (40) $[M+Na]^+$,

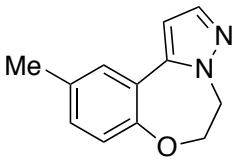
663.29 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{20}H_{21}N_2O_2$ $[M+H]^+$ 321.1598 found 321.1560. **mp** 99-101 °C.

5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2m):



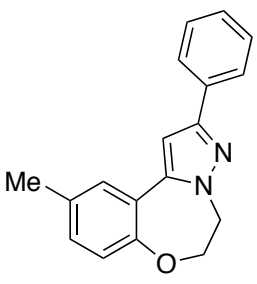
The general procedure **G** was adapted using 1-[2-(2-bromophenoxy)ethyl]-1H-pyrazole (80 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **2m** (45 mg, 81 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.0, 1.5 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.24 (dt, J = 8.0, 1.6 Hz, 1H), 7.10-7.04 (m, 2H), 6.65 (d, J = 2.1 Hz, 1H), 4.67 (dd, J = 6.2, 4.3 Hz, 2H), 4.46 (dd, J = 5.8, 4.3 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.41 (C_q), 140.24 (C_q), 139.13 (CH), 129.40 (CH), 129.01 (CH), 127.72 (CH), 121.08 (CH), 117.45 (C_q), 104.77 (CH), 68.44 (CH_2), 54.24 (CH_2). **IR (υ max in CH_2Cl_2)**: 2939, 1613, 1463, 1208, 1035, 764 cm^{-1}. **MS (ESI)** m/z (relative intensity) 187.09 (100) $[M+H]^+$, 209.07 (50) $[M+Na]^+$, 395.15 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{11}N_2O$ $[M+H]^+$ 187.0866 found 187.0869. **mp** 63-66 °C.

10-methyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2n):



The general procedure **G** was adapted using 1-[2-(2-bromo-4-methylphenoxy)ethyl]-1H-pyrazole (70 mg, 0.25 mmol), $Pd(OAc)_2$ (2.5 mol%) and $PCy_3{*}HBF_4$ (3.8 mol%). After 20 h, purification by column chromatography (Hex/MTBE 8:2) yielded **2n** (43 mg, 86 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.53-7.50 (m, 2H), 7.04 (dd, J = 8.2, 2.0 Hz, 1H), 6.95 (d, J = 8.3 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H), 4.66 (dd, J = 5.5, 2.6 Hz, 2H), 4.45 (dd, J = 6.0, 2.7 Hz, 2H), 2.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) 153.40 (C_q), 140.39 (C_q), 139.06 (CH), 132.04 (C_q), 130.27 (CH), 129.06 (CH), 120.89 (CH), 117.20 (C_q), 104.62 (CH), 68.50 (CH_2), 54.23 (CH_2), 20.49 (CH_3). **IR (υ max in CH_2Cl_2):** 2923, 1490, 1221, 1055, 820 cm^{-1}. **MS (ESI)** m/z (relative intensity) 201.10 (100) $[M+H]^+$, 223.08 (40) $[M+Na]^+$, 423.18 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{13}N_2O$ $[M+H]^+$ 201.1022 found 201.1025. **mp** 106-108 °C.

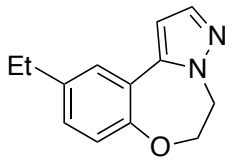
10-methyl-2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2o):



The general procedure **G** was adapted using 1-[2-(2-bromo-4-methylphenoxy)ethyl]-3-phenyl-1H-pyrazole (89 mg, 0.25 mmol), $Pd(OAc)_2$ (5.0 mol%) and $PCy_3{*}HBF_4$ (7.5 mol%). After 20 h, purification by column chromatography (Hex/MTBE 8:2) yielded **2o** (52 mg, 75 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.90 (d, J = 1.3 Hz, 1H), 7.87 (s, 1H), 7.60 (s,

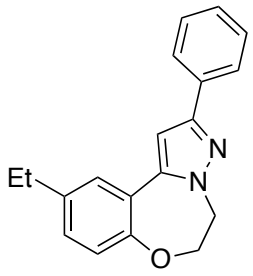
1H), 7.48-7.43 (m, 2H), 7.38-7.36 (m, 1H), 7.09 (dd, J = 8.3, 1.8 Hz, 1H), 7.00 (s, 1H), 6.98 (s, 1H), 4.72 (dd, J = 6.1, 4.2 Hz, 2H), 4.49 (dd, J = 5.9, 4.5 Hz, 2H), 2.39 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) 153.57 (C_q), 150.84 (C_q), 141.81 (C_q), 133.04 (C_q), 132.09 (C_q), 130.40 (CH), 129.09 (CH), 128.58 (CH), 127.71 (CH), 125.44 (CH), 120.93 (CH), 117.17 (C_q), 101.72 (CH), 68.54 (CH_2), 54.47 (CH_2), 20.55 (CH_3). **IR (υ max in CH_2Cl_2):** 2920, 1510, 1221, 1057, 763 cm^{-1}. **MS (ESI)** m/z (relative intensity) 277.13 (100) $[M+H]^+$, 299.12 (40) $[M+Na]^+$, 575.24 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$ 277.1335 found 277.1338. **mp** 92-94 °C.

10-ethyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4] (2p):



The general procedure **G** was adapted using 1-[2-(2-bromo-4-ethylphenoxy)ethyl]-1H-pyrazole (74 mg, 0.25 mmol), $Pd(OAc)_2$ (2.5 mol%) and $PCy_3{*}HBF_4$ (3.8 mol%). After 20 h, purification by column chromatography (Hex/EtOAc 8:2) yielded 2p (46 mg, 86 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.54-7.53 (m, 2H), 7.10 (dd, J = 8.3, 2.0 Hz, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.67 (d, J = 2.0 Hz, 1H), 4.68 (dd, J = 6.2, 4.2 Hz, 2H), 4.47 (dd, J = 6.0, 4.2 Hz, 2H), 2.66 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) 153.51 (C_q), 140.51 (C_q), 139.04 (CH), 138.50 (C_q), 129.11 (CH), 127.98 (CH), 120.99 (CH), 117.20 (C_q), 104.62 (CH), 68.51 (CH_2), 54.22 (CH_2), 27.96 (CH_2), 15.59 (CH_3). **IR (υ max in CH_2Cl_2):** 2964, 1490, 1222, 1124, 1056, 828, 775 cm^{-1}. **MS (ESI)** m/z (relative intensity) 215.12 (100) $[M+H]^+$, 237.10 (40) $[M+Na]^+$, 451.21 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{13}H_{15}N_2O$ $[M+H]^+$ 215.1179 found 215.1182. **mp** 93-96 °C.

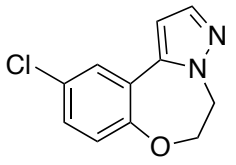
10-ethyl-2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2q):



The general procedure **G** was adapted using 1-[2-(2-bromo-4-ethylphenoxy)ethyl]-3-phenyl-1H-pyrazole (111 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **2q** (57 mg, 73 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 (dd, J = 8.4, 1.4 Hz, 2H), 7.62 (d, J = 1.7 Hz, 1H), 7.46-7.36 (m, 3H), 7.13 (dd, J = 8.4, 1.9 Hz, 1H), 7.03 (s, 1H), 7.00-6.99 (m, 1H), 4.72 (dd, J = 6.3, 4.2 Hz, 2H), 4.50 (dd, J = 5.8, 4.4 Hz, 2H), 2.70 (q, J = 7.6 Hz, 2H), 1.31 (t, J = 7.6 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.67 (C_q), 150.86 (C_q), 141.90 (C_q), 138.54 (C_q), 133.05 (C_q), 129.22 (CH), 128.56 (CH), 128.00 (CH), 127.70 (CH), 125.45 (CH), 121.04 (CH), 117.20 (C_q), 101.70 (CH), 68.57 (CH_2), 54.45 (CH_2), 28.02 (CH_2), 15.66 (CH_3). **IR (υ max in CH_2Cl_2)**: 2951, 2359, 1489, 1216, 1053, 762 cm^{-1}. **MS (ESI**) m/z (relative intensity) 291.15 (100) $[M+H]^+$, 313.13 (30) $[M+Na]^+$, 603.27 (15)

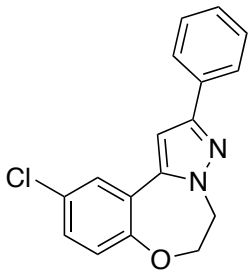
[2M+Na]$^+$. **HR-MS (ESI)** m/z calcd for $C_{19}H_{19}N_2O$ [M+H]$^+$ 291.1492 found 291.1495. **mp** 72-75 °C.

10-chloro-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2r):



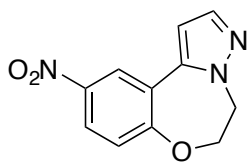
The general procedure **G** was adapted using 1-[2-(2-bromo-4-chlorophenoxy)ethyl]-1H-pyrazole (75 mg, 0.25 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **2r** (42 mg, 76 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67 (d, J = 5.5 Hz, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.18 (dd, J = 8.7, 2.4 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 4.67 (dd, J = 6.2, 4.2 Hz, 2H), 4.46 (dd, J = 6.2, 4.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.95 (C_q), 139.26 (CH), 138.98 (C_q), 129.13 (CH), 128.28 (CH), 127.69 (C_q), 122.57 (CH), 118.80 (C_q), 105.28 (CH), 68.56 (CH_2), 54.22 (CH_2). **IR (υ max in CH_2Cl_2)**: 2977, 1481, 1384, 1223, 828, 774 cm^{-1}. **MS (ESI**) m/z (relative intensity) 221.05 (100) [M+H]$^+$, 243.03 (60) [M+Na]$^+$, 463.07 (40) [2M+Na]$^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{10}ClN_2O$ [M+H]$^+$ 221.0476 found 221.0480. **mp** 143-145 °C.

10-chloro-2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2s):



The general procedure **G** was adapted using 1-[2-(2-bromo-4-chlorophenoxy)ethyl]-3-phenyl-1H-pyrazole (113 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **2s** (48 mg, 65 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.76 (d, J = 2.5 Hz, 1H), 7.47-7.43 (m, 2H), 7.38-7.36 (m, 1H), 7.21 (dd, J = 8.8, 2.5 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 6.96 (s, 1H), 4.74 (dd, J = 6.1, 4.2 Hz, 2H), 4.51 (dd, J = 6.0, 4.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.11 (C_q), 151.07 (C_q), 140.39 (C_q), 132.65 (C_q), 129.26 (CH), 128.60 (CH), 128.29 (CH), 127.89 (CH), 127.76 (C_q), 125.44 (CH), 122.61 (CH), 118.76 (C_q), 102.26 (CH), 68.62 (CH_2), 54.42 (CH_2). **IR (υ max in CH_2Cl_2)**: 2973, 1646, 1479, 1218, 1052, 763 cm^{-1}. **MS (ESI**) m/z (relative intensity) 297.08 (100) [M+H]$^+$, 319.06 (55) [M+Na]$^+$, 615.13 (25) [2M+Na]$^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{14}ClN_2O$ [M+H]$^+$ 297.0789 found 297.0792. **mp** 120-123 °C.

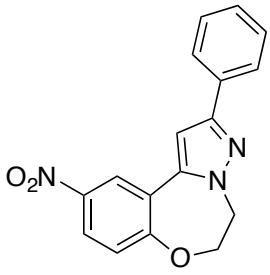
10-nitro-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2t):



The general procedure **G** was adapted using 1-[2-(2-bromo-4-nitrophenoxy)ethyl]-1H-pyrazole (78 mg, 0.25 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **2t** (51 mg, 88 %) as a

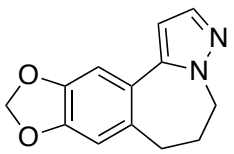
white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.64 (d, J = 2.7 Hz, 1H), 8.09 (dd, J = 9.1, 2.7 Hz, 1H), 7.57 (d, J = 1.7 Hz, 1H), 7.16 (d, J = 9.1 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 4.75 (dd, J = 7.9, 3.9 Hz, 2H), 4.59 (dd, J = 7.7, 4.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.46 (C_q), 139.54 (CH), 138.12 (C_q), 125.77 (C_q), 125.35 (CH), 124.13 (CH), 122.16 (CH), 114.40 (C_q), 106.10 (CH), 68.92 (CH_2), 53.99 (CH_2). **IR (υ max in CH_2Cl_2)**: 2944, 2359, 1504, 1349, 743 cm^{-1}. **MS (ESI)** m/z (relative intensity) 232.07 (100) $[M+H]^+$, 254.05 (45) $[M+Na]^+$, 485.12 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{10}N_3O_3$ $[M+H]^+$ 232.0717 found 232.0714. **mp** 136-138 °C.

10-nitro-2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2w):



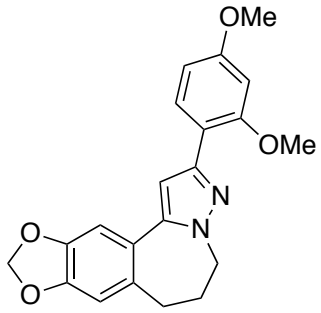
The general procedure **G** was adapted using 1-[2-(2-bromo-4-nitrophenoxy)ethyl]-3-phenyl-1H-pyrazole (155 mg, 0.4 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **2w** (77 mg, 63 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.73 (d, J = 2.7 Hz, 1H), 8.12 (ddd, J = 9.0, 2.6, 0.3 Hz, 1H), 7.87 (d, J = 7.1 Hz, 2H), 7.49-7.44 (m, 2H), 7.40-7.38 (m, 1H), 7.18 (d, J = 9.0 Hz, 1H), 7.12 (s, 1H), 4.80 (dd, J = 6.3, 4.0 Hz, 2H), 4.64 (dd, J = 5.8, 4.1 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.63 (C_q), 151.40 (C_q), 142.68 (C_q), 139.45 (C_q), 132.34 (C_q), 128.67 (CH), 128.09 (CH), 125.45 (CH), 125.37 (CH), 124.24 (CH), 122.23 (CH), 117.03 (C_q), 102.99 (CH), 68.95 (CH_2), 54.22 (CH_2). **IR (υ max in CH_2Cl_2)**: 2979, 2360, 1522, 1506, 1349, 1102, 761 cm^{-1}. **MS (ESI)** m/z (relative intensity) 308.10 (100) $[M+H]^+$, 330.08 (40) $[M+Na]^+$, 637.18 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{14}N_3O_3$ $[M+H]^+$ 308.1030 found 308.1027. **mp** 118-121 °C.

6,7-dihydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2-c]pyrazolo[1,5-a]azepine (2x):



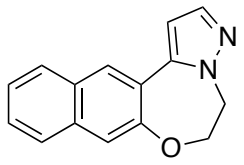
The general procedure **G** was adapted using 1-[3-(6-bromobenzo[d][1,3]dioxol-5-yl)propyl]-1H-pyrazole (93 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **2x** (46 mg, 67 %) as a colurless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.50 (d, J = 1.8 Hz, 1H), 6.90 (s, 1H), 6.79 (s, 1H), 6.30 (d, J = 1.9 Hz, 1H), 5.99 (s, 2H), 4.17 (t, J = 6.9 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.35 (p, J = 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 147.64 (C_q), 146.39 (C_q), 142.88 (C_q), 138.08 (CH), 132.49 (C_q), 124.05 (C_q), 109.81 (CH), 108.36 (CH), 103.86 (CH), 101.13 (CH_2), 47.66 (CH_2), 31.99 (CH_2), 30.59 (CH_2). **IR (υ max in CH_2Cl_2)**: 2943, 1617, 1501, 1478, 1398, 1252, 1039, 783 cm^{-1}. **MS (ESI)** m/z (relative intensity) 229.10 (100) $[M+H]^+$, 251.08 (60) $[M+Na]^+$, 479.17 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{13}H_{13}N_2O_2$ $[M+H]^+$ 229.0972 found 229.0975.

2-(2,4-dimethoxyphenyl)-6,7-dihydro-5H-[1,3]dioxolo[4',5':4,5]benzo[1,2-c]pyrazolo[1,5-a]azepine (2y):



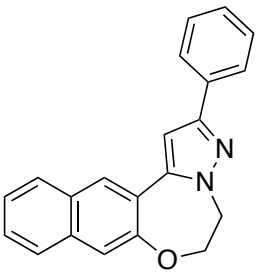
The general procedure **G** was adapted using 1-[3-(6-bromobenzo[d][1,3]dioxol-5-yl)propyl]-3-(2,4-dimethoxyphenyl)-1H-pyrazole (134 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **2y** (84 mg, 77 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.92 (d, J = 8.2 Hz, 1H), 7.00 (s, 1H), 6.80 (d, J = 2.8 Hz, 2H), 6.61-6.58 (m, 2H), 5.99 (s, 2H), 4.21 (t, J = 6.9 Hz, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 2.65 (t, J = 7.1 Hz, 2H), 2.37 (p, J = 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.22 (C_q), 157.65 (C_q), 147.51 (C_q), 146.85 (C_q), 146.35 (C_q), 143.40 (C_q), 132.57 (C_q), 129.01 (CH), 124.38 (C_q), 115.48 (C_q), 109.81 (CH), 108.36 (CH), 104.76 (CH), 104.52 (CH), 101.11 (CH_2), 98.71 (CH), 55.38 (CH_3), 55.26 (CH_3), 47.74 (CH_2), 31.97 (CH_2), 30.69 (CH_2). **IR (υ max in CH_2Cl_2)**: 2943, 1612, 1475, 1207, 1038, 737 cm^{-1}. **MS (ESI)** m/z (relative intensity) 365.15 (100) $[M+H]^+$, 387.13 (35) $[M+Na]^+$, 751.27 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{21}H_{21}N_2O_4$ $[M+H]^+$ 365.1496 found 365.1500. **mp** 135-138 °C.

5,6-dihydronaphtho[2,3-f]pyrazolo[1,5-d][1,4]oxazepine (2z):



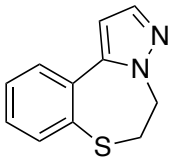
The general procedure **G** was adapted using 1-{2-[(3-bromonaphthalen-2-yl)oxy]ethyl}-1H-pyrazole (79 mg, 0.25 mmol). After 20 h, purification by column chromatography (DCM/EtOAc 98:2) yielded **2z** (38 mg, 65 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 7.52-7.29 (m, 3H), 6.80 d, J = 2.0 Hz, 1H), 4.72 (dd, J = 6.0, 4.5 Hz, 2H), 4.58 (dd, J = 6.2, 4.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 153.53 (C_q), 140.53 (C_q), 139.35 (CH), 133.84 (C_q), 129.92 (C_q), 128.53 (CH), 127.82 (CH), 126.94 (CH), 126.49 (CH), 125.14 (CH), 120.46 (C_q), 117.05 (CH), 105.34 (CH), 69.67 (CH_2), 53.44 (CH_2). **IR (υ max in CH_2Cl_2)**: 2966, 1596, 1407, 1354, 1170, 745 cm^{-1}. **MS (ESI)** m/z (relative intensity) 237.10 (100) $[M+H]^+$, 259.08 (30) $[M+Na]^+$, 495.18 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{15}H_{13}N_2O$ $[M+H]^+$ 237.1022 found 237.1025. **mp** 141-144 °C.

2-phenyl-5,6-dihydronaphtho[2,3-f]pyrazolo[1,5-d][1,4]oxazepine (2aa):



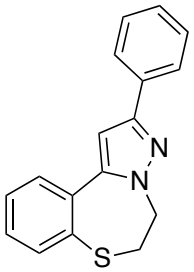
The general procedure **G** was adapted using 1-{2-[(3-bromonaphthalen-2-yl)oxy]ethyl}-3-phenyl-1H-pyrazole (95 mg, 0.3 mmol). After 20 h, purification by column chromatography (pure DCM) yielded **2aa** (60 mg, 64 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.93-7.87 (m, 3H), 7.76 (d, J = 7.8 Hz, 1H), 7.55-7.37 (m, 6H), 7.11 (s, 1H), 4.76 (dd, J = 6.1, 4.3 Hz, 2H), 4.61 (dd, J = 6.2, 4.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.10 (C_q), 151.83 (C_q), 133.45 (C_q), 133.24 (C_q), 132.25 (CH), 129.52 (C_q), 128.51 (CH), 127.52 (CH), 126.66 (CH), 126.58 (CH), 126.56 (CH), 125.56 (CH), 124.64 (CH), 113.26 (C_q), 107.69 (CH), 103.02 (CH), 67.82 (CH_2), 51.59 (CH_2). **IR (υ max in CH_2Cl_2)**: 2942, 1637, 1352, 1262, 1169, 767 cm^{-1}. **MS (ESI**) m/z (relative intensity) 313.13 (100) $[M+H]^+$, 335.12 (55) $[M+Na]^+$, 647.24 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{21}H_{17}N_2O$ $[M+H]^+$ 313.1335 found 313.1338. **mp** 118-121 °C.

5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]thiazepine (2ab):



The general procedure **G** was adapted using 1-{2-[(2-bromophenyl)thio]ethyl}-1H-pyrazole (90 mg, 0.3 mmol). After 20 h, purification by column chromatography (DCM/EtOAc 98:2) yielded **2ab** (33 mg, 54 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.5, 0.9 Hz, 1H), 7.60 (d, J = 1.8 Hz, 1H), 7.51 (dd, J = 7.5, 1.5 Hz, 1H), 7.43 (dt, J = 7.5, 1.3 Hz, 1H), 7.35 (dt, J = 7.5, 1.3 Hz, 1H), 6.43 (d, J = 1.8 Hz, 1H), 4.46 (t, J = 6.2 Hz, 2H), 3.60 (t, J = 6.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 142.56 (C_q), 138.67 (CH), 135.23 (C_q), 134.50 (CH), 131.16 (C_q), 129.61 (CH), 129.19 (CH), 128.68 (CH), 105.12 (CH), 47.88 (CH_2), 38.71 (CH_2). **IR (υ max in CH_2Cl_2)**: 3060, 2932, 1501, 1227, 1020, 747 cm^{-1}. **MS (ESI**) m/z (relative intensity) 203.06 (100) $[M+H]^+$, 225.05 (50) $[M+Na]^+$, 427.10 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{11}N_2S$ $[M+H]^+$ 203.0637 found 203.0640. **mp** 58-68 °C.

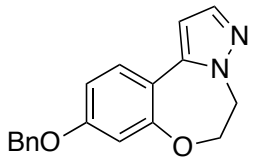
2-phenyl-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]thiazepine (2ac):



The general procedure **G** was adapted using 1-{2-[(2-bromophenyl)thio]ethyl}-3-phenyl-1H-pyrazole (85 mg, 0.3 mmol). After 20 h, purification by column chromatography (pure DCM) yielded **2ac** (43 mg, 51 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.3 Hz, 2H), 7.70 (dd, J = 7.5, 0.8 Hz, 1H), 7.58 (dd, J = 7.5, 1.0 Hz, 1H), 7.48-7.43 (m, 3H), 7.40-7.33 (m, 2H), 6.73 (s, 1H), 4.49 (t, J = 6.0 Hz, 2H), 3.64 (t, J = 5.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 150.70 (C_q), 144.04 (C_q), 135.11 (C_q), 134.55 (CH), 133.14 (C_q), 131.30 (C_q), 129.60 (CH), 129.30

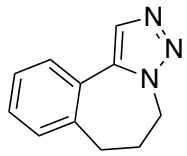
(CH), 128.71 (CH), 128.56 (CH), 127.66 (CH), 125.54 (CH), 102.33 (CH), 48.13 (CH_2), 38.70 (CH_2). **IR (υ max in CH_2Cl_2)**: 2936, 1671, 1510, 1243, 1053, 821, 723 cm-1. **MS (ESI)** m/z (relative intensity) 279.10 (100) $[M+H]^+$, 301.08 (40) $[M+Na]^+$, 579.16 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{15}N_2S$ $[M+H]^+$ 279.0950 found 279.0953. **mp** 99-101 °C.

9-(benzyloxy)-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2ad):



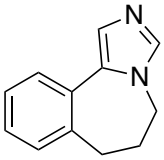
The general procedure **G** was adapted using 1-{2-[5-(benzyloxy)-2-bromophenoxy]ethyl}-1H-pyrazole (149 mg, 0.4 mmol), $Pd(OAc)_2$ (5.0 mol%) and $PCy_3{*}HBF_4$ (7.5 mol%). After 20 h, purification by column chromatography (pure DCM) yielded **2ad** (79 mg, 68 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.47-7.34 (m, 5H), 6.76 (dd, J = 8.8, 2.6 Hz, 1H), 6.66 (d, J = 2.6 Hz, 1H), 6.56 (d, J = 2.1 Hz, 1H), 5.09 (s, 2H), 4.71-4.65 (m, 2H), 4.49-4.47 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) 159.59 (C_q), 156.52 (C_q), 140.24 (C_q), 139.12 (CH), 136.37 (C_q), 130.09 (CH), 128.54 (CH), 128.02 (CH), 127.37 (CH), 110.74 (CH), 110.38 (C_q), 105.94 (CH), 103.76 (CH), 70.01 (CH_2), 68.45 (CH_2), 54.19 (CH_2). **IR (υ max in CH_2Cl_2):** 2978, 1511, 1229, 1053, 743 cm^{-1}. **MS (ESI)** m/z (relative intensity) 293.13 (100) $[M+H]^+$, 315.11 (40) $[M+Na]^+$, 607.23 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1285 found 293.1288.

6,7-dihydro-5H-benzo[c][1,2,3]triazolo[1,5-a]azepine (2ae):



The general procedure **G** was adapted using 1-[3-(2-bromophenyl)propyl]-1H-1,2,3-triazole (80 mg, 0.3 mmol). After 20 h, purification by column chromatography (pure DCM) yielded **2ae** (52 mg, 94 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.46 (dd, J = 6.2, 1.2 Hz, 1H), 7.39-7.35 (m, 3H), 4.43 (t, J = 6.9 Hz, 2H), 2.72 (t, J = 7.0 Hz, 2H), 2.44 (p, J = 7.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.34 (C_q), 137.77 (C_q), 131.45 (CH), 129.86 (CH), 129.58 (CH), 128.20 (CH), 127.22 (CH), 127.08 (C_q), 46.34 (CH_2), 30.66 (CH_2), 30.35 (CH_2). **IR (υ max in CH_2Cl_2)**: 2945, 1455, 1208, 1109, 980, 766 cm^{-1}. **MS (ESI)** m/z (relative intensity) 186.10 (100) $[M+H]^+$, 208.08 (40) $[M+Na]^+$, 393.18 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{12}N_3$ $[M+H]^+$ 186.1026 found 186.1030.

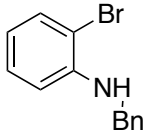
6,7-dihydro-5H-benzo[c]imidazo[1,5-a]azepine (2af):



The general procedure **G** was adapted using 1-[3-(2-bromophenyl)propyl]-1H-imidazole (149 mg, 0.4 mmol). After 20 h, purification by column chromatography (pure DCM) yielded **2af** (50 mg, 67 %) as a colourless oil. **^{1}H NMR** (300 MHz,

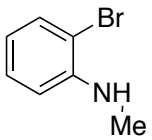
$CDCl_3$) δ 7.80 (dd, J = 8.9, 2.3 Hz, 1H), 7.40-7.33 (m, 2H), 7.31-7.25 (m, 1H), 7.16 (s, 1H), 7.03 (s, 1H), 3.93 (t, J = 6.8 Hz, 2H), 2.74 (t, J = 7.0 Hz, 2H), 2.34 (p, J = 6.9 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.10 (C_q), 137.93 (C_q), 131.03 (C_q), 129.12 (CH), 128.87 (CH), 128.45 (CH), 127.94 (CH), 127.00 (CH), 120.54 (CH), 44.39 (CH_2), 31.20 (CH_2), 30.71 (CH_2). **IR (υ max in CH_2Cl_2)**: 2941, 1469, 1454, 1293, 1108, 770 cm^{-1}. **MS (ESI**) m/z (relative intensity) 185.11 (100) $[M+H]^+$, 207.09 (40) $[M+Na]^+$, 391.19 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{12}H_{13}N_2$ $[M+H]^+$ 185.1073 found 185.1076.

N-benzyl-2-bromoaniline:



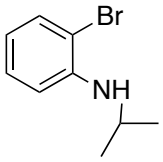
The general procedure **H** was followed using 2-bromo-aniline (172 mg, 1.0 mmol) and benzyl bromide (131 μL). After 10 h, purification by column chromatography (pure Hexane) afforded the alkylated aniline (235 mg, 90 %) as a colourless oil. The spectral data were in agreement with those reported in the literature. [8]

2-bromo-N-methylaniline:



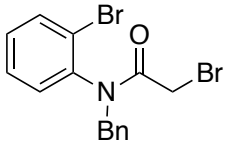
The general procedure **H** was followed using 2-bromo-aniline (172 mg, 1.0 mmol) and methyl iodide (68 μL). After 10 h, purification by column chromatography (pure Hexane) afforded the alkylated aniline (164 mg, 88 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[9]

2--bromo-N-isopropylaniline:



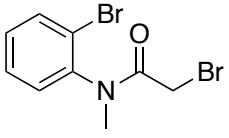
The general procedure **H** was followed using 2-bromo-aniline (172 mg, 1.0 mmol) and 2-iodo propane (110 μL). After 10 h, purification by column chromatography (pure Hexane) afforded the alkylated aniline (186 mg, 80 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[9]

N-benzyl-2-bromo-N-(2-bromophenyl)acetamide



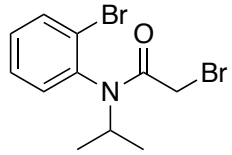
The general procedure **I** was followed using N-benzyl-2-bromoaniline (1 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 9:1) afforded the acetamide (291 mg, 76 %) as a white solid. The spectral data were in agreement with those reported in the literature.[10]

2-bromo-N-(2-bromophenyl)-N-methylacetamide



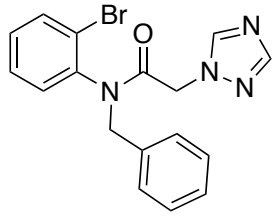
The general procedure **I** was followed using 2-bromo-N-methylaniline (1 g, 5.38 mmol). After 10 h, purification by column chromatography (pure Hexane) afforded the acetamide (1.57 g, 95 %) as a colourless oil. The spectral data were in agreement with those reported in the literature.[10]

2-bromo-N-(2-bromophenyl)-N-isopropylacetamide



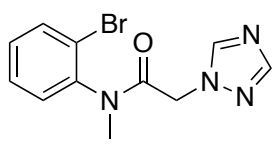
The general procedure **I** was followed using 2-bromo-N-isopropylaniline (1 g, 4.65 mmol). After 10 h, purification by column chromatography (pure Hexane) afforded the acetamide (1.20 g, 77 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.20 (d, J = 7.8 Hz, 1H), 7.47-7.27 (m, 3H), 4.81 (ept, J = 6.7 Hz, 1H), 3.67 (d, J = 11.2 Hz, 1H), 3.42 (d, J = 11.2 Hz, 1H), 1.63 (d, J = 3.0 Hz), 1.58 (d, J = 3.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.78 (C_q), 141.13 (C_q), 134.05 (CH), 130.39 (CH), 128.92 (CH), 129.18 (CH), 52.16 (CH), 41.65 (CH_2), 22.23 (CH_3), 20.14 (CH_3). **MS (ESI)** m/z (relative intensity): 335.94 (100) $[M+H]^+$, 337.94 (55) $[M+H]^+$, 357.92 (40) $[M+Na]^+$, 359.92 (35) $[M+Na]^+$, 692.86 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{14}Br_2NO$ $[M+H]^+$ 333.9437 found 333.9432.

N-benzyl-N-(2-bromophenyl)-2-(1H-1,2,4-triazol-1-yl)acetamide (5a):



The general procedure **F** was followed using N-benzyl-2-bromo-N-(2-bromophenyl)acetamide (575 mg, 1.5 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 6:4) yielded **5a** (489 mg, 88 %) as a pale yellow foam. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.94 (s, 1H), 7.75 (dd, J = 7.5, 2.4 Hz, 1H), 7.31-7.25 (m, 5H), 7.19-7.17 (m, 2H), 6.89 (dd, J = 6.1, 2.1 Hz, 1H), 5.56 (d. J = 14.2 Hz, 1H), 4.66 (dd, J = 25.4, 16.7 Hz, 2H), 4.14 (d, J = 14.2 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.90 (C_q), 151.50 (CH), 144.65 (CH), 138.37 (C_q), 135.56 (C_q), 134.19 (CH), 131.26 (CH), 130.79 (CH), 129.41 (CH), 128.91 (CH), 128.46 (CH), 127.90 (CH), 123.52 (C_q), 52.23 (CH_2), 51.09 (CH_2). **IR (υ max in CH_2Cl_2)**: 3206, 1760, 1430, 1243, 1042, 713 cm^{-1}. **MS (ESI**) m/z (relative intensity) 371.05 (100) $[M+H]^+$, 373.05 (95) $[M+H]^+$, 393.03 (40) $[M+Na]^+$, 395.03 (20) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{16}BrN_4O$ $[M+H]^+$ 371.0502 found 371.0505.

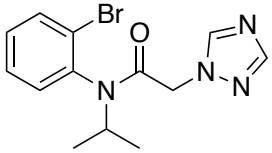
N-(2-bromophenyl)-N-methyl-2-(1H-1,2,4-triazol-1-yl)acetamide (5b):



The general procedure **F** was followed using 2-bromo-N-(2-bromophenyl)-N-methylacetamide (307 mg, 1.0 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 1:1) yielded **5b** (245 mg, 83 %) as a colurless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.90 (s, 1H), 7.75 (dd, J = 8.0, 1.2 Hz, 1H), 7.47-7.34 (m, 3H), 4.66 (dd, J = 24.3, 15.9 Hz, 2H), 3.26 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.92 (C_q), 151.52 (CH), 144.63 (CH), 140.42 (C_q), 134.22 (CH), 130.77 (CH), 129.71 (CH), 129.60 (CH), 123.07 (C_q), 50.78 (CH_2), 36.30 (CH_3). **MS (ESI)** m/z (relative intensity): 295.02 (100) $[M+H]^+$, 297.02 (90) $[M+H]^+$, 317.00 (45) $[M+Na]^+$, 319.00 (35) $[M+Na]^+$, 613.01 (10) $[2M+Na]^+$.

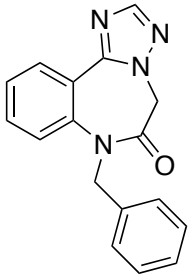
HR-MS (ESI) m/z calcd for $C_{11}H_{12}BrN_4O$ $[M+H]^+$ 295.0189 found 295.0192.

N-(2-bromophenyl)-N-isopropyl-2-(1H-1,2,4-triazol-1-yl)acetamide (5c):



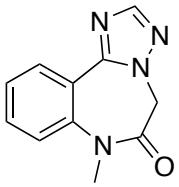
The general procedure **F** was followed using 2-bromo-N-(2-bromophenyl)-N-isopropylacetamide (335 mg, 1.0 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **5c** (235 mg, 73 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.89 (s, 1H), 7.75 (dd, J = 7.6, 2.2 Hz, 1H), 7.40-7.34 (m, 3H), 4.65 (dd, J = 25.0, 16.6 Hz, 2H), 4.79 (ept, J = 6.7 Hz, 1H), 3.68 (d, J = 11.2 Hz, 3H), 3.40 (d, J = 11.2 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.78 (C_q), 141.13 (C_q), 134.05 (CH), 130.39 (CH), 128.92 (CH), 129.18 (CH), 52.16 (CH), 41.65 (CH_2), 22.23 (CH_3), 20.14 (CH_3). **MS (ESI)** m/z (relative intensity): 323.05 (100) $[M+H]^+$, 325.05 (90) $[M+H]^+$, 345.03 (45) $[M+Na]^+$, 347.03 (35) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{13}H_{16}BrN_4O$ $[M+H]^+$ 323.0502 found 323.0505.

7-benzyl-5H-benzo[f][1,2,4]triazolo[1,5-d][1,4]diazepin-6(7H)-one (6a):



The general procedure **G** was adapted using N-benzyl-N-(2-bromophenyl)-2-(1H-1,2,4-triazol-1-yl)acetamide (111 mg, 0.3 mmol), $Pd(OAc)_2$ (10 mol%) and $PCy_3{*}HBF_4$ (15 mol%). After 20 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **3a** (49 mg, 56 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.10 (s, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.55-7.50 (m, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.31-7.24 (m, 3H), 7.08 (d, J = 7.8 Hz, 2H), 5.10 (s, 2H), 4.97 (bs, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) 165.50 (C_q), 151.45 (CH), 150.41 (C_q), 139.69 (C_q), 136.18 (C_q), 131.76 (CH), 129.75 (CH), 128.68 (CH), 127.45 (CH), 126.69 (CH), 126.63 (CH), 123.54 (CH), 120.92 (C_q), 53.65 (CH_2), 52.35 (CH_2). **IR (υ max in CH_2Cl_2):** 3002, 2353, 1649, 1627, 1245, 768 cm^{-1}. **MS (ESI)** m/z (relative intensity) 291.12 (100) $[M+H]^+$, 313.11 (40) $[M+Na]^+$, 603.22 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{17}H_{15}N_4O$ $[M+H]^+$ 291.1240 found 291.1244.

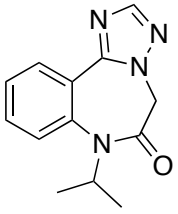
7-methyl-5H-benzo[f][1,2,4]triazolo[1,5-d][1,4]diazepin-6(7H)-one (6b):



The general procedure **G** was adapted using N-benzyl-N-(2-bromophenyl)-2-(1H-1,2,4-triazol-1-yl)acetamide (59 mg, 0.2 mmol), $Pd(OAc)_2$ (10 mol%) and $PCy_3{*}HBF_4$ (15 mol%). After 20 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **6b** (29 mg, 68 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.98 (dd, J = 8.2, 1.8 Hz, 1H), 7.62 (dt, 8.1, 1.7 Hz, 1H), 7.45-7.41 (m, 2H), 4.86 (bs, 2H), 3.42 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.22 (C_q), 151.72

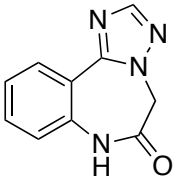
(CH), 151.48 (C_q), 140.44 (C_q), 131.60 (CH), 129.55 (CH), 126.18 (CH), 122.99 (CH), 120.49 (C_q), 52.19 (CH_2), 37.42 (CH_3). **IR (υ max in CH_2Cl_2):** 2956, 2352, 1669, 1494, 1269, 784 cm^{-1}. **MS (ESI)** m/z (relative intensity): 215.09 (100) $[M+H]^+$, 237.07 (50) $[M+Na]^+$, 451.16 (25) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{11}N_4O$ $[M+H]^+$ 215.0927 found 215.0930.

7-isopropyl-5H-benzo[f][1,2,4]triazolo[1,5-d][1,4]diazepin-6(7H)-one (6c):



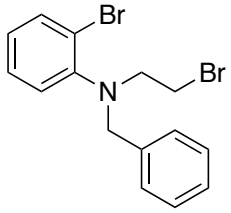
The general procedure **G** was adapted using N-(2-bromophenyl)-N-isopropyl-2-(1H-1,2,4-triazol-1-yl)acetamide (64 mg, 0.2 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 6:4) yielded **6c** (29 mg, 60 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.5, 1.3 Hz, 1H), 8.03 (s, 1H), 7.51 (dt, 7.2, 1.4 Hz, 1H), 7.39 (dt, J = 7.4, 1.1 Hz, 1H), 7.18 (dd, J = 7.4, 0.8 Hz, 1H), 4.92 (s, 2H), 4.80 (ept, J = 6.5 Hz, 1H), 3.70 (d, J = 11.0 Hz, 3H), 3.38 (d, J = 11.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.93 (C_q), 151.54 (CH), 151.75 (C_q), 134.19 (C_q), 13213 (CH), 129.44 (CH), 124.35 (CH), 121.67 (CH), 118.31 (C_q), 51.25 (CH_2), 52.16 (CH), 21.98 (CH_3), 20.00 (CH_3). **MS (ESI)** m/z (relative intensity): 243.12 (100) $[M+H]^+$, 265.11 (60) $[M+Na]^+$, 507.22 (25) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{13}H_{15}N_4O$ $[M+H]^+$ 243.1240 found 243.1243.

Synthesis of 5H-benzo[f][1,2,4]triazolo[1,5-d][1,4]diazepin-6(7H)-one (7):



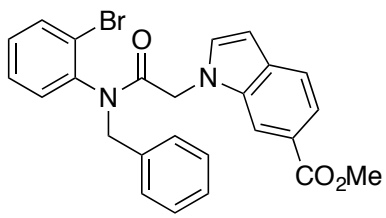
To a solution of 7-benzyl-5H-benzo[f][1,2,4]triazolo[1,5-d][1,4]diazepin-6(7H)-one (100 mg, 0.35 mmol) in trifluoroacetic acid (0.70 mL, 0.5 M), was added triflic acid (15 µL, 0.18 mmol) dropwise. The solution was stirred at room temperature overnight. The mixture was quenched with water, basified with $NaHCO_3$ sat. and extracted with DCM (3 x 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated to afford a white solid. The crude was purified by chromatography on silica gel eluting with pure EtOAc to yield 51 mg (75 %) of **7** as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.71 (bs, 1H), 8.10 (dd, J = 7.8, 1.5 Hz, 1H), 8.05 (s, 1H), 7.58 (dt, 7.5, 1.6 Hz, 1H), 7.41 (dt, J = 7.7, 1.1 Hz, 1H), 7.20 (dd, J = 7.4, 0.8 Hz, 1H), 4.97 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) 167.13 (C_q), 151.93 (CH), 151.86 (C_q), 134.28 (C_q), 131.99 (CH), 129.88 (CH), 125.85 (CH), 121.56 (CH), 118.01 (C_q), 52.24 (CH_2). **IR (υ max in CH_2Cl_2):** 3421, 3007, 2361, 1684, 1648, 1263, 748 cm^{-1}. **MS (ESI)** m/z (relative intensity) 201.08 (100) $[M+H]^+$, 223.06 (40) $[M+Na]^+$, 423.13 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{10}H_9N_4O$ $[M+H]^+$ 201.0771 found 201.0775. The product decomposes at 220 °C.

Synthesis of N-benzyl-2-bromo-N-(2-bromoethyl)aniline:



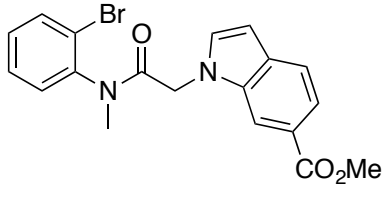
To a 0 °C solution of N-benzyl-2-bromo-N-(2-bromophenyl)acetamide (383 mg, 1 mmol) in THF (5 ml, 0.2 M) was added was added dropwise BH_3*THF complex 1.0 M in THF (5 mL, 5 mmol) and the reaction was stirred at room temperature for 5 h. The reaction was quenched by the addition of MeOH (10 mL) and the mixture contentrated. The residue was purified by column chromatography to afford the correspondin bromide (198 mg, 54 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.62 (dd, J = 7.8, 1.1 Hz, 1H), 7.39-7.13 (m, 7H), 7.01-6.94 (m, 1H), 4.30 (s, 2H), 3.53-3.33 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.60 (C_q), 136.24 (C_q), 131.62 (CH), 128.34 (CH), 128.00 (CH), 127.18 (CH), 125.39 (CH), 123.89 (CH), 122.98 (C_q), 120.23 (CH), 59.43 (CH_2), 51.05 (CH_2), 43.87 (CH_2). **MS (ESI)** m/z (relative intensity): 369.96 (100) $[M+H]^+$, 371.96 (70) $[M+H]^+$, 391.94 (45) $[M+Na]^+$, 393.94 (35) $[M+Na]^+$, 760.90 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{15}H_{16}Br_2N$ $[M+H]^+$ 367.9644 found 367.9641.

Methyl 1-{2-[benzyl(2-bromophenyl)amino]-2-oxoethyl}-1H-indole-6-carboxylate (8a):



The general procedure **L** was followed using N-benzyl-2-bromo-N-(2-bromophenyl)acetamide (383 mg, 1.0 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 8:2) yielded **8a** (295 mg, 62%) as a colourless oil.**^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.81-7.78 (m, 2H), 7.63 (d, J = 8.3 Hz, 1H), 7.32-7.20 (m, 8H), 6.85 (dd, J = 7.0, 2.0 Hz, 1H), 6.58 (d, J = 3.0 Hz, 1H), 5.59 (d, J = 14.2 Hz, 1H), 4.63 (s, 2H), 4.31 (d, J = 14.2 Hz, 1H), 3.95 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.99 (C_q), 166.70 (C_q), 138.94 (C_q), 135.99 (C_q), 135.85 (C_q), 134.17 (CH), 132.14 (C_q), 131.87 (CH), 131.13 (CH), 130.46 (CH), 129.44 (CH), 128.77 (CH), 128.39 (CH), 127.75 (CH), 123.66 (C_q), 123.30 (C_q), 120.60 (CH), 120.44 (CH), 111.40 (CH), 102.49 (CH), 52.20 (CH_2), 51.77 (CH_3), 48.39 (CH_2). **MS (ESI)** m/z (relative intensity): 477.08 (100) $[M+H]^+$, 479.08 (80) $[M+H]^+$, 499.06 (40) $[M+Na]^+$, 501.06 (35) $[M+Na]^+$, 977.13 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{25}H_{22}BrN_2O_3$ $[M+H]^+$ 477.0808 found 477.0811.

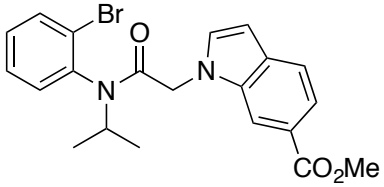
Methyl 1-(2-((2-bromophenyl)(methyl)amino)-2-oxoethyl)-1H-indole-6-carboxylate (8b):



The general procedure **L** was adapted using 2-bromo-N-(2-bromophenyl)-N-methylacetamide (307 mg, 1.0 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 6:4) yielded **8b** (268 mg, 67 %) as a colourless oil.**^{1}H NMR** (300 MHz, $CDCl_3$)

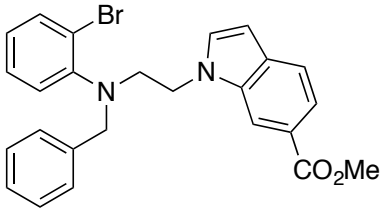
δ 8.35 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.80-7.72 (m, 3H), 7.45-7.34 (m, 3H), 6.82 (s, 1H), 5.20 (d, J = 13.9 Hz, 1H), 4.67 (d, J = 14.0 Hz, 1H), 3.95 (s, 3H), 3.40 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.03 (C_q), 166.95 (C_q), 140.51 (C_q), 140.34 (C_q), 135.61 (C_q), 131.43 (C_q), 130.22 (CH), 129.67 (CH), 126.10 (CH), 125.54 (C_q), 123.13 (CH), 122.91 (CH), 121.32 (CH), 120.11 (CH), 111.63 (CH), 100.02 (CH), 51.98 (CH_3), 47.62 (CH_2), 36.84 (CH_3). **MS (ESI)** m/z (relative intensity): 401.05 (100) $[M+H]^+$, 403.05 (90) $[M+H]^+$, 423.03 (35) $[M+Na]^+$, 425.03 (25) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{19}H_{18}BrN_2O_3$ $[M+H]^+$ 401.0495 found 401.0498.

Methyl 1-(2-((2-bromophenyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylate (8c):



The general procedure **L** was adapted using 2-bromo-N-(2-bromophenyl)-N-isopropylacetamide (333 mg, 1.0 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **8c** (248 mg, 58 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.83-7.75 (m, 2H), 7.59 (d, J = 8.3 Hz, 1H), 7.45-7.27 (m, 4 H), 6.53 (d, J = 2.8 Hz, 1H), 4.83 (p, J = 6.7 Hz, 1H), 4.55 (dd, J = 16.6, 8.5 Hz, 2H), 3.94 (s, 3H), 3.63 (d, J = 11.2 Hz, 2H), 3.40 (d, J = 11.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.99 (C_q), 166.74 (C_q), 140.29 (C_q), 138.53 (C_q), 135.57 (C_q), 131.61 (C_q), 130.48 (CH), 129.02 (CH), 128.29 (CH), 126.90 (CH), 125.15 (CH), 123.79 (C_q), 121.28 (CH), 120.36 (CH), 112.01 (CH), 99.79 (CH), 52.13 (CH), 52.01 (CH_3), 48.20 (CH_2), 22.51 (CH_3), 21.23 (CH_3). **MS (ESI)** m/z (relative intensity): 429.08 (100) $[M+H]^+$, 431.08 (90) $[M+H]^+$, 451.06 (35) $[M+Na]^+$, 451.06 (25) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{19}H_{18}BrN_2O_3$ $[M+H]^+$ 429.0808 found 429.0811.

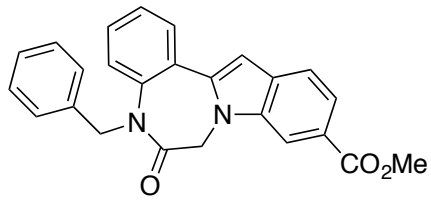
Methyl 1-(2-(benzyl(2-bromophenyl)amino)ethyl)-1H-indole-6-carboxylate (8d):



The general procedure **L** was adapted using N-benzyl-2-bromo-N-(2-bromoethyl)aniline (367 mg, 1.0 mmol). After 10 h, purification by column chromatography (Hex/EtOAc 6:4) yielded **8d** (240 mg, 52 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.85 (dd, J = 9.5, 1.2 Hz, 1H), 7.70-7.67 (m, 2H), 7.32-7.28 (m, 1H), 7.21-7.14 (m, 7H), 7.03 (dt, J = 8.8, 0.91 Hz, 1H), 6.54 (d, J = 2.7 Hz, 1H), 4.22 (t, J = 6.5 Hz, 2H), 4.17 (s, 2H), 3.99 (s, 3H), 3.46 (t, J = 6.4 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.08 (C_q), 148.02 (C_q), 135.17 (C_q), 134.26 (CH), 132.22 (C_q), 131.62 (CH), 128.34 (CH), 128.16 (CH), 127.97 (CH), 127.16 (CH), 125.39 (CH), 123.89 (CH), 122.91 (C_q), 121.97 (C_q), 120.33 (CH), 120.31 (CH), 111.55 (CH), 101.52 (CH), 59.30 (CH_2), 51.77 (CH_3), 50.75 (CH_2), 44.31 (CH_2). **MS (ESI)** m/z (relative intensity): 463.10 (100) $[M+H]^+$, 465.10 (80) $[M+H]^+$, 485.08 (40) $[M+Na]^+$,

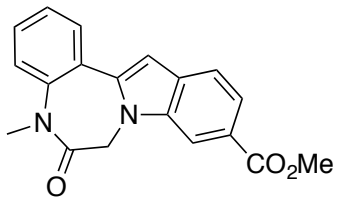
487.08 (30) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{25}H_{24}BrN_2O_2$ $[M+H]^+$ 463.1016 found 463.1019.

Methyl 5-benzyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[1,7-a]indole-10-carboxylate (9a):



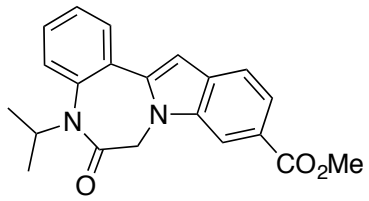
The general procedure **G** was adapted using Methyl 1-{2 [benzyl(2-bromophenyl)amino]-2-oxoethyl}-1H-indole-6-carboxylate (143 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **9a** (78 mg, 66 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.74-7.68 (m, 2H), 7.41-7.39 (m, 2H), 7.36-7.28 (m, 1H), 7.19-7.17 (m, 3H), 7.02-6.99 (m, 2H), 6.82 (s, 1H), 5.20-5.14 (m, 2H), 5.02 (d, J = 15.4 Hz, 1H), 4.61 (d, J = 14.0 Hz, 1H), 3.98 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.72 (C_q), 166.76 (C_q), 140.19 (C_q), 139.36 (C_q), 136.60 (C_q), 135.45 (C_q), 131.67 (C_q), 130.44 (CH), 129.65 (CH), 128.43 (CH), 127.11 (CH), 126.76 (CH), 126.53 (CH), 126.43 (C_q), 123.70 (CH), 123.56 (CH), 121.36 (C_q), 120.39 (CH), 111.62 (CH), 52.43 (CH_2), 51.89 (CH_3), 47.49 (CH_2). **MS (ESI)** m/z (relative intensity): 397.16 (100) $[M+H]^+$, 419.14 (40) $[M+Na]^+$, 815.28 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{25}H_{21}N_2O_3$ $[M+H]^+$ 397.1547 found 397.1550.

Methyl 5-methyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[1,7-a]indole-10-carboxylate (9b):



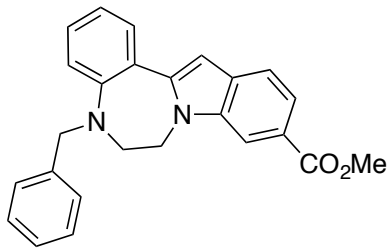
The general procedure **G** was adapted using Methyl 1-(2-((2-bromophenyl)(methyl)amino)-2-oxoethyl)-1H-indole-6-carboxylate (120 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 95:5) yielded **9b** (68 mg, 71 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.76-7.70 (m, 2H), 7.54 (t, J = 7.7 Hz, 1H), 7.42-7.36 (m, 2H), 6.84 (s, 1H), 5.23 (d, J = 14.2 Hz, 1H), 4.67 (d, J = 14.1 Hz, 1H), 3.98 (s, 3H), 3.39 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.73 (C_q), 167.16 (C_q), 140.40 (C_q), 140.14 (C_q), 135.51 (C_q), 131.57 (C_q), 130.31 (CH), 129.74 (CH), 126.14 (CH), 125.45 (C_q), 123.62 (C_q), 122.92 (CH), 121.32 (CH), 120.31 (CH), 111.49 (CH), 100.14 (CH), 51.90 (CH_3), 47.42 (CH_2), 36.73 (CH_3). **MS (ESI)** m/z (relative intensity): 321.12 (100) $[M+H]^+$, 343.11 (50) $[M+Na]^+$, 663.22 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$ 321.1234 found 321.1237.

Methyl 5-isopropyl-6-oxo-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[1,7-a]indole-10-carboxylate (9c):



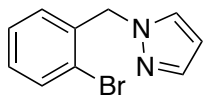
The general procedure **G** was adapted using Methyl 1-(2-((2-bromophenyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylate (128 mg, 0.3 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **9c** (56 mg, 54 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.88 (dd, J = 8.6, 1.3 Hz, 1H), 7.74-7.70 (m, 2H), 7.50-7.41 (m, 3H), 6.85 (s, 1H), 5.00 (d, J = 14.1 Hz, 1H), 4.47-4.42 (m, 2H), 3.98 (s, 3H), 1.48 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.76 (C_q), 166.81 (C_q), 140.09 (C_q), 138.43 (C_q), 135.57 (C_q), 131.59 (C_q), 130.58 (CH), 129.02 (CH), 127.71 (C_q), 126.89 (CH), 125.05 (CH), 123.59 (C_q), 121.25 (CH), 120.29 (CH), 111.61 (CH), 99.68 (CH), 52.36 (CH), 51.87 (CH_3), 48.27 (CH_2), 22.29 (CH_3), 20.21 (CH_3). **MS (ESI)** m/z (relative intensity): 345.16 (100) $[M+H]^+$, 371.14 (35) $[M+Na]^+$, 719.28 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 345.1547 found 345.1549.

Methyl 5-benzyl-6,7-dihydro-5H-benzo[5,6][1,4]diazepino[1,7-a]indole-10-carboxylate (9d):



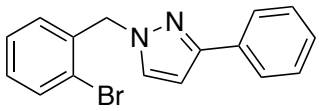
The general procedure **G** was adapted using Methyl 1-(2-(benzyl(2-bromophenyl)amino)ethyl)-1H-indole-6-carboxylate (139 mg, 0.3 mmol). After 20 h, purification by column chromatography (DCM/EtOAc 98:2) yielded **9d** (68 mg, 59 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.93-7.86 (m, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.35-7.09 (m, 8H), 6.79 (s, 1H), 4.46 (s, 2H), 4.38 (t, J = 5.4 Hz, 2H), 3.96 (s, 3H), 3.65 (t, J = 5.2 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 192.25 (C_q), 168.12 (C_q), 135.96 (C_q), 134.34 (C_q), 131.67 (C_q), 131.55 (C_q), 130.11 (CH), 129.64 (CH), 128.89 (CH), 128.47 (CH), 128.36 (CH), 128.32 (CH), 128.11 (CH), 127.91 (CH), 120.24 (C_q), 119.86 (CH), 111.48 (CH), 110.96 (CH), 101.46 (C_q), 57.86 (CH_2), 55.73 (CH_2), 51.81 (CH_3), 42.66 (CH_2). **MS (ESI)** m/z (relative intensity): 383.18 (100) $[M+H]^+$, 405.16 (35) $[M+Na]^+$, 787.33 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 383.1754 found 383.1759.

1-(2-bromobenzyl)-1H-pyrazole (10a):



The general procedure **E** was followed using 2-Bromobenzyl bromide (250 mg, 1.0 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 7:3) yielded **10a** (237 mg, 89 %) as a white solid. The spectral data were in agreement with those reported in the literature.[11]

1-(2-bromobenzyl)-3-phenyl-1H-pyrazole (10b):

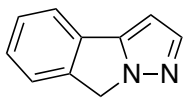


The general procedure **E** was followed using 2-Bromobenzyl bromide (2.1 g, 8.4 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **10b** (1.98 g, 91 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.89-7.84 (m, 2H), 7.60 (dd, J = 4.5, 1.5 Hz, 1H), 7.48-7.16 (m, 6H), 6.95 (dd, J = 4.3, 1.2 Hz, 1H), 6.64 (d, J = 1.3 Hz, 1H), 5.47 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 152.10 (C_q), 136.52 (C_q), 133.61 (C_q), 133.02 (CH), 131.53 (CH), 130.04 (CH), 129.50 (CH), 128.86 (CH), 127.91 (CH), 125.90 (CH), 122.93 (C_q), 103.60 (C_q), 56.11 (CH_2). **MS (ESI)** m/z (relative intensity): 313.03 (100) $[M+H]^+$, 315.03 (95) $[M+H]^+$, 335.01 (50) $[M+Na]^+$, 337.01 (40) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{16}H_{14}BrN_2$ $[M+H]^+$ 313.0335 found 313.0338.

1-(2-bromobenzyl)-3-(2,4-dimethoxyphenyl)-1H-pyrazole (10c):

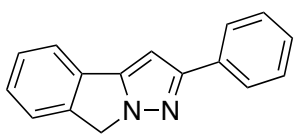
The general procedure **E** was followed using 2-Bromobenzyl bromide (500 mg, 2.0 mmol). After 11 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **10c** (682 mg, 92 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.97 (dd, J = 8.0, 0.9 Hz, 1H), 7.59 (dd, J = 7.8, 1.1 Hz, 1H), 7.47 (d, J = 2.3 Hz, 1H), 7.24-7.14 (m, 2H), 6.49 (dd, J = 7.5, 1.3 Hz, 1H), 6.84 (d, J = 2.3 Hz, 1H), 6.58 (d, J = 7.7 Hz, 2H), 5.48 (s, 2H), 3.90 (s, 3H), 3.84 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.50 (C_q), 157.92 (C_q), 148.94 (C_q), 136.70 (C_q), 132.75 (CH), 130.44 (CH), 129.56 (CH), 129.42 (CH), 127.90 (CH), 122.61 (C_q), 106.92 (CH), 104.90 (CH), 98.93 (CH), 55.82 (CH_2), 55.55 (CH_3), 55.48 (CH_3). **MS (ESI)** m/z (relative intensity): 373.05 (100) $[M+H]^+$, 375.05 (95) $[M+H]^+$, 395.04 (50) $[M+Na]^+$, 395.04 (40) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{18}BrN_2O_2$ $[M+H]^+$ 373.0546 found 373.0550.

8H-pyrazolo[5,1-a]isoindole (11a):



The general procedure **G** was followed using 1-(2-bromobenzyl)-3-phenyl-1H-pyrazole (47 mg, 0.2 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **11b** (26 mg, 82 %) as a white solid. The spectral data were in agreement with those reported in the literature.[11]

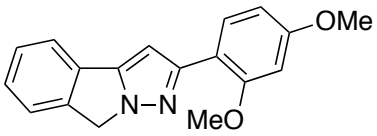
2-phenyl-8H-pyrazolo[5,1-a]isoindole (11b):



The general procedure **G** was followed using 1-(2-bromobenzyl)-1H-pyrazole (62 mg, 0.2 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **11b** (24 mg, 52 %) as a white

solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.93-7.90 (m, 2H), 7.60 (s, 1H), 7.49-7.28 (m, 6H), 6.70 (s, 1H), 5.15 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156.21 (C_q), 147.70 (C_q), 140.42 (C_q), 134.23 (C_q), 131.25 (CH), 128.90 (CH), 128.53 (CH), 127.96 (CH), 127.50 (CH), 123.61 (CH), 93.62 (C_q), 52.50 (CH_2). **MS (ESI**) m/z (relative intensity): 233.11 (100) $[M+H]^+$, 255.09 (50) $[M+Na]^+$, 487.19 (40) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{16}H_{13}N_2$ $[M+H]^+$ 233.1073 found 233.1075.

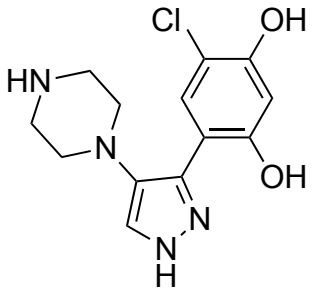
2-(2,4-dimethoxyphenyl)-8H-pyrazolo[5,1-a]isoindole (11c):



The general procedure **G** was followed using 1-(2-bromobenzyl)-1H-pyrazole (74 mg, 0.2 mmol). After 20 h, purification by column chromatography (Hex/EtOAc 9:1) yielded **11c** (25 mg, 43 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 1H), 7.64 (d, J = 7.5, 1H), 7.50-7.29 (m, 3H), 6.87 (s, 1H), 6.61 (d, J = 7.6 Hz, 2H), 5.19 (s, 2H), 3.96 (s, 3H), 3.88 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 160.71 (C_q), 158.02 (C_q), 153.05 (C_q), 147.11 (C_q), 140.47 (C_q), 131.58 (CH), 129.53 (C_q), 128.43 (CH), 127.21 (CH), 126.60 (CH), 123.62 (CH), 120.69 (CH), 116.04 (C_q), 105.05 (CH), 99.12 (CH), 97.28 (CH), 55.73 (CH_3), 55.11 (CH_3), 52.23 (CH_2). **MS (ESI**) m/z (relative intensity): 293.13 (100) $[M+H]^+$, 315.11 (50) $[M+Na]^+$, 607.23 (40) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1285 found 193.1287.

10.2.1 Docking analysis

Docking Calculations - The crystal structure of the receptor were obtained from the RCSB Protein Data Bank (PDB), PDB code 2CCS (resolution 1.79 Å), where the N-terminal domain of Hsp90 has been co-crystalized with the piperazine-containing compound **A**:



Scheme S-X. Compound **A**

The protein has been prepared using the Protein Preparation Wizard module of Schrödinger Suite implemented in the Maestro software package (**Schrodinger, LLC, NY, 2017**). It consists in assigning bond orders, adding hydrogens and in removing all crystallization waters. The protonation states of the protein residues have been predicted using PROPKA with a target pH of 7.0 ± 2. Histidines tautomers and side-chains were flipped in order to optimize the H-bond network. Possible atom clashes in the crystal structure have been released with a constrained minimization of heavy atoms using the OPLS3 force field, with a maximum RMSD of 0.3 Å between the initial and final structure.

Compound **2** has been obtained from the PDB structure 2CCS, while the others was manually built in Maestro. All ligands have been prepared, adding hydrogens and assigning bond orders. LigPrep (**LigPrep, Schrödinger, LLC, New York, NY, 2017**) and Epik (**Epik, Schrödinger, LLC, New York, NY, 2017**) were used to generate initial 3D geometries and possible stereoisomers. The most probable protonation and tautomeric states were calculated at pH of 7.0 ± 2.

Docking calculations were performed using the Schrödinger Suite release 2017-1 (Schrödinger, LLC, New York, NY, 2017). Complexes have been generated through the **Schrödinger Induced Fit Docking (IFD) protocol**. Unlike standard docking studies where the binding site of the receptor is held rigid and the ligand is free to move, this procedure allows the putative binding site of the receptor to undergo side-chain and/or backbone movements, so that it changes its shape according to the binding mode of the ligand. The IFD protocol is based on "Glide" and the Refinement module "Prime" for the prediction of ligand binding modes and consequent structural modification in the receptor:

Each ligand is docked with Glide using a softened potential, consisting in a scaling of the van der Waals radii. A maximum 20 poses per ligand are retained.

Protein-ligand complexes undergo a Prime side-chain prediction for on residues within 5 Å of any ligand pose.

The same set of residues and the ligand for each complex are minimized.

Complexes within 30 Kcal/mol of the lowest-energy structure are redocked with Glide. The ligands are docked into the induced-fit receptor structure.

Finally, and estimate of the binding energy (IFDScore) is calculated for each output pose and they are ranked accordingly.

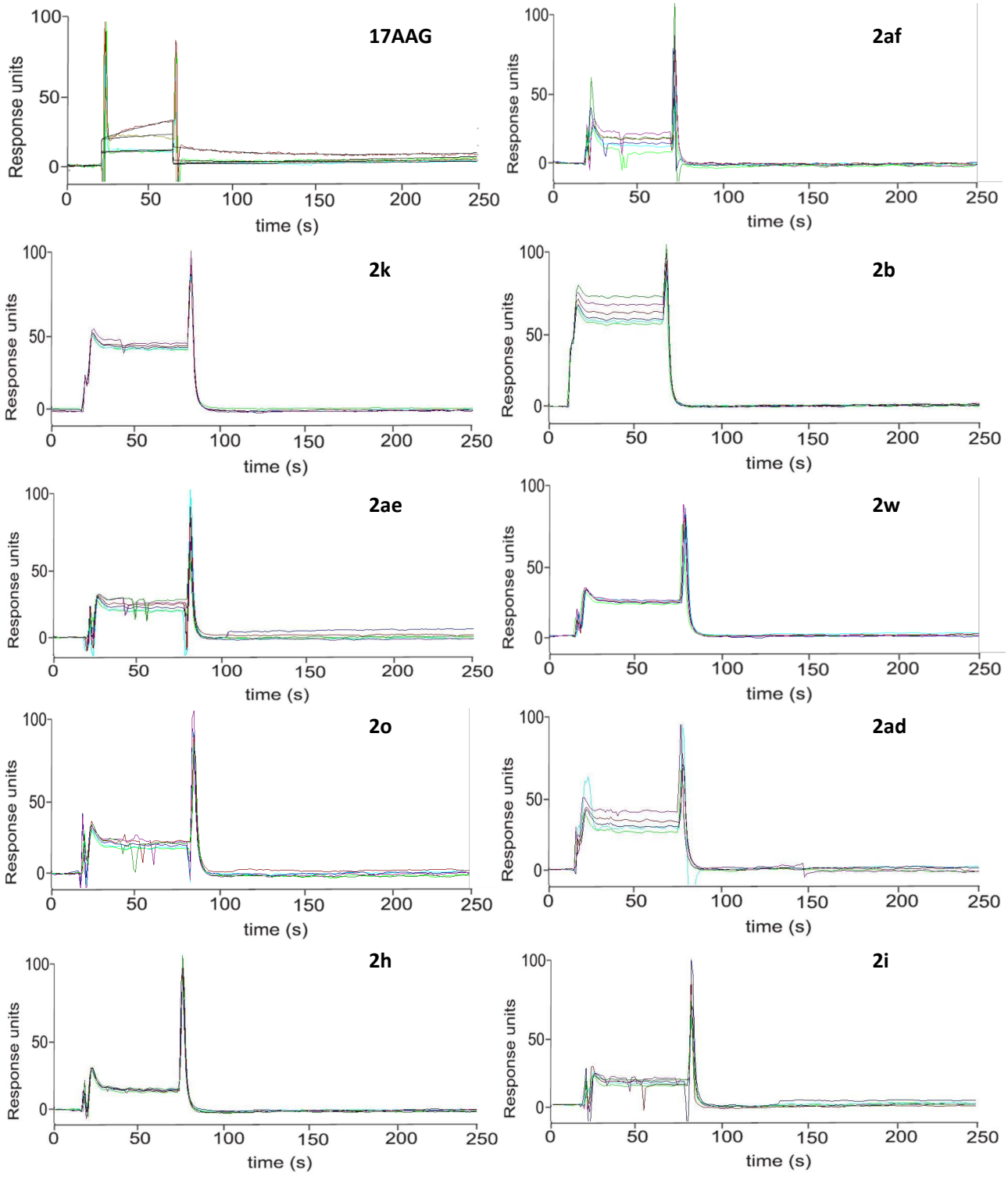
10.2.2 Biological tests

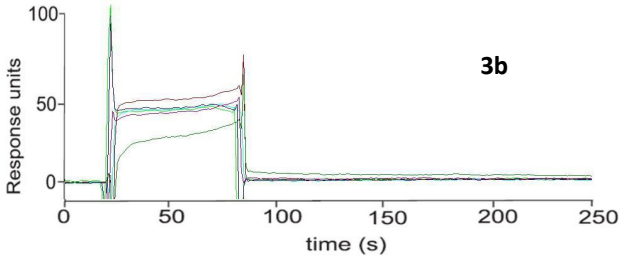
Surface Plasmon Resonance Spectroscopy (SPR) experimental part

SPR experiments were performed using a Biacore 3000 optical biosensor, equipped with research-grade CM5 sensor chips (GE Healthcare, Milano, Italy). Recombinant human Hsp90α (Abcam, Cambridge UK, 100μg mL^{-1} in CH_3COONa 50mM, pH 5.0) was immobilized on a CM5 sensor chip surface using standard amine-coupling protocols and flow rate of 5 μLmin−1 to obtain densities of 8–12 kRU. Twelve compounds, as well as 17-AAG used as positive control, were dissolved in 100% DMSO to obtain 4 mM solutions, and diluted 1:200 (v/v) in PBS (10mM NaH_2PO_4, 150mM NaCl, pH 7.4) to a final DMSO concentration of 0.1%. For each molecule a six-point concentration series were set up, spanning 1nM–10nM–100nM–500nM–1μM–4μM, and for each sample the complete binding study was carried out using triplicate aliquots. SPR experiments were performed at 25 °C, using a flow rate of 50 μLmin^{-1}, with 60 s monitoring of association and 300 s monitoring of dissociation.

Changes in mass, due to the binding response, were recorded as resonance units (RU). To obtain the dissociation constant (KD), these responses were fit to a 1:1 Langmuir binding model by nonlinear regression, using the BiaEvaluation sofware program provided by GE Healthcare. Simple interactions were suitably fitted to a single-site bimolecular interaction model (A+B=AB), yielding a single KD.

Surface Plasmon Resonance (SPR)
Supporting informations




3b
Response units
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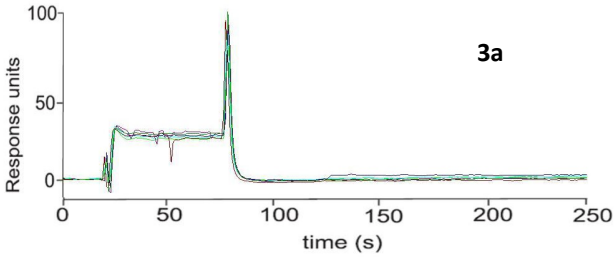
50
0
0
50
100
150
200
250
time (s)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0
50
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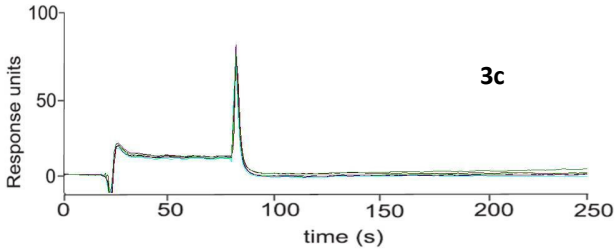
time (s)


3c
Response units
100
50
0
0
50
100
150
200
250
time (s)

10.2.3 References

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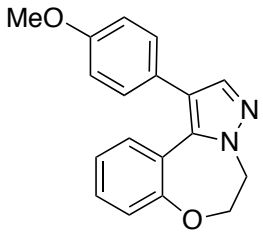
10.3 Representative procedure for the intermolecular C-H activation of azepines

General procedure

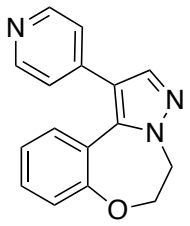
A solution of azepine **2m/2j** (0.2 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %), iodo arene (0.6 mmol), Ag_2CO_3 (110 mg, 0.40 mmol) in anhydrous DMF (2 mL) was heated at 100 ºC for 24 h. After the reaction period, the reaction mixture was diluted with EtOAc (5 mL) and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 - 200 mesh) furnished the corresponding functionalized azepine.

1-(4-methoxyphenyl)-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (12a):



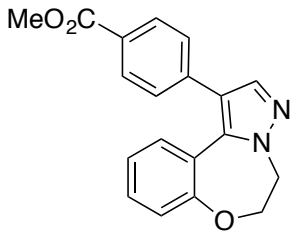
The general procedure was followed using 5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine **2m** (90 mg, 0.48 mmol) and 4-Iodoanisole (337 mg, 1.44 mmol). After 24 h, purification by column chromatography (n-Hexane/MTBE 1:1) yielded **12a** (59 mg, 42 %) as a white solid. **^{1}H NMR** (300 MHz, CDCl3) δ 7,85-7,48 (m, 2H), 7,31-6,97 (m, 7H), 3,87 (s, 3H), 4,55 (t, J = 3,0 Hz, 2H), 4,75 (t, J = 2,5 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 156,64 (C_q), 139,25 (C_q), 131,04 (C_q), 130,40 (CH), 129,35 (CH), 129,35 (CH), 128,79 (C_q), 124,33 (C_q), 123,61 (CH), 121,95 (CH), 114,80 (CH), 106,59 (C_q), 69,56 (CH_2), 56,04 (CH_3), 55,26 (CH_2). **MS (ESI)** m/z (relative intensity): 293.13 (100) $[M+H]^+$, 315.11 (100) $[M+Na]^+$, 607.23 (47) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{17}N_2O$ $[M+H]^+$ 293.1285 found 293.1281.

1-(pyridin-4-yl)-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (12d):



The general procedure was followed using 5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine **2m** (90 mg, 0.48 mmol) and 4-Iodopyridine (295 mg, 1.44 mmol). After 24 h, purification by column chromatography (n-Hexane/MTBE 1:1) yielded **12d** (few mg, < 10 %) as a colourless oil. Unfortunately, the amount was not enough for a fully characterization and was observed only in **MS (ESI)** m/z (relative intensity): 264.11 (100) $[M+H]^+$, 286.29 (40) $[M+Na]^+$.

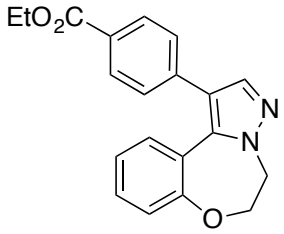
Methyl 4-(5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepin-1-yl)benzoate (12b):



The general procedure was followed using 5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine **2m** (90 mg, 0.48 mmol) and Methyl 4-Iodobenzoate (377 mg, 1.44 mmol). After 24 h, purification by column chromatography (n-Hexane/MTBE 1:1) yielded **12b** (57 mg,

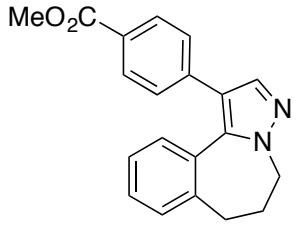
37 %) as a white solid. **^{1}H NMR** (300 MHz, CDCl3) δ 7.48-7.35 (m, 3H), 7.25 (d, J = 8.8, 2H), 7.2 (d, J = 6.5 Hz, 1H), 6.85 (d, J = 9.0 Hz, 2H), 6.42 (s, 1H), 4.20-4.13 (m, 4H), 3.81 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 140.23 (C_q), 139.44 (C_q), 138.8 (CH), 137.81 (C_q), 131.8 (C_q), 130.4 (CH), 129.7 (CH), 129.63 (C_q), 129.5 (CH), 128.9 (CH), 127.8 (CH), 127.33 (C_q), 125.13 (C_q), 114.8 (CH), 56.1 (CH_3), 48.9 (CH_2), 31.5 (CH_2). **MS (ESI)** m/z (relative intensity): 321.12 (100) $[M+H]^+$, 343.10 (60) $[M+Na]^+$, 663.22 (25) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{19}H_{17}N_2O_3$ $[M+H]^+$ 321.1234 found 321.1237.

Ethyl 4-(5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepin-1-yl)benzoate (12c):



The general procedure was followed using 5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine **2m** (90 mg, 0.48 mmol) and Ethyl 4-Iodobenzoate (397 mg, 1.44 mmol). After 24 h, purification by column chromatography (n-Hexane/MTBE 1:1) yielded **12c** (49 mg, 33 %) as a white solid. **^{1}H NMR** (300 MHz, CDCl3) δ 7.97 (t, J = 8.4 Hz, 2H), 7.52 (d, J = 8.5 Hz, 2H), 7.28 (m, 3H), 6.94 (q, J = 8.7 Hz, 2H) 4.73 (t, J = 5.3 Hz, 2H), 4.54 (t, J = 5.4 Hz, 2H), 4.43-4.34 (m, 5H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 169.99 (C_q), 155.25 (C_q), 148.72 (C_q), 139.60 (C_q), 138.86 (C_q), 138.37 (C_q), 131.3 (CH), 131.1 (CH), 130.6 (CH), 130.1 (CH), 128.6 (CH), 124.4 (CH), 123.5 (CH), 122.53 (C_q), 75.2 (CH_2), 61.7 (CH_2), 50.3 (CH_2), 14.9 (CH_3). **MS (ESI)** m/z (relative intensity): 335.14 (100) $[M+H]^+$, 357.12 (60) $[M+Na]^+$, 691.25 (25) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{20}H_{19}N_2O_3$ $[M+H]^+$ 335.1390 found 335.1393.

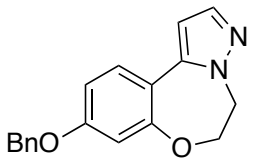
Methyl 4-(6,7-dihydro-5H-benzo[c]pyrazolo[1,5-a]azepin-1-yl)benzoate (13a):



The general procedure was followed using 5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine **2m** (90 mg, 0.49 mmol) and Methyl 4-Iodobenzoate (377 mg, 1.44 mmol). After 24 h, purification by column chromatography (n-Hexane/MTBE 1:1) yielded **12e** (47 mg, 34 %) as a white solid. **^{1}H NMR** (300 MHz, CD_2Cl_2) δ 8.15 (d, J = 1.8 Hz, 2H), 7.77 (d, J = 1.8 Hz, 2H), 7.37-7.25 (m, 5H), 3.96 (s, 3H), 4.13-4.22 (m, 6H). **^{13}C NMR** (75 MHz, CD_2Cl_2) δ (ppm): 167.37 (C_q), 145.04 (C_q), 130.9 (CH), 130.5 (CH), 130.4 (C_q), 130.2 (CH), 130.09 (C_q), 129.7 (CH), 129.2 (CH), 129.08 (C_q), 128.82 (C_q), 128.1 (CH), 127.8 (CH), 126.03 (C_q), 49.7 (CH_2), 33.9 (CH_2), 31.8 (CH_3), 31.2 (CH_2). **MS (ESI)** m/z (relative intensity): 319.14 (100) $[M+H]^+$, 341.13 (50) $[M+Na]^+$, 659.26 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{20}H_{19}N_2O_2$ $[M+H]^+$ 319.1441 found 319.1445.

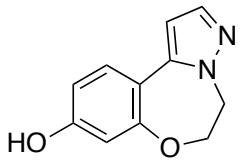
10.4 Representative procedures for the synthesis of PDE10 inhibitor

Synthesis of 9-(benzyloxy)-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (2ad):



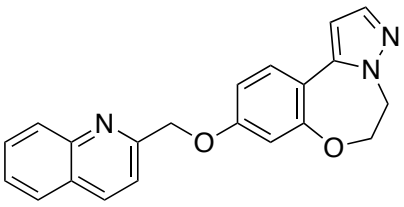
A solution of 1-[2-(5-(benzyloxy)-2-bromophenoxy)ethyl]-1H-pyrrole **1ad** (387.5 mg, 1.04 mmol), $Pd(OAc)_2$ (11.7 mg, 5 mol %), $PCy_3{*}HBF_4$ (28.7 mg, 7.5 mol%), KOAc (122.5 mg, 1.25 mmol) in anhydrous DMF (14.8 mL) was heated at 140 °C for 20 h. After 20 h, the reaction mixture was diluted with EtOAc (5 mL) and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 - 200 mesh) with pure DCM yielding **x** (79 mg, 68 %) as a colourless oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.64 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 2.0 Hz, 1H), 7.47-7.34 (m, 5H), 6.76 (dd, J = 8.8, 2.6 Hz, 1H), 6.66 (d, J = 2.6 HZ, 1H), 6.56 (d, J = 2.1 Hz, 1H), 5.09 (s, 2H), 4.68 (t, J = 7.2 Hz, 2H), 4.48 (t, J = 7.0 Hz, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.59 (C_q), 156.52 (C_q), 140.24 (C_q), 139.12 (CH), 136.37 (C_q), 130.09 (CH), 128.54 (CH), 128.02 (CH), 127.37 (CH), 110.74 (CH), 110.38 (C_q), 105.94 (CH), 103.76 (CH), 70.01 (CH_2), 68.45 (CH_2), 54.19 (CH_2). **IR (υ max in CH_2Cl_2)**: 2978, 1511, 1229, 1053, 743 cm^{-1}. **MS (ESI**) m/z (relative intensity) 293.13 (100) $[M+H]^+$, 315.11 (40) $[M+Na]^+$, 607.23 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{18}H_{17}N_2O_2$ $[M+H]^+$ 293.1285 found 293.1288.

Synthesis of 5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepin-9-ol (14):



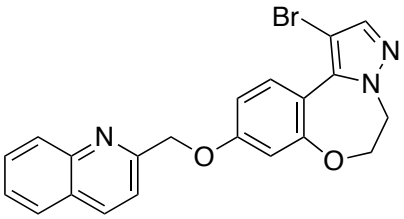
The catalyst Pd/C (50 mg, 10% w/w) was added to a solution of **2ad** (460 mg, 1.57 mmol) in methanol (15 mL) and AcOH (1 mL). The flask was evacuated and backfilled three times with H_2 and the mixture stirred at room temperature overnight under H_2 pressure (1 bar). After 12 h, the reaction mixture filtered and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 - 200 mesh) with DCM/EtOAc 9:1 yielding **14** (283.7 mg, 90 %) as a white solid. **^{1}H-NMR** (300 MHz, CD_3OD) δ 7.64 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 2.1 Hz, 1H), 6.63 (d, J = 2.1 Hz, 1H), 6.58 (dd, J = 8.7, 2.5 Hz, 1H), 6.46 (d, J = 2.5 Hz, 1H), 4.60 (t, J = 3.8 Hz, 2H), 4.44 (t, J = 2.3 Hz, 2H). **^{13}C-NMR** (75 MHz, CD_3OD) δ 160.63 (C_q), 158.88 (C_q), 142.87 (C_q), 140.31 (CH), 131.82 (CH), 112.44 (CH), 110.58 (C_q), 108.03 (CH), 104.84 (CH), 69.95 (CH_2), 55.50 (CH_2). **MS (ESI**) m/z (relative intensity) 203.08 (100) $[M+H]^+$, 225.06 (30) $[M+Na]^+$, 427.13 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{11}H_{11}N_2O_2$ $[M+H]^+$ 203.0815 found 203.0818.

Synthesis of 9-(quinolin-2-ylmethoxy)-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (15):



A solution 2-bromo methyl quinolone (297.6 mg, 1.34 mmol) in dry acetone (2 mL) under argon was added to a 0 °C solution of **14** (270 mg, 1.34 mmol) and Cs_2CO_3 (764 mg, 2,35 mmol) in acetone (26.8 mL, 0.05 M). The mixture was stirred at the same temperature for 30 minutes, upon which it was allowed to warm up to ambient temperature for 10 h. The solvent was removed and the residue portioned between DCM and H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel with (DCM/EtOAc 7:3) yielding **15** (377 mg, Resa = 82 %) as a white solid. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.22 (d, J = 8.5 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.77 (dd, J = 7.0, 2.7 Hz, 1H), 7.67-7.55 (m, 3H), 7.5 (d, J = 2.0 Hz, 1H), 6.8 (dd, J= 8.9, 2.66 Hz, 1H), 6.7 (d, J = 2.6 Hz, 1H), 6.55 (d, J = 2.1 Hz, 1H), 5.41 (s, 2H), 4.66 (t, J = 4.0 Hz, 2H), 4.46 (t, J = 4.1 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 158.82 (Cq), 156.4 (Cq), 156.15 (Cq), 147.10 (Cq), 139.74 (Cq), 138.72 (CH), 136.58 (CH), 129.80 (CH), 129.35 (CH), 128.48 (CH), 127.21 (C_q), 127.11 (CH), 126.11 (CH), 118.51 (CH), 110.30 (C_q), 110.15 (CH), 105.87 (CH), 103.42 (CH), 70.90 (CH_2), 68.04 (CH_2), 53.77 (CH_2). **MS (ESI**) m/z (relative intensity) 344.14 (100) $[M+H]^+$, 366.12 (30) $[M+Na]^+$, 709.25 (10) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{21}H_{18}N_3O_2$ $[M+H]^+$ 344.1394 found 344.1398.

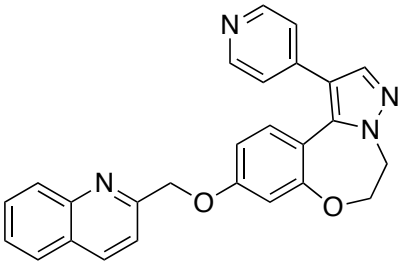
Synthesis of 1-bromo-9-(quinolin-2-ylmethoxy)-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (17):



To a 0 °C solution of **15** (30 mg, 0.09 mmol) in dry DCM (0.3 mL, 0.33 M) under argon NBS (16.2 mg, 0.11 mmol) was added in portion. The mixture was stirred at the same temperature for 30 minutes, upon which it was allowed to warm up to ambient temperature for 10 h protected from light. The solvent was removed and the residue portioned between DCM and H_2O. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel with (Hex/MTBE 7:3) yielding **17** (24 mg, Resa = 65 %) as a white solid. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 8.28 (d, J = 8.5 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.80-7.76 (m, 2H), 7.70 (d, J = 8.5 Hz, 1H), 7.61 (dd, J= 8.0, 1.0 Hz, 1H), 7.52 (s, 1H), 6.95 (dd, J= 8.7, 2.6 Hz, 1H), 6.88 (d, J= 2.6 Hz, 1H), 5.43 (s, 2H), 4.57 (t, J = 4.8 Hz, 2H), 4.44 (t, J= 5.1 Hz, 2H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 177.87 (C_q), 161.21 (C_q), 158.09 (C_q), 156.30 (C_q),

148.48 (C_q), 137.70 (C_q), 113.31 (C_q), 140.9 (CH), 137.8 (CH), 131.6 (CH), 130.6 (CH), 129.9 (CH), 128.6 (CH), 127.5 (CH), 120.0 (CH), 111.4 (CH), 109.2 (CH), 74.6 (CH_2), 72.6 (CH_2), 51.6 (CH_2). **MS (ESI**) m/z (relative intensity) 422.05 (100) $[M+H]^+$, 424.05 (90) $[M+H]^+$, 444.03 (30) $[M+Na]^+$, 446.03 (20) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{21}H_{17}BrN_3O_2$ $[M+H]^+$ 422.0499 found 422.0497.

Synthesis of 1-(pyridin-4-yl)-9-(quinolin-2-ylmethoxy)-5,6-dihydrobenzo[f]pyrazolo[1,5-d][1,4]oxazepine (PDE10 inhibitor 16) :



Under argon atmosphere, a solution of **17** (13,2 mg, 0,031 mmol), $Pd(OAc)_2$ (0,7 mg, 10 mol%), XPhos (2,96 mg, 20 mol%), K_2CO_3 (8,57 mg, 0,062 mmol) in anhydrous 1,4-dioxane (94 µL, 0,33 M) was added H_2O (31,3 µL) and the reaction mixture was heated at 100 °C for 24 h. After the reaction period, the reaction mixture was diluted with EtOAc (2 mL) and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 - 200 mesh) with (EtOAc/DCM 8:2) yielding **16** (8 mg, Resa = 63 %) as a white solid. **^{1}H-NMR** (300 MHz, CD_2Cl_2) δ 8.51 (s, 2H), 8.29 (d, J = 8.5 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 6.25 (d, J = 7.9 Hz, 1H), 7.81-7.7 (m, 3H), 7.61 (t, J = 8.0 1H), 7.35 (s, 2H), 7.18 (d, J=8.7 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 6.8 (dd, J = 8.7, 2.6 Hz, 1H), 5.42 (s, 2H), 4.65 (t, J = 5.1 Hz, 2H), 4.45 (t, J = 5.3 Hz, 2H). **^{13}C-NMR** (75 MHz, CD_2Cl_2) δ 161.38 (C_q), 157.93 (C_q), 156.41 (C_q), 150.38 (C_q), 142.33 (C_q), 139.31 (CH), 138.15 (C_q), 137.73 (CH), 131.95 (CH), 130.54 (CH), 129.75 (CH), 128.50 (CH), 128.43 (C_q), 127.39 (CH), 119.99 (CH), 118.25 (C_q), 114.62 (C_q), 111.93 (CH), 105.91 (CH), 74.28 (CH_2), 75.29 (CH_2), 50.14 (CH_2). **MS (ESI**) m/z (relative intensity) 421.17 (100) $[M+H]^+$, 443.15 (60) $[M+Na]^+$, 863.30 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{26}H_{21}N_4O_2$ $[M+H]^+$ 421.1659 found 421.1662.

10.5 Representative procedures for Azetidine C-H activation

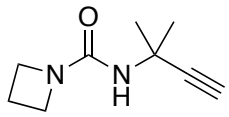
The Preparation of Bis-aryl allyl urea 21-24 (General Procedure A)

A solution of azetidinecarboxamide **19** (0.2 mmol), $Pd(OAc)_2$ (6.6 mg, 0.02 mmol, 10 mol %), iodo arene (0.24 mmol), AgOAc (66.8 mg, 0.40 mmol) in anhydrous $PhCH_3$ (2 mL) was heated at 50 ^oC for 24 h. After the reaction period, the reaction mixture was diluted with EtOAc (5 mL) and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 - 200 mesh) furnished the corresponding Bis-arylatedcyclobutanecarboxamides.

Preparation of N-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]azetidine-1-carboxamide:

Procedure 1:

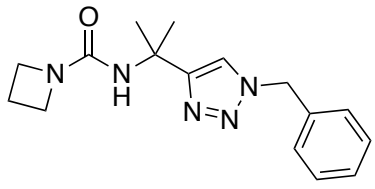
STEP A (synthesis of N-(2-methylbut-3-yn-2-yl)azetidine-1-carboxamide 18)



Triphosgene (237 mg, 0.8 mmo1) was dissolved in CH_2Cl_2 (4.4 mL). A mixture of 2-Methyl-3-butyn-2-amine (210 µL, 2 mmol) and N,N-diisopropylethylamine (DIPEA, 383 µL, 1.1 mmol) in CH_2Cl_2 (6.6 mL) was slowly added to the stirred solution of triphosgene over a period of 30 min using a syringe pump. After a further 10 min of stirring, a solution of azetidine (2 mmol, 135 µL) and DIPEA (383 µL, 1.1 mmol) in CH_2Cl_2 (4.0 mL) was added in one portion.

The reaction mixture was stirred for 3 h at rt, evaporated to dryness and the crude was purified by column chromatography (n-Hexane/EtOAc 1:1) yielded **18** (210 mg, 64 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 4.12 (bs, 1H), 3.96 (t, J = 7.5 Hz, 4 H), 2.34 (s, 1H), 2.24 (p, J = 7.7 Hz, 2H), 1.65 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.86 (C_q), 88.04 (C_q), 68.52 (CH), 48.83 (CH_2), 47.20 (C_q), 29.59 (CH_3), 15.01 (CH_2). **MS (ESI)** *m/z* (relative intensity): 167.11 (100) $[M+H]^+$, 189.10 (45) $[M+Na]^+$, 572 (20) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_9H_{15}N_2O$ $[M+H]^+$ 167.1179 found 167.1177.

STEP B (synthesis of N-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]azetidine-1-carboxamide 19)

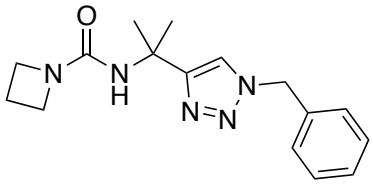


$CuSO_4 \cdot 5H_2O$ (7.5 mg, 0.03 mmol) and sodium ascorbate (12 mg, 0.03 mmol) were added to benzyl azide (83 µL, 0.06 mmol) in t-BuOH:H_2O (2 mL, 1:1) at ambient temperature. N-(2-methylbut-3-yn-2-yl)azetidine-1-carboxamide (100 mg, 0.6 mmol) was added slowly to the mixture at ambient temperature and the resulting mixture was stirred for 24 h. The reaction mixture was diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (3 × 10 mL). The organic

layers were washed with aqueous NH_4OH (2 × 10 mL), brine (2 × 20 mL) and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (pure EtOAc) yielded **19** (140 mg, 78 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.40-7.37 (m, 3H), 7.31-7.28 8m, 2H), 5.50 (s, 2H), 4.76 (bs, 1H), 3.93 (t, J = 7.5 Hz, 4 H), 2.21 (p, J = 7.5 Hz, 2H), 1.73 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.39 (C_q), 154.40 (C_q), 144.67 (C_q), 128.94 (CH), 128.51 (CH), 127.98 (CH), 120.25 (CH), 53.98 (CH_2), 50.62 (C_q), 48.80 (CH_2), 28.53 (CH_3), 14.91 (CH_2). **MS (ESI)** *m/z* (relative intensity): 300.18 (100) $[M+H]^+$, 322.16 (45) $[M+Na]^+$, 621.34 (20) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{16}H_{22}N_5O$ $[M+H]^+$ 300.1819 found 300.1822.

Procedure 2:

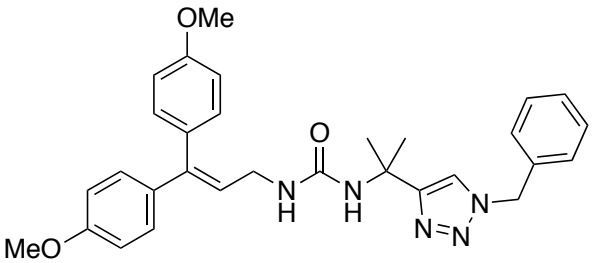
Synthesis of N-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]azetidine-1-carboxamide:



Triphosgene (1.76 g, 5.9 mmo1) was dissolved in CH_2Cl_2 (30 mL). A mixture of 2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-amine (3.2 g, 14.8 mmol) and N,N-diisopropylethylamine (DIPEA, 2.8 mL, 1.1 mmol) in CH_2Cl_2 (50 mL) was slowly added to the stirred solution of triphosgene over a period of 30 min using a syringe pump. After a further 10 min of stirring, a solution of azetidine (14.8 mmol, 1.4 g) and DIPEA (5.3 mL, 2.1 mmol) in CH_2Cl_2 (30 mL) was added in one portion.

The reaction mixture was stirred for 3 h at rt, evaporated to dryness and the crude was purified by column chromatography (pure EtOAc) yielded **19** (1.77 g, 40 %) as a white solid.

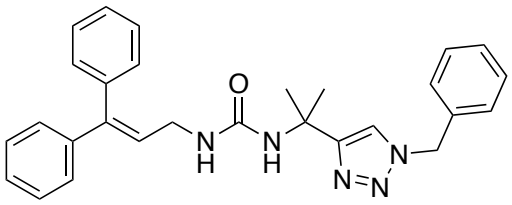
1-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]-3-[3,3-bis(4-methoxyphenyl)allyl]urea (21):



The general procedure **A** was followed using N-(2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl)azetidine-1-carboxamide **19** (60 mg, 0.2 mmol) and 4-Iodo anisole (56 mg, 0.6 mmol). After 24h, purification by column chromatography (Hex/ iPrOH 8:2) yielded **21** (40 mg, 38 %) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.41-7.25 (m, 6H), 7.15 (d, J = 8.6 Hz, 2H), 7.06 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.5 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 5.90 (t, J = 6.8 Hz, 1H), 5.45 (s, 2H), 3.91-3.81 (m, 9H), 1.66 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.08 (C_q), 158.92 (C_q), 143.57 (C_q), 134.54 (C_q), 134.35 (C_q), 132.12 (CH), 130.89 (CH), 130.43 (CH), 128.99 (CH), 128.69 (CH), 128.67 (C_q), 127.98 (CH), 122.80 (CH), 113.64 (CH), 113.41 (CH), 111.01 (C_q), 55.36 (C_q), 55.15 (CH_3), 54.10 (CH_2), 50.32 (C_q), 39.97 (CH_2), 28.40 (CH_3). **MS (ESI)** m/z (relative intensity):

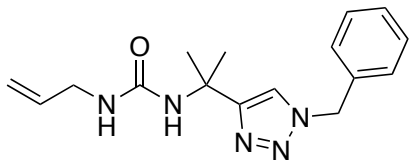
512.27 (100) $[M+H]^+$, 534.25 (40) $[M+Na]^+$, 1045.51 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{30}H_{34}N_5O_3$ $[M+H]^+$ 512.2656 found 512.2659.

1-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]-3-(3,3-diphenylallyl)urea (24):



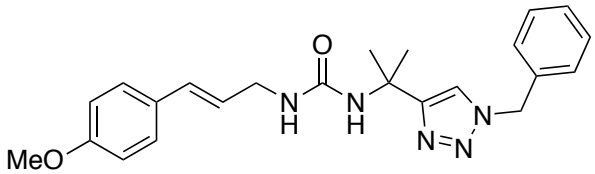
The general procedure **A** was followed using N-(2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl)azetidine-1-carboxamide **19** (60 mg, 0.2 mmol) and 4-Iodo benzene (27 µL, 0.6 mmol). After 24h, purification by column chromatography (Hex/ iPrOH 8:2) yielded **24** (32 mg, 35 %) as a pale yellow oil. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.40-7.19 (m, 16 H), 6.03 (t, J = 6.9 Hz, 1H), 5.51 (s, 2H), 5.47 (s, 1H), 4.44 (bs, 1H), 3.83 (d, J = 6.9 Hz, 1H), 1.72 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 158.41(C_q), 153.03 (C_q), 144.72 (C_q), 141.47 (C_q), 138.68 (C_q), 131.46 (C_q), 129.59 (CH), 129.17 (CH), 128.94 (CH), 128.76 (CH), 128.49 (CH), 128.32 (CH), 128.09 (CH), 127.53 (CH), 127.44 (CH), 126.57 (CH), 124.28 (CH), 54.53 (CH_2), 50.22 (C_q), 39.97 (CH_2), 28.18 (CH_3). **MS (ESI**) m/z (relative intensity): 452.24 (100) $[M+H]^+$, 474.23 (40) $[M+Na]^+$, 925.46 (20) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{28}H_{30}N_5O$ $[M+H]^+$ 452.2445 found 452.2449.

Synthesis of N-(2-methylbut-3-yn-2-yl)azetidine-1-carboxamide (22):



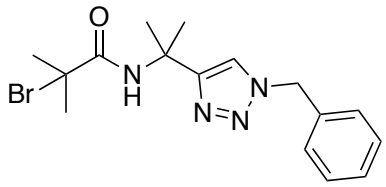
Triphosgene (237 mg, 0.8 mmo1) was dissolved in CH_2Cl_2 (5 mL). A mixture of 2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-amine (432 mg, 2 mmol) and N,N-diisopropylethylamine (DIPEA, 380 µL, 1.1 mmol) in CH_2Cl_2 (7 mL) was slowly added to the stirred solution of triphosgene over a period of 30 min using a syringe pump. After a further 10 min of stirring, a solution of propargyl amine (2 mmol, 150 µL) and DIPEA (380 µL, 1.1 mmol) in CH_2Cl_2 (5 mL) was added in one portion. The reaction mixture was stirred for 1.5 h at rt, evaporated to dryness and the crude was purified by column chromatography (n-Hexane/iPr-OH 95:5) yielded **22** (260 mg, 44 %) as a white solid. **^{1}H NMR** (500 MHz, Chloroform-*d*) δ 7.40 (s, 1H), 7.37-7.31 (m, 3H), 7.26-7.21 (m, 2H), 5.74 (ddt, *J* = 17.2, 10.5, 5.4 Hz, 1H), 5.46 (s, 2H), 5.41 (bs, 1H), 5.06 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.00 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.96 (t, *J* = 5.3 Hz, 1H), 3.69 (td, *J* = 5.4, 2.7 Hz, 2H), 1.67 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.26 (C_q), 154.52 (C_q), 135.38 (CH), 134.60 (C_q), 129.06 (CH), 128.66 (CH), 128.04 (CH), 120.40 (CH), 115.33 (C_q), 54.13 (CH_2), 50.37 (CH_2), 42.61 (CH_2), 28.74 (CH_3). **MS (ESI)** *m/z* (relative intensity): 300.18 (100) $[M+H]^+$, 322.16 (45) $[M+Na]^+$, 621.34 (20) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{16}H_{22}N_5O$ $[M+H]^+$ 300.1819 found 300.1821.

Synthesis of (E)-1-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]-3-(3-(4-methoxyphenyl)allyl)urea (23):



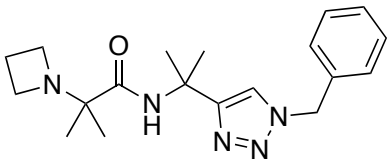
A solution of urea **22** (0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol, 10 mol %), 4-Iodo anisole (0.24 mmol), AgOAc (40 mg, 0.24 mmol) in anhydrous $PhCH_3$ (2 mL) was heated at 50 °C for 20 h. After the reaction period, the reaction mixture was diluted with EtOAc (5 mL) and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 - 200 mesh) furnished the corresponding opened structure (20 mg, 50 %). **^{1}H NMR** (300 MHz, Chloroform-*d*) δ 7.38 (bs, 1H), 7.36-7.30 (m, 3H), 7.27-7.18 (m, 5H), 6.86-6.77 (m, 2H), 6.38 (d, *J* = 15.8 Hz, 1H), 5.98 (dt, *J* = 15.8, 6.1 Hz, 1H), 5.43 (s, 2H), 3.86-3.81 (m, 2H), 3.78 (s, 3H), 1.69 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 159.03 (C_q), 134.50 (C_q), 130.67 (CH), 129.52 (C_q), 129.00 (CH), 128.60 (CH), 127.96 (CH), 127.44 (CH), 124.47 (CH), 120.30 (C_q), 120.26 (C_q), 113.89 (CH), 55.30 (CH), 54.21 (CH_2), 50.63 (C_q), 42.52 (CH_2), 28.86 (CH_3). **MS (ESI)** *m/z* (relative intensity): 406.22 (100) $[M+H]^+$, 428.21 (60) $[M+Na]^+$, 833.42 (30) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{23}H_{28}N_5O_2$ $[M+H]^+$ 406.2238 found 406.2240.

Synthesis of N-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]-2-bromo-2-methylpropanamide (25):



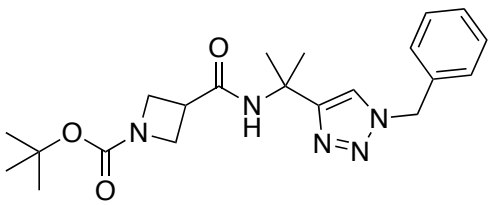
To a 0 °C solution of 2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-amine (350 mg, 1.6 mmol) and triethylamine (250 µL, .8 mmol) in dry DCM (7.4 mL, 025 M) under argon α–bromoisobutyryl bromide (200 µL, 1.6 mmol) was added dropwise. The mixture was stirred at the same temperature for 30 minutes, upon which it was allowed to warm up to ambient temperature for 3 h. The mixture was quenched with H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography on silica gel with (Hex/EtOAc 7:3) yielding **25** (580 mg, Resa = 99 %) as a white solid. **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.40-7.36 (m, 4H), 7.30-7.26 (m, 2H), 5.52 (s, 2H), 1.97 (s, 1H), 1.91 (s, 6H), 1.76 (s, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 171.04 (C_q), 153.13 (C_q), 134.47 (C_q), 128.99 (CH), 128.60 (CH), 127.95 (CH), 120.17 (CH), 62.32 (C_q), 54.08 (CH_2), 51.68 (C_q), 32.10 (CH_3), 27.46 (CH_3). **MS (ESI)** m/z (relative intensity) 365.10 (100) $[M+H]^+$, 367.10 (85) $[M+H]^+$, 387.08 (30) $[M+Na]^+$, 389.08 (20) $[M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{16}H_{22}BrN_4O$ $[M+H]^+$ 365.0972 found 365.0975.

Synthesis of 2-(azetidin-1-yl)-N-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]-2-methylpropanamide (26):



To a mixture of azetidine (100 µL, 1.5 mmol) and N-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]-2-bromo-2-methylpropanamide (274 mg, 0.75 mmol) in acetonitrile (2 mL) and water (0.1 mL), silver oxide (693 mg, 3 mmol) is added in one portion. The heterogeneous reaction mixture is stirred at room temperature overnight. The crude reaction mixture is filtered through a disposable frit and solids rinsed with ethyl acetate (2 mL). The combined filtrates are concentrated and subsequently purified by column chromatography (silica gel, 100 - 200 mesh) furnished the corresponding product **26** as a white solid (240 mg, 80 %). **^{1}H-NMR** (300 MHz, $CDCl_3$) δ 7.96 (bs, 1H), 7.41-7.34 (m, 4H), 7.28-7.25 (m, 2H), 5.50 (s, 2H), 3.19 (t, J = 7.0 Hz, 4 H), 1.99 (p, J = 7.0 Hz, 2H), 1.74 (s, 6H), 1.08 (s, 6H). **^{13}C-NMR** (75 MHz, $CDCl_3$) δ 175.18 (C_q), 153.75 (C_q), 134.76 (C_q), 128.91 (CH), 128.45 (CH), 127.89 (CH), 120.28 (CH), 60.88 (C_q), 53.90 (CH_2), 50.29 (C_q), 47.27 (CH_2), 27.83 (CH_3), 19.08 (CH_3), 16.28 (CH_2). **MS (ESI)** m/z (relative intensity) 342.23 (100) $[M+H]^+$, 364.21 (55) $[M+Na]^+$, 705.43 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{19}H_{28}N_5O$ $[M+H]^+$ 342.2288 found 342.2291.

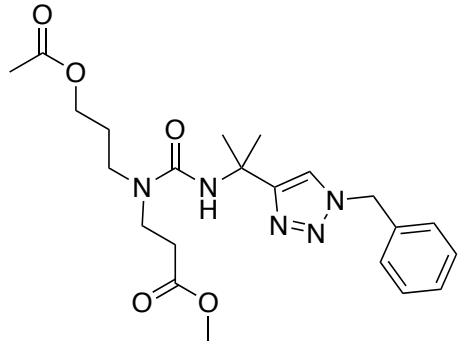
Synthesis of tert-butyl 3-{[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]carbamoyl}azetidine-1-carboxylate (27):



Oxalyl chloride (51 µL, 0.6 mmol) was added dropwise to a mixture of the 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (100 mg, 0.5 mmol), DMF (cat.) in dry DCM (5 mL, 0.1 M) under a N_2 atmosphere at 0 °C. The mixture was stirred at the same temperature for 2 h, upon which it was allowed to warm up to ambient temperature. The crude acid chloride was cooled to 0 °C and it was then added dropwise to a solution of the corresponding amine (119 mg, 0.6 mmol), NEt_3 (208 µL, 1.5 mmol) in dry DCM (0.1 M) at 0 °C. The mixture was initially stirred at the same temperature and then at ambient temperature for 3h. To the reaction mixture was added sat. aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with sat. aqueous NH_4Cl, brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography (EtOAc/n-Hex 7:3) yielded **27** (175 mg, 88 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42-7.37 (m, 4H), 7.33-7.28 (m, 2H), 6.34 (bs, 1H), 5.52 (s, 2H), 4.08-4.00 (m, 4H), 3.20-3.12 (m, 1H), 1.76 (s, 6H), 1.44 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.37 (C_q), 155.66 (C_q), 153.12 (C_q), 134.04 (C_q), 128.68 (CH), 128.31 (CH), 128.24 (CH), 119.71 (CH), 79.11 (C_q), 66.1379 (C_q), 53.77 (CH_2), 51.13 (CH_2), 33.40 (CH), 27.88 (CH_3), 27.35 (CH_3). **MS (ESI)** *m/z* (relative intensity): 400.23

(100) $[M+H]^+$, 422.22 (35) $[M+Na]^+$, 821.44 (20) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{21}H_{30}N_5O_3$ $[M+H]^+$ 400.2343 found 400.2347.

Methyl 3-{1-(3-acetoxypropyl)-3-[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]ureido}propanoate (30):



A solution of carboxamide **19** (0.15 mmol), $Pd(OAc)_2$ (3.7 mg, 0.015 mmol, 10 mol %), methyl acrylate (0.45 mmol), AgOAc (55 mg, 0.33 mmol) and HFIP (79 µL, 0.75 mmol) in anhydrous $PhCH_3$ (1.5 mL) was heated at 100 °C for 20 h. After the reaction period, the reaction mixture was diluted with EtOAc (5 mL) and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 - 200 mesh) furnished the corresponding opened structure as a colurless oil (31 mg, 44 %). **^{1}H NMR** (400 MHz, Chloroform-*d*) δ 7.36 (s, 1H), 7.33-7.29 (m, 3H), 7.25-7.21 (m, 2H), 5.68 (bs, 1H), 5.45 (s, 2H), 4.03 (t, *J* = 6.2 Hz, 2H), 3.63 (s, 3H), 3.45 (t, *J* = 6.6 Hz, 2H), 3.20 (t, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 6.5 Hz, 2H), 2.00 (s, 3H), 1.81 (dq, *J* = 7.9, 6.2 Hz, 2H), 1.67 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.90 (C_q), 170.86 (C_q), 156.64 (C_q), 154.62 (C_q), 134.81 (C_q), 128.92(CH), 128.46 (CH), 127.94 (CH), 120.23 (CH), 61.86 (C_q), 53.93 (CH_2), 51.85(CH_3), 50.96 (CH_2), 44.22 (CH_2), 43.32 (CH_2), 33.46(CH_2), 28.65(CH_3), 27.38 (CH_2), 20.88 (CH_3). **MS (ESI)** *m/z* (relative intensity): 446.24 (100) $[M+H]^+$, 468.51 (45) $[M+Na]^+$, 913.45 (20) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{16}H_{22}N_5O$ $[M+H]^+$ 466.2398 found 446.2411.

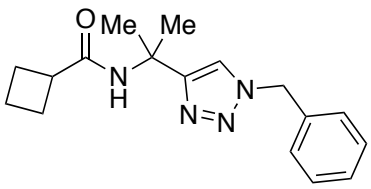
10.6 Representative procedures for Cyclobutane C-H activation
The synthesis of cyclobutanecarboxamides (General procedure A)

Oxalyl chloride (1.1 equiv) was added dropwise to a mixture of the cyclobutanecarboxylic acid (1.0 equiv), DMF (cat.) in dry DCM (0.06 M) under a N_2 atmosphere at 0 °C. The mixture was stirred at the same temperature for 3 h, upon which it was allowed to warm up to ambient temperature. The crude acid chloride was cooled to 0 °C and it was then added dropwise to a solution of the corresponding amine (1.2 equiv), NEt_3 (3.0 equiv) in dry DCM (0.1 M) at 0 °C. The mixture was initially stirred at the same temperature and then at ambient temperature for 3h. To the reaction mixture was added sat. aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were washed with sat. aqueous NH_4Cl, brine and dried over Na_2SO_4. The filtrate was concentrated under reduced pressure and the crude product was purified by column chromatography on silica gel.

The Preparation of Bis-arylated Cyclobutanecarboxamides 33a-33u, 35 and 36 (General Procedure B)

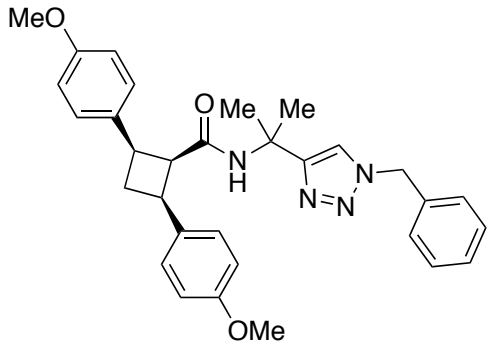
A solution of cyclobutanecarboxamide **31** (0.2 mmol), $Pd(TFA)_2$ (6.6 mg, 0.02 mmol, 10 mol %), iodo arene (0.8 mmol), AgOAc (73 mg, 0.44 mmol) in anhydrous *o*-Xylene (2 mL) was heated at 130 ^oC for 20 h. After the reaction period, the reaction mixture was diluted with EtOAc (5 mL) and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 - 200 mesh) furnished the corresponding Bis-arylatedcyclobutanecarboxamides.

***N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]cyclobutanecarboxamide (31)** :



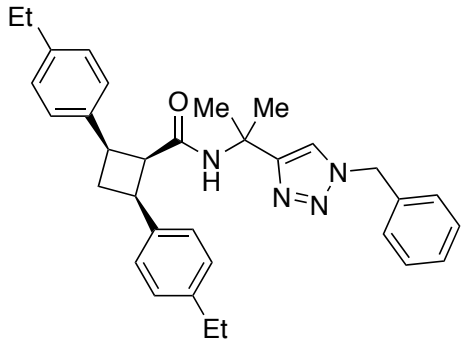
The general procedure **A** was followed using cyclobutanecarboxylic acid (1.15 mL, 12.00 mmol) and 2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (3.1 g, 14.4 mmol). After 6 h, purification by column chromatography (DCM/ MeOH 98:2) yielded **31** (2.5 g, 70 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42-7.32 (m, 4H), 7.30-7.23 (m, 2H), 6.03 (bs, 1H), 5.49 (s, 2H), 2.93 (qd, *J* = 8.4, 0.9 Hz, 1H), 2.29-2.03 (m, 4H), 1.99-1.77 (m, 2H), 1.72 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.2 (C_q), 153.8 (C_q), 134.6 (C_q), 129.0 (CH), 128.6 (CH), 128.0 (CH), 120.2 (CH), 54.2 (CH_2), 51.1 (C_q), 40.6 (CH), 28.0 (CH_3), 25.2 (CH_2), 18.1 (CH_2). **IR (ATR)**: 2978, 1499, 1171, 1020, 728, 457 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 321 (100) $[M+Na]^+$, 299 (60) $[M+H]^+$, 619 (55) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{17}H_{23}N_4O$ $[M+H]^+$ 299.1866 found 299.1870.

***N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(4-methoxyphenyl)cyclobutane-1-carboxamide (33a) :**



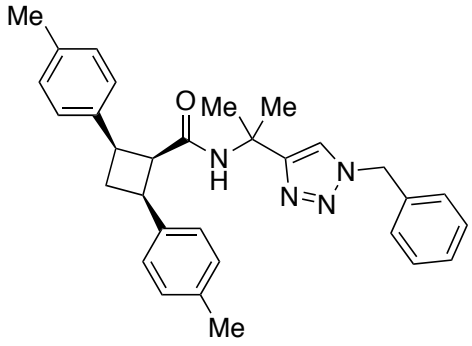
The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (45 mg, 0.15 mmol) and 4-I-anisole (140 mg, 0.6 mmol). After 20h, purification by column chromatography (n-Hexane/ EtOAc 7:3) yielded **33a** (63 mg, 83 %) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.39-7.29 (m, 3H), 7.19-7.11 (m, 6H), 6.84-6.74 (m, 4H), 6.60 (s, 1H), 5.74 (bs, 1H), 5.27 (s, 2H), 3.84 (dt, J = 11.0, 7.9 Hz, 2H), 3.74 (s, 6H), 3.59 (td, J = 8.3, 3.1 Hz, 1H), 3.28 (q, J = 10.9 Hz, 1H), 2.56 (dtd, J = 10.0, 7.9, 3.1 Hz, 1H), 1.27 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.5 (C_q), 157.7 (C_q), 153.1 (C_q), 135.0 (C_q), 132.9 (C_q), 128.8 (CH), 128.3 (CH), 128.1 (CH), 127.6 (CH), 120.7 (CH), 113.3 (CH), 55.3 (CH_3), 53.6 (CH_2), 53.4 (CH), 51.3 (C_q), 37.7 (CH), 29.8 (CH_2), 27.9 (CH_3). **IR (ATR)**: 2936, 1671, 1510, 1243, 1053, 821, 723 cm-1. **MS (ESI**) m/z (relative intensity): 511 (100) $[M+H]^+$, 533 (40) $[M+Na]^+$, 1043 (30) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{31}H_{35}N_4O_3$ $[M+H]^+$ 511.2704 found 511.2703.

***N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(4-ethylphenyl)cyclobutane-1-carboxamide (33b) :**



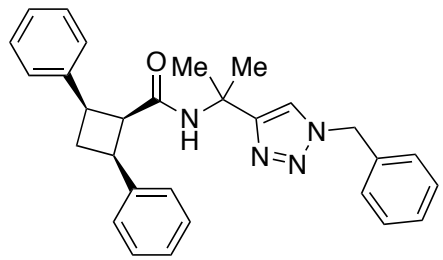
The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (45 mg, 0.15 mmol) and 1-Ethyl-4-Iodobenzene (87 µL, 0.6 mmol). After 20h, purification by column chromatography n-Hexane/EtOAc 6:4) yielded **33c** (52 mg, 69 %) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.38-7.30 (m, 3H), 7.17-7.10 (m, 6H), 7.09-7.02 (m, 4H), 6.74 (s, 1H), 5.74 (bs, 1H), 5.27 (s, 2H), 3.88 (dt, J = 11.2, 8.1 Hz, 2H), 3.65 (td, J = 8.3, 3.0 Hz, 1H), 3.27 (q, J = 11.0 Hz, 1H), 2.64-2.57 (m, 1H), 2.56 (q, J = 7.6 Hz, 4H), 1.21 (s, 6H), 1.16 (t, J = 7.6 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.6 (C_q), 153.4 (C_q), 141.8 (C_q), 138.1 (C_q), 134.8 (C_q), 128.9 (CH), 128.4 (CH), 127.6 (CH), 127.4 (CH), 127.0 (CH), 120.8 (CH), 53.7 (CH_2), 53.2 (CH), 51.2 (C_q), 38.0 (CH), 29.5 (CH_2), 28.5 (CH_2), 27.6 (CH_3), 15.8 (CH_3). **IR (ATR)**: 2959, 1650, 1530, 1227, 1047, 823, 726 cm-1. **MS (ESI)** m/z (relative intensity): 507 (100) $[M+H]^+$, 529 (30) $[M+Na]^+$, 1035 (25) $[2M+Na]^+$. **HR-MS (ESI)** m/z calcd for $C_{33}H_{39}N_4O$ $[M+H]^+$ 507.3118 found 507.3114.

***N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-di-*p*-tolylcyclobutane-1-carboxamide (33c) :**



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (45 mg, 0.15 mmol) and 4-Iodotoluene (131 mg, 0.6 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 7:3) yielded **33b** (52 mg, 73 %) as a white solid. Synthesis of **33b** on gram scale: A solution of cyclobutanecarboxamide **31** (0.2 mmol), $Pd(TFA)_2$ (133 mg, 0.4 mmol (10 mol %)), 4-I-toluene (16 mmol) AgOAc (1.5 g, 8.8 mmol) in anhydrous o-xylene (40 mL) was heated at 130 ° C for 20 h. After the reaction period, the reaction mixture was diluted with EtOAc and concentrated in vacuum and the resulting mixture was purified by column chromatography (silica gel, 100 – 200 mesh) furnished the corresponding bisarylatedcyclobutanecarboxamides in 71 % yield. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 3H), 7.15-7.08 (m, 6H), 7.07-7.01 (m, 4H), 6.66 (s, 1H), 5.73 (bs, 1H), 5.27 (s, 2H), 3.87 (dt, *J* = 11.4, 8.0 Hz, 2H), 3.64 (td, *J* = 8.3, 3.2 Hz, 1H), 3.28 (q, *J* = 10.8 Hz, 1H), 2.59 (dtd, *J* = 10.0, 7.9, 3.1 Hz, 1H), 2.27 (s, 6H), 1.25 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.4 (C_q), 153.2 (C_q), 137.8 (C_q), 135.1 (C_q), 134.9 (C_q), 128.8 (CH), 128.5 (CH), 128.3 (CH), 127.5 (CH), 126.8 (CH), 120.8 (CH), 53.6 (CH_2), 53.3 (CH), 51.3 (C_q), 38.1 (CH), 29.6 (CH_2), 27.8 (CH_3), 21.1 (CH_3). **IR (ATR)**: 2974, 1674, 1531, 1232, 1056, 809, 725 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 479 (100) $[M+H]^+$, 501 (70) $[M+Na]^+$, 979 (30) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{31}H_{35}N_4O$ $[M+H]^+$ 479.2805 found 479.2805.

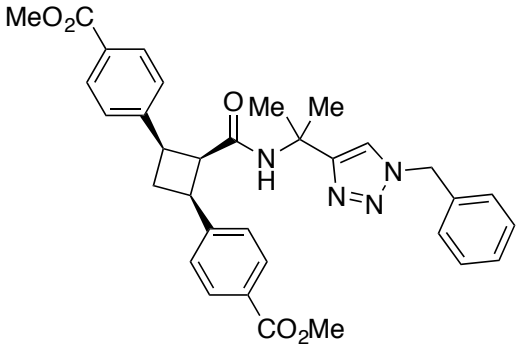
***N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-diphenylcyclobutane-1-carboxamide (33d) :**



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and Iodobenzene (90 µL, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 7:3) yielded **33d** (63 mg, 70 %) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 5.1, 2.0 Hz, 3H), 7.22 (d, *J* = 4.3 Hz, 8H), 7.12 (ddt, *J* = 6.5, 5.0, 2.4 Hz, 4H), 6.53 (s, 1H), 5.74 (bs, 1H), 5.27 (s, 2H), 3.93 (dt, *J* = 11.1, 8.2 Hz, 2H), 3.69 (td, *J* = 8.3, 3.1 Hz, 1H), 3.36 (q, *J* = 10.9 Hz, 1H), 2.62 (dtd, *J* = 10.8, 8.0, 3.1 Hz, 1H), 1.23 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.3 (C_q), 153.2 (C_q), 140.8 (C_q), 134.9 (C_q), 128.8 (CH), 128.3 (CH), 127.8 (CH), 127.6 (CH), 126.9 (CH), 125.8(CH),120.6 (CH), 53.7 (CH_2), 53.4 (CH), 51.4 (C_q), 38.4 (CH), 29.2 (CH_2), 27.9 (CH_3). **IR**

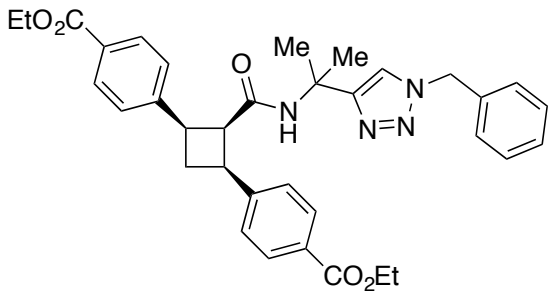
(ATR: 2922, 1672, 1528, 1234, 1055, 761, 697 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 451 (100) $[M+H]^+$, 473 (35) $[M+Na]^+$, 923 (24) $[2M+Na]^+$, 200 (6). **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{31}N_4O$ $[M+H]^+$ 451.2492 found 451.2493.

Dimethyl 4,4'-{2-{[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]carbamoyl}cyclobutane-1,3-diyl)}dibenzoate (33e) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and Methyl-4-iodobenzoate (210 mg, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 7:3) yielded **33e** (84 mg, 74 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.01-7.80 (m, 4H), 7.33-7.29 (m, 3H), 7.28-7.22 (m, 4H), 7.16-7.11 (m, 2H), 6.84 (s, 1H), 6.18 (bs, 1H), 5.28 (s, 2H), 3.99-3.84 (m, 8H), 3.73 (td, *J* = 8.2, 3.1 Hz, 1H), 3.40 (q, *J* = 10.7 Hz, 1H), 2.67 (dtd, *J* = 9.9, 8.0, 3.0 Hz, 1H), 1.22 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.7 (C_q), 166.9 (C_q), 153.1 (C_q), 146.3 (C_q), 134.6 (C_q), 129.1 (CH), 128.9 (CH), 128.4 (CH), 127.7 (C_q), 127.7 (CH), 126.8 (CH), 120.2 (CH), 53.8 (CH_2), 53.1 (CH), 51.9 (CH_3), 51.4 (C_q), 38.3 (CH), 29.6 (CH_2), 27.6 (CH_3). **IR (ATR)**: 2970, 1708, 1546, 1276, 1105, 722, 696 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 567 (100) $[M+H]^+$, 589 (60), $[M+Na]^+$, 1155 (15) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{33}H_{35}N_4O_5$ $[M+H]^+$ 567.2602 found 567.2606.

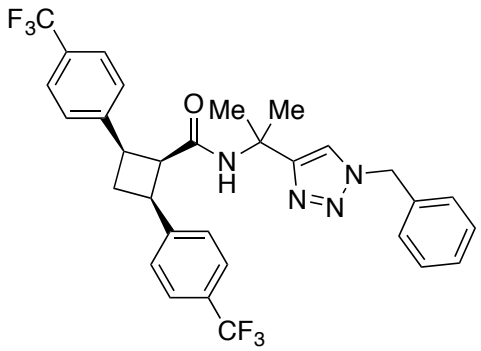
Diethyl 4,4'-{2-{[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]carbamoyl}cyclobutane-1,3-diyl)}dibenzoate (33f) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and Ethyl-4-iodobenzoate (134 µL, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 1:1) yielded **33f** (85 mg, 72 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.04-7.79 (m, 4H), 7.31 (dd, *J* = 5.0, 1.9 Hz, 3H), 7.28-7.22 (m, 4H), 7.16-7.12 (m, 2H), 6.83 (s, 1H), 6.14 (bs, 1H), 5.28 (s, 2H), 4.33 (q, *J* = 7.1 Hz, 4H), 3.93 (dt, *J* = 10.9, 7.9 Hz, 2H), 3.73 (td, *J* = 8.2, 3.0 Hz, 1H), 3.40 (q, *J* = 10.7 Hz, 1H), 2.68 (dtd, *J* = 9.9, 8.0, 3.0 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 6H), 1.23 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.8 (C_q), 166.5 (C_q), 153.1 (C_q), 146.2 (C_q), 134.6 (C_q), 129.1 (CH), 128.9 (CH), 128.4 (CH), 128.1 (C_q), 127.8 (CH), 126.7 (CH), 120.2 (CH), 60.8 (CH_2), 53.8 (CH_2), 53.0 (CH), 51.4 (C_q), 38.4 (CH),

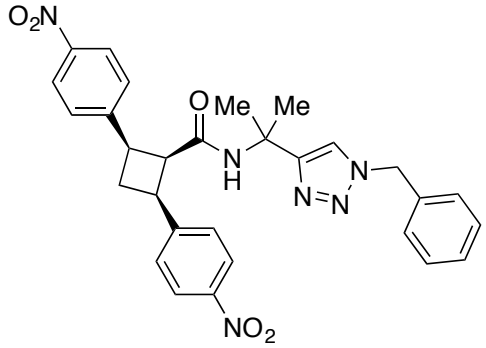
29.6 (CH_2), 27.6 (CH_3), 14.4 (CH_3). **IR (ATR)**: 2976, 1712, 1608, 1270, 1098, 775, 724 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 595 (100) $[M+H]^+$, 617 (40), $[M+Na]^+$, 1211 (20) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{35}H_{39}N_4O_5$ $[M+H]^+$ 595.2915 found 595.2925.

***N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis[4-(trifluoromethyl)phenyl)] cyclobutane-1-carboxamide (33g) :**



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (45 mg, 0.15 mmol) and 4-Iodobenzotrifluoride (88 µL, 0.6 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 7:3) yielded **33g** (67 mg, 78 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.48 (dd, *J* = 8.7, 0.8 Hz, 4H), 7.35-7.26 (m, 7H), 7.19-7.14 (m, 2H), 6.99 (s, 1H), 6.27 (bs, 1H), 5.33 (s, 2H), 3.94 (dt, *J* = 11.2, 8.0 Hz, 2H), 3.74 (td, *J* = 8.3, 3.4 Hz, 1H), 3.36 (q, *J* = 10.8 Hz, 1H), 2.70 (dtd, *J* = 10.0, 8.1, 3.1 Hz, 1H), 1.21 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.7 (C_q), 153.3 (C_q), 144.9 (C_q), 134.5 (C_q), 128.9 (CH), 128.5 (CH), 128.0 (C_q, q, J_{C-F} = 32 Hz), 127.8 (CH), 127.1 (CH), 124.6 (CH, q, J_{C-F} = 3.8 Hz), 124.4 (C_q, q, J_{C-F} = 271 Hz), 120.0 (CH), 53.9 (CH_2), 52.9 (CH), 51.2 (C_q), 38.0 (CH), 29.6 (CH_2), 27.2 (CH_3). **IR (ATR)**: 2924, 1668, 1322, 1109, 1064, 827, 599 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 587 (100) $[M+H]^+$, 609 (35) $[M+Na]^+$, 1195 (40) $[2M+Na]^+$, 1173 (6) $[2M+H]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{31}H_{29}F_6N_4O$ $[M+H]^+$ 587.2240 found 587.2245.

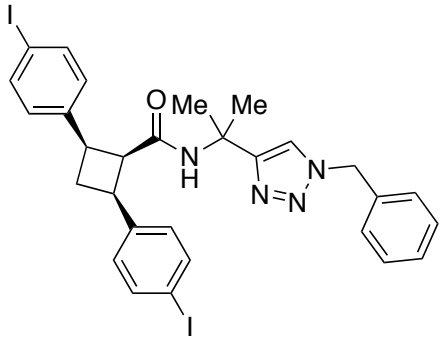
***N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(4-nitrophenyl)cyclobutane-1-carboxamide (33h) :**



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (45 mg, 0.15 mmol) and 1-Iodo-4-nitrobenzene (150 mg, 0.6 mmol). After 20 h, purification by column chromatography (DCM/MeOH 95:5) yielded **33h** (47 mg, 58 %) as a pale yellow solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11-8.08 (m, 4H), 7.38-7.29 (m, 7H), 7.21-7.14 (m, 2H), 7.04 (s, 1H), 6.45 (bs, 1H), 5.37 (s, 2H), 4.00 (dt, *J* = 10.6, 8.4 Hz, 2H), 3.80 (td, *J* = 8.2, 3.0 Hz, 1H), 3.39 (q, *J* = 10.7 Hz, 1H), 2.82-2.72 (dtd, *J* = 10.6, 8.1, 3.0 Hz, 1H), 1.23 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.3 (C_q), 153.3 (C_q), 148.4 (C_q), 146.3 (C_q), 134.2 (C_q), 129.0 (CH), 128.7 (CH), 127.9 (CH), 127.6 (CH), 123.1 (CH), 119.7 (CH), 54.1 (CH_2), 53.2

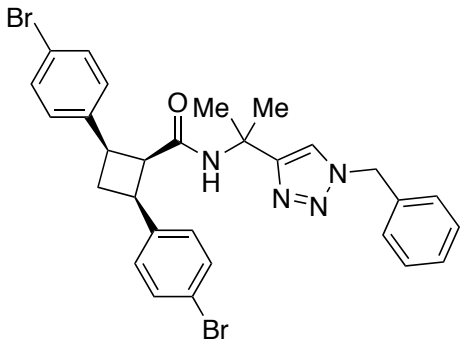
(CH), 51.4 (C_q), 38.0 (CH), 29.9 (CH_2), 27.4 (CH_3). **IR (ATR)**: 2972, 1671, 1510, 1343, 1211, 852, 722, 691 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 541 (100) $[M+H]^+$, 563 (75) $[M+Na]^+$, 1103 (45) $[2M+H]^+$, 420 (15), 264 (15). **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{29}N_6O_5$ $[M+H]^+$ 541.2194 found 541.2190.

_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(4-iodophenyl)cyclobutane-1-carboxamide (33i) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 1,4-Diiodobenzene (264 mg, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 9:1) yielded **33i** (70 mg, 50 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65-7.47 (m, 4H), 7.41-7.30 (m, 3H), 7.21 (dd, *J* = 7.5, 2.1 Hz, 2H), 6.96-6.87 (m, 5H), 5.99 (s, 2H), 5.40 (bs, 1H), 3.80 (dt, *J* = 11.0, 8.0 Hz, 2H), 3.60 (td, *J* = 8.2, 3.1 Hz, 1H), 3.23 (q, *J* = 10.8 Hz, 1H), 2.58 (dtd, *J* = 11.1, 8.0, 3.1 Hz, 1H), 1.28 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.9 (C_q), 153.2 (C_q), 140.6 (C_q), 136.8 (CH), 134.8 (C_q), 129,0 (CH), 128.9 (CH), 128.5 (CH), 127.9 (CH), 120.4 (CH), 91.1 (C_q), 54.1 (CH_2), 52.7 (CH), 51.2 (C_q), 37.8 (CH), 29.5 (CH_2), 27.5 (CH_3). **IR (ATR)**: 2936, 1670, 1482, 1004, 807, 721, 586 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 703 (100) $[M+H]^+$, 577 (47), 725 (25) $[M+Na]^+$, 1427 (5) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{29}I_2N_4O$ $[M+H]^+$ 703.0425 found 703.0418.

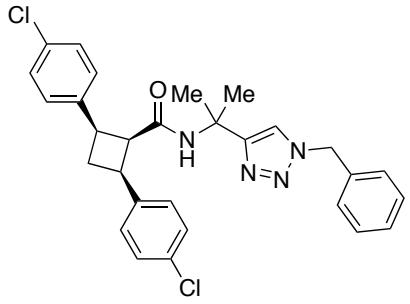
_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(4-bromophenyl)cyclobutane-1-carboxamide (33j) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (45 mg, 0.15 mmol) and 1-Bromo-4-iodobenzene (160 mg, 0.6 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc (8:2) yielded **33j** (65 mg, 71 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.32 (m, 7H), 7.22-7.16 (m, 2H), 7.11 (d, *J* = 8.5 Hz, 4H), 6.85 (s, 1H), 6.00 (bs, 1H), 5.36 (s, 2H), 3.84 (dt, *J* = 11.1, 8.1 Hz, 2H), 3.61 (td, *J* = 8.2, 3.0 Hz, 1H), 3.27 (q, *J* = 10.8 Hz, 1H), 2.60 (qd, *J* = 7.9, 4.0 Hz, 1H), 1.28 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.9 (C_q), 153.1 (C_q), 139.3 (C_q), 134.7 (C_q), 131.5 (C_q), 129.0 (CH), 128.5 (CH), 128.3 (CH), 127.9 (CH), 127.8 (CH), 120.3 (CH), 53.9 (CH_2), 53.0 (CH), 51.3 (C_q), 37.7 (CH), 29.7 (CH_2), 27.6 (CH_3). **IR (ATR)**: 2943, 1668, 1486, 1217, 1009, 811, 718 cm^{-1}. **MS (ESI)** *m/z*

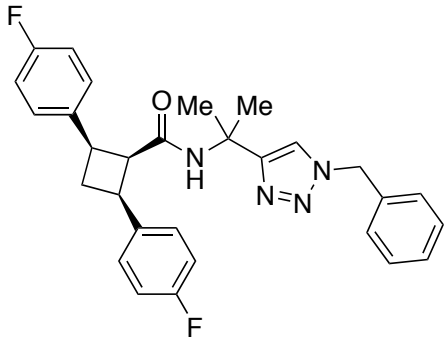
(relative intensity): 631 (100) $[M+Na]^+$, 607 (52) $[M+H]^+$, 1239 (30) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{29}Br_2N_4O$ $[M+H]^+$ 607.0703 found 607.0689.

_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(4-chlorophenyl)cyclobutane-1-carboxamide (33k) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (45 mg, 0.15 mmol) and 1-Chloro-4-iodobenzene (143 mg, 0.6 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 8:2) yielded **33k** (50 mg, 64 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.38-7.31 (m, 7H), 7.23-7.17 (m, 2H), 7.11-7.00 (m, 4H), 6.87 (s, 1H), 6.01 (bs, 1H), 5.38 (s, 2H), 3.81 (dt, *J* = 11.0, 8.0 Hz, 2H), 3.61 (td, *J* = 8.3, 3.2 Hz, 1H), 3.26 (q, *J* = 10.8 Hz, 1H), 2.59 (dtd, *J* = 10.7, 8.0, 2.8 Hz, 1H), 1.29 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.9 (C_q), 153.1 (C_q), 139.8 (C_q), 134.7 (C_q), 130.8 (CH), 128.9 (CH), 128.7 (CH), 128.5 (CH), 127.8 (CH), 120.3 (CH), 119.6 (C_q), 54.0 (CH_2), 52.9 (CH), 51.3 (C_q), 37.8 (CH), 29.7 (CH_2), 27.6 (CH_3). **IR (ATR)**: 2980, 1669, 1490, 1210, 1089, 815, 721 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 541 (100) $[M+Na]^+$, 519 (68) $[M+H]^+$, 1061 (35) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{29}Cl_2N_4O$ $[M+Na]^+$ 541.1532 found 541.1529.

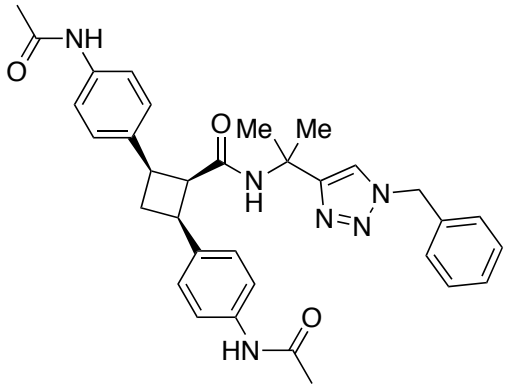
_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(4-fluorophenyl)cyclobutane-1-carboxamide (33l) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (45 mg, 0.15 mmol) and 1-Fluoro-4-iodobenzene (69 µL, 0.6 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 8:2) yielded **33l** (42 mg, 57 %) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$ δ 7.42-7.30 (m, 3H), 7.16 (ddt, *J* = 11.6, 5.3, 2.8 Hz, 6H), 6.96-6.85 (m, 4H), 6.78 (s, 1H), 5.98 (bs, 1H), 5.32 (s, 2H), 3.84 (dt, *J* = 11.1, 8.1 Hz, 2H), 3.60 (td, *J* = 8.2, 3.1 Hz, 1H), 3.29 (q, *J* = 10.8 Hz, 1H), 2.59 (dtd, *J* = 9.9, 8.0, 3.1 Hz, 1H), 1.26 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.2 (C_q), 161.2 (C_q, d, J_{C-F} = 243.5 Hz), 153.3 (C_q), 136.5 (C_q, d, J_{C-F} = 3.1 Hz), 134.7 (C_q), 128.9 (CH), 128.5 (CH), 128.4 (CH, d, J_{C-F} = 7.8 Hz), 127.8 (CH), 120.3 (CH), 114.5 (CH, d, J_{C-F} = 21.1 Hz), 53.8 (CH_2), 53.1 (CH), 51.2 (C_q), 37.5 (CH), 29.7 (CH_2), 27.6 (CH_3). **IR (ATR)**: 2965, 1667, 1534, 1235, 1052, 827, 719 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 487 (100) $[M+H]^+$, 509

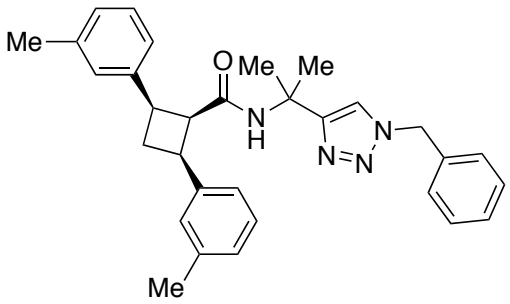
(59) $[M+Na]^+$, 995 (59) $[2M+Na]^+$. **HR-MS** (ESI) *m/z* calcd for $C_{29}H_{29}F_2N_4O$ $[M+H]^+$ 487.2304 found 487.2305.

***N*,*N*'-{{2-{[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]carbamoyl}cyclobutane-1,3-diyl}bis(4,1-phenylene)}diacetamide (33m) :**



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and *N*-(4-iodophenyl)acetamide (209 mg, 0.8 mmol). After 20 h, purification by column chromatography (DCM/MeOH 9:1) yielded **33m** (82 mg, 73 %) as a white solid. **^{1}H NMR** (600 MHz, CD_3OD) δ 7.46 (d, *J* = 8.6 Hz, 4H), 7.31-7.26 (m, 3H), 7.17 (d, *J* = 8.6 Hz, 4H), 7.04-7.01 (m, 2H), 6.49 (s, 1H), 5.24 (s, 2H), 3.93-3.85 (m, 3H), 3.29-3.22 (m, 1H), 2.56-2.48 (m, 1H), 2.00 (s, 6H), 1.26 (s, 6H). **^{13}C NMR** (126 MHz, CD_3OD) δ 172.2 (C_q), 171.2 (C_q), 154.3 (C_q), 138.5 (C_q), 137.7 (C_q), 136.8 (C_q), 129.7 (CH), 129.1 (CH), 128.4 (CH), 128.3 (CH), 123.0 (CH), 120.5 (CH), 54.4 (CH_2), 53.3 (CH), 52.1 (C_q), 39.1 (CH), 30.1 (CH_2), 28.7 (CH_3), 23.8 (CH_3). **IR (ATR)**: 2977, 1643, 1514, 1246, 820, 722 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 565 (100) $[M+H]^+$, 587 (40) $[M+Na]^+$, 381 (20), 603 (5). **HR-MS (ESI)** *m/z* calcd for $C_{33}H_{37}N_6O_3$ $[M+H]^+$ 565.2922 found 565.2911.

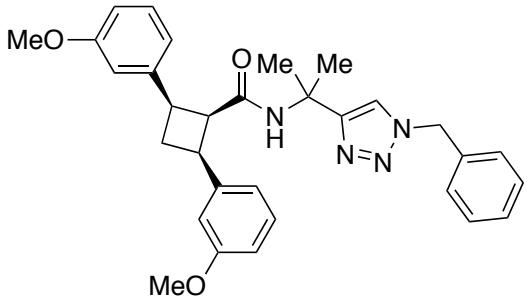
***N*-[2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-di-*m*-tolylcyclobutane-1-carboxamide (33n) :**



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 3-Iodotoluene (102 µL, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 6:4) yielded **33n** (62 mg, 65 %) as a white solid. **^{1}H NMR** (600 MHz,$CDCl_3$) δ 7.36-7.31 (m, 3H), 7.15- 7.07 (m, 4H), 7.04 (dq, *J* = 1.9, 0.9 Hz, 2H), 7.00 (dq, *J* = 7.6, 1.0 Hz, 2H), 6.93 (ddt, *J* = 7.4, 1.9, 0.9 Hz, 2H), 6.51 (s, 1H), 5.77 (bs, 1H), 5.27 (s, 2H), 3.89 (dt, *J* = 11.3, 8.2 Hz, 2H), 3.68 (tdd, *J* = 8.3, 3.0, 0.8 Hz, 1H), 3.30 (tdd, *J* = 11.3, 10.0, 0.8 Hz, 1H), 2.61 (dtd, *J* = 10.0, 8.0, 3.1 Hz, 1H), 2.27 (s, 6H), 1.25 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.4 (C_q), 153.2 (C_q), 140.9 (C_q), 137.3 (C_q), 135.0 (C_q), 128.8 (CH), 128.2 (CH), 127.7 (CH), 127.6 (CH), 127.4 (CH), 126.5 (CH), 123.9 (CH), 120.6 (CH), 53.6 (CH_2), 53.2 (CH), 51.4 (C_q), 38.2 (CH), 29.4 (CH_2), 27.9 (CH_3), 21.5 (CH_3). **IR (ATR)**: 2975, 1655, 1454, 1207, 1055, 780, 722,

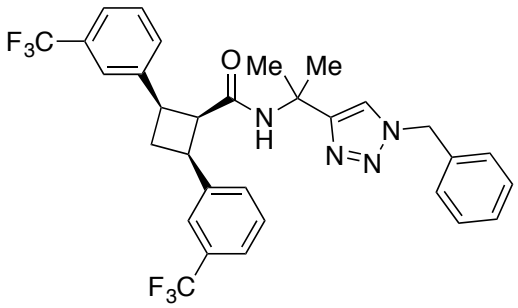
695 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 479 (100) $[M+H]^+$, 501 (30) $[M+Na]^+$, 979 (5) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{31}H_{35}N_4O$ $[M+H]^+$ 479.2805 found 479.2806.

_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(3-methoxyphenyl)cyclobutane-1-carboxamide (33o) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 3-Iodoanisole (95 µL, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 7:3) yielded **33o** (82 mg, 80 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.30 (m, 3H), 7.17-7.11 (m, 4H), 7.10 (s, 1H), 6.82-6.74 (m, 3H), 6.68 (dt, *J* = 8.1, 1.6 Hz, 2H), 6.64 (s, 1H), 5.79 (bs, 1H), 5.30 (s, 2H), 3.90 (dt, *J* = 11.3, 8.1 Hz, 2H), 3.74 (s, 7H), 3.29 (q, *J* = 10.7 Hz, 1H), 2.69-2.57 (m, 1H), 1.28 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.3 (C_q), 159.3 (C_q), 153.2 (C_q), 142.6 (C_q), 135.0 (C_q), 128.9 (CH), 128.8 (CH), 128.3 (CH), 127.6 (CH), 120.6 (CH), 119.2 (CH), 112.3 (CH), 111.7 (CH), 55.2 (CH_3), 53.7 (CH_2),53.2 (CH), 51.5 (C_q), 38.3 (CH), 29.6 (CH_2), 27.9 (CH_3). **IR (ATR)**: 2937, 1673, 1600, 1255, 1039, 778, 722, 691 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 511 (65) $[M+H]^+$, 533 (100) $[M+Na]^+$, 1021 (6) $[2M+H]^+$, 1043 (47) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{31}H_{35}N_4O_3$ $[M+H]^+$ 511.2704 found 511.2703.

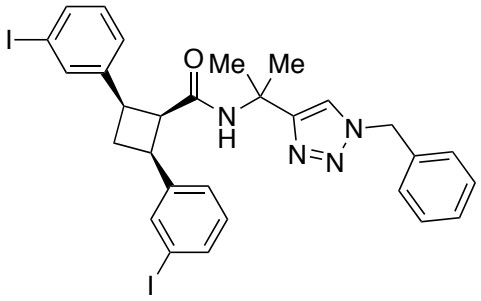
_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis[3-(trifluoromethyl)phenyl] cyclobutane-1-carboxamide (33p) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 3-Iodobenzotrifluoride (116 µL, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 7:3) yielded **33p** (84 mg, 72 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.44 (dq, *J* = 1.8, 0.8 Hz, 2H), 7.41-7.30 (m, 9H), 7.18-7.11 (m, 2H), 6.88 (s, 1H), 6.27 (bs, 1H), 5.33 (s, 2H), 3.94 (dt, *J* = 10.7, 7.8 Hz, 2H), 3.74 (td, *J* = 8.5, 3.7 Hz, 1H), 3.39 (q, *J* = 10.9 Hz, 1H), 2.71 (dtd, *J* = 9.9, 8.0, 3.1 Hz, 1H), 1.22 (s, 6H).**^{13}C NMR** (126 MHz,$CDCl_3$) δ 168.7 (C_q), 153.4 (C_q), 141.8 (C_q), 134.5 (C_q), 130.2 (CH), 130.0 (C_q, q, J_{C-F} = 31 Hz), 128.9 (CH), 128.5 (CH), 128.3 (CH), 127.7 (CH), 124.2 (C_q, q, J_{C-F} = 272 Hz), 123.4 (CH, q, J_{C-F} = 3.7 Hz), 122.7 (CH, q, J_{C-F} = 3.8 Hz), 119.9 (CH), 53.9 (CH_2), 52.7 (CH), 51.4 (C_q), 38.0 (CH), 29.7 (CH_2), 27.3 (CH_3). **IR (ATR)**: 2953, 1672, 1540, 1323, 1152, 1115, 723,

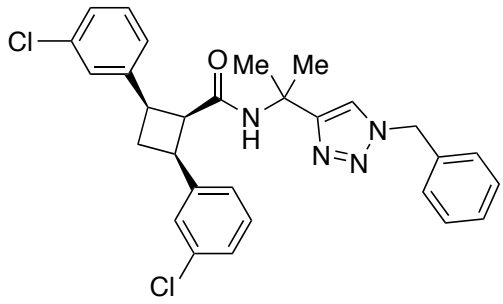
697 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 587 (100) $[M+H]^+$, 609 (12) $[M+Na]^+$, 1195 (20) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{31}H_{29}F_6N_4O$ $[M+H]^+$ 587.2240 found 587.2247.

_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(3-iodophenyl)cyclobutane-1-carboxamide (33q) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 1,3-Diiodobenzene (232 mg, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 8:2) yielded **33q** (62 mg, 44 %) as a white solid. **^{1}H NMR** (500 MHz,$CDCl_3$) δ 7.52 (q, *J* = 1.5 Hz, 2H), 7.44 (ddt, *J* = 7.8, 1.6, 0.8 Hz, 2H), 7.20-7.14 (m, 3H), 7.14 (ddt, *J* = 7.8, 1.9, 1.0 Hz, 4H), 6.93 (t, *J* = 7.8 Hz, 2H), 6.83 (s, 1H), 6.04 (bs, 1H), 5.37 (s, 2H), 3.82 (dt, *J* = 10.4, 8.0 Hz, 2H), 3.62 (td, *J* = 8.2, 3.1 Hz, 1H), 3.25 (q, *J* = 10.8 Hz, 1H), 2.60 (dtd, *J* = 9.9, 8.0, 3.0 Hz, 1H), 1.32 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.9 (C_q), 153.3 (C_q), 143.5 (C_q), 135.7 (CH), 134.9 (CH), 134.8 (C_q), 129.7 (CH), 128.9 (CH), 128.5 (CH), 127.8 (CH), 126.1 (CH), 120.4 (CH), 94.1 (C_q), 53.9 (CH_2), 52.6 (CH), 51.5 (C_q), 37.6 (CH), 30.1 (CH_2), 27.7 (CH_3). **IR (ATR)**: 2931, 1668, 1468, 1210, 1055, 720, 691 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 725 (100) $[M+Na]^+$, 703 (70) $[M+H]^+$, 1427 (70) $[2M+Na]^+$, 599 (5). **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{29}I_2N_4O$ $[M+H]^+$ 703.0425 found 703.0423.

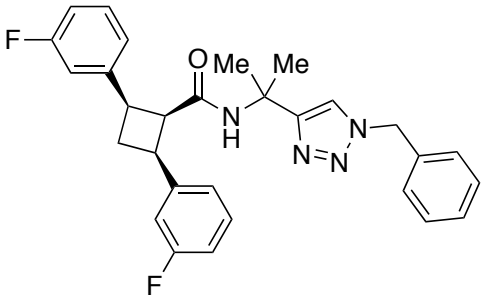
_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(3-chlorophenyl)cyclobutane-1-carboxamide (33r) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 3-Chloroiodobenzene (100 µL, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 8:2) yielded **33r** (62 mg, 60 %) as a white solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.35-7.31 (m, 3H), 7.18 (d, *J* = 1.9 Hz, 2H), 7.17-7.14 (m, 2H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.10-7.04 (m, 4H), 6.82 (s, 1H), 6.07 (bs, 1H), 5.35 (s, 2H), 3.85 (dt, *J* = 10.7, 8.0 Hz, 2H), 3.65 (td, *J* = 8.1, 2.9 Hz, 1H), 3.29 (q, *J* = 10.7 Hz, 1H), 2.62 (dtd, *J* = 9.9, 8.0, 3.0 Hz, 1H), 1.30 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.9 (C_q), 153.3 (C_q), 143.1 (C_q), 134.7 (C_q), 133.7 (C_q), 129.2 (CH), 128.9 (CH), 128.5 (CH), 127.7 (CH), 126.9 (CH), 126.1 (CH), 126.0 (CH), 120.4 (CH), 53.8 (CH_2), 52.7 (CH), 51.4 (C_q), 37.8 (CH), 29.5 (CH_2), 27.6 (CH_3). **IR (ATR)**: 2939, 1667, 1539, 1207, 1056, 789, 717 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 541 (100) $[M+Na]^+$, 519

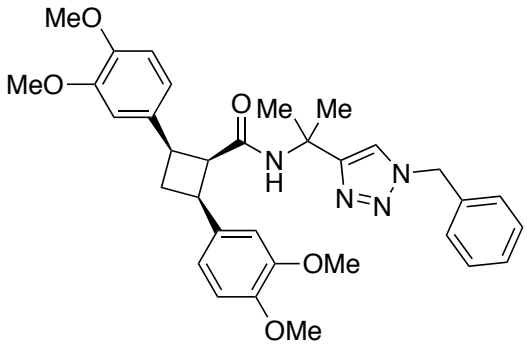
(25) $[M+H]^+$, 1061 (85) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{29}Cl_2N_4O$ $[M+H]^+$ 519.1713 found 519.1703.

_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(3-fluorophenyl)cyclobutane-1-carboxamide (33s) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 3-Fluoroiodobenzene (94 µL, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 8:2) yielded **33s** (64 mg, 66 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 3H), 7.16 (td, *J* = 8.1, 6.1 Hz, 4H), 6.97-6.89 (m, 4H), 6.84-6.77 (m, 3H), 6.08 (bs, 1H), 5.33 (s, 2H), 3.86 (dt, *J* = 10.8, 8.1 Hz, 2H), 3.66 (td, *J* = 8.2, 3.1 Hz, 1H), 3.29 (q, *J* = 10.8 Hz, 1H), 2.61 (dtd, *J* = 9.9, 8.0, 3.1 Hz, 1H), 1.28 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.0 (C_q), 162.7 (C_q, d, J_{C-F} = 245 Hz), 153.3 (C_q), 143.6 (C_q, d, J_{C-F} = 7.1 Hz), 134.8 (C_q), 129.3 (CH, d, J_{C-F} = 8.3 Hz), 128.9 (CH), 128.5 (CH), 127.7 (CH), 122.5 (CH, d, J_{C-F} = 2.7 Hz), 120.3 (CH), 113.8 (CH, d, J_{C-F} = 21 Hz), 112.7 (CH, d, J_{C-F} = 21 Hz), 53.8 (CH_2), 52.8 (CH), 51.4 (C_q), 37.9 (CH), 29.5 (CH_2), 27.6 (CH_3). **IR (ATR)**: 2946, 1667, 1584, 1211, 1054, 781, 720 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 995 (100) $[2M+Na]^+$, 509 (85) $[M+Na]^+$, 487 (40) $[M+H]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{29}F_2N_4O$ $[M+H]^+$ 487.2304 found 487.2300.

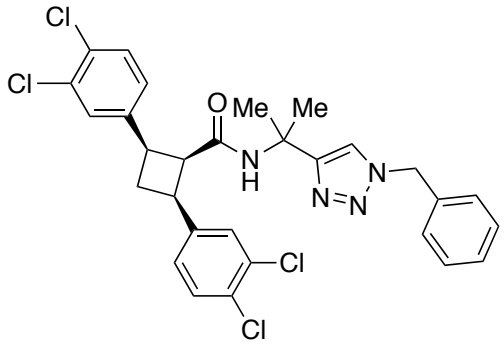
_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(3,4-dimethoxyphenyl)cyclobutane-1-carboxamide (33t) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 4-Iodo-1,2-dimethoxybenzene (211 mg, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 1:1) yielded **33t** (mg, 65 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.33-7.28 (m, 3H), 7.17-7.11 (m, 2H), 6.78-6.73 (m, 7H), 5.97 (bs, 1H), 5.31 (s, 2H), 3.87-3.79 (m, 14H), 3.63 (td, *J* = 8.2, 3.1 Hz, 1H), 3.25 (q, *J* = 10.7 Hz, 1H), 2.60 (dtd, *J* = 9.8, 7.9, 3.1 Hz, 1H), 1.28 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.5 (C_q), 153.4 (C_q), 148.4 (C_q), 147.1 (C_q), 134.8 (C_q), 133.6 (C_q), 128.8 (CH), 128.3 (CH), 127.6 (CH), 120.3 (CH), 118.9 (CH), 110.9 (CH), 110.3 (CH), 55.9 (CH_3), 55.8 (CH_3), 53.6 (CH_2), 53.3 (CH), 51.3 (C_q), 38.0 (CH), 30.3 (CH_2), 27.8 (CH_3). **IR (ATR)**: 2962, 1671, 1513, 1239, 1139, 1026, 734 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 593 (100) $[M+Na]^+$,

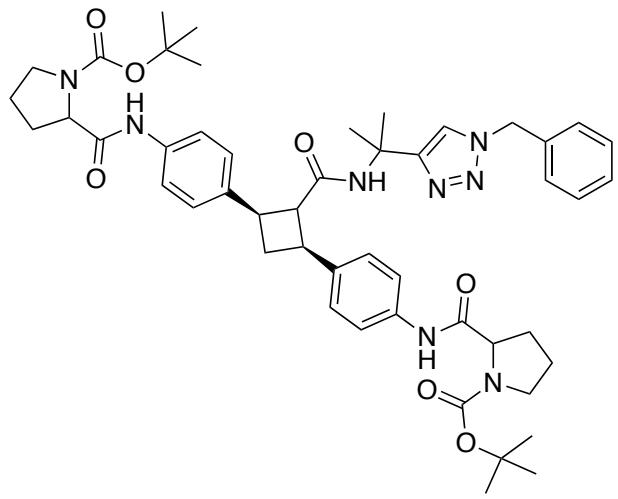
1163 (55) $[2M+Na]^+$, 572 (20) $[M+H]^+$, 1027 (10). **HR-MS (ESI)** *m/z* calcd for $C_{33}H_{39}N_4O_5$ $[M+H]^+$ 571.2915 found 571.2915.

_N_-[2-(1-benzyl-1_H_-1,2,3-triazol-4-yl)propan-2-yl]-2,4-bis(3,4-dichlorophenyl)cyclobutane-1-carboxamide (33u) :



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and 1,2-dichloro-4-iodobenzene (218 mg, 0.8 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 7:3) yielded **33u** (69 mg, 59 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36-7.31 (m, 3H), 7.30 (s, 1H), 7.28-7.25 (m, 3H), 7.22-7.17 (m, 2H), 7.02-6.96 (m, 3H), 6.22 (bs, 1H), 5.39 (s, 2H), 3.80 (dt, *J* = 10.9, 8.3 Hz, 2H), 3.61 (td, *J* = 8.2, 3.1 Hz, 1H), 3.21 (q, *J* = 10.7 Hz, 1H), 2.63 (dtd, *J* = 9.9, 8.1, 3.1 Hz, 1H), 1.33 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.5 (C_q), 153.2 (C_q), 141.1 (C_q), 134.5 (C_q), 131.8 (C_q), 129.8 (C_q), 129.7 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 127.9 (CH), 126.3 (CH), 120.0 (CH), 54.1 (CH_2), 52.6 (CH), 51.5 (C_q), 37.4 (CH), 30.1 (CH_2), 27.5 (CH_3). **IR (ATR)**: 2947, 1667, 1471, 1222, 1029, 815, 720, 631 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 589 (100) $[M+H]^+$, 611 (40) $[M+Na]^+$, 1199 (40) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{27}Cl_4N_4O$ $[M+H]^+$ 587.0933 found 587.0925.

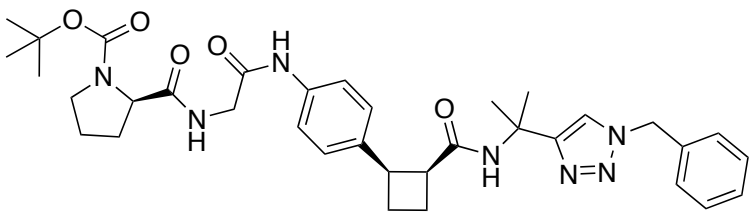
Di-tert-butyl-2,2'-{{{{(1R,3S)-2-{[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2 yl]carbamoyl}cyclobutane-1,3-diyl}bis(4,1 phenylene)bis(azanediyl)}bis(carbonyl}}bis(pyrrolidine-1-carboxylate) (35):



The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and tert-butyl 2-[(4-iodophenyl)carbamoyl]pyrrolidine-1-carboxylate (333 mg, 0.8 mmol). After 20 h, purification by column chromatography (DCM/MeOH 98:2) yielded **35** (116 mg, 66 %) as a white solid. **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.49-7.37 (m, 4H), 7.36-7.29 (m, 3H), 7.24-7.12 (m, 6H), 6.72 (s, 1H), 5.85 (bs, 1H), 5.29 (s, 2H), 4.38 (bs, 2H), 3.85 (q, J = 9.1 Hz, 2H), 3.63 (td, J = 8.2, 3.0 Hz,

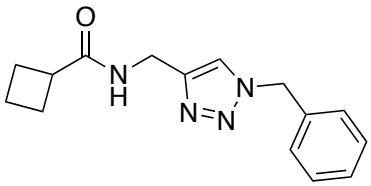
1H), 3.47-3.22 (m, 5H), 2.71-2.48 (m, 4H), 1.91-1.88 (m, 2H), 1.48-1.44 (m, 21H), 1.27 (s, 6H), 0.98-0.72 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.44 (C_q), 154.66 (C_q), 153.54 (C_q), 136.19 (d, J = 101.3 Hz, C_q), 133.01 (C_q), 128.98 (CH), 128.41 (CH), 128.01 (CH), 127.70 (d, J = 11.1 Hz, CH),125.71 (CH), 122.95 (C_q), 122.93 (CH), 121.61 (CH), 120.88 (C_q), 119.31 (CH), 80.78 (C_q), 51.62 (CH), 51.5 (C_q), 50.31 (CH_2), 47.53 (CH_2) , 38.31 (d, J = 13.3 Hz, CH_2), 36.27 (CH_2), 30.13 (CH_3), 30.03 (CH_2), 28.45 (CH_3). **MS (ESI)** *m/z* (relative intensity): 875.48 (100) $[M+Na]^+$, 897.46 (60) $[M+H]^+$, 1772.94 (15) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{49}H_{63}N_8O_7$ $[M+H]^+$ 875.4814 found 875.4817.

Tert-butyl(R)-2-{{2-{{4-{(1R,2S)-2-{[2-(1-benzyl-1H-1,2,3-triazol-4-yl)propan-2-yl]carbamoyl}cyclobutyl}phenyl}amino}-2-oxoethyl}carbamoyl}pyrrolidine-1-carboxylate (36):



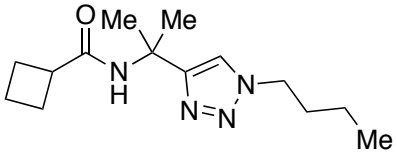
The general procedure **B** was followed using *N*-(2-(1-benzyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl)cyclobutanecarboxamide **31** (60 mg, 0.2 mmol) and tert-butyl (R)-2-{{2-[(4-iodophenyl)amino]-2-oxoethyl}carbamoyl}pyrrolidine-1-carboxylate (378 mg, 0.8 mmol). After 20 h, purification by column chromatography (DCM/MeOH 98:2) yielded **35** (116 mg, 66 %) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.60-7.45 (m, 1H), 7.38-7.28 (m, 3H), 7.21 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.5 Hz, 3H), 7.03-6.89 (m, 1H), 5.41 (s, 2H), 4.20 (q, J = 5.6, 4.9 Hz, 1H), 4.00 (qd, J = 16.8, 15.0, 6.4 Hz, 2H), 3.79 (qd, J = 8.9, 3.9 Hz, 1H), 3.51-3.36 (m, 2H), 3.25 (td, J = 8.7, 4.5 Hz, 1H), 2.58-2.39 (m, 1H), 2.32 (ddt, J = 14.7, 9.6, 4.7 Hz, 1H), 2.21 (ddd, J = 9.0, 4.7, 2.3 Hz, 1H), 2.13-2.03 (m, 7H), 1.39 (s, 9H), 1.33-1.18 (m, 5H), 0.91-0.75 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 172.65 (C_q), 171.26 (C_q), 167.09 (C_q), 155.50 (C_q), 153.44 (CH), 136.95 (C_q), 136.26 (C_q), 134.86 (C_q), 128.88 (CH), 128.39 (CH), 127.91 (CH), 120.61 (CH), 119.81 (CH), 80.80 (C_q), 60.93 (CH_2), 53.41 (C_q), 51.00 (CH), 47.43 (CH), 46.30 (CH), 43.90 (CH), 42.49 (CH_2), 31.62 (CH_3), 28.43 (CH_3) , 27.70 (CH_2), 24.77 (CH_2), 22.69 (CH_2), 20.30 (CH_2). **MS (ESI)** *m/z* (relative intensity): 644.36 (100) $[M+Na]^+$, 666.34 (70) $[M+H]^+$, 1309.69 (15) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{35}H_{46}N_7O_5$ $[M+H]^+$ 644.3555 found 644.35558.

***N*-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]cyclobutanecarboxamide (37) :**



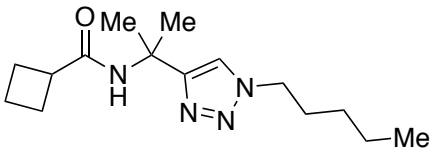
The general procedure **A** was followed using cyclobutanecarboxylic acid (0.29 mL, 3.00 mmol) and (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanamine (677 mg, 3.6 mmol). After 6h, purification by column chromatography (DCM/MeOH 98:2) yielded **37** (551 mg, 68 %) as a white solid. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.40-7.33 (m, 3H), 7.28-7.23 (m, 2H), 6.14 (bs, 1H), 5.48 (s, 2H), 4.46 (d, *J* = 5.5 Hz, 2H), 2.98 (pd, *J* = 8.6, 1.0 Hz, 1H), 2.35-2.17 (m, 2H), 2.16-.2.05 (m, 2H), 2.00-1.77 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.0 (C_q), 145.2 (C_q), 134.4 (C_q), 129.1 (CH), 128.8 (CH), 128.1 (CH), 122.1 (CH), 54.2 (CH_2), 39.7 (CH), 34.8 (CH_2), 25.2 (CH_2),18.1 (CH_2). **IR (ATR)**: 2942, 1635, 1543, 1221, 1041, 718, 452 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 293 (100) $[M+Na]^+$, 271 (75) $[M+H]^+$, 563 (35) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{15}H_{19}N_4O_1$ $[M+H]^+$ 271.1553 found 271.1552.

***N*-[2-(1-butyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]cyclobutanecarboxamide (40a) :**



The general procedure **A** was followed using cyclobutanecarboxylic acid (0.58 mL, 6.00 mmol) and 2-(1-butyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (1.3 g, 7.2 mmol). After 6h, purification by column chromatography (n-Hex/ EtOAc 1:1) yielded **37a** (950 mg, 60 %) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.06 (bs, 1H), 4.31 (t, *J* = 7.4 Hz, 2H), 2.95 (pd, *J* = 8.5, 1.0 Hz, 1H), 2.25-2.18 (m, 2H), 2.13-2.05 (m, 2H), 1.97-1.78 (m, 4H), 1.75 (s, 6H), 1.41-1.31 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.2 (C_q), 153.3 (C_q), 120.1 (CH), 51.2 (C_q), 50.1 (CH_2), 40.6 (CH), 32.3 (CH_2), 28.1 (CH_3), 25.2 (CH_2), 19.8 (CH_2), 18.0 (CH_2), 13.5 (CH_3). **IR (ATR)**: 2957, 1665, 1534, 1257, 1059, 846, 674 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 265 (100) $[M+H]^+$, 287 (53) $[M+Na]^+$, 551 (10) $[2M+Na]^+$, 166 (15), 138 (15). **HR-MS (ESI)** *m/z* calcd for $C_{14}H_{25}N_4O$ $[M+H]^+$ 265.2023 found 265.2028.

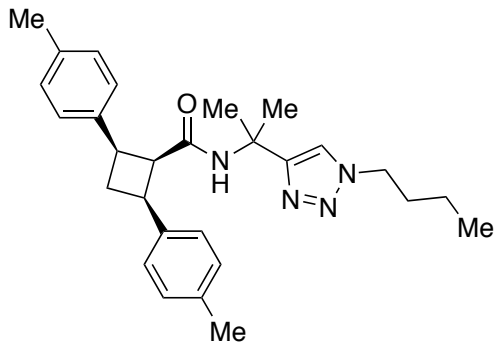
***N*-[2-(1-pentyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]cyclobutanecarboxamide (40b) :**



The general procedure **A** was followed using cyclobutanecarboxylic acid (0.58 mL, 6.00 mmol) and 2-(1-pentyl-1*H*-1,2,3-triazol-4-yl)propan-2-amine (1.4 g, 7.2 mmol). After 6h, purification by column chromatography (nHex/EtOAc 1:1) yielded **37b** (967 mg, 58%) as a white solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.47 (s, 1H), 6.07 (bs, 1H), 4.29 (t, *J* = 6.5 Hz, 2H), 2.94 (pd, *J* = 8.5, 1.0 Hz, 1H), 2.26-2.16 (m, 2H), 2.12-2.06 (m, 2H), 1.95-1.85 (m, 4H), 1.75 (s, 6H), 1.40-1.26 (m, 4H), 0.89 (t, *J* = 7.1 Hz, 3H). **^{13}C**

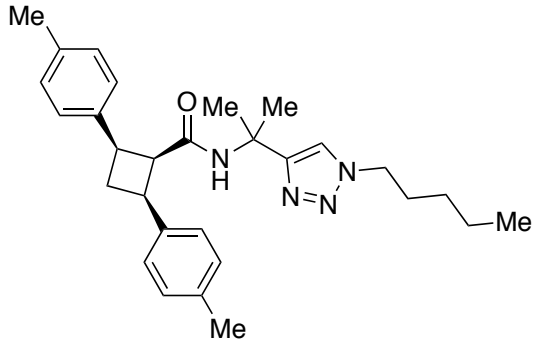
NMR (126 MHz, $CDCl_3$) δ 174.2 (C_q), 153.8 (C_q), 120.1 (CH), 51.1 (C_q), 50.4 (CH_2), 40.6 (CH), 30.0 (CH_2), 28.7 (CH_2), 28.1 (CH_3), 25.2 (CH_2), 22.1 (CH_2), 18.0 (CH_2), 13.9 (CH_3). **IR (ATR)**: 2933, 1663, 1533, 1383, 1256, 1055, 855 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 279 (100) $[M+H]^+$, 301 (80) $[M+Na]^+$, 579 (45) $[2M+Na]^+$, 180 (15), 152 (15). **HR-MS (ESI)** *m/z* calcd for $C_{15}H_{27}N_4O$ $[M+H]^+$ 279.2179 found 279.2184.

(1*s*,2*R*,4*S*)-*N*-[2-(1-butyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-di-*p*-tolylcyclobutane-1-carboxamide (42a) :



The general procedure **B** was followed using *N*-[2-(1-butyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]cyclobutanecarboxamide (**1b**) (40 mg, 0.15 mmol) and 4-iodotoluene (131 mg, 0.6 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 6:4) yielded **42a** (49 mg, 74 %) as a white solid.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.08 (d, *J* = 7.8 Hz, 4H), 7.04 (d, *J* = 7.8 Hz, 4H), 6.70 (s, 1H), 6.08 (bs, 1H), 4.07 (t, *J* = 7.4 Hz, 2H), 3.85 (dt, *J* = 11.2, 8.2 Hz, 2H), 3.67 (td, *J* = 8.3, 3.1 Hz, 1H), 3.24 (q, *J* = 10.9 Hz, 1H), 2.57 (dtd, *J* = 10.1, 8.0, 3.1 Hz, 1H), 2.29 (s, 6H), 1.83-1.64 (m, 2H), 1.29-1.19 (m, 8H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 185.2 (C_q), 169.8 (C_q), 137.9 (C_q), 134.9 (C_q), 128.4 (CH), 126.8 (CH), 120.6 (CH), 52.9 (CH), 50.9 (C_q), 49.9 (CH_2), 38.6 (CH_2), 38.0 (CH), 32.2 (CH_2), 27.0 (CH_3), 21.1 (CH_3), 19.8 (CH_2), 13.5 (CH_3). **IR (ATR)**: 2931, 1672, 1514, 1234, 1053, 810, 521 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 445 (100) $[M+H]^+$, 467 (15) $[M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{28}H_{37}N_4O$ $[M+H]^+$ 445.2962 found 445.2954.

(1*s*,2*R*,4*S*)-*N*-[2-(1-pentyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]-2,4-di-*p*-tolylcyclobutane-1-carboxamide (42b) :



The general procedure **B** was followed using *N*-[2-(1-pentyl-1*H*-1,2,3-triazol-4-yl)propan-2-yl]cyclobutanecarboxamide (**1c**) (42 mg, 0.15 mmol) and 4-iodotoluene (131 mg, 0.6 mmol). After 20 h, purification by column chromatography (n-Hexane/EtOAc 6:4) yielded **42b** (48 mg, 70 %) as a white solid.**^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.13 (d, *J* = 7.9 Hz, 4H), 7.07 (d, *J* = 7.8 Hz, 4H), 6.54 (s, 1H), 5.69 (bs, 1H), 4.04 (t, *J* = 7.5 Hz, 2H), 3.87 (dt, *J* = 11.3, 8.2 Hz, 2H), 3.64 (td, *J* = 8.3, 3.1 Hz, 1H), 3.30 (q, *J* = 11.0 Hz, 1H), 2.58 (dtd, *J* = 10.0, 8.0, 3.1 Hz, 1H), 2.30 (s, 6H), 1.79-1.72 (m, 2H), 1.37-1.30 (m, 2H), 1.28-1.22 (m, 8H), 0.90 (t, *J* =

7.3 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 169.4 (C_q), 152.7 (C_q), 137.8 (C_q), 135.1 (C_q), 128.5 (CH), 126.9 (CH), 120.4 (CH), 53.3 (CH), 51.4 (C_q), 50.0 (CH_2), 38.1 (CH), 29.9 (CH_2), 29.5 (CH_2), 28.7 (CH_2), 28.0 (CH_3), 22.2 (CH_2), 21.1 (CH_3), 13.9 (CH_3). **IR (ATR)**: 2967, 1672, 1434, 1217, 1053, 810, 522 cm^{-1}. **MS (ESI)** *m/z* (relative intensity): 459 (100) $[M+H]^+$, 481 (25) $[M+Na]^+$, 939 (5) $[2M+Na]^+$. **HR-MS (ESI)** *m/z* calcd for $C_{29}H_{39}N_4O$ $[M+H]^+$ 459.3118 found 459.3120.

10.7 Aknowledgments

First of all, I would like to thank my family, everything was possible because you followed me (bear for some situation is the correct word) each step of this long and sometimes tiring experience.

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