FROM CLICK CHEMISTRY TO CATALYTIC CLEAVAGE OF UNSTRAINED C-C BONDS

Míriam Sau Roca

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DOCTORAL THESIS

From Click Chemistry to catalytic cleavage of unstrained C-C bonds

Míriam Sau Roca

Supervised by Prof. Miquel. A. Pericàs Brondo and Prof. Ruben Martin Romo

Institut Català d'Investigació Química (ICIQ)

UNIVERSITAT ROVIRA I VIRGILI

Tarragona, 2016

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Prof. **MIQUEL A. PERICÀS**, group leader at the Institute of Chemical Research of Catalonia (ICIQ) and Prof. **RUBEN MARTIN**, ICREA Research Professor and group leader at the Institute of Chemical Research of Catalonia (ICIQ),

CERTIFY, that the present Doctoral Thesis entitled "**FROM CLICK CHEMISTRY TO CATALYTIC CLEAVAGE OF UNSTRAINED C-C BONDS**" presented by **Míriam Sau Roca** to obtain the degree of Doctor, has been carried out under their supervision at the Institute of Chemical Research of Catalonia (ICIQ).

Tarragona, June 2, 2016

PhD Thesis supervisors

Prof. Miquel. A. Pericàs

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Abbreviations

AAC	Alkyne and azide cycloaddition
CuAAC	Copper alkyne and azide cycloaddition
t-BuOH	*tert*-butanol
DMF	Dimethylformamide
MeCN	Acetonitrile
THF	Tetrahyfrofuran
DCE	Dichloroethane
TBHP	*tert*-butyl hydroperoxide
MW	Microwave irradiation
rt	room temperature (approx 22-25ºC)
TMS	Trimethyl silyl ether
δ	Chemical shift
J	Coupling constant
$CDCl_3$	Deuterated chloroform
d	Doublet
s	Singulet
t	Triplet
m	Multiplet
NMR	Nuclear magnetic resonance
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
mCPBA	*Meta*-chloroperbenzoic acid
$NaClO_2$	Sodium chlorite

The rest of abbreviations and acronyms: "Guideline for authors" *J. Org. Chem.* **2008**, 73, 23A-24A

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Publications

1) Copper-free Intramolecular Alkyne-Azide cycloadditions leading to seven membered heterocycles.
Sau, M.; Escrich. C. R.; Pericàs, M. A. *Org. Lett*. **2011**, *13*, 5044-5047.

2) Palladium catalyzed arylative functionalization of unsatrained bonds of 1,2-amino alcohols.
Míriam Sau, Miquel. A. Pericàs and Ruben Martin. Manuscript in preparation.

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Chapter 1. General introduction to Click Chemistry

1.1 Triazole as essential scaffold

Nowadays it is known that Nature is able to carry out from the simplest to the most challenging transformation in an efficient and straightforward manner. It is the most perfect chemist there will ever be because it has the ability to perform and to control an astonishing range of chemical reactions in a very selective way using extremely efficient catalysts. This notion has arisen an interest within the scientific community to try and mimic Nature's approach to chemical synthesis. Although the formation of the C-C bond is the most widely applied process by Nature and consequently one of the most studied processes by humans, the creation of the C-heteroatom bonds is a close competitor in the field of organic chemistry. C-Heteroatom bond making strategies are essential for the building of biomolecules. Particularly, the presence of *N*-heterocyclic compounds is really abundant in drugs and biological natural products such as amino acids (proline or histidine), pyrimidines or purines among others. In particular, triazoles are one of the most relevant and well known heterocycles present like vital structural motive in many of different drug categories such as anti-inflammatory, analgesic, antihypertensive or antiparkinson among many others (Figure 1.1).[1] This broad and potent biological activity[2] is the reason why, still nowadays, they are extensively investigated. In addition to their powerful pharmacological activity, they are also used in a wide range of

[1] a) Kharb, R.; Sharma, P. C.; Yar, M. S. *J. Enzym. Inh. Medic. Chem*. **2011**, *26*, 1-21. b) Almerico, A.; Barone, G.; Martorana, A.; Terenzi, A.; Mingoia, F.; Delisi, R.; Lauria, A. *Eur. J. Org*. **2014**, 3289-3306.

[2] a) Alvarez, R.; Velázquez, S.; Félix, A.; Aquaro, S.; Clercq, R.; Perno, C.; Karlsson, A.; Balzarini, J.; Camarasa, M. *J. Med. Chem*. **1994**, *37*, 4185-4194. b) Velázquez. S.; Alvarez, R.; Pérez, C.; Gago, F.; Clercd, E.; Balzarini, J.; Camarasa, M. *Antivir. Chem. Chemother*. **1998**, *9*, 481-489. c) Yagi, B.; Stapert, D.; Schaadt, R.; Hamel, J.; Zurenko, G.; Ford, C.; Reischer, R.; Morris, J.; Hutchinson, D. K.; Hester, J. B.; Grega, K. C.; Graber, D. R.; Garmon, S. A.; Emmert, D. E.; Barbachyn, M. R.; Anderson, D. J.; Allwine, A. A.; Genin, M. J. *J. Med. Chem*. **2000**, *43*, 953-970.

industrial applications like dyes, corrosion inhibition, photostabilization or agrochemicals.[3]

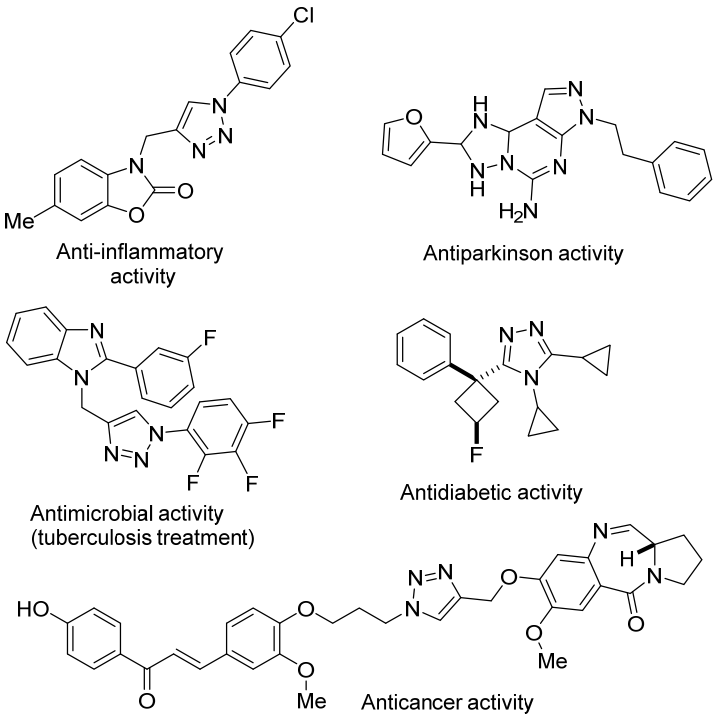


Figure 1.1

1.2 Click Chemistry concept

Different strategies are reported in the literature for the synthesis of triazoles.[4] Among them, the 1,3-dipolar cycloadditions between an azide and an alkyne is the most widely used. This reaction was discovered at the beginning of 20th century but it was not until 1960's that Huisgen and co-workers proposed a more accurate mechanism.[5] Theoretically, 1,3-dipolar cycloadditions could provide a wide variety of functionalized five-

[3] Fan, W. Q.; Katritzky, A. R. *In comprehensive heterocyclic chemistry II*. Elsevier Science: Oxford, **1996**, *4*, 1-126.

[4] Haider, S.; Alam, M. S.; Hamid, H. *Inflammation & Cell Signaling*, **2014**, *1*, 1-10.

[5] Huigen, R. *Angew. Chem. In. Ed*. **1963**, *2*, 565-632.

membered heterocycles combining a 1,3-dipole with a dipolarophile to form an uncharged five-membered ring (Figure 1.2).

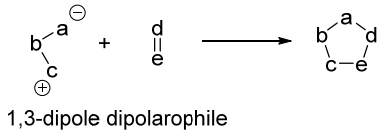


Figure 1.2

An important set of 1,3-dipoles are described in the literature[6] but without any doubt the azide functional group is the most relevant and commonly used in combination with an alkyne (Figure 1.3).

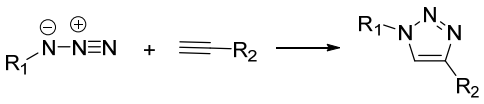


Figure 1.3

Even though this is a very efficient and straightforward methodology for the preparation of triazoles, associated drawbacks like the lack of regioselectivity (mixtures of 1,4 and 1,5 regioisomers are normally obtained), the need of long reaction time and also the use of high temperatures blocked its application until the beginning of the present century.

In 2001, the group of Sharpless reported the Click Chemistry concept.[7] This term is again an inspiration from the nature and is based in a rapid assembly of potential interesting compounds. Aside from straightforward reactions, Click Chemistry transformations must meet a set of requirements. According with the definition of Sharpless, all transformations included in the Click Chemistry concept should be carried out with:

- Available starting materials
- Simple reaction conditions (not sensitive to water or oxygen)

---

[6] Huisgen, R. *Angew. Chem. In. Ed*. **1963**, *2*, 565-632.

[7] Kolb, H. C.; Finn, M. G.; Sharples, K. B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004-2021.

- Without the use of protecting group

And the reaction should be:

- Modular
- Wide in reaction scope
- With high yields

and only inoffensive by-products, easily removable by crystallization or distillation, should be formed.

Different methodologies are included in the Click Chemistry field such as addition to multiple carbon-carbon bonds (epoxidation, dihydroxylation or aziridination), nucleophilic ring opening reactions of strained heterocycles (epoxides, aziridines), non-aldol carbonyl chemistry like formation of ureas, thioureas or hidrazones and cycloaddition reactions like Diels Alder or 1,3-dipolar cycloadditions. [8]

1.3 Cu(I)-catalyzed 1,3-dipolar cycloaddition between an alkyne and an azide (CuAAC)

In 2002, Sharpless[9] and Meldal[10] independently found out that Cu(I) is able to catalyze 1,3-dipolar cycloadditions reactions between an azide and an alkyne (Figure 1.4). This fact implied the development of a very general and useful tool for organic chemists and it contributed to the popularization of the Click Chemistry concept. This Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) provides 1,4-substituted triazoles with complete regioselectivity and is by far the most used and representative reaction belonging to Click Chemistry (to the point that both concepts tend to be mixed up in the recent literature). Meldal reported the synthesis of peptidotriazoles on solid support via Cu(I)-catalyzed 1,3-dipolar

[8] Kolb, H. C.; Finn, M. G.; Sharples, K. B. *Angew.Chem. Int. Ed*. **2001**, *40*, 2004-2021.

[9] Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew.Chem. Int. Ed*. **2002**, *41*, 2596-22599.

[10] Tornoe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem*. **2002**, *67*, 3057-3064.

cycloaddition of an azide and a peptide previously functionalized with an alkyne moiety (Figure 1.4 (b)).

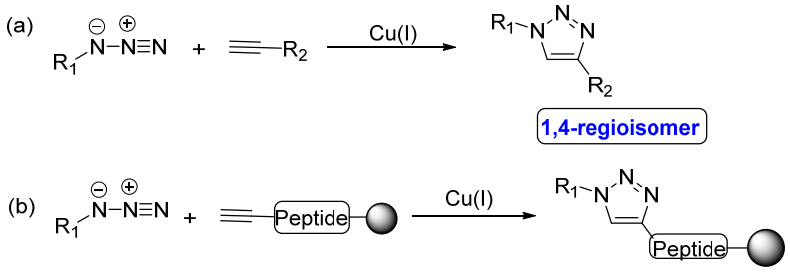


Figure 1.4

This transformation was carried out with a simple experimental procedure: low catalyst loading ($CuSO_4$, 1 mol%), in water (among other solvents) for 6 to 36 hours, at ambient temperature with high yields and complete regioselectivity. They used a Cu(I)-catalyst prepared in situ from Cu(II)-salts and a reducing agent (5-10 mol% of sodium ascorbate). The scope of this transformation was relevant because a broad range of both azides and alkynes, were employed. On the one hand, primary, secondary and tertiary, aromatic azides were used and, on the other hand, different terminal alkynes were also successfully applied. No reactivity was observed with internal alkynes (Figure 1.5).

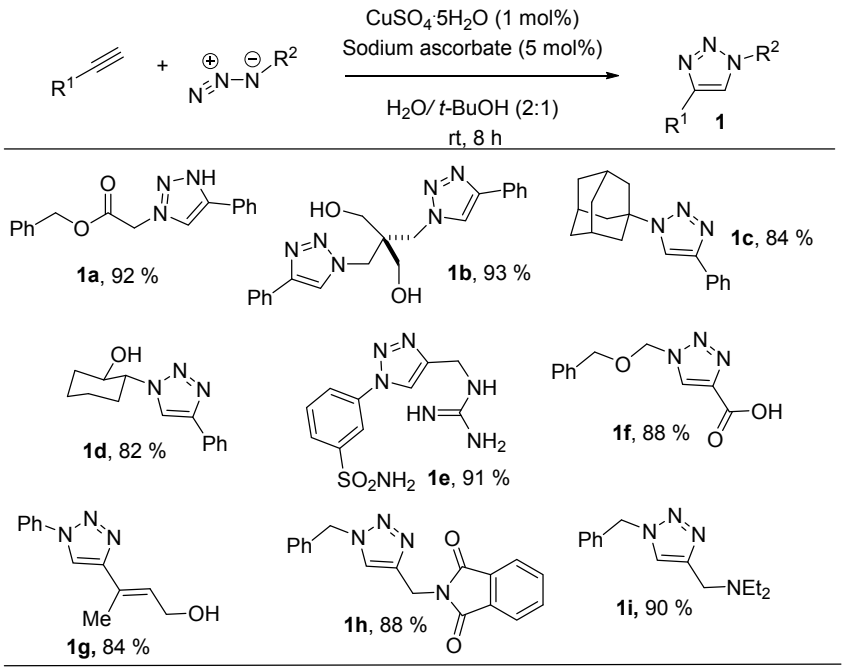


Figure 1.5

Despite the initial reluctance to use azides, probably because of safety concerns associated with their handling, nowadays they are the most popular moiety to carry out 1,3-dipolar cycloadditions. Azide functionality is special because it is stable towards water, oxygen, the most common reaction conditions (wide variety of solvents and temperature) and even inside the living cells. Both azide and alkyne, are not present in nature, they are very selective in terms of reactivity and it is really easy to introduce them into organic compounds. In this manner, exclusive reaction sites are created for further transformations. This is especially interesting when working with complex biological systems. Sharpless in 2003, reported the introduction of azide or alkyne functionalities in the coat protein of CPMV (cowpea mosaic virus, a plant virus) **2** or **3**. They followed the degree of functionalization through the fluorescein derivatives obtained after the click

reaction with the corresponding counter partner **4** or **5** (Figure 1.6).[11] They demonstrated that this methodology is also reliable for complex and real systems.

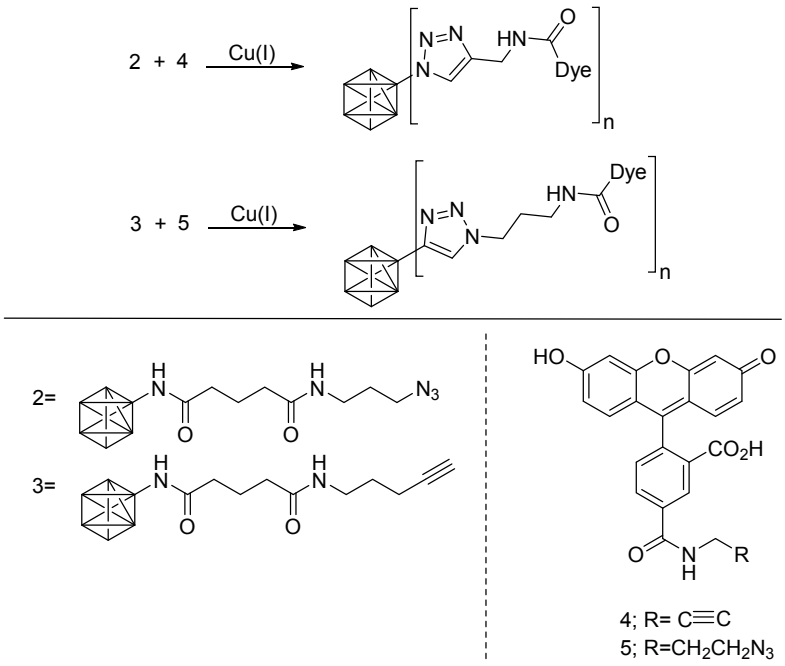


Figure 1.6

1.3.1 Proposed mechanism for CuAAC

Some time later, the same group reported a propousal stepwise mechanism for the CuAAC.[12]

[11] Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sarpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192-3193.

[12] Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210-216.

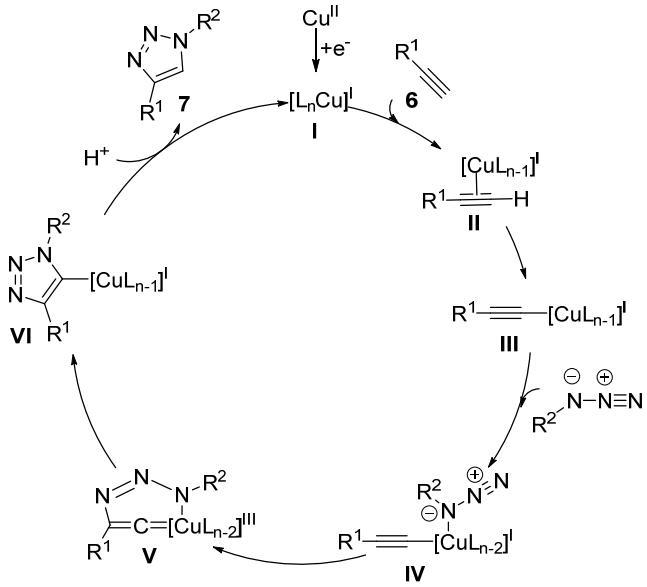


Figure 1.7

The proposed mechanism starts with the coordination of the alkyne **6** to the Cu(I) species **I** displacing one of the solvent ligands to form **II**. This step, in water, is exothermic (11.7 kcal/mol) and it is in agreement with the experimental observation that it is not necessary to use of a base for the proton abstraction; it also explains why the reaction is faster in water. The Cu-acetylide **III** is proposed as intermediate in many of C-C bond forming processes. It is postulated that the first coordination of acetylene to the Cu(I) species is necessary to induce an essential decrease in the pka, rendering a Cu(I)-acetilyde complex in aqueous media. Subsequently, they proposed a stepwise mechanism due to the high energetic barriers obtained in theoretical calculations for the concerted cycloaddition. The next step is the azide coordination to the copper (**IV)** through the displacement of another ligand. Subsequently, the more distal nitrogen attacks the C2 carbon of the acetylide, forming **V**. Next, ring contraction takes place to obtain complex **VI** and finally protodemetalation of the triazolyl copper species generates the final triazole **7**.

Later, further mechanistic investigation from the same group and others exposed that this reaction apparently elapses through dinuclear or tetranuclear Cu(I) species.[13] Indeed, the facility of copper to form aggregates is well known. Straub showed that the cycloaddition through a hypothetical mononuclear Cu-complex (Figure 1.8 (black pathway)) is disfavored because it entails much higher energetic barriers than the one obtained with the hypothetical polynuclear copper intermediates (Figure 1.8 (blue pathway)).[13c]

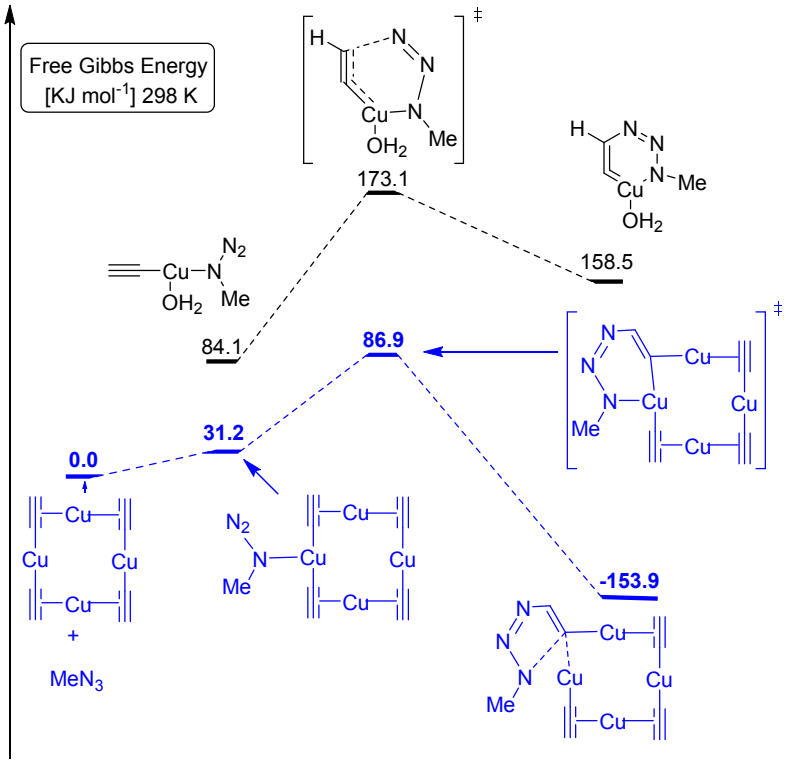


Figure 1.8

In 2013, Fokin *et al*. made a step further and proposed another catalytic cycle based on dinuclear copper species (Figure 1.9). The authors

[13] a) Rodionov, V.V.; Fokin, V. V.; Finn. M. G. *Angew.Chem. Int. Ed*. **2005**, *44*, 2210-2215. b) Ahlquist. M.; Fokin, V.V. *Organometallics* **2007**, *26*, 4389-4391. c) Straub, B. F. *Chem. Commun*. **2007**, 3868-3870.

demonstrated that the two copper atoms have different roles in the course of the reaction. They proposed first formation of σ-bond Cu-acetylide complex followed by the incorporation of the second copper atom through π-interaction forming the catalytic active species **VIII**. Subsequently, azide coordination to the triple bond takes place followed by the stepwise annulation events to obtain the triazole **9**.[14]

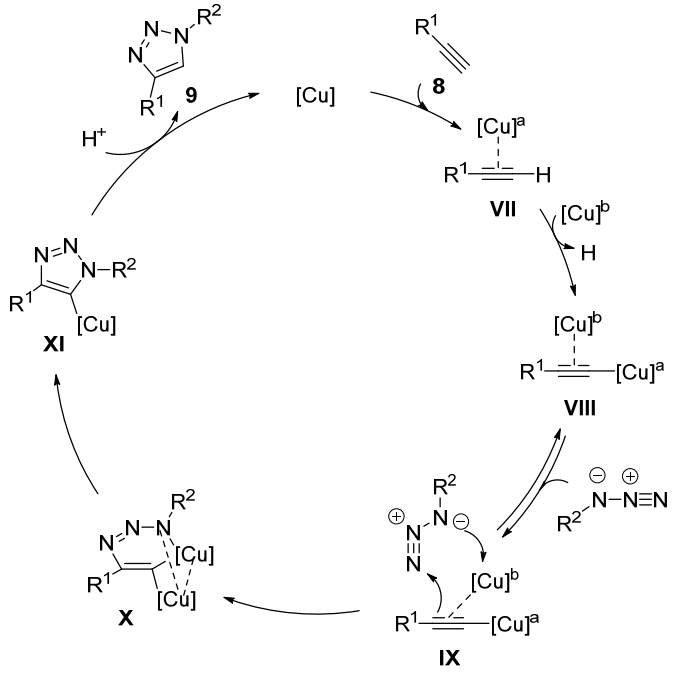


Figure 1.9

1.4 Ru(II)-catalyzed 1,3-dipolar cycloaddition between an alkyne and an azide (RuAAC)

Shortly after the impressive success of Cu(I)-catalyzed cycloaddition of alkynes and azides to afford 1,4-disubstituted 1,2,3-triazoles, the same

[14] Worrel, B. T.; Malik, J. A.; Fokin, V.V *Science,* **2013**, *340*, 457-461.

group reported the obtention of the other regioisomer (1,5-disubstituted triazoles) using the Cp*RuCl(PPh$_3$)$_2$ complex as a catalyst (Figure 1.10).[15]

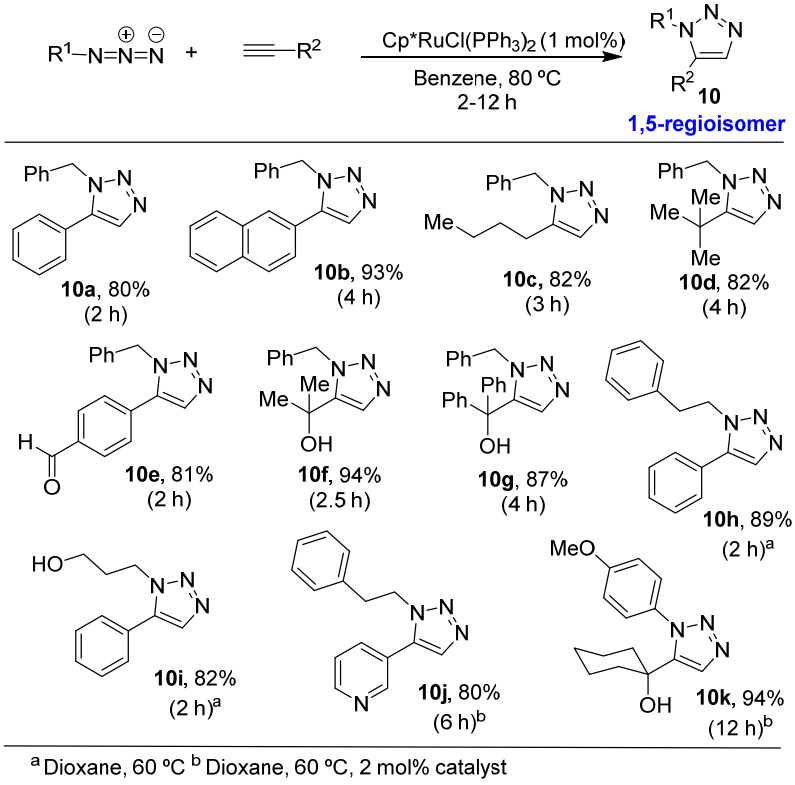


Figure 1.10

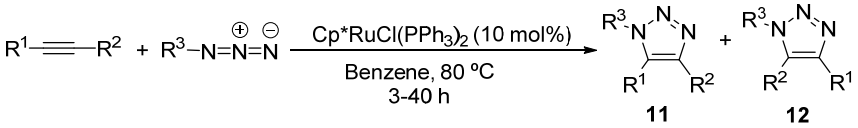
As shown in Figure 1.10, this transformation has also a wide substrate scope. Aryl and alkyl azides as well as different alkynes were successfully employed. Also different functional groups were well tolerated.

The same publication features one example with the use of an internal alkyne, but the scope with such species would be widely extended in a paper reported by Weinreb[16] in 2006. Therein, the cycloaddition reaction

[15] a) Zhang, Li.; Chen, X.; Xue, P.; Sun, H. H. Y.; Williams, I. D.; Sharpless, K. B.; Fokin, V. V.; Jia, G. *J. Am. Chem. Soc.* **2005**, *127*, 15998-15999.

[16] a) Majireck, M. M.; Weinreb, S. M. *J. Org. Chem.* **2006**, *71*, 8680-8683.

with a wide set of internal alkynes is reported, affording in general good regioselectivities (Figure 1.11).



Entry	R^1	R^2	R^3	Yield (%)	11:12 ratio
1	Ph	Me	CH_2Ph	95	38:62
2	Ph	CO_2Et	CH_2Ph	85	100:0
3	Ph	COMe	CH_2Ph	100	100:0
4	Ph	CH_2OH	CH_2Ph	70	0:100
5	Ph	$CH(OEt)_2$	CH_2Ph	75	50:50
6	Me	CH_2NEt_2	CH_2Ph	70	0:100
7	Me	*t*-Bu	CH_2Ph	15	0:100
8	Me	CH_2CH_2OH	CH_2Ph	90	23:77
9	Bu	CO_2Me	CH_2Ph	90	100:0
10	Et	COMe	CH_2Ph	90	100:0
11	Ph	Me	1-adamantyl	10	0:100

Figure 1.11

1.4.1 Proposed mechanism for RuAAC

These two papers present the same mechanistic proposal (Figure 1.12). The Ru-acetylide intermediate is unlikely and even impossible for internal alkynes. Therefore, this transformation could start by coordination of the azide and the alkyne to the ruthenium (**XII**), then carboruthenation of the alkyne takes place to produce a six-membered ruthenacycle (**XIII** or **XIV**; **XIII** is more convenient than **XIV**) that further undergoes reductive elimination providing the desired triazole **13**.

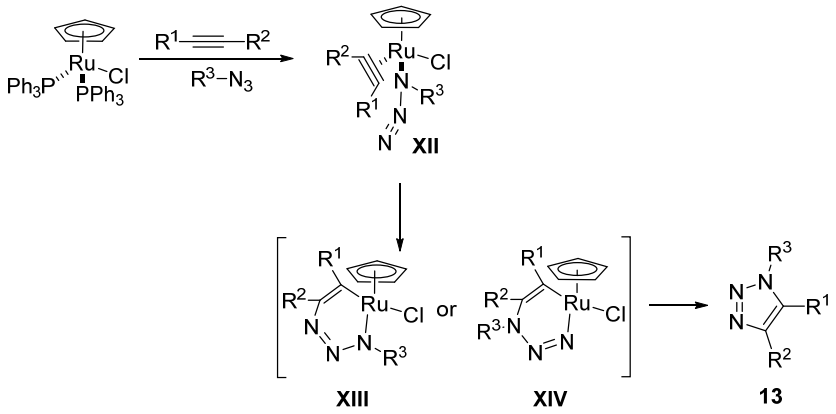


Figure 1.12

1.5 Drawbacks of Click Chemistry

Despite the fact that CuAAC has very important practical advantages such as the mild temperatures required for reactions, wide range of pH tolerance, broad substrate scope and high chemoselectivity, among others, it has also some associated disadvantages. The most important are the following:

1. Azide and alkyne have to be introduced into the target molecules when working in a biological field. Unlike the case of amines or carboxylic acids, azides and alkynes are hardly found in Nature.

2. Instability of the copper catalysts.[17] Copper(I) in aqueous solution is unstable toward disproportionation, which leads to inactive Cu(0) and Cu(II) species. It is also known that copper(I)-complexes are oxidized to Cu(II) and really reactive oxygen species such as peroxides or hydroxyl radicals. This can result, on the one hand, in a loss of active Cu(I) complex, although it has already been mentioned that some reducing agents like sodium ascorbate are added to reduce the obtained Cu(II) species. On the other hand, and probably the most important inconvenient, the formation of

[17] a) Simons, M. G. et al. *J. Chem. Soc., Dalton Trans*. **1980**, 1827-1838. b) Merrill, C. L. et al. *J. Chem. Soc., Dalton Trans*. **1984**, 2207-2211.c) Ciavatta, L.; Ferri, D.; Palombari, R. *J. Inorg. Nucl. Chem.* **1983**, *23*, 1201-1205.

extremely reactive oxygen species is an issue, since they are able to oxidize an important variety of molecules like biomolecules.

3. Copper toxicity is also a remarkable drawback when biological systems are employed. It is well known that copper is cytotoxic in micromolar concentration. Despite the fact that a lot of applications have been developed with Click Chemistry methodology, the toxicity of copper has been a significant handicap for medicine and biological applications.

1.6 Cu(I)-stabilization through protecting ligands

With the aim of solving this problem, organic chemists have developed better catalytic systems with the use of different ligands to try to stabilize Cu(I) against oxidation (Figure 1.13).[18-24]

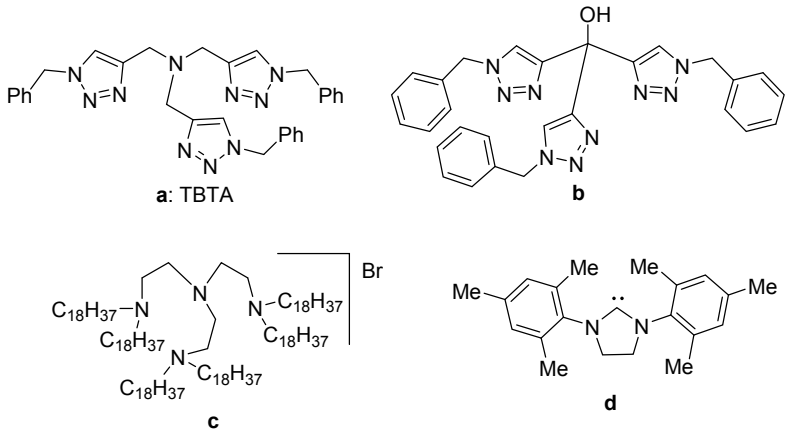


Figure 1.13

In 2004, the group of Sharpless studied the metal binding character of different ligands as well as their catalytic activity. They realized that polytriazole species could enhance the reactivity at the same time that Cu(I) was better protected in front of oxidation. Among all ligands tested, *tris*-(benzyltriazolylmethyl) amine (TBTA) (**a** in Figure 1.13) exhibited the best results in terms of reactivity and stability. Probably, their tetradentate binding ability occupying all possible coordination sites, is the responsible

for the Cu(I) stabilization.[18] Shortly after, mechanistic insights were reported revealing that in this case the prediction of the process was even more difficult that in the previous case (CuAAC without stabilizing ligands). The rate of the reaction depens on a lot of variables such as concentration of the ligand and the Cu(I), the binding affinity and the lability of the copper complexes among others.[19] More recently, the X-ray structure of Cu(I)-TBTA was reported showing a dimeric copper species (Figure 1.14). It is shown that the tertiary amine is not directly attached to the Cu atom and one triazole is the bridge between both copper atoms.[20]

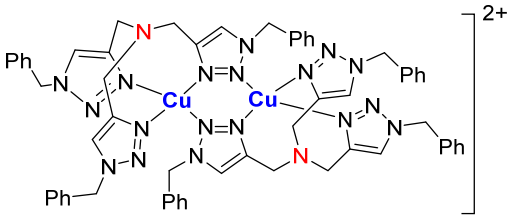


Figure 1.14

The group of Nolan also proved that [(IMes)CuBr] is also a reliable catalyst for CuAAC (**d** Figure 1.13). This catalyst meets all requirements of Click Chemistry. The excellent yields and extremely high reactivities together with the fact that this catalyst is useful both for terminal and for internal alkynes make it is a strong competitor for TBTA.[21] The following year, Straub *et al*. isolated and characterized a mononuclear Cu complex proving that at least in this case a mononuclear copper intermediate is possible for CuAAC (Figure 1.15).[22]

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[18] Chan, T. R.; Hilgraf, R.; Sharplese, K. B.; Fokin, V. V. *Org. Lett*. **2004**, *6*, 2853-2855.

[19] Rodionov, V. O.; Presolski, S. I.; Díaz, D. D. Fokin, V. V.; Finn, M. G. *J. Am. Chem. Soc*. **2007**, *129*, 12705-12712.

[20] Dannelly, P. S.; Zanatta, S. D.; Zammit, S. C. White, J. M.; Williams, S. *J. Chem. Commun*. **2008**, 2459-2461.

[21] González, S. D.; Correa, A.; Cavallo, L.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 7558-7564.

[22] Nolte, C.; Mayer, P.; Straub, B. F. *Angew. Chem. Int. Ed*. **2007**, *46*, 2101-2103.

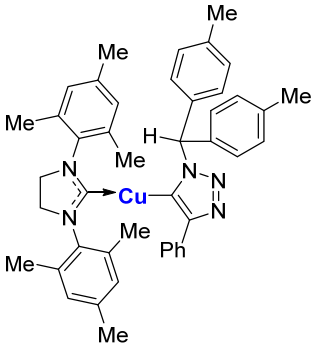

Figure 1.15

Tetradentate tripodal ligands (**c** in Figure 1.13) are another class of copper stabilizing agent. Their higher stability allows their preparation in open air conditions, improving other ligands where an in situ preparation is required. It has been shown that [Cu(C18$_6$tren)]Br (**c** in Figure 1.13) is also useful for internal alkynes, in addition to terminal ones.[23]

Our group has also developed a ligand with a powerful complexing character for Cu(I) (**b** in Figure 1.13). The ligand contains two well differentiated parts: a hydrophilic zone established by a hydroxyl group and the rest of the ligands possessing more strong hydrophobic character. The hydroxyl provides good conditions to work in water, as well as an anchoring point. This fact allows attaching the catalyst onto polymeric supports offering the possibility of easy recovering of the catalyst. This catalyst can also be easily fine-tuned by changing the nature of the azide and alkyne in a simple and efficient CuAAC reaction.[24]

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[23] Candelon, N.; Lastécouères, D.; Diallo, A. K.; Aranzaes, J. R.; Astruc, D.; Vincent, J. M. *Chem. Commun*. **2008**, 741-743.

[24] a) Özçubukçu, S.; Ozkal, E.; Jimeno, C.; Pericàs. M. A. *Org. Lett*. **2009**, *11*, 4680-4683. b) Ozkal, E.; Özçubukçu, S.; Jimeno, C.; Pericàs. M. A. *Catal. Sci. Technol*. **2012**, *2*, 195-200. c) Ozkal, E.; Llanes, P.; Bravo, F.; Ferrali, A.; Pericàs, M. A. *Adv. Synth. Catal*. **2014**, *356*, 857-869. d) Etayo, P.; Ayats, C.; Pericàs, M. A. *Chem. Commun*. **2016**, *52*, 1997-2010.

1.7 Copper-free alkyne azide cycloaddition for biological applications

The previously mentioned toxicity of copper has prevented the development in vivo applications of Click Chemistry like labeling of biomolecules or monitoring cell processes. We have previously shown that this can be partially controlled and improved by using some Cu-stabilizing ligands that prevent the interaction of the copper with the biological system (section 1.6). However, the ideal approach should consist in the development of copper free methodologies useful for in vivo applications. Recently, different possibilities have been reported using 1,3-dipolar cycloaddition reactions between an azide and an alkyne without the use of copper. Different inter- and intramolecular proposals have been developed, which are compatible with biological and medicinal chemistry.

1.7.1 Copper-free intermolecular processes

Indeed Huisgen was the pioneer for 1,3-cycloaddition reaction but the need of too high temperatures blocked the development of this methodology in 1960's. In 2004, the group of Bertozzi, reported the use of the Cu-free AAC for the selective modification of biomolecules and labeling of live cells. On the one hand, they synthesized biotinylated cyclooctyne **14** and, on the other, the modified GlyCAM-Ig (**15**; protein from Chinese hamster ovary cells) for the further AAC reaction (Figure 1.16). They realized that with the use of strained alkynes the AAC was viable (faster than with a terminal alkyne) and a good alternative to Cu(I) catalysis for biological systems without apparent cytodamage.[25]

[25] a) Agard, N. J.; Prescher, J. A.; Bertozzi, C. R. *J. Am. Chem. Soc*. **2004**, *126*, 15046-15047.

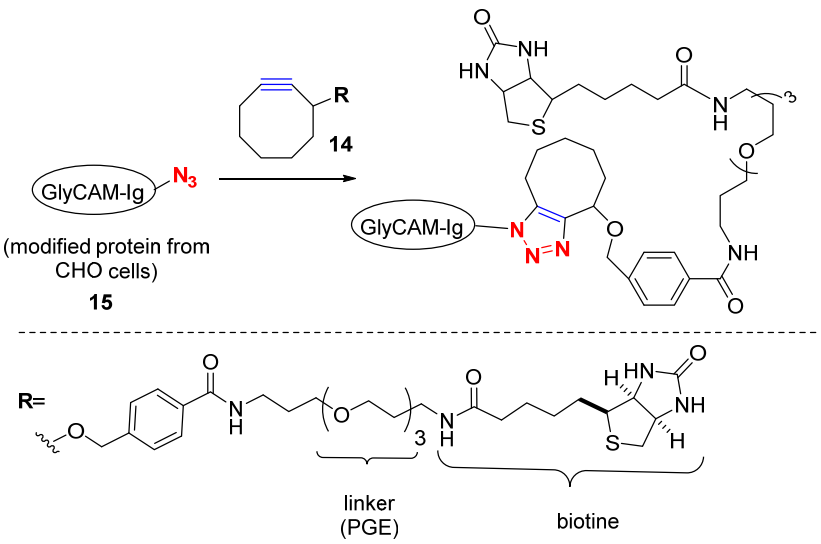
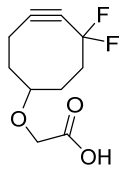


Figure 1.16

Although the transformation was feasible, the reaction was not fast and sensitive enough for useful applications (sensitivity is described as the number of azides that are reacted in a period of time). To try to circumvent these drawbacks, the same group reported that the introduction of electron withdrawing fluorine atoms in the propargylic position of the cyclooctyne (DIFO, (**16**)) accelerated up to 63 times the rate of the reaction, compared with the simple cyclooctyne (Figure 1.17).[26] The combination of ring strain and electron withdrawing groups in the adjacent carbon of the alkyne produce a drastic energy decrease in the LUMO of the alkyne, favoring the cycloaddition.

[26] a) Agard, N. J.; Baskin, J. M.; Prescher, J. A.; Lo, A.; Bertozzi, C. R. *Chem. Biol*. **2006**, *1*, 644-648. b) Baskin, J. M.; Prescher, J. A.; Laughlin, S. T.; Agard, N. J.; Chang, P. V.; Miller, I. A.; Lo, A.; Codelli, J. A.; Bertozzi, C. R. *Proc Natl. Acad. Sci. USA,* **2007**, *104*, 16793-16797.



DIFO, **16**

Figure 1.17

The in vivo labelling of molecules such as glycans, lipids or proteins in more complex systems like living cells is essential for biological chemistry (Figure 1.18). One known and useful approach is called biorthogonal reporter strategy.[26a] It consists in the introduction of the reporter (azide group) through metabolic strategies or chemical transformations and then the covalent labelling of the reporter with a probe through a selective reaction like cycloaddition with the proper cyclooctyne (e.g. DIFO). Azides are the most widely used chemical reporters because of their small size and metabolic stability. This technique helps in the labeling of targets in vivo without the requirement of genetic manipulation. Following this procedure, the Bertozzi group labeled living cells of mice and living zebrafish as well as different types of biomolecules such as glycans or lipids. They introduced the azide through the metabolism due to their stability and lack of reactivity with natural biofunctionalities. Then, labelling through 1,3-dipolar cycloaddition reaction with the strained cyclooctynes like DIFO produced a system ready to be visualized (Figure 1.18).[27]

[27] a) Chang, P. V.; Prescher, J. A.; Sletten, E. M.; Baskin, J. M.; Miller, I. A.; Agard, N. J.; Lo, A.; Bertozzi, C. R. *Proc. Nat. Acad. Sci. USA* **2010**, *107*, 1821-1826. b) Laughlin, S.; Baskin, J. M.; Amacher, S. L.; Bertozzi, C. R. *Sience* **2008**, *320*, 664-667.

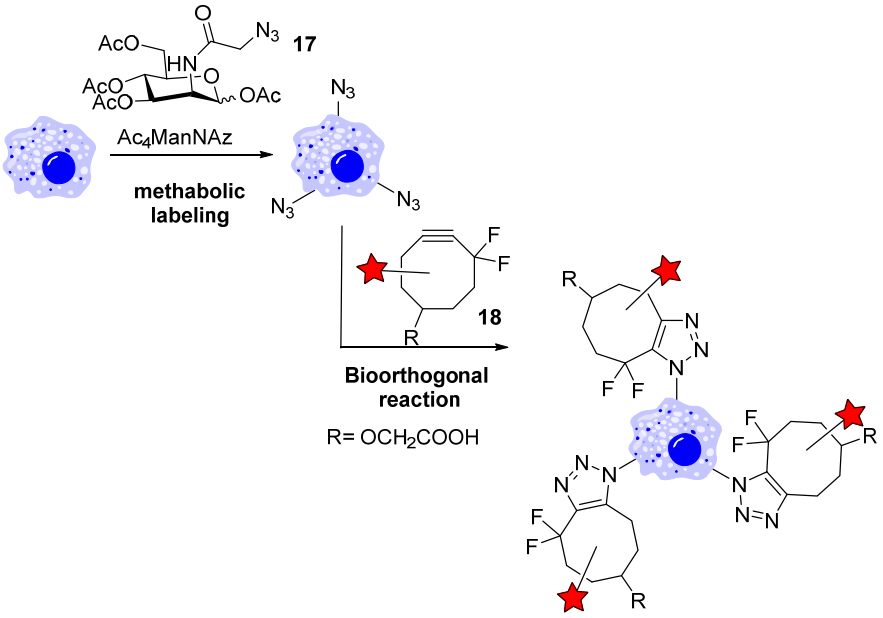


Figure 1.18

Nevertheless, this approach is not free of inconvenients: the labeling agent requires a long synthesis and low yields are obtained. Other strategies have been reported in the literature improving the alkyne moiety for the cycloaddition. In the first one, the cyclooctyne is fused with two phenyl rings with the purpose that the aromaticity of the arenes rings could enhance the reactivity of the cycloalkyne (Figure 1.19 **a**). The second one is a combination of DIFO and the previous one (Figure 1.19 **b**). It has two fluorine atoms in the carbon adjacent to the alkyne and also contains one fused benzene ring. And in the last case (Figure 1.19 **c**), the cyclooctyne possesses an amido group fused with two benzene rings. These molecules are termally stable, much more reactives in front of azides than simple cyclooctyne and their syntheses are easier. [28] In spite of the great

[28] a) Chenoweth, K.; Chenweth, D.; Goddard III, W. A. *Org. Biomol. Chem*. **2009**, *7*, 5255-5258. b) Ning, X.; Guo, J.; Wolfert, M. A.; Boon, G. *Angew. Chem. In. Ed*. **2008**, *47*, 2253-2255. c) Jewett, J. C.; Sletten, E. M.; Bertozzi, C. R. *J. Am. Chem. Soc*. **2010**, *132*, 3688-3691. d) Codelli, J. A.; Baskin, J. M.; Agard, N. J.; Bertozzi, C. R. *J. Am. Chem. Soc*. **2008**, *130*, 11468-1476.

improvement achieved, these reagents have not found general application up to date. In any case, it seems easy to predict that they will play a central role in an interesting methodology for further in vivo applications in the field of biochemistry.

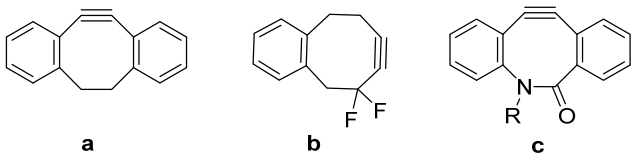


Figure 1.19

In 2010, the group of Ma reported another copper-free strategy in the solid state (Figure 1.20).[29] They exploited the known arene-perfluoroarene interactions to facilitate the 1,3-dipolar cycloaddition reaction at room temperature. Displaying the corresponding azide and alkyne in the proper position allows the 1,3-dipolar cycloaddition reaction to take place with high levels of regioselectivity towards the 1,4-triazole product. This strategy was based in an imine linkage between both arene rings, which upon hydrolysis gave rise to the triazole monomer product.

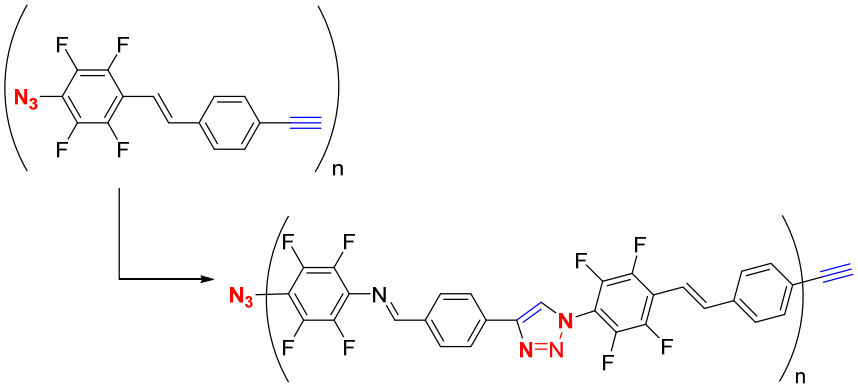


Figure 1.20

These transformations based on supramolecular interactions will offer new ways to control and promote chemical reactions.

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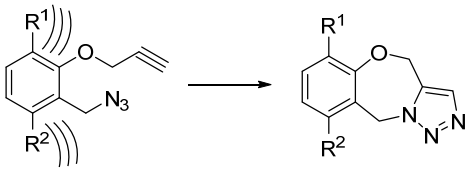
[29] Ni, B. B.; Wang, C.; Wu, H.; Pei, J.; Ma. Y. *Chem. Commun*. **2010**, *46*, 782-784.

1.7.2 Copper-free intramolecular processes

Intramolecular cycloadditions belong to a type of essential transformations.[30] They represent a really versatile strategy, providing a huge range of fused rings. Different approaches have been developed to force the cycloaddition reaction such as the use of a catalyst or high temperatures among others. The spatial distribution is another resource available that can facilitate the cycloaddition by avoiding the activation entropy related with intermolecular processes. Targets functional groups, in this case, an azide and an alkyne are already installed in the proper position to favor the reaction (Figure 1.21). An increase in the reaction rate is produced due to the more facile interaction between both functional groups when they are tethered to the same backbone.

In 1993, the group of Sharpless reported a work based on intramolecular 1,3-dipolar cycloaddition reactions between an azide and an alkyne in a simple chemical system (Figure 1.21). In this case both functional groups were linked to a benzene ring in *o*-position through two different arms.[31]



19 **20**

Figure 1.21

They also studied the steric effect of different substitution patterns, observing different result in the rate of the reaction. Having both arms in close proximity (*o*-substituted) together with the fact that R^1 and R^2 do not allow their free rotation, enhanced the reaction rate through some kind of Thorpe-Ingold effect.

---

[30] Mazzu, A.; Ku, H.; Ku, A.; Padwa, A. *J. Org. Chem*. **1978**, *43*, 66-69.

[31] Weller, D. J.; Sammes, P. G.; Sharpless, B. *Tetrahedron*, **1993**, *49*, 8179-8194.

The group of Hotha reported an intramolecular 1,3-dipolar cycloaddition reaction on carbohydrates. Sugar derivatives bearing either an azide or an alkyne functionality undergo the 1,3-dipolar cycloaddition reaction affording the corresponding chiral fused polycyclic triazole (Figure 1.22).[32]

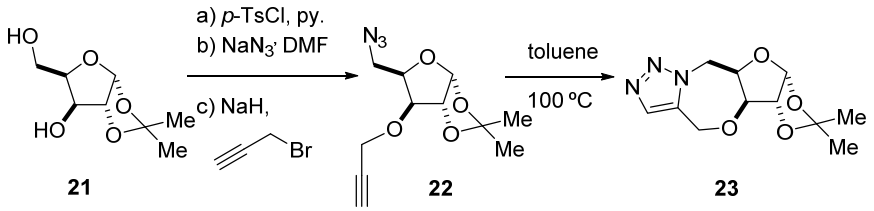


Figure 1.22

In 2006, the group of Eycken, reported the synthesis of bisbenzocyclooctadiene-aza analogues of (–)-Steganacin, (–)-Steganone displaying high antileukemic activity (Figure 1.23).

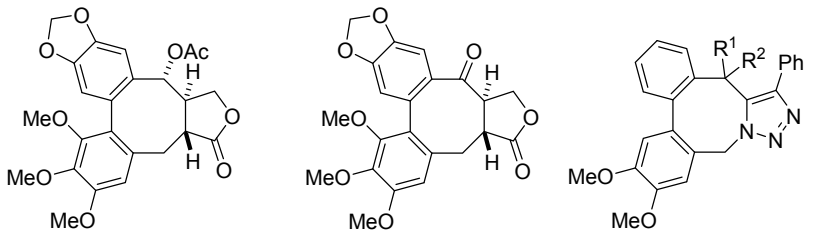


Figure 1.23

They proposed an approach for the synthesis of Steganacin and Steganone 7-aza derivatives (**26**-**27**) (Figure 1.24). This methodology consists in (a) Suzuki-Miyura coupling, (b) proper introduction of the azide and the alkyne moieties in the resulting biaryl and (c) the cycloaddition reaction.[33]

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[32] Natu, A. A.; Anegundi, R. I.; Hotha, S. *Tetrahedron Lett*. **2005**, 4585-4588. b) Anegundi, R. I.; Puranki, Puranik, V. G.; Hota, S. *Org. Biomol. Chem*. **2008**, *6*, 779-786.

[33] Beryozkina, T.; Appukkuttan, P.; Mont, N.; Eyecken, E. V. *Org. Lett*. **2006**, *8*, 487-490.

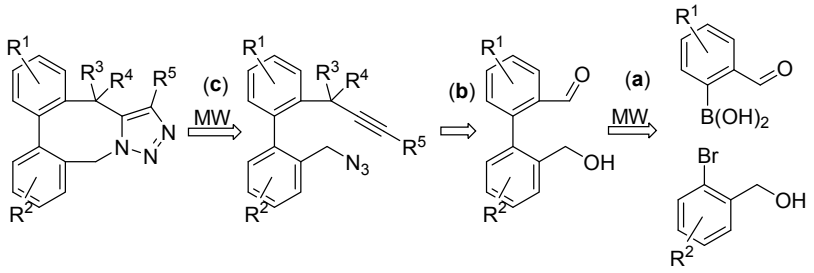


Figure 1.24

Although the synthesis is not straightforward they realized that the use of microwave irradiation enhanced both the rate of the Suzuki-Miyaura reaction and the rate of the 1,3-dipolar cycloaddition.

In 2008, our group published another intramolecular 1,3-dipolar cycloaddition reaction in the absence of copper.[34] This strategy started from the corresponding pyrrolidine-fused epoxide **28** followed by azidolysis (**29**), propargylation of the resulting alcohol **30** and finally intramolecular cycloaddition (**31**) (Figure 1.25). The sequence could be easily adapted to the preparation of enantiopure tricyclic systems by performing a Jacobsen-type desymmetrization of the starting meso epoxide **28**.

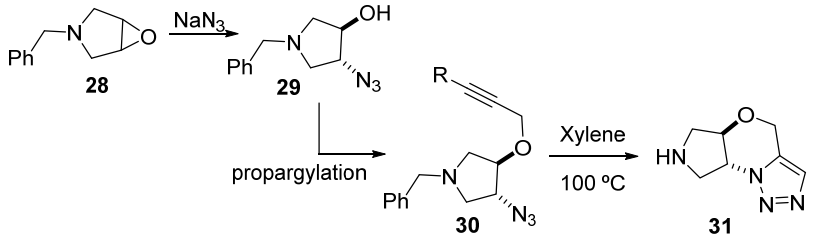


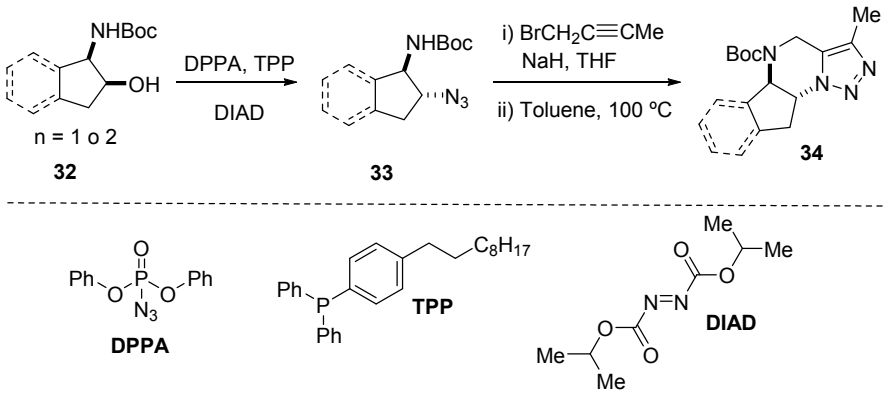
Figure 1.25

One year later, the group of Datta reported a similar investigation, using Boc-protected propargylamines instead of propargylic ethers.[35] They carried

[34] Oliva, A. I.; Christmann, U.; Font, D.; Cuevas, F.; Ballester, P.; Buschmann, H.; Torrens, A.; Yenes, S.; Pericàs, M. A. *Org. Lett*. **2008**, *10*, 1617-1619.

[35] Li, R.; Jansen, D. J.; Datta, A. *Org. Biomol. Chem*. **2009**, *7*, 1921-1930.

out a systematic research providing an important set of new heterocycles (Figure 1.26).



DPPA = diphenylphosphoryl azide, TPP = triphenylphosphine derivative,
DIAD = diisopropyl azodicarboxylate

Figure 1.26

In the same year, Taddei and co-workers, presented a microwave assisted intramolecular 1,3-dipolar cycloaddition reaction on propargyl α-azido amides **35** (Figure 1.27).[36]

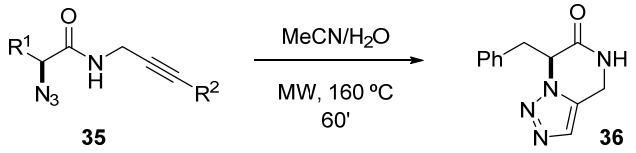


Figure 1.27

Almost simultaneously, the group of Lamaty described a sequential azidation, alkylation and intramolecular cycloaddition process starting from SES-protected aza-Baylis-Hillman β-amino ester **37** (Figure 1.28).[37]

[36] Balducci, E.; Bellucci, L.; Petricci, E.; Tafi, A.; Taddei, M. *J. Org. Chem*. **2009**, *74*, 1314-1321.

[37] Declerck, V.; Toupet, L.; Martinez, J.; Lamaty, F. *J. Org. Chem*. **2009**, *74*, 2004-2007.

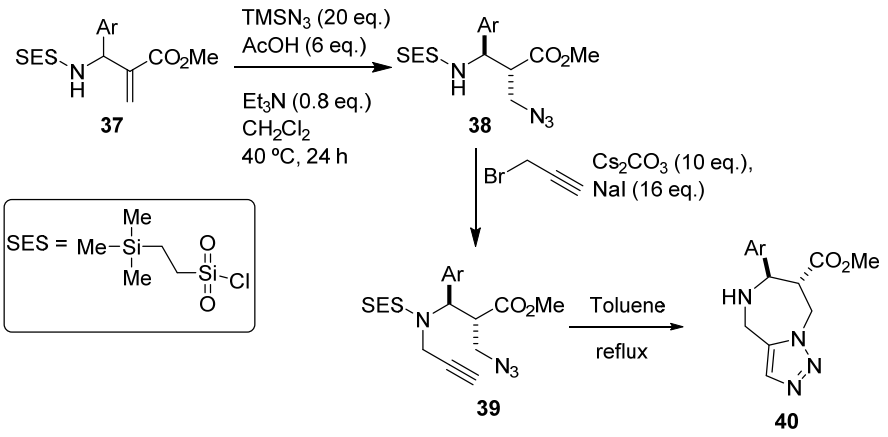


Figure 1.28

In 2010, the Panek research group used enantioenriched allenylsilanes **41** as starting materials for the preparation of fully functionalized triazoles **42** with excellent diastereoselectivities (≥ 20:1) (Figure 1.29).[38]

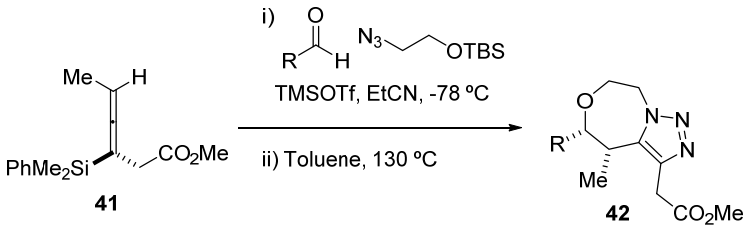
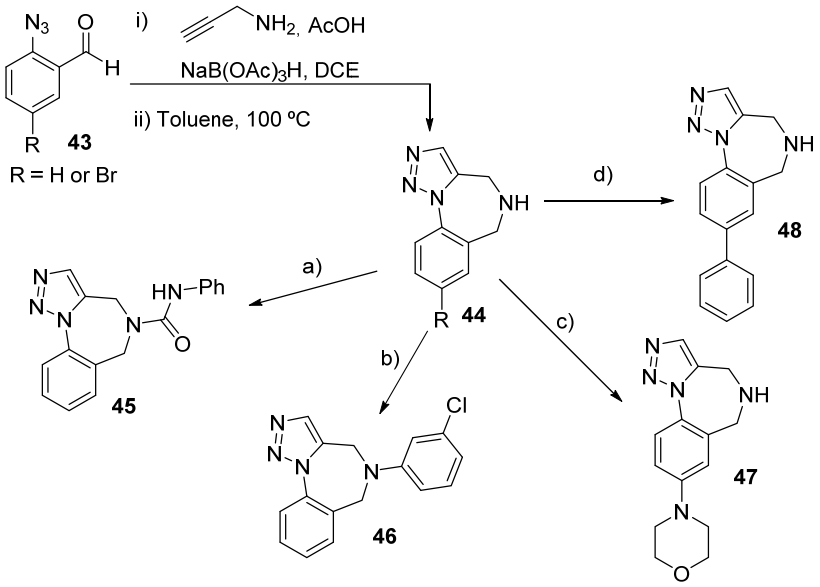


Figure 1.29

Just one year later, the Martin group reported the first obtention of 1,2,3-triazolo-1,4-benzodiazepine scaffolds **44** from α-azido benzaldehyde derivatives **43**. Interestingly, these building blocks admitted further functionalization (Figure 1.30).[39]

[38] Brawn, R. A.; Welzel, M.; Lowe, J. T.; Panek, J. S. *Org. Lett*. **2010**, *12*, 336-339.

[39] Donald, J. R.; Martin, S. F. *Org. Lett*. **2011**, *13*, 852-855.



a) PhNCO, CH_2Cl_2 b) 1-Br-3-Cl-C_6H_4, $Pd(OAc)_2$, rac-BINAP, NaO*t*-Bu, toluene, 80 ºC
c) Morpholine, $Pd(OAc)_2$, rac-BINAP, NaO*t*-Bu, toluene, 80 ºC. d) $Pd[P(t\text{-}Bu)_3]_2$)

Figure 1.30

Chapter 2. Copper-free intramolecular alkyne-azide cycloaddition

2.1 Objectives

The objectives of the research described in this chapter are the following:

1- To develop a new straightforward methodology to obtain enantiopure triazole rings fused to seven-membered heterocycles.

2- The use of Cu-free Click Chemistry to carry out the desired transformation, which should facilitate the study of the biological activity of the resulting cycloadducts.

2.2 Benzodiazepines and their derivatives

A wide range of existing drugs contain a core structure based on a series of consecutive fused rings. Different strategies have been developed for their construction but as it was already mentioned the cycloaddition reaction is one of the most useful. In particular, the 1,3-dipolar cycloaddition between and alkyne and an azide has played an important role for the synthesis of complex molecules bearing a large and sophisticate scaffolds with fused rings. Among others, benzodiazepines and derivatives are commonly used drugs for the treatment of central nervous system disorders and they are an example of structures that contain different fused rings in their cores.[40] Due to the high pharmacological activity associated to 1,4-benzodiazepines and to their economical impact, the synthesis of these compounds has gained an enormous interest in the last decades. One of the most common modification of the benzodiazepine scaffold is the introduction of another fused heterocycle. For instance, Alprazolam or Estazolam posses a triazole ring fused to the seven-membered ring of the benzodiazepine core structure (Figure 2.1). Despite the significant interest for their preparation, synthetic methods leading to them are still limited.[31, 37-39]

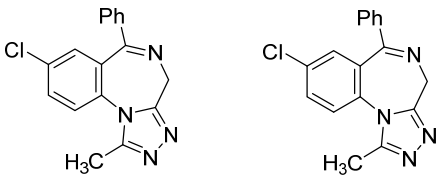


Figure 2.1

As it was already mentioned in the general introduction of Click Chemistry (Chapter 1) the ideal synthetic protocol for compounds with

[40] Villalgordo, J. M.; Pastor, A.; Cabrera, J.; Alajarín, M. *Tetrahedron Lett*. **2007**, 3495-3499.

biological applications are those avoiding the use of metals. The preparation of potentially useful scaffolds with the total warranty that not even traces of metals are present in those materials represents a significant advantage in view of the implementation of production processes. Purification for the removal of metal traces is compulsory from the regulatory point of view and often represents an important added cost.

2.3 Results and discussions

At this point, we realized that a new metal-free strategy for the synthesis of triazole-fused rings to seven-membered heterocycles could be an interesting expansion of the range of synthetic methods. Thus, we envisioned a simple and new approach starting with optically pure propargyl ethers of phenylglycidol (**50**), followed by epoxide ring opening (**51**) and 1,3-dipolar cycloaddition reaction (**52**) (Figure 2.2).[41] According to our plans, the intramolecular AAC was expected to take place without the involvement of any catalyst.

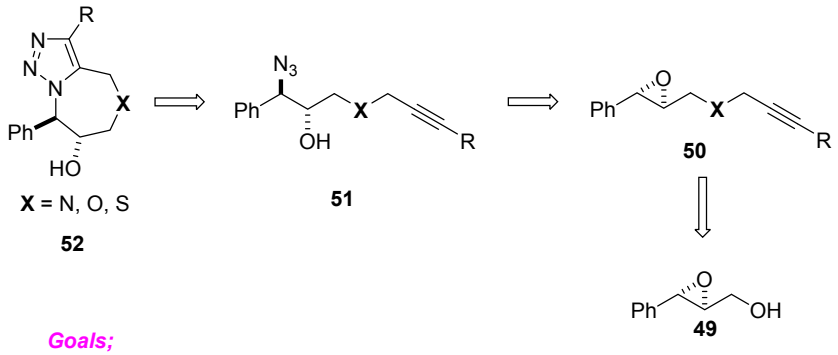


Figure 2.2

[41] Sau, M.; Escrich. C. R.; Pericàs, M. A. *Org. Lett*. **2011**, *13*, 5044-5047.

2.3.1 Synthesis of the model substrate

We chose **54** as our model substrate because it is the easiest one to prepare (Figure 2.3). The first step involves the enantioselective epoxidation of the commercially available *trans*-cinnamyl alcohol (**53**), following the classic protocol reported by Sharpless.[42] In this manner we could obtain the enantiopure phenylglycidol (**49**) in large scale (42 g) using a Labmax reactor. We next carried out the propargylation with sodium hydride and proparyl bromide to obtain the desired starting material **54**.

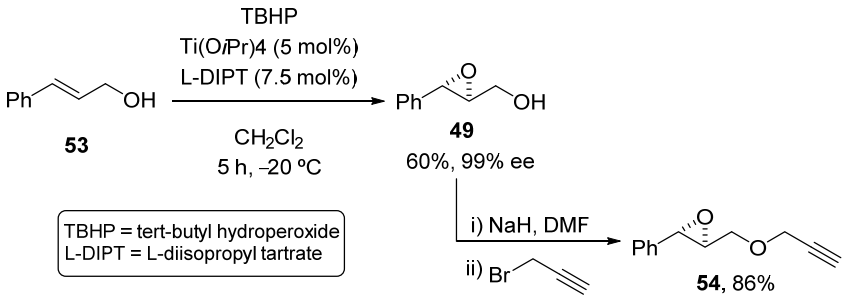


Figure 2.3

2.3.2 Optimization of the reaction conditions with 54

With a substantial amount of terminal alkyne **54** in hand, we started with the optimization of the reaction conditions for the epoxide ring opening with sodium azide (Figure 2.4). In the first tests, the azido-alcohol intermediate **55** was always observed together with the desired final product **56**. It is worth noting that **55** was never detected as the only product in the crude of the reaction mixture.

[42] Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, B. K. *J. Am. Chem.Soc*. **1987**, *109*, 5765-5780.

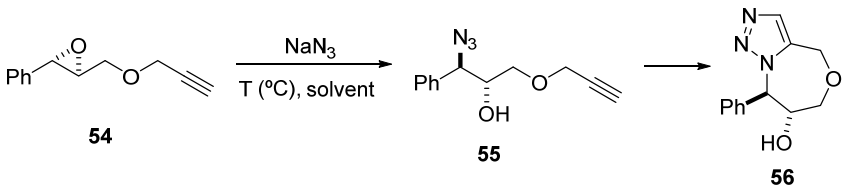
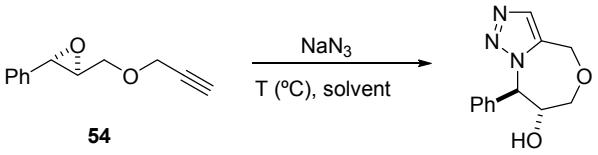


Figure 2.4

We quickly realized that this fact could play to our advantage, since with an appropriate fine tuning of reaction conditions it could be possible to carry out both reactions (azide introduction and 1,3-dipolar cycloaddition) in a one pot procedure. Thus, it would be possible to avoid the isolation of potentially dangerous organic azides **55**, increasing the safety of the process.

The optimization of the reaction conditions (Table 1) was carried out fixing the use of 1 equivalent of the model substrated (**54**) and 3 equivalents of sodium azide, to ensure that the epoxide ring opening was complete and fast. As working in a homogeneous system is preferred, polar solvents such as MeCN, DMF or *t*-BuOH/H_2O (1:1) were tested to solubilize the azide, being the latter the most convenient. At the beginning, conventional heating was used but the reaction times were much too long (entry 1 and 2). Nevertheless, employing microwave irradiation reactions were faster within the same range of temperatures (entries 3-7). As it is shown in Table 1, temperatures around 100 ºC were necessary in all the studied solvents to achieve complete conversions and good yields. With the use of the optimized reaction conditions (*t*-BuOH/water (1:1) as solvent at 110 ºC under microwave irradiation for 3 hours), 70% isolated yield was obtained for the two-step, one pot procedure (Entry 7).

Table 1. Optimization of the reaction conditions using 54



54 **56**

Entry	Solvent	T (ºC)	t	54:55:56[c] ratio (%)
1	MeCN	100[a]	12 h	100:0:0
2	*t*-BuOH/H_2O	100[a]	18 h	0:0:100
3	DMF	95[b]	30 min	100:0:0
4	*t*-BuOH/H_2O	95[b]	40 min	24:67:9
5	*t*-BuOH/H_2O	95/ 120[b]	60/ 30 min	0:18:82
6	*t*-BuOH/H_2O	95/ 120[b]	45/ 60 min	0:4:96
7	*t*-BuOH/H_2O	110[b]	3h	0:0:100

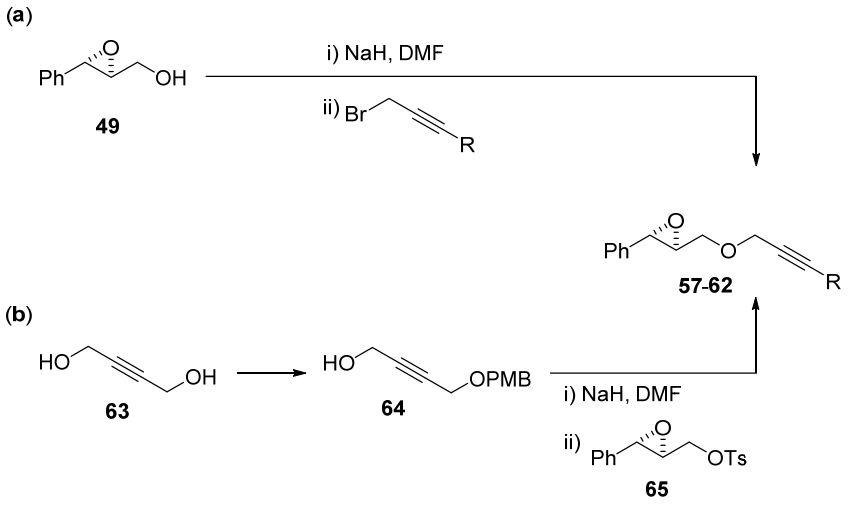
a) Normal heating. b) Microwave irradiation. c) Starting material:intermediate:product ratio, determined by ^{1}H NMR of the crude of the reaction mixture.

After the optimization carried out for the terminal alkyne we set out to test the reaction with internal alkynes.

2.3.3 Synthesis of different internal alkynes

First of all, we synthesized a set of internal alkynes. Two different synthetic methodologies were used to obtain them (Table 2). Route **a**, was the same employed for the preparation of the model substrate, using sodium hydride to deprotect the alcohol of the phenylglycidol (**49**) followed by alkylation with the corresponding propargyl bromide to obtain **57**-**60**. Route **b** entails first monoprotection of the commercially available but-2-yne-1,4-diol (**63**) with 4-methoxybenzyl chloride (PMBCl), followed by the deprotonation of the alcohol with sodium hydride and the alkylation of the phenylglycidol tosyl derivative **65** to obtain **61**-**62**.

Table 2. Starting materials with internal alkynes



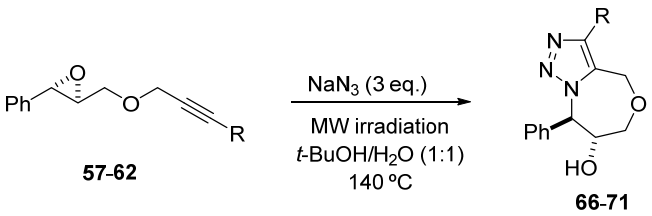
Product	R	Method	Yield[a] (%)
57	Me	**a**	80
58	Ph	**a**	78
59	1-naphthyl	**a**	80
60	*n*-pentyl	**a**	85
61	CH_2OPMB	**b**	53
62	CH_2OH	**b**[b]	74

a) Isolated yields. b) Obtained by deprotection of **61** with DDQ.

2.3.4 Scope with different internal alkynes

With ethers **57-62** in hand, the next step was to submit them to the optimized reaction conditions for the azide introduction and click reaction one pot procedure. The resultant triazolo oxepanes **66-71** were formed stereospecifically, although an increase of the reaction temperature was necessary. Thus, reaction times had to be reoptimized to obtain satisfactory yields taking into consideration that we are carrying out two consecutive reactions in one pot (Table 3).

Table 3. Scope of 1,3-cycloaddition reaction with internal alkynes



Product	R	t (min)	Yield[a] (%)
66	Me	150	60
67	Ph	90	80
68	1-naphthyl	120	68
69	*n*-pentyl	90	70
70	CH_2OPMB	90	63
71	CH_2OH	120	60

a) Isolated yields

It is worth highlighting that only one diastereomer was observed in all cases. A cristal of **70** was obtained and X-ray diffraction analysis was used to confirm the relative configuration (Figure 2.5).

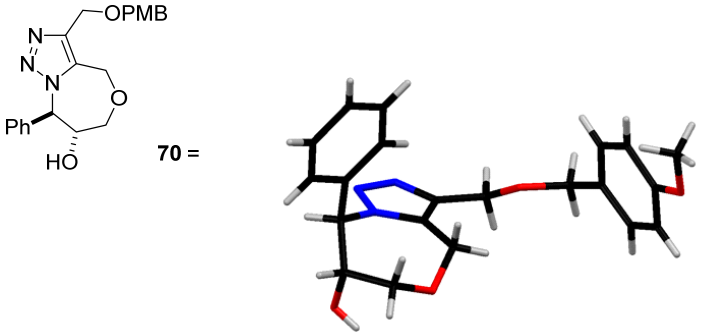


Figure 2.5

2.3.5 Synthesis of starting materials containing nitrogen and sulfur

Encouraged by previous results for both terminal and internal alkynes, we next envisioned to expand the scope of this transformation. Our idea was

to install other heteroatoms such as nitrogen or sulfur instead of the oxygen derived from the ether (Figure 2.6). With this aim, we strived to place a nitrogen or sulfur atom between the epoxide and the alkyne moieties.

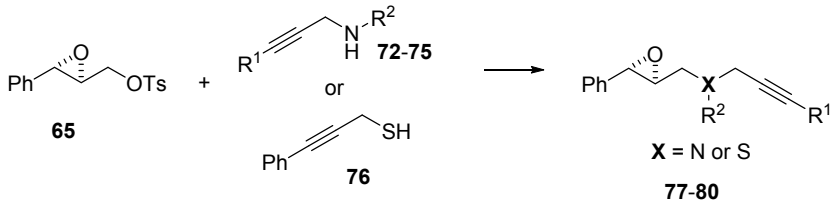


Figure 2.6

2.3.5.1 Synthesis of propargylic secondary amines (72-75) and propargylic thiol (76)

With this idea, it was first essential to synthesize a set of representative secondary propargyl amines (Figure 2.7) and a propargyl thiol (Figure 2.8). Four representative secondary propargyl amines were prepared (Figure 2.7). In the first two cases, **a** and **b** in Figure 2.7, reductive amination was used to obtain the desired propargyl amine **72** and **73**. Using benzaldehyde, formation of the undesired dialkylated product was observed, which accounts for the drop in the obtained yield (37%). In the second case, with butanal, dialkylation was never observed and as a consequence the yield was higher (65%). In Figure 2.7**c**, a simple acylation of propargylamine with acetyl chloride takes place to obtain **74**, whereas process **d**, is a copper catalyzed three component coupling under microwave irradiation following a procedure described in the literature (**75**).[43]

[43] Pereshivko, O. P.; Peshkov, V. A.; Van der Eycken, E. V. *Org. Lett*. **2010**, *12*, 2638-2641.

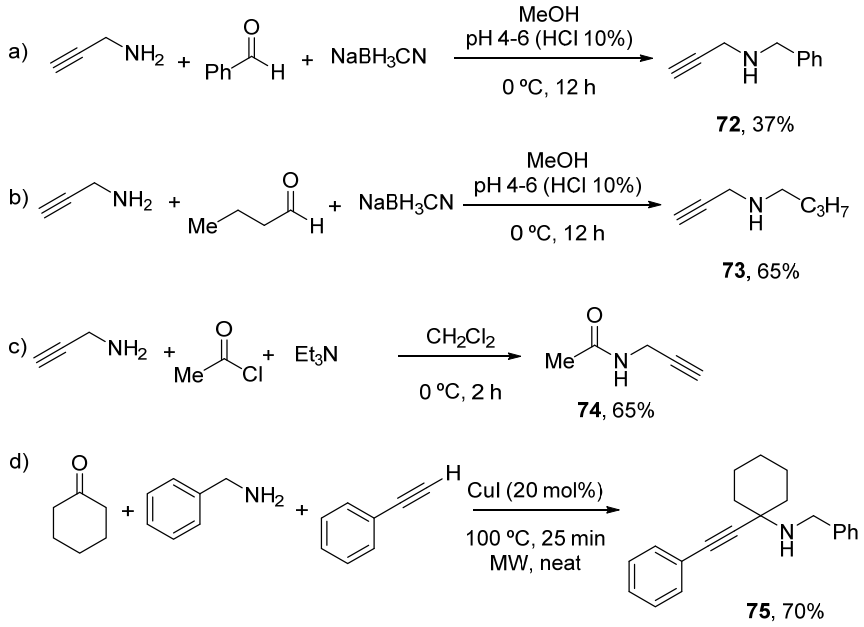


Figure 2.7

Next, the preparation of phenylpropargyl thiol **76** was carried out from the corresponding chloride **81** and thiourea (**82**), following a procedure reported in the literature.[44] Although a mixture of the desired product with little amounts of disulfide **83** was always observed (Figure 2.8).

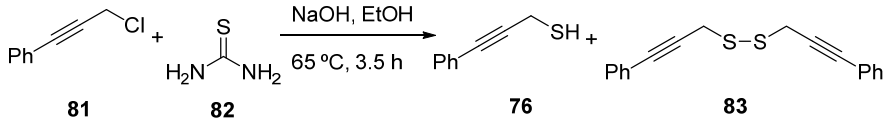


Figure 2.8

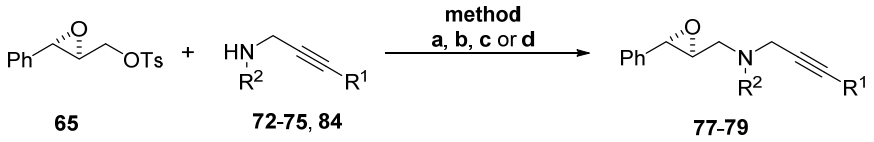
2.3.5.2 Synthesis of arylglycidol-derived propargylic amines and thiols

With the secondary amines **72-75** and the phenylpropargyl thiol (**76**) in hand, the next step was to assemble them with the phenylglycidyl *p*-toluenesulfonate (**65**) to form the desired starting materials. In the case of

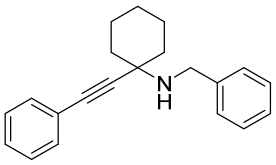
[44] Zheng, Y. F.; Oehlschlager, C. A.; Georgopapadakou, H. N.; Hartman, G. P.; Scheliga, P. *J. Am. Chem. Soc*. **1995**, *117*, 670-680.

the amines, four different strategies were used to this end; **a**, **b**, **c** or **d** method (Table 4).[45]

Table 4. Starting materials with propargyl amines



65 **72-75**, **84** **77-79**

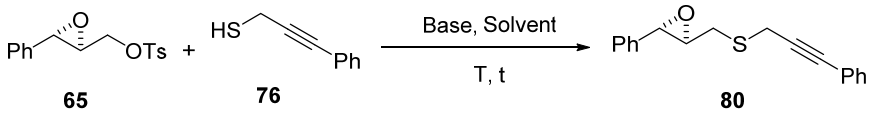
Amine	Method used	R^1	R^2	Product (Yield[e](%))
84	**a**	H	H	**77** (20)
72	**a**	H	CH_2Ph	**78** (70)
73	**a**	H	C_4H_9	**79** (80)
74	**a, b, c**	H	Ac	0
75	**a, d**			0

Method a) KI, DMF, 3 days. **Method b**) KOH, TBAI, THF, rt, 12 h. **Method c**) NaH, DMF, rt, 12 h. **Method d**) Et_3N, MW, 100 ºC. e) Isolated yields.

For the preparation of thioethers, three different sets of conditions were employed: **e**, **f** or **g** method using the mixture obtained in the propargyl thiol preparation (**76**+**83**) (Table 5). The best conditions (entry 3) involved the use of an aqueous solution of NaOH and toluene while heating the reaction mixture at 40 ºC for 3.5 h.

[45] Thurner, A.; Faigl, F.; László, T.; Mordini, A.; Valacchi, M.; Reginato, G.; Czira, G. *Tetrahedron* **2001**, *57*, 8173-8180.

Table 5. Starting materials with propargyl thioethers



65 **76** **80**

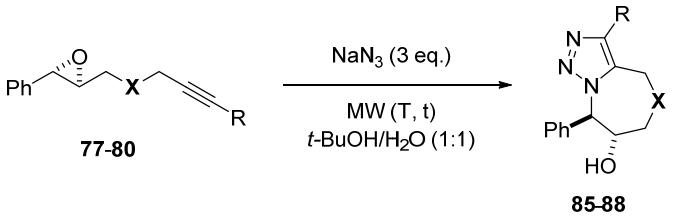
Entry	Base	Solvent	T (ºC)	t (h)	Yield [a] 80 (%)
1	Et_3N	CH_2Cl_2	0	12	0
2	NaH	THF	0	3.5	0
3	NaOH, (n-Oct)$_4$NBr	H_2O/Toluene	40	3.5	76

a) Isolated yields

2.3.6 Scope with starting materials containing nitrogen and sulfur

With our desired starting materials **77-80** in hand, we then set out to study the azide introduction and cyclization in one pot procedure. Initially, these starting materials were submitted to the previously optimized reaction conditions, albeit some parameters (namely, temperature and time) had to be reoptimized for the achievement of satisfactory yields (Table 6).

Table 6. Two-step one pot procedure with different heteroatoms



77-80 **85-88**

Product	X	R	T (ºC)	t (min)	Yield [a] (%)
85	NH	H	110	150	60
86	NBn	H	130	180	70
87	NBu	H	130	180	85
88	S	Ph	140	90	53

a) Isolated yields

As shown in Table 6, for the propargyl amine derivative starting materials good yields were obtained although the temperature had to be fine-tuned for each *N*-protecting group. The thioether starting material being an internal alkyne, required temperatures even a little bit higher to get full conversions, but only moderate yields were obtained anyway (53%).

2.3.7 Expanding the scope with larger size heterocycles

Encouraged by these good results, we thought to expand the reaction scope focusing our attention on the synthesis of heterocycles with larger ring size.

2.3.7.1 Synthesis of starting material

To try the reaction for the formation of a triazole system fused to a larger heterocycle, the corresponding starting material was first prepared (Figure 2.9). The employed methodology was the alkylation with phenylglycidyl tosylate (**65**) of 5-hexyn-1-ol (**89**) under Williamson conditions to afford **90** in 73% yield.

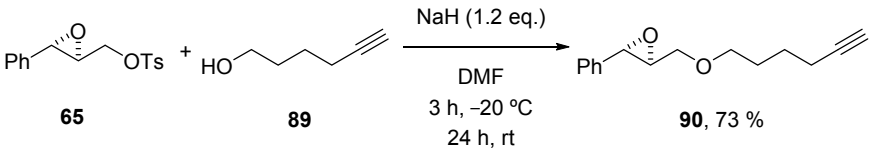
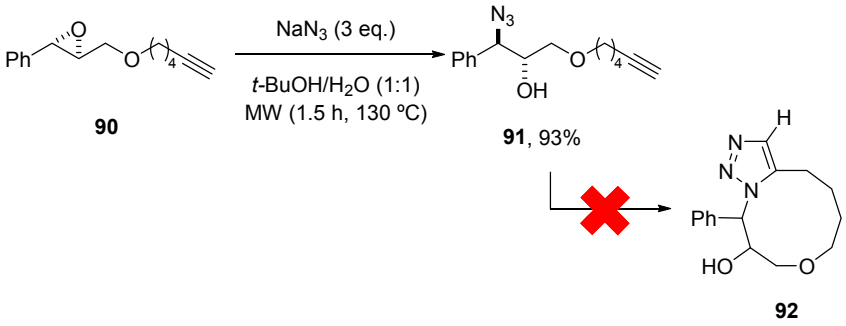


Figure 2.9

2.3.7.2 Azide introduction and click reaction for the preparation of triazoles fused to ten-membered heterocyclic rings

With **90** in hand, we set out to study the desired azide substitution and 1,3-cycloaddition reaction (Figure 2.10). Although different attempts were tried, we were never able to observe the triazole fused to the ten-membered ring. Indeed, the two-step one pot procedure with and without copper, as

well as the reaction in two steps, were tested without success. The only product observed was the intermediate **91**, isolated in 93% yield, but the cyclization product **92** was never observed.



90 **91**, 93% **92**

Figure 2.10

2.4 Conclusions

- An efficient intramolecular metal-free cycloaddition reaction for the generation of triazole fused to seven members heterocycles has been developed.

- The procedure allows the introduction of an azide and the 1,3-dipolar cyclization in a one pot transformation under microwave irradiation using simple precursors.

- A wide substrate scope was achieved and the resulting molecules are stable.

- The molecules obtained were submitted to initial biological studies by Laboratorios Esteve, S. A. but, unfortunately their biological activity discouraged further investigations.

2.5 Experimental section

2.5.1 General considerations

Reagents. Reagents were weighed in open air. All reagents were purchased and directly used from commercial sources. Flash column chromatography was carried out with ultra pure silica gel flash 60 (230-240 mesh)

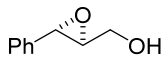
Analytical methods. ^{1}H NMR, ^{13}C NMR and melting point, where applicable, are attached for all compounds. ^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz and 400 MHz Bruker apparatus at 20 ºC. All NMR spectra are presented in part per million (ppm) and were measured relative to the signal of $CHCl_3$ (7.27 ppm in the case of ^{1}H NMR and 77.0 ppm for the ^{13}C NMR). All ^{13}C NMR were obtained with ^{1}H decoupling. Coupling constants (*J*), are reported in hertz. Melting points were measured using open glass capillaries in a Mettler Toledo MP70 apparatus. Infrared spectra were carried out on a Bruker Tensor 27. Mass spectra were recorded on a Waters LCT Premier spectrometer.

2.5.2 Synthesis of starting materials

2.5.2.1 Large scale synthesis of (2*S*,3*S*)-phenylglycidol (49)[42]

In a Labmax reactor, at room temperature, molecular sieves (30 g) were introduced, followed by the addition of dry CH_2Cl_2 (3 L), via canula. The system was cooled down to –20 ºC. Then, L-diisopropyl tartrate (DIPT) (4.9 mL, 23.6 mmol) was introduced via canula, washing with additional dry CH_2Cl_2 (20 mL) and followed by the addition of titanium (IV) isopropoxide (4.6 mL, 15.7 mmol) and *tert*-butyl hydroperoxide (TBHP) (79 mL, 630 mmol) with Teflon canula. The resulting mixture was stirred for 1 h at –20 ºC. Then, *trans*-cinnamyl alcohol (42.2 g, 315 mmol) was transferred via canula over 1 h. In this step, the additional rate must be controlled in order

to avoid the reaction mixture to warm up. The reaction was stirred at –20 ºC for 4 h following the reaction progress by TLC. The reaction was quenched with a solution containing NaOH (2.5 g) and NaCl (2.5 g) in water (25 mL) and diethyl ether (330 mL). The system was warmed up to 10 ºC over 25 min and stirred at this temperature for additional 10 min. Then, Celite and $MgSO_4$ were added and the mixture was warmed up to 25 ºC over 10 min and stirred at this temperature for 10 min more. At this point, the reaction mixture was filtered through Celite, washed with diethyl ether and the filtrate was concentrated under reduced pressure, yielding a yellow oil which contained the epoxide with excess of TBHP. TBHP was then removed by azeotropic distillation with toluene yielding a yellow oil which became solid slowly. Finally, the product was purified by crystallization from hexanes/Et_2O (1:1), yielding **49** in 73% (34.4 g, 0.637 mols) as a pale yellow powder. As the enantiomeric excess of **49** was 97%, it was recrystallized again with hexanes/Et_2O (1:1) obtaining 60% yield (28.4 g, 0.526 mols) of the enantiopure product (**49**) (99.9% ee).



49

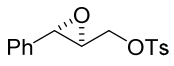
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52-7.20 (m, 5H), 4.18 (dd, J = 13.1, 3.2 Hz, 1H), 3.95 (d, J = 3.2 Hz, 1H), 3.81 (dd, J = 13.1, 5.0 Hz, 1H), 3.25-3.32 (m, 1H), 2.24 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.5, 128.5, 128.3, 125.7, 62.5, 61.2, 55.6 ppm.

2.5.2.2 Synthesis of (2*S*,3*S*)-3-phenyl-2-tosyloxymethyloxirane (65)[46]

Triethylamine (3.3 mL, 22.6 mmol) and 4-dimethylaminopyridine (DMAP) (199 mg, 1.55 mmol) were introduced in a flame-dried flask under

[46] Marcos, R.; Rodríguez-Escrich, C.; Herrerías, I.; Pericàs. M. A. *J. Am. Chem. Soc*. **2008**, *130*, 16838.

argon. A solution of tosyl chloride (2.8 g, 14.6 mmol) in dry CH_2Cl_2 (60 mL) was added to the mixture and cooled to –20 ºC. Then, a solution of (2*S*,3*S*)-3-phenyl-2,3-epoxipropan-1-ol (**49**) (2.0 g, 13.3 mmol) in dry CH_2Cl_2 (4 mL) was added and the solution was stirred for 16 h at this temperature. Afterwards, the reaction mixture was washed with 10% aqueous tartaric acid solution (3 x 5 mL), saturated aqueous $NaHCO_3$ solution (3 x 5 mL) and brine (3 x 5 mL). The organic phase was dried with anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The solid obtained was purified by flash column chromatography on silica get treated with Et_3N 2.5% (hexanes/EtOAc (80:20)). The desired product was obtained as a white solid in 82% yield (3.3 g, 12.5 mmol)



65

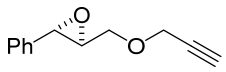
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, J = 8.4 Hz, 2H), 7.37-7.19 (m, 7H), 4.33 (dd, J = 11.4, 3.6 Hz, 1H), 4.14 (dd, J = 11.4, 5.8 Hz, 1H), 3.75 (d, J = 2.2 Hz, 1H), 3.24 (ddd, J = 5.8, 3.6, 2.2 Hz, 1H), 2.45 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.2, 135.5, 132.6, 130.0, 128.6, 128.5, 128.0, 125.7, 69.4, 58.5, 56.4, 21.7 ppm.

2.5.2.3 Synthesis of phenylglycidyl propargyl ethers (54, 57-62)

General procedure I[46]

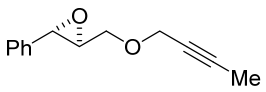
A solution of (2*S*,3*S*)-phenylglycidol (**49**) (500 mg, 3.33 mmol) in DMF (6 mL) was added dropwise to a suspension of NaH (96 mg, 4.0 mmol) in DMF (8 mL) under nitrogen at –20 ºC. The reaction mixture was stirred for 20 min, then a solution of the corresponding propargylic halide (4.3 mmol) was added dropwise and the reaction mixture was stirred at –20 ºC for 3 h and at room temperature overnight. The reaction was quenched with water (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic solvents were washed with brine (75 mL), dried over anhydrous Na_2SO_4,

filtered and removed under reduced pressure. Purification by flash column chromatography on silica gel afforded the desired products **54**, **57**-**62**.



54

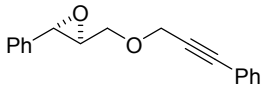
(2*S*,3*S*)-2-Phenyl-3-((prop-2-yn-1-yloxy)methyl)oxirane (54). General procedure **I** was followed using propargyl bromide (482 μL, 4.33 mmol). Column chromatography: silica gel (hexanes/EtOAc (90:10), R_f = 0.40). Pale yellow oil, yield = 86% (540 mg). $[\alpha]_D$: −81.0 (*c* 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.25 (m, 5H), 4.26 (d, *J* = 2.4 Hz, 2H), 3.92 (dd, *J* = 11.4, 3.1 Hz, 1H), 3.82 (d, *J* = 2.0 Hz, 1H), 3.70 (dd, *J* = 11.4, 5.3 Hz, 1H), 3.24 (m, 1H), 2.47 (t, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.0, 128.9, 128.7, 126.1, 79.6, 75.3, 69.7, 61.0, 58.9, 56.2 ppm. IR (neat, cm^{-1}): 2857, 1461, 1099. MS (ESI+) *m/z* (%) 211 (M+Na). HRMS *calcd*. for ($C_{12}H_{12}NaO_2$): 211.0735, *found* 211.0727.



57

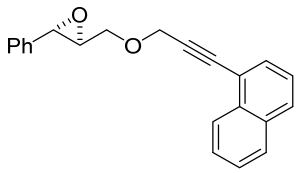
(2*S*,3*S*)-2-((But-2-yn-1-yloxy)methyl)-3-phenyloxirane (57). General procedure **I** was followed using 1-bromo-2-butyne (391 μL, 4.33 mmol). Column chromatography: silica gel (hexanes/EtOAc (90:10), R_f = 0.45). Pale yellow oil, yield = 80% (538 mg). $[\alpha]_D$: −68.0 (*c* 0.11, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 4.21 (m, 2H), 3.87 (dd, *J* = 11.6, 3.3 Hz, 1H), 3.81 (d, *J* = 2.0 Hz, 1H), 3.68 (dd, *J* = 11.6, 5.2 Hz, 1H), 3.23 (m, 1H), 1.85(dd, *J* = 2.6, 2.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.8, 128.4, 128.2, 125.7, 83.0, 74.7, 69.2, 60.8, 59.1, 55.9, 33.6

ppm. IR (neat, cm^{-1}): 2920, 2242, 1707. MS (IC) *m/z* (%) 203 (M+H). HRMS *calcd*. for ($C_{13}H_{15}O_2$): 203.1072, *found* 203.1082.



58

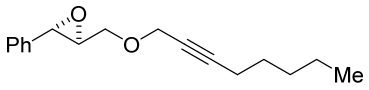
(2*S*,3*S*)-2-Phenyl-3-(((3-phenylprop-2-yn-1-yl)oxy)methyl)oxirane (58). General procedure **I** was followed using 3-chloro-1-phenyl-1-propyne (595 μL, 4.33 mmol). Column chromatography: silica gel (hexanes/EtOAc (90:10), R_f = 0.45). Yellow oil, yield = 78% (686 mg). $[\alpha]_D$: –35.9 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49-7.26 (m, 10H), 4.48 (m, 2H), 3.98 (dd, *J* = 11.4, 3.3 Hz, 1H), 3.85 (d, *J* = 2.0 Hz, 1H), 3.77 (dd, *J* = 11.4, 5.0 Hz, 1H), 3.28 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.1, 132.4, 132.1, 128.9, 128.8, 128.6, 126.1, 122.8, 87.1, 84.9, 69.8, 61.1, 59.7, 56.3 ppm. IR (neat, cm^{-1}): 2925, 2223, 1280. MS (IC) *m/z* (%) 265 (M+H). HRMS *calcd*. for ($C_{18}H_{17}O_2$): 265.1229, *found* 265.1231.



59

(2*S*,3*S*)-2-(((3-Naphthalen-1-yl)prop-2-yn-1-yl)oxy)methyl)-3-phenyloxirane (59). General procedure **I** was followed using 1-(3-bromo-1-propynyl)naphthalene (979 mg, 4.00 mmol). Column chromatography: silica gel (hexanes/EtOAc (95:5), R_f = 0.20). Yellow oil, yield = 80% (839 mg). $[\alpha]_D$: –53.3 (*c* 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35-7.25 (m, 12H), 4.63 (s, 2H), 4.05 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.87 (d, *J* = 2.0 Hz, 1H), 3.84 (dd, *J* = 11.4, 5.3 Hz, 1H), 3.31 (m, 1H) ppm. ^{13}C NMR (101

MHz, $CDCl_3$): δ 136.7, 133.3, 133.1, 130.6, 129.0, 128.5, 128.3, 128.2, 126.8, 126.4, 126.0, 125.7, 125.1, 120.1, 89.4, 84.8, 69.5, 60.8, 59.5, 55.9 ppm. IR (neat, cm^{-1}): 2897, 2852, 1355, 1104. MS (IC) *m/z* (%) 337 (M+Na). HRMS *calcd*. for ($C_{22}H_{18}NaO_2$): 337.1204, *found* 337.1201.



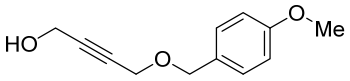
60

(2*S*,3*S*)-2-((Oct-2-yn-1-yloxy)methyl)-3-phenyloxirane (60). General procedure **I** was followed using 1-chloro-2-octyne (672 µL, 4.33 mmol). Column chromatography: silica gel (hexanes/EtOAc (95:5), R_f = 0.25). Pale orange oil, yield = 85% (728 mg). $[\alpha]_D$: –59.2 (*c* 0.14, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.25 (m, 5H), 4.25-4.22 (m, 2H), 3.87 (dd, *J* = 11.5, 3.4 Hz, 1H), 3.81 (d, *J* = 2.0 Hz, 1H), 3.68 (dd, *J* = 11.5, 5.3 Hz, 1H), 3.26-3.21 (m, 1H), 2.25-2.17 (m, 2H), 1.57-1.46 (m, 2H), 1.41-1.24 (m, 4H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.9, 128.5, 128.3, 125.7, 87.8, 75.4, 69.2, 60.9, 59.2, 56.1, 31.1, 28.3, 22.2, 18.8, 14.0 ppm. IR (neat, cm^{-1}): 2955, 2931, 2852, 1461, 1094. MS (ESI) *m/z* (%) 281 (M+Na). HRMS *calcd*. for ($C_{17}H_{22}NaO_2$): 281.1517, *found* 281.1510.

4-((4-Methoxybenzyl)oxy)but-2-yn-1-ol (64).[47] A solution of 2-butyn-1,4-diol (**63**) (200 mg, 2.32 mmol) in DMF (3 mL) was added dropwise to a suspention of NaH (28 mg, 1.16 mmol) in DMF (2 mL) under nitrogen at 0 ºC for 30 min. Then, TBAI (43 mg, 0.12 mmol) and PMBCl (157 µL, 1.16 mmol) were added and the mixture was stirred overnight at room temperature. The reaction was quenched with water (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (75 mL), dried over anhydrous Na_2SO_4, filtered and concentrated

[47] Ashfeld, B. L.; Martin, S. F. *Tetrahedronn* 2006, 62, 10497-10506.

under reduced pressure. Purification by flash column chromatography (hexanes/EtOAc (60:40), R_f = 0.35) on silica gel afforded the desired product **64** as a yellow oil in 58% yield (140 mg).

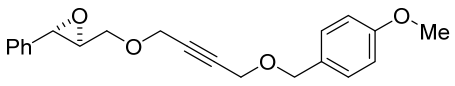


64

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.27 (m, 2H), 6.91-6.87 (m, 2H), 4.53 (s, 2H), 4.33 (s, 2H), 4.18 (t, J = 1.77 Hz, 2H), 3.81 (s, 3H), 1.79 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 129.7, 129.3, 113.8, 84.7, 81.8, 71.3, 57.0, 55.3, 51.1 ppm. IR (neat, cm^{-1}): 3400, 2935, 2838, 1611, 1512. MS (IC) *m/z* (%) 229 (M+Na). HRMS *calcd*. for ($C_{12}H_{14}NaO_3$): 229.0841, *found* 229.0841.

(2*S*,3*S*)-2-(((4-((4-Methoxybenzyl)oxy)but-2-yn-1-yl)oxy)methyl)-3-phenyloxirane (61).[48] A solution of **64** (140 mg, 0.68 mmol) in DMF (1.2 mL) was added dropwise to a suspension of NaH (23 mg, 0.95 mmol) in DMF (2 mL) under nitrogen at –20 ºC for 20 min. Then, a solution of (2*S*,3*S*)-3-phenyl-2-tosyloxymethyloxirane (**65**) (248 mg, 0.81 mmol) in DMF (1.5 mL) was added dropwise and the reaction mixture was stirred for 3 h at –20 ºC and then at room temperature overnight. The reaction was quenched with water (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic phase were washed with brine (75 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (hexanes/EtOAc (80:20), R_f = 0.40) on silica gel afforded the desired product as a pale yellow oil in 53% yield (120 mg).

[48] Dittmer, D. C.; Discordia, R. P.; Zhang, Y.; Murphy, C. K.; Kumar, A.; Pepito, S. A.; Wang, Y. *J. Org. Chem*. **1993**, *58*, 718-731.

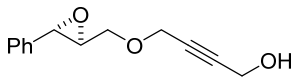


61

$[\alpha]_D$ = –47.3 (*c* 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (m, 7H), 6.91-6.84 (m, 2H), 4.53 (s, 2H), 4.32 (m, 2H), 4.18 (t, *J* = 1.8 Hz, 2H), 3.91 (dd, *J* = 11.5, 3.2 Hz, 1H), 3.81 (d, *J* = 2.2 Hz, 1H), 3.80 (s, 3H), 3.70 (dd, *J* = 11.5, 5.3 Hz, 1H), 3.24 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.4, 136.7, 129.7, 129.4, 128.5, 128.3, 125.7, 113.8, 83.0, 82.0, 71.3, 69.4, 60.7, 58.9, 57.0, 56.0, 55.3 ppm. IR (neat, cm^{-1}): 2854, 1611, 1513. MS (IC) *m/z* (%) 361 (M+Na). HRMS *calcd*. for ($C_{21}H_{22}NaO_4$): 361.1416.1517, *found* 361.1424.

4-(((2*S*,3*S*)-Phenyloxiran-2-yl)methoxy)but-2-yn-1-ol (62).

DDQ (131mg, 0.58 mmol) was added to a solution of **61** (140 mg, 0.41 mmol) in CH_2Cl_2/buffer solution (pH = 7) at 0 ºC for 3 h. The reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic phases were washed with saturated $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (hexanes/EtOAc (60:40), R_f = 0.23) on silica get afforded the desired product as an oil in 74% yield (67 mg).



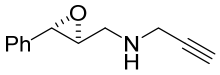
62

$[\alpha]_D$ = –64.9 (*c* 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.20 (m, 5H), 4.30 (s, 4H), 3.91 (dd, *J* = 11.4, 3.2 Hz, 1H), 3.82 (d, *J* = 1.9 Hz, 1H), 3.68 (dd, *J* = 11.4, 5.3 Hz, 1H), 3.24 (m, 1H), 1.77 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.6, 128.5, 128.3, 125.7, 85.1, 81.3, 69.5, 60.8, 58.8, 55.9, 51.1 ppm. IR (neat, cm^{-1}): 3421, 2921, 2860, 1461. MS (IC) *m/z* (%) 241 (M+Na). HRMS *calcd*. for ($C_{13}H_{14}NaO_3$): 241.0841, *found* 241.0831.

2.5.2.4 Synthesis of phenylglycidyl propargyl amines (77-79)

General procedure II[43, 45]

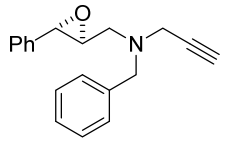
The corresponding propargyl amine was added dropwise to a solution of (2*S*,3*R*)-3-phenyl-2-tosyloxymethyloxirane (**65**) (200 mg, 0.66 mmol) and KI (5.5 mg, 0.033 mmol) in DMF (2.6 mL) at 0 ºC. The reaction mixture was stirred for 3 days at room temperature. The reaction was quenched with water (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic phase was washed with brine (75 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexanes/EtOAc (90:10)) treated with Et_3N 2.5% afforded the desired products **77-79**.



77

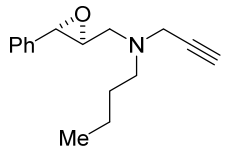
***N*-(((2*S*,3*S*)-3Phenyloxiran-2-yl)methyl)prop-2-yn-1-amine (77).**

General procedure **II** was followed using propargyl amine **84** (84 µL, 1.31 mmol). Column chromatography: silica gel (hexanes/EtOAc (60:40), R_f = 0.40). Yellow oil, yield = 20% (25 mg). $[\alpha]_D$: –43.3 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.24 (m, 5H), 3.81 (d, *J* = 1.5 Hz, 1H), 3.52 (d, *J* = 2.4 Hz, 2H), 3.19 (m, 1H), 3.16 (dd, *J* = 12.2. 3.6 Hz, 1H), 2.91 (dd, *J* = 12.2, 5.0 Hz, 1H), 2.25 (t, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.0, 128.5, 128.2, 125.6, 81.7, 71.8, 61.8, 56.7, 49.3, 38.2 ppm. IR (neat, cm^{-1}): 3288, 2923, 2841, 1496. MS (IC) *m/z* (%) 188 (M+H). HRMS *calcd*. for ($C_{12}H_{14}NO$): 188.1075, *found* 188.1084.



78

***N*-Benzyl-*N*-(((2*S*,3*S*)-3-phenyloxiran-2-yl)methyl)prop-2-yn-1-amine (78).** General procedure **II** was followed using *N*-benzylprop-2-yn-1-amine (**72**) (191 mg, 1.31 mmol). Column chromatography: silica gel (hexanes/EtOAc (80:20), R_f = 0.70). Yellow oil, yield = 70% (128 mg). $[\alpha]_D$: −78.9 (*c* 0.13, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.22 (m, 10H), 3.80 (d, *J* = 13.1 Hz, 1H), 3.71 (d, *J* = 2.1 Hz, 1H), 3.69 (d, *J* = 13.1Hz, 1H), 3.46 (d, *J* = 2.4 Hz, 2H), 3.14 (m, 1H), 2.91 (dd, *J* = 13.5, 4.6 Hz, 1H), 2.82 (dd, *J* = 13.5, 5.8 Hz, 1H), 2.82 (t, *J* = 2.4 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.2, 137.1, 129.1, 128.5, 128.4, 128.1, 127.3, 125.6, 78.3, 73.6, 61.3, 58.3, 56.9, 55.0, 42.4 ppm. IR (neat, cm^{-1}): 3291, 3028, 2830, 1455. MS (IC) *m/z* (%) 278 (M+H). HRMS *calcd*. for ($C_{19}H_{20}NO$): 278.1545, *found* 278.1537.



79

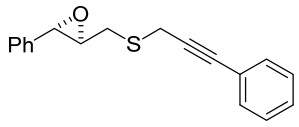
***N*-(((2S,3S)-3-phenyloxiran-2-yl)methyl)-*N*-(prop-2-yn-1-yl)butan-1-amine (79).** General procedure **II** was followed using *N*-(prop-2-yn-1-yl)butan-1-amine (**73**) (144.5 mg, 1.30 mmol). Column chromatography: silica gel (hexanes/EtOAc (80:20), R_f = 0.70). Yellow oil, yield = 80% (129 mg). $[\alpha]_D$: −79.1 (*c* 0.14, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 5H), 3.70 (d, *J* = 2 Hz, 1H), 3.51 (d, *J* = 2.0 Hz, 2H), 3.10 (m, 1H), 2.85 (dd, *J* = 13.4, 4.6 Hz, 1H), 2.76 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.58 (m, 2H), 2.21 (t, *J* = 2.2 Hz, 1H), 1.46 (m, 2H), 1.35 (m, 2H), 0.92 (t, *J* = 7.2 Hz, 3H)

ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.2, 128.5, 128.1, 125.6, 78.4, 73.1, 61.3, 57.1, 55.5, 53.7, 42.6, 29.6, 20.5, 14.0 ppm. IR (neat, cm^{-1}): 3295, 2956, 2929, 2862, 2824, 1496. MS (ESI+) *m/z* (%) 266 (M+Na). HRMS *calcd*. for ($C_{16}H_{21}NONa$): 266.1521, *found* 266.1536.

2.5.2.5 Synthesis of phenylglycidyl propargyl thioether (80)[44]

(2*S*,3*R*)-2-Phenyl-3-(((3-phenylprop-2-yn-1-yl)thio)methyl)oxirane (80)

To a solution of NaOH (2.5 g) in 11.5 mL of water and 11.5 mL of toluene were added tetraoctyl ammonium bromide (164 mg, 0.30 mmol), (2*S*,3*R*)-3-phenyl-2-tosyloxymethyloxirane (**65**) (912 mg, 3.0 mmol) and 3-phenylprop-2-yne-1-thiol (**76**) (370 mg, 2.49 mmol). The reaction mixture was heated for 48 h at 45 ºC. The reaction mixture was allowed to cool to room temperature, quenched with water (15 mL) and extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed with brine (75 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (hexanes/EtOAc (90:10), R_f = 0.4) treated with Et_3N 2.5% afforded the desired product in 76% yield (535 mg).



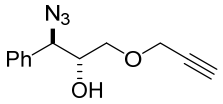
80

$[\alpha]_D$ = –36.0 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.26 (m, 10H), 3.84 (d, *J* = 1.9 Hz, 1H), 3.64 (d, *J* = 16.9 Hz, 1H), 3.57 (d, *J* = 16.9 Hz, 1H), 3.28 (ddd, *J* = 6.0, 4.6, 2.0 Hz, 1H), 3.07 (dd, *J* = 14.4, 5.1 Hz, 1H), 3.02 (dd, *J* = 14.4, 5.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.7, 131.7, 128.5, 128.3, 128.2, 128.1, 125.5, 122.7, 84.8, 83.7, 61.6, 58.6, 32.9, 20.5 ppm. IR (neat, cm^{-1}): 3062, 2956, 1719, 1597, 1489. MS

(ESI+) *m/z* (%) 303 (M+Na). HRMS *calcd*. for ($C_{18}H_{16}NaOS$): 303.0820, *found* 303.0821.

2.5.3 Isolated intermediate (55)

(1*R*,2*R*)-1-Azido-1-phenyl-3-(prop-2-yn-1-yloxy)propan-2-ol (55).



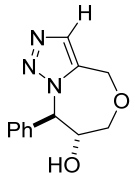
55

Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.34 (m, 5H), 4.66 (d, J = 8.0 Hz, 1H), 4.20 (d, J = 4.0 Hz, 2H), 4.01 (m, 1H), 3.63 (m, 2H), 2.46 (t, J = 4.0 Hz, 1H), 2.23 (d, J = 4.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.7, 128.6, 128.4, 127.6, 78.9, 74.8, 72.5, 69.8, 66.5, 58.4 ppm. IR (neat, cm^{-1}): 3433, 2887, 2096. MS (IC) *m/z* (%) 254 (M+Na). HRMS *calcd*. for ($C_{12}H_{13}NaO_2$): 254.0907, *found* 254.0905.

2.5.4 Click reaction products (56, 66-71, 85-88)

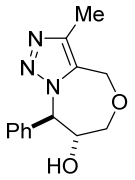
General procedure III.

A solution of the corresponding substrate (1.0 eq., 0.1 M) and NaN_3 (3 eq.) in *t*-BuOH/H_2O (1:1) was stirred in a microwave apparatus (constant temperature mode) at the indicated temperature and time. The reaction was quenched with water (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel treated with Et_3N 2.5% (hexanes/EtOAc (50:50)) afforded the desired product.



56

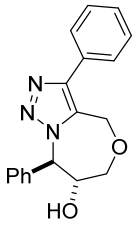
(7*R*,8*R*)-8-Phenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo[5,1-*c*][1,4] oxazepin-7-ol (56). General procedure **III** was followed using substrate **54** (50.0 mg, 0.266 mmol) and NaN_3 (51 mg, 0.797 mmol) in 2.2 mL of *t*-BuOH/water for 3 h at 100 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.20). White solid, yield = 70% (42.9 mg). mp: 140-144 ºC. $[\alpha]_D$ = +35.2 (*c* 0.10, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.40-7.29 (m, 3H), 6.88 (d, *J* = 7.6 Hz, 2H), 6.51 (d, *J* = 4.5 Hz, 1H), 5.03 (d, *J* = 14.9, 1H), 4.47 (dd, *J* = 5.1, 4.2 Hz, 1H), 4.38 (d, *J* = 14.9 Hz, 1H), 4.10 (dd, *J* = 13.2, 3.6 Hz, 1 H), 3.77 (d, *J* = 13.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.3, 135.3, 133.0, 129.4, 128.3, 125.3, 71.8, 69.8, 69.2, 62.9 ppm. IR (neat, cm^{-1}): 3347, 3063, 2957, 2922, 2853, 1449. MS (ESI$^-$) *m/z* (%) 230 (M–H). HRMS *calcd*. for ($C_{12}H_{12}N_3O_2$): 230.0930, *found* 230.0940.



66

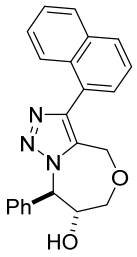
(7*R*,8*R*)-3-Methyl-8-phenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo[5,1-*c*][1,4] oxazepin-7-ol (66). General procedure **III** was followed using substrate **57** (50.0 mg, 0.247 mmol) and NaN_3 (48.2 mg, 0.742 mmol) in 2.2 mL of *t*-BuOH/water for 2.5 h at 140 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.35). White solid, yield = 60% (36.3 mg). mp: 140-143 ºC. $[\alpha]_D$ = +35.6 (*c* 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.38-7.29 (m, 3H), 6.81 (m, 2H), 6.43 (d, J = 4.7 Hz, 2H), 4.92 (d, J = 14.6, 1H), 4.45 (m, 1H), 4.31 (d, J = 14.6 Hz, 1H), 4.08 (dd, J = 13.1, 3.7 Hz, 1 H), 3.76 (d, J = 13.1 Hz, 1H), 3.29 (br s, 1H), 2.35 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.2, 135.5, 132.7, 129.3, 128.1, 125.3, 71.9, 69.9, 69.2, 62.3, 10.2 ppm. IR (neat, cm^{-1}): 3301, 2922, 2853, 1449. MS (ESI+) *m/z* (%) 264 (M+H). HRMS *calcd*. for ($C_{13}H_{16}N_3O_2$): 246.1243, *found* 246.1245.



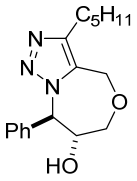
67

(7*R*,8*R*)-3,8-Diphenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo[5,1-*c*][1,4] oxazepin-7-ol (67). General procedure **III** was followed using substrate **58** (50.0 mg, 0.189 mmol) and NaN_3 (36.9 mg, 0.567 mmol) in 1.9 mL of *t*-BuOH/water for 1.5 h at 140 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.45). Colourless oil, yield = 80% (46.4 mg). $[\alpha]_D$ = +33.9 (*c* 0.17, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66-7.29 (m, 8H), 6.92-6.84 (m, 2H), 6.55 (d, J = 4.6 Hz, 1H), 5.20 (d, J = 14.9, 1H), 4.49 (d, J = 14.9 Hz, 1H), 4.50 (m, 1H), 4.10 (dd, J = 13.3, 3.7 Hz, 1H), 3.82 (dd, J = 13.3, 0.8 Hz, 1H), 3.13 (d, J = 7.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.6, 135.4, 133.0, 130.4, 129.3, 128.8, 128.4, 128.3, 128.1, 125.4, 72.1, 69.8, 69.6, 62.9 ppm. IR (neat, cm^{-1}): 3361, 2924, 2856, 1495. MS (ESI+) *m/z* (%) 308 (M+H). HRMS *calcd*. for ($C_{18}H_{18}N_3O_2$): 308.1399, *found* 308.1391.



68

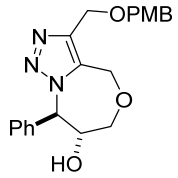
(7*R*,8*R*)-3-(Naphthalen-1-yl)-8-phenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo [5,1-*c*][1,4]oxazepin-7-ol (68). General procedure **III** was followed using substrate **59** (50.0 mg, 0.159 mmol) and NaN_3 (31.0 mg, 0.477 mmol) in 1.6 mL of *t*-BuOH/water for 2 h at 140 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.30). White solid, yield = 68% (38.6 mg). mp: 143-145 ºC. $[\alpha]_D$ = +20.5 (*c* 0.14, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06-7.28 (m, 10H), 6.90 (m, 2H), 6.60 (d, *J* = 4.6 Hz, 1H), 4.84 (d, *J* = 15.1, 1H), 4.50 (m, 1H), 4.37 (d, *J* = 15.1 Hz, 1H), 4.05 (dd, *J* = 13.1, 3.5 Hz, 1H), 3.76 (d, *J* = 13.1 Hz, 1H), 2.80 (d, *J* = 7.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.7, 133.3, 133.1, 130.8, 129.1, 128.5, 128.3, 128.2, 126.8, 126.4, 126.0, 125.7, 125.1, 120.1, 89.4, 84.8, 69.5, 60.8, 59.5, 56.0 ppm. IR (neat, cm^{-1}): 3424, 2922, 2854, 2349, 1460. MS (ESI+) *m/z* (%) 358 (M+H). HRMS *calcd*. for ($C_{22}H_{20}N_3O_2$): 358.1556, *found* 358.1546.



69

(7*R*,8*R*)-3-Phenyl-8-phenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo[5,1-*c*][1,4] oxazepin-7-ol (69). General procedure **III** was followed using substrate **60** (50.0 mg, 0.194 mmol) and NaN_3 (37.7 mg, 0.581 mmol) in 1.9 mL of *t*-BuOH/water for 1.5 h at 140 ºC. Column chromatography: silica gel

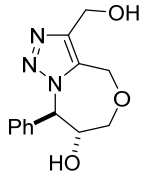
(hexanes/EtOAc (50:50), R_f = 0.37). White solid, yield = 70% (40.8 mg). mp: 148-150 ºC. $[\alpha]_D$ = +22.3 (*c* 0.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.25 (m, 3H), 6.83-6.77 (m, 2H), 6.45 (d, *J* = 4.7 Hz, 1H), 4.92 (d, *J* = 14.8, 1H), 4.49-4.41 (m, 1H), 4.30 (d, *J* = 14.8 Hz, 1H), 4.08 (dd, *J* = 13.1, 3.9 Hz, 1 H), 3.76 (d, *J* = 13.1 Hz, 1H), 2.68 (m, 2H), 1.73 (m, 2H), 1.35 (m, 4H), 0.91 (dd, *J* = 8.3, 6.9 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.8, 135.6, 132.4, 129.3, 128.1, 125.3, 72.0, 69.9, 69.1, 62.4, 31.5, 29.6, 24.9, 22.4, 14.0 ppm. IR (neat, cm^{-1}): 3200, 2954, 2928, 2856, 1449. MS (ESI+) *m/z* (%) 302 (M+H). HRMS *calcd*. for ($C_{17}H_{24}N_3O_2$): 302.1869, *found* 302.1868.



70

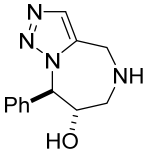
(7*R*,8*R*)-3-(((4-Methoxybenzyl)oxy)methyl)-8-phenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo[5,1-*c*][1,4]oxazepin-7-ol (70). General procedure **III** was followed using substrate **61** (50.0 mg, 0.148 mmol) and NaN_3 (28.8 mg, 0.443 mmol) in 1.5 mL of *t*-BuOH/water for 1.5 h at 140 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.12). White solid, yield = 63% (35.5 mg). mp: 147-149 ºC. $[\alpha]_D$ = +40.5 (*c* 0.13, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 6.93-6.86 (m, 2H), 6.83-6.77 (m, 2H), 6.47 (d, *J* = 4.7, 1H), 5.13 (d, *J* = 15.1 Hz, 1H), 4.71 (d, *J* = 12.2 Hz, 1H), 4.68 (d, *J* = 12.2 Hz, 1H), 4.56 (s, 2H), 4.43 (m, 1H), 4.31 (d, *J* = 15.1 Hz, 1H), 4.08 (dd, *J* = 13.1, 3.9 Hz, 1H), 3.81 (s, 3H), 3.76 (d, *J* = 13.1 Hz, 1H), 2.62 (d, *J* = 9.6 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.7, 142.6, 135.7, 135.5, 130.0, 129.9, 129.6, 128.5, 125.7, 114.2, 72.6, 72.2, 70.2, 69.8, 63.2, 62.5, 55.6 ppm. IR (neat, cm^{-1}):

3390, 2920, 2855, 1512. MS (ESI+) *m/z* (%) 382 (M+H). HRMS *calcd*. for ($C_{21}H_{24}N_3O_4$): 382.1767, *found* 382.1759.



71

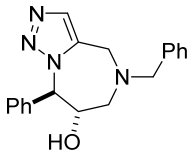
(7*R*,8*R*)-3-(Hydroxymethyl)-8-phenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo [5,1-*c*][1,4]oxazepin-7-ol (71). General procedure **III** was followed using substrate (**62**) (50.0 mg, 0.229 mmol) and NaN_3 (44.7 mg, 0.687 mmol) in 2.3 mL of *t*-BuOH/water for 2 h at 140 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.15). Yield = 60% (35.9 mg). White solid. mp: 105-107 ºC. $[\alpha]_D$ = +29.6 (*c* 0.11, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.28 (m, 3H), 6.84-6.78 (m, 2H), 6.47 (d, *J* = 4.8 Hz, 1H), 5.12 (d, *J* = 14.8, 1H), 4.76 (s, 2H), 4.46 (m, 1H), 4.33 (d, *J* = 14.8 Hz, 1H), 4.11 (dd, *J* = 13.4, 3.6 Hz, 1H), 3.95 (d, *J* = 8.4 Hz, 1H), 3.76 (d, *J* = 13.4 Hz, 1H), 3.32 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 144.7, 135.2, 134.4, 129.4, 128.3, 125.3, 72.0, 69.9, 69.5, 62.1, 55.7 ppm. IR (neat, cm^{-1}): 3302, 2959, 2923, 2855, 1449. MS (ESI+) *m/z* (%) 284 (M+Na). HRMS *calcd*. for ($C_{13}H_{15}N_3O_3Na$): 284.1011, *found* 284.1009.



85

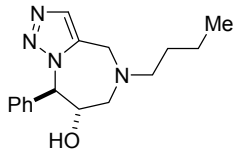
(7*R*,8*R*)-8-Phenyl-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*][1,4] diazepin-7-ol (85). General procedure **III** was followed using substrate (**77**) (50.0 mg, 0.267 mmol) and NaN_3 (52.1 mg, 0.801 mmol) in 2.6 mL of *t*-

BuOH/water for 2.5 h at 110 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.20). Yield = 60% (36.9 mg). Pale yellow oil. $[\alpha]_D$ = +27.3 (*c* 0.13, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1H), 7.38-7.28 (m, 3H), 6.80-6.75 (m, 2H), 6.47 (d, *J* = 4.7 Hz, 1H), 4.49 (m, 1H), 4.25 (d, *J* = 15.7 Hz, 1H), 3.64 (d, *J* = 15.7, 1H), 3.20 (dd, *J* = 14.1, 5.1 Hz, 1H), 2.94 (d, *J* = 14.1 Hz, 1H), 2.94 (br s, 1H), 2.94 (br s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.9, 134.9, 131.5, 128.2, 126.9, 124.3, 68.6, 67.1, 49.2, 41.8 ppm. IR (neat, cm^{-1}): 3302, 3054, 2985, 2928, 1264. MS (ESI+) *m/z* (%) 231 (M+H). HRMS *calcd*. for ($C_{12}H_{15}N_4O$): 231.1246, *found* 231.1251.



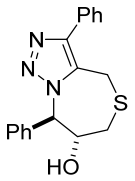
86

(7*R*,8*R*)-5-Benzyl-8-phenyl-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*] [1,4] diazepin-7-ol (86). General procedure **III** was followed using substrate **78** (50.0 mg, 0.180 mmol) and NaN_3 (35.2 mg, 0.541 mmol) in 1.8 mL of *t*-BuOH/water for 3 h at 130 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.20). Yield = 70% (40.4 mg). White solid. mp: 187-190 ºC. $[\alpha]_D$ = +77.9 (*c* 0.13, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (s, 1H), 7.40-7.24 (m, 8H), 6.81-6.73 (m, 2H), 6.45 (d, *J* = 4.6 Hz, 1H), 4.47 (br s, 1H), 4.08 (dd, *J* = 14.8, 2.2 Hz, 1H), 3.76 (d, *J* = 13.2, 1H), 3.69 (d, *J* = 13.2 Hz, 1H), 3.52 (br s, 1H), 3.36 (d, *J* = 14.8 Hz, 1H), 3.10 (ddd, *J* = 13.0, 6.0, 1.8 Hz, 1H), 2.72 (d, *J* = 13.0 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 137.1, 135.8, 134.9, 133.2, 129.2, 128.7, 127.9, 127.9, 125.5, 69.1, 68.5, 63.2, 56.9, 48.7 ppm. IR (neat, cm^{-1}): 3376, 2917, 2791, 2349, 1450. MS (ESI+) *m/z* (%) 321 (M+H). HRMS *calcd*. for ($C_{19}H_{21}N_4O$): 321.1715, *found* 321.1717.



87

(7*S*,8*R*)-5-Butyl-8-phenyl-5,6,7,8-tetrahydro-4*H*-[1,2,3]triazolo[1,5-*a*] [1,4] diazepin-7-ol (87). General procedure **III** was followed using substrate **79** (50.0 mg, 0.205 mmol) and NaN_3 (40.1 mg, 0.616 mmol) in 2 mL of *t*-BuOH/water for 3 h at 130 ºC. Column chromatography: silica gel (hexanes/EtOAc (60:40), R_f = 0.21). Yield = 85% (50.0 mg). Pale yellow oil. $[\alpha]_D$ = +78.9 (*c* 0.11, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (s, 1H), 7.38-7.27 (m, 3H), 6.80-6.74 (m, 2H), 6.43 (d, *J* = 4.6 Hz, 1H), 4.46 (m, 1H), 4.05 (dd, *J* = 14.8, 2.4 Hz, 1H), 3.62 (br s, 1H), 3.42 (d, *J* = 14.8 Hz, 1H), 3.01 (ddd, *J* = 13.2, 6.4, 2.0, 1H), 2.69 (d, *J* = 13.2 Hz, 1H), 2.66-2.51 (m, 2H), 1.53-1.41 (m, 2H), 1.35-1.24 (m, 2H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 136.0, 135.2, 132.9, 129.1, 127.9, 125.5, 69.3, 68.3, 59.0, 57.2, 49.5, 29.3, 20.2, 13.9 ppm. IR (neat, cm^{-1}): 3293, 2954, 2929, 2861, 1449. MS (ESI+) *m/z* (%) 287 (M+H). HRMS *calcd*. for ($C_{16}H_{23}N_4O$): 287.1872, *found* 287.1886.

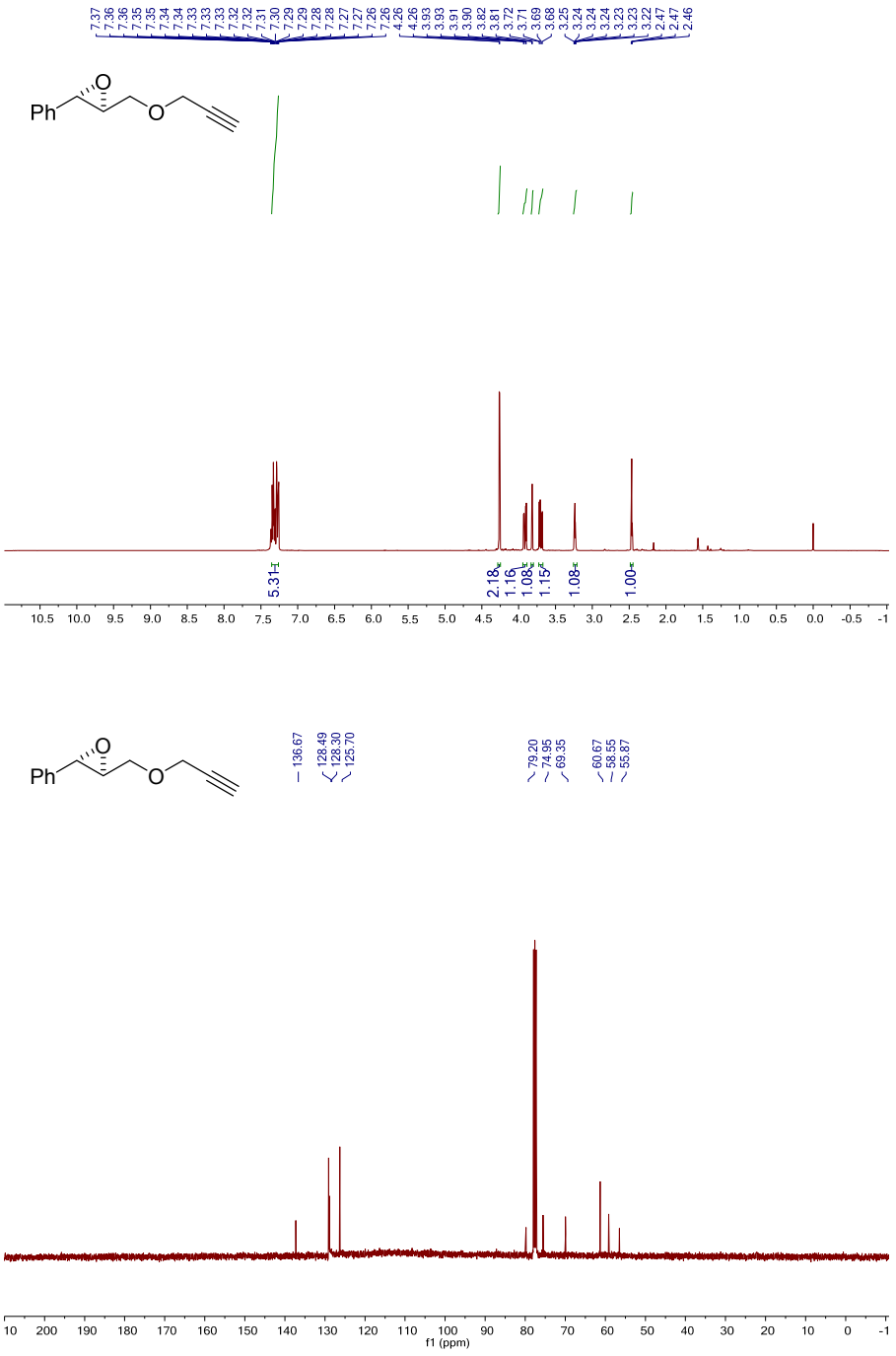


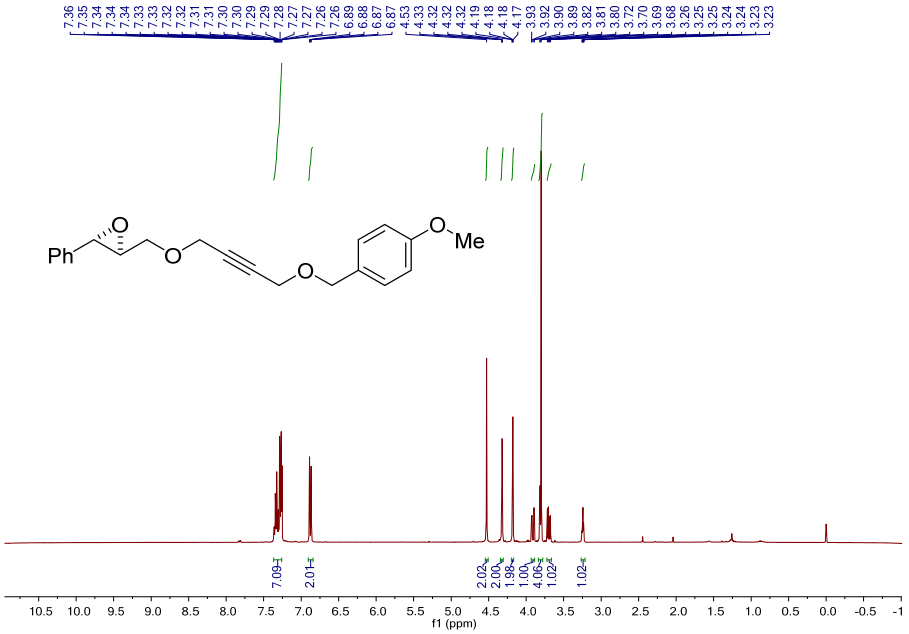
88

(7*R*,8*R*)-3,8-Diphenyl-4,6,7,8-tetrahydro-[1,2,3]triazolo[1,5-*c*][1,4] thiazepin-7-ol (88). General procedure **III** was followed using substrate **80** (50.0 mg, 0.178 mmol) and NaN_3 (34.8 mg, 0.535 mmol) in 1.8 mL of *t*-BuOH/water for 1.5 h at 140 ºC. Column chromatography: silica gel (hexanes/EtOAc (50:50), R_f = 0.23). Yield = 53% (30.5 mg). Pale yellow oil. $[\alpha]_D$ = +37.5 (*c* 0.11, acetone). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.29

(m, 8H), 6.88-6.82 (m, 2H), 5.96-5.92 (d, *J* = 3.2 Hz, 1H), 4.59-4.50 (m, 1H), 4.13 (d, *J* = 15.6 Hz, 1H), 4.06 (d, *J* = 15.6 Hz, 1H), 3.17 (dd, *J* = 13.4, 2.0 Hz, 1H), 3.00-2.88 (m, 1H), 2.88-2.82 (dd, *J* = 13.4, 5.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.1, 138.0, 137.7, 129.2, 128.9, 128.6, 128.5, 126.6, 125.7, 123.4, 67.5, 66.0, 31.7, 27.4 ppm. IR (neat, cm^{-1}): 3285, 2920, 2850, 1494, 1452. MS (ESI+) *m/z* (%) 346 (M+Na). HRMS *calcd*. for ($C_{18}H_{17}N_3ONaS$): 346.0990, *found* 346.1007.

2.5.5 Selected NMR spectra




7.36
7.35
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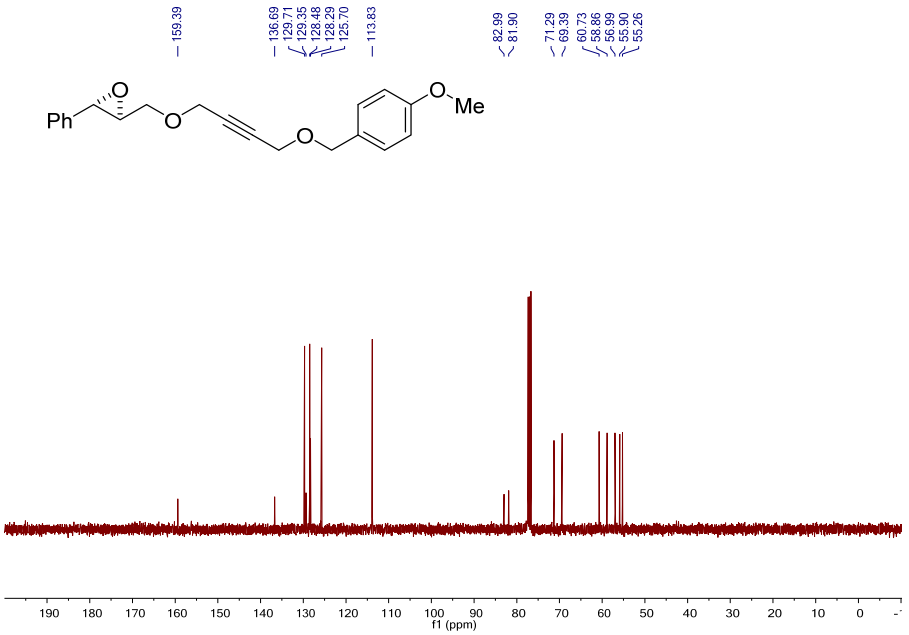
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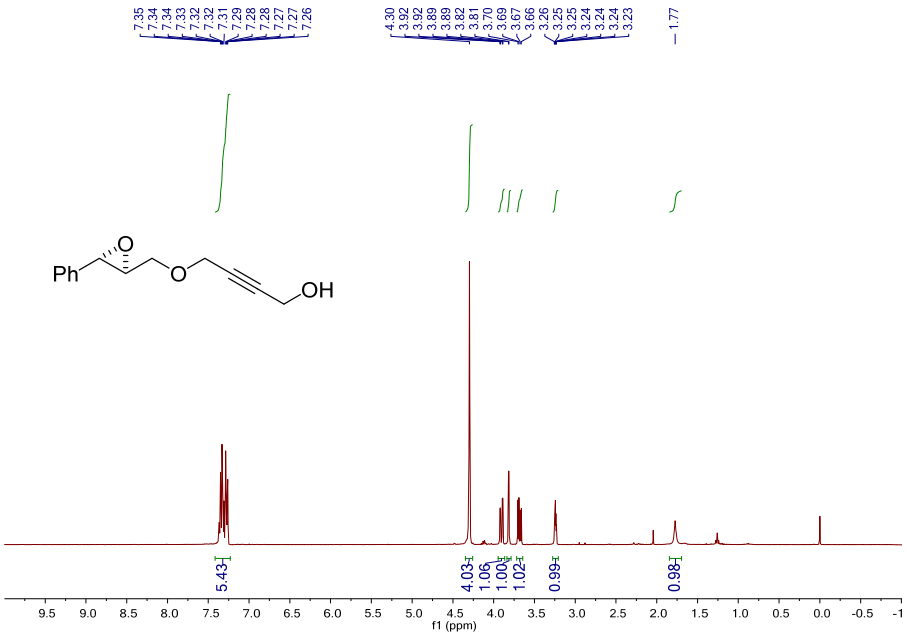
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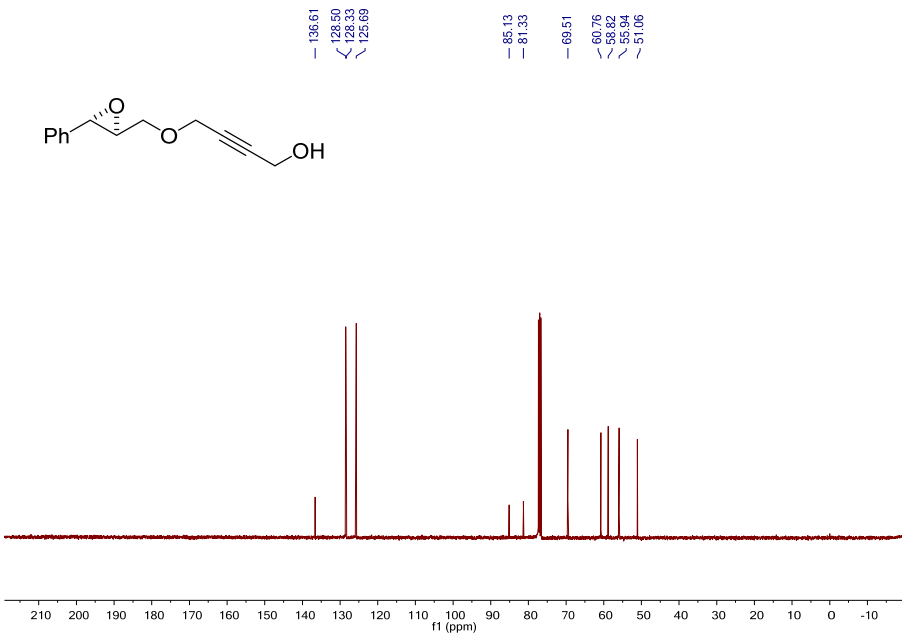
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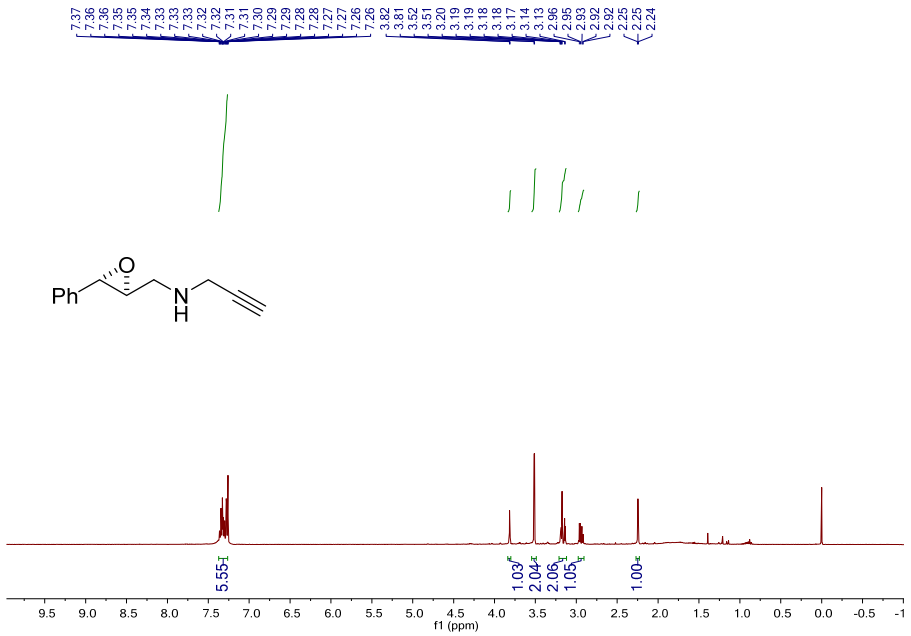
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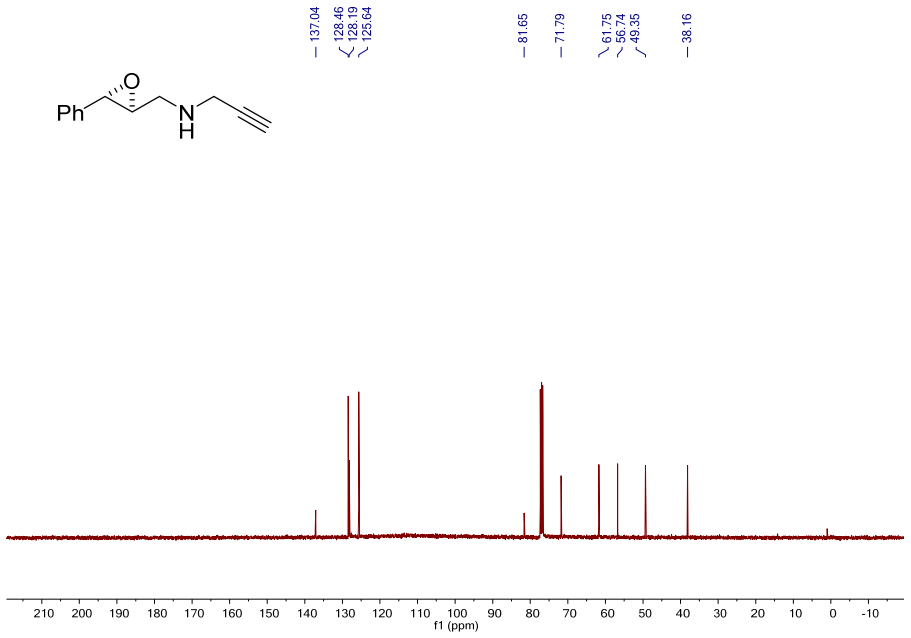
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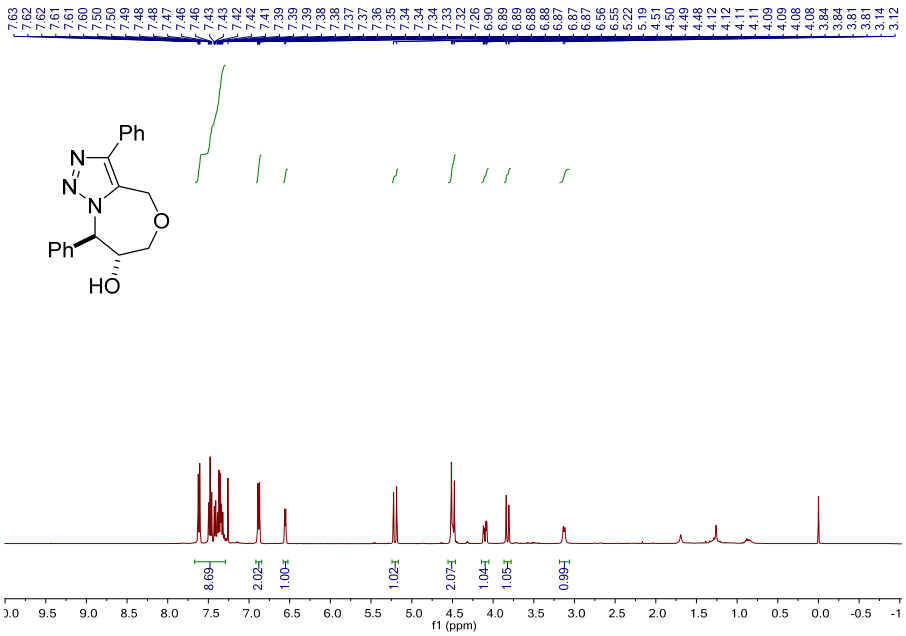
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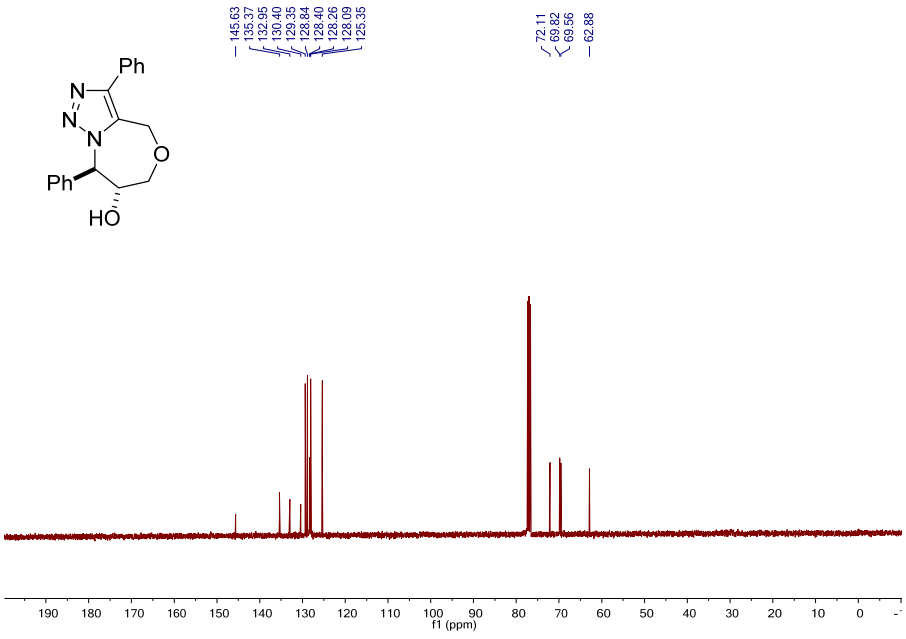
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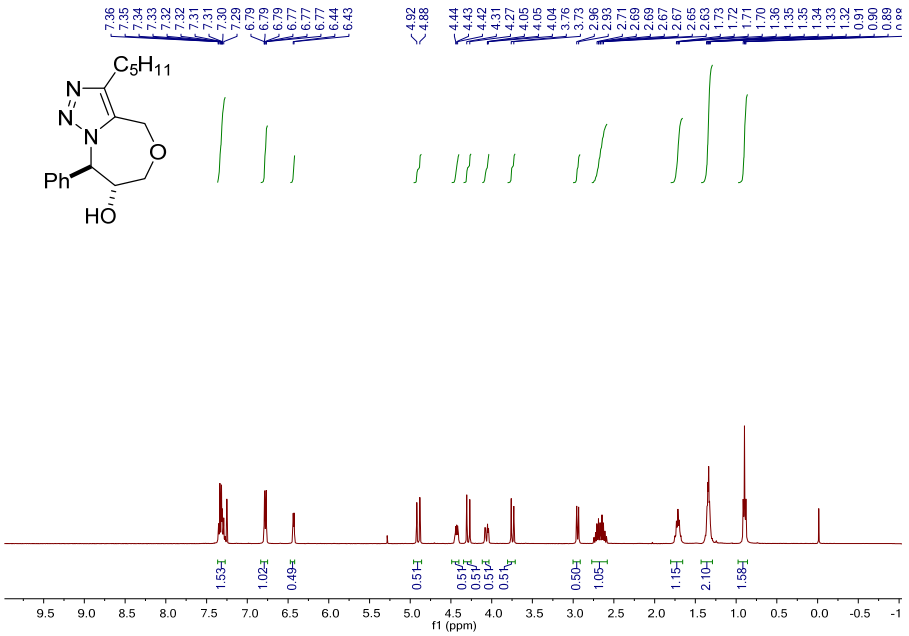
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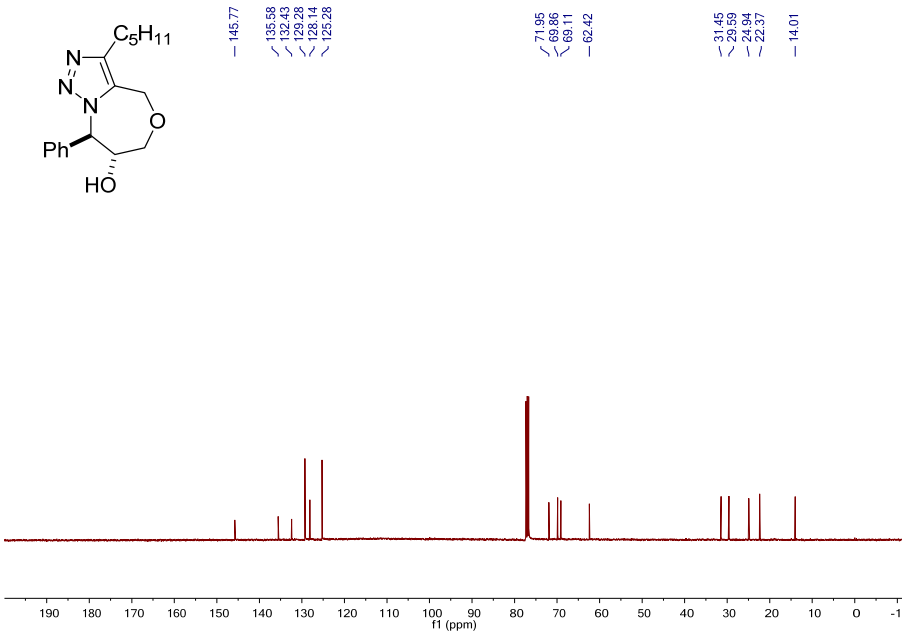
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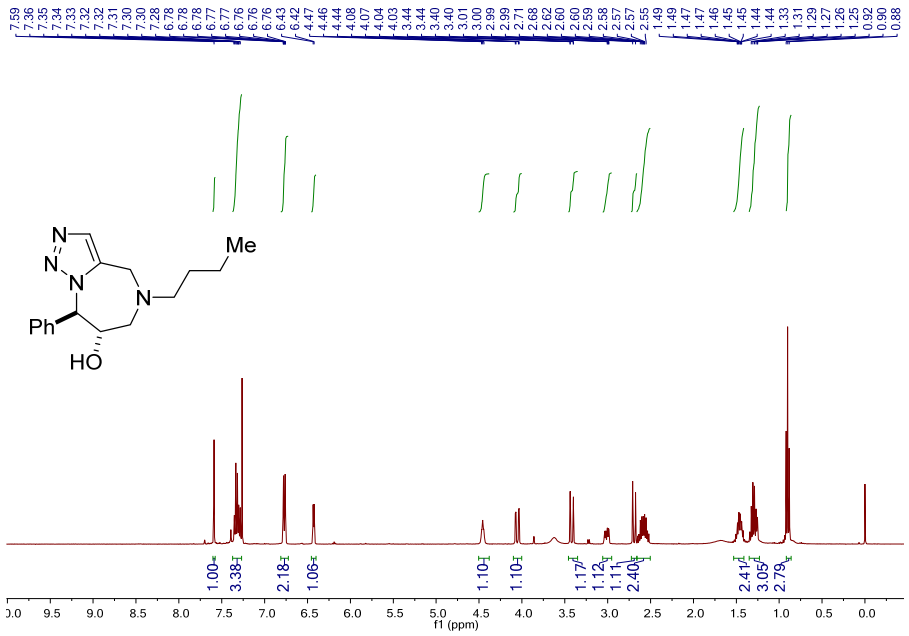
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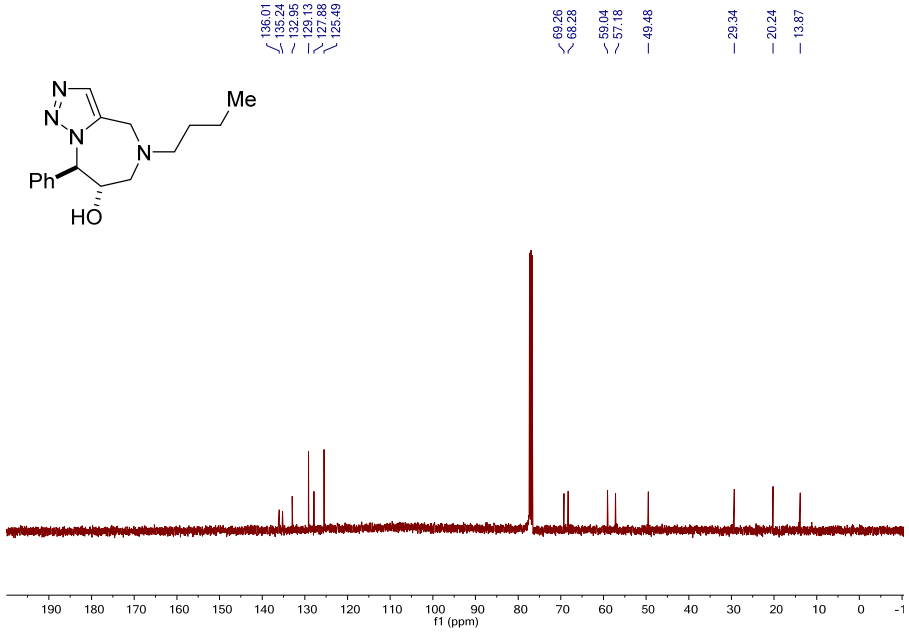
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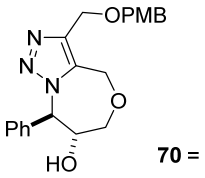
2.5.6 X-Ray crystallographic data for 70



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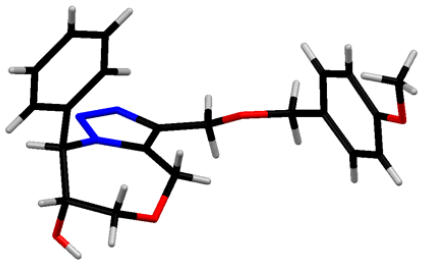

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Z, Z': **Z**: 4 **Z'**: 0

R-Factor (%) 3.4

Chapter 3. General introduction to C-C bond cleavage

3.1 Introduction to C-C bond cleavage

In the early 1970s, it was discovered that Ni or Pd complexes were able to catalyze the coupling of two different hydrocarbon fragments (Figure 3.1). This seemingly trivial discovery triggered unimaginable consequences in synthetic organic chemistry, setting the stage for a powerful, general and practical strategy for the construction of C-C bonds.[49] Although in the last decades formidable advances have been realized in this field, these methodologies still have some important limitations that need to be addressed. Among these, the utilization of well-defined, stoichiometric and in many instances, air-sensitive organometallic reagent (R^1-M) and the considerable amount of waste produced are important aspects worth considering for the future applications.

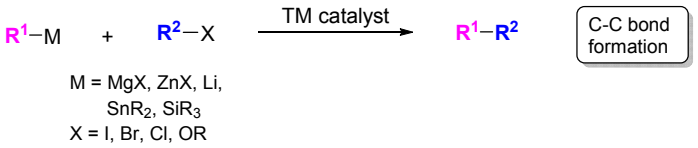

Figure 3.1

While reductive elimination (C-C bond formation) typically constitutes the last step within the catalytic cycle of a myriad of cross-coupling reactions,[49] the microscopic reverse of this transformation (C-C bond activation) has been relatively less explored (Figure 3.2).[50] By definition, however, such a concept possesses a number of advantages: (a) no organometallic reagents would be required; (b) simple starting materials

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[49]For reviews about metal-catalyzed cross-coupling reactions, see: (a) Johanasson, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed*. **2012**, *51*, 5062-5085. (b) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457-2483.

[50] For reviews about C-C bond activation, see: (a) Crabtree, R. H. *Chem. Rev*. **1985**, *85*, 245-269. (b) Rybtchinski, B.; Milstein, D. *Angew. Chem. Int. Ed*. **1999**, *38*, 870-883. (c) Murakami, M.; Matsuda, T. *Chem. Commun*. **2011**, *47*, 1100-1105. (d) Chen, F.; Wang, T.; Jiao, N. *Chem. Rev*. **2014**, *114*, 8613-8661. (e) Dermenci, A.; Coe, J. W.; Dong, G. *Org. Chem. Front*. **2014**, *1*, 567-581.

could be employed; (c) more atom-economical processes than preactivation techniques and (d) no prefunctionalization are needed. Although impressive advances have been made in the field of C-H activation, the C-C bond activation is still largely undeveloped.

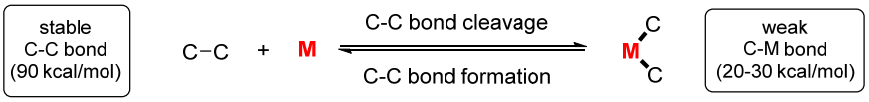

Figure 3.2

Probably, the main challenge for the C-C bond activation is related to the thermodynamic stability, strength and low polarization of the C-C bond. Indeed, two moderately weak carbon-metal bonds (C-M-C; 20-30 kcal/mol) are formed from a much more stable carbon-carbon bond (C-C; 90 kcal/mol) (Figure 3.2). [51] From a kinetic standpoint, the difficulties associated to the cleavage of C-C bonds are based on the following: (1) the directionality of its σ-orbital and (2) the steric interaction of C-C bonds with proximal C-H bond orbitals and metal orbitals (Figure 3.3). The π-orbital of C-C double bond is oriented sideways, allowing the interaction with the metal orbital without significant difficulties. As for the C-H bond, the σ-orbital that connects both atoms lies along the bond axis; although the directionality with the metal orbital is not appropriate, the 1s orbital of the hydrogen atom is spherical, thus facilitating the interaction with the metal center (Figure 3.3).[52]

[51] Jun, Ch-Ho. *Chem. Soc. Rev*. **2004**, *33*, 610-618.

[52] Murakami, M. Cleavage of Carbon-Carbon single Bonds by Transition Metals. Wiley-VCH Verlag GmbH & Co. kGaA, Weinheim, Germany.

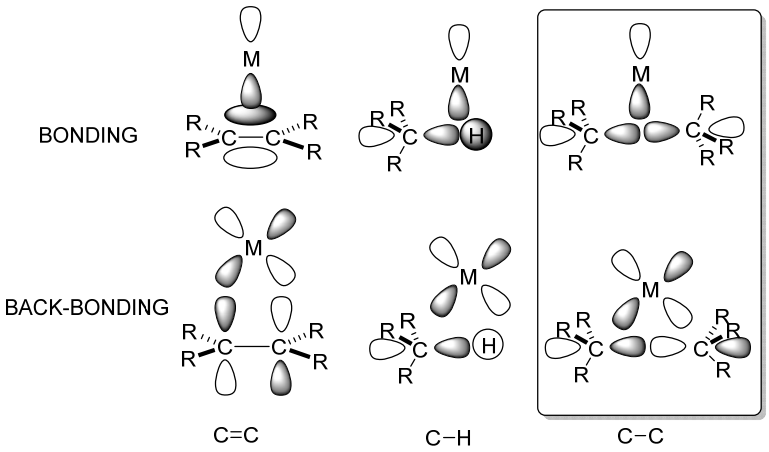

Figure 3.3

Despite the numerous drawbacks related to the C-C bond activation, several strategies have been developed to tackle such challenge. Prompted by seminal discoveries utilizing stoichiometric transition metals complexes, the recent years have witnessed the design of powerful catalytic C-C bond cleavage events.[50-52] The most common used strategies to promote C-C bond cleavage are the following:

(1) Strain-relief of cyclopropanes or cyclobutanes.

(2) Aromaticity as a driving force.

(3) Chelation control, bringing the metal in close proximity to the targeted C-C bond.

(4) Activation of polarized C-C single bonds.

3.2 Stoichiometric approaches for the activation of C-C single bonds

Metal mediated C-C bond activation technologies were initially reported using strained molecules and stoichiometric amounts of metal complexes. In 1955, Tipper[53] and few years later Chatt[54] demonstrated the structure of platinacyclobutane **XV** after an oxidative addition of

[53] Tipper, C. F. H. *J. Chem. Soc*. **1955**, 2045-2048.

[54] Adams, D. A.; Chatt, J.; Guy, R. G.; Sheppard, N. *J. Chem. Soc*. **1961**, 738-739

cyclopropane (**93**) to a Pt(II) complex in the presence of pyridine, giving acces to **XVI** (Figure 3.4).

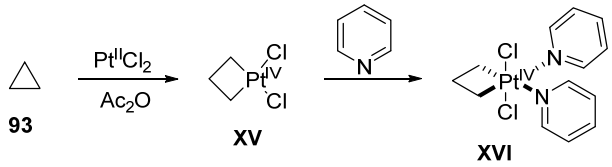

Figure 3.4

The driving force for effecting C-C bond cleavage of cyclopropanes is associated to the correct orientation and the proper symmetry of the HOMO and LUMO orbitals, hence facilitating the interaction with transition metal orbitals while lowering down the kinetic barrier of the reaction. These conceptions have been taken by others, thus becoming a useful strategy for promoting C-C cleavage of strained rings.[55]

In 1969, Müller and co-workers reported that $RhCl(PPh_3)_3$ (**XVII**) (Wilkinson catalyst) can activate the sp-sp^2 carbon bonds of diynones (**94**) (Figure 3.5). Decarbonylation and further reductive elimination takes place to afford the corresponding diynes (**95**) and $RhCl(CO)(PPh_3)_2$ species (**XVIII**). The authors demonstrated that this reaction was general for different types of diynones with diverse electronic and steric properties, affording the corresponding dyines in moderate to good yields. [56]

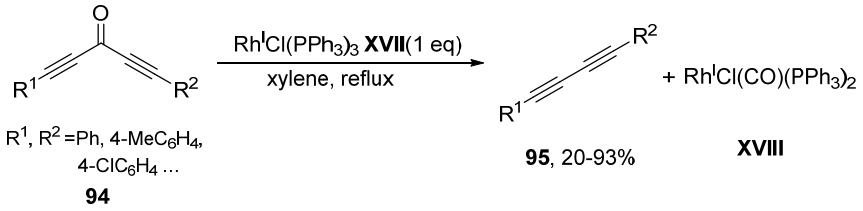

Figure 3.5

[55] Seiser, T.; Cramer, N. *Org. Biomol. Chem*. **2009**, *7*, 2835-2840.

[56] Müller, E.; Segnitz, A.; Langer, E. *Tetrahedron Lett*. **1969**, *14*, 1129-1132.

Subsequently, the Teranishi's group [57] described an efficient decarbonylation of unstrained 1,2- and 1,3-diketones (**96**) with $RhCl(PPh_3)_3$ (**XVII**). Under these conditions, **97** was obtained together with the inactive $RhCl(CO)(PPh_3)_2$ (**XVIII**) and $RhCl(acac)_2(PPh_3)$ (**XIX**) (Figure 3.6). Interestingly, the decarbonylation of acetylacetone en route to 2-butanone was observed when treated with **XIX**.

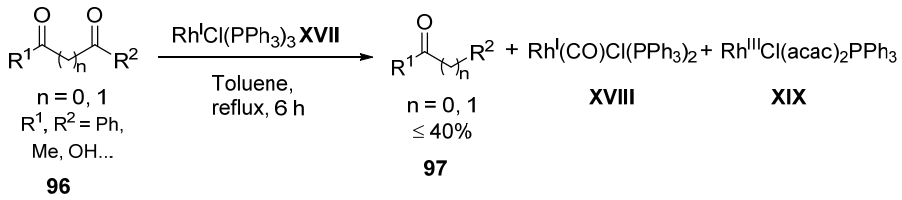

Figure 3.6

In 1977, Eilbracht and Dahler[58] showed one of the first examples where an aromatization event was critical for effecting the C-C bond activation (Figure 3.7). In such reaction, the $Fe_2(CO)_9$ complex is coordinated with the cyclopentadienyl ring (**98)** in THF under mild conditions to give the complex **XX**. Further addition of more $Fe_2(CO)_9$ and an increase of the temperature generates the cyclopentadienyl iron complex **XXI** through C-C bond activation.

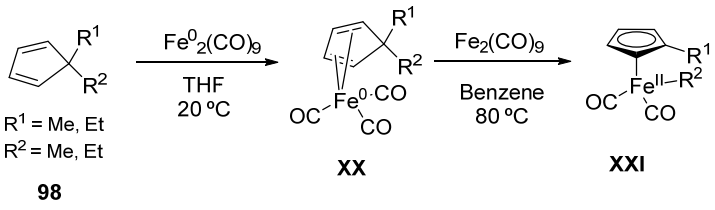

Figure 3.7

It has also been reported that other metal species like iridium can form

[57] Kaneda, K.; Azuma, H.; Wayaku, M.; Teranishi, S. *Chem. Lett*. **1974**, 215-216.

[58] Eilbracht, P.; Dahler, P. *J. Organometallic Chem*. **1977**, *135*, C23-C25.

Cp-complexes via C-C bond activation. Crabtree[59] and co-workers used substituted cyclopentanes (**99)** with $[IrH_2(Me_2CO)((p\text{-}FC_6H_4)_3P)]_2$ (**XXII**) to such purposes. The Ir complex **XXII** first underwent dehydrogenolysis to form complex **XXIII** and subsequent demethylation (C-C bond activation) to provide the final Cp-Ir complex **XXIV** (Figure 3.8).

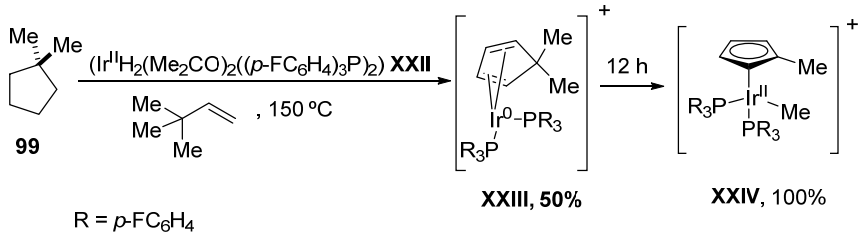

Figure 3.8

Another example where aromatization can drive the C-C bond activation was applied by Chaudret,[60] in which a methyl group was removed from steroid-type compounds (Figure 3.9). Specifically, Cp^*Ru^+ was able to aromatize the B-ring of ergosterol 5 (**100**) via initial C-H activation ending up in $[Cp^*Ru(H)(\eta^5\text{-cyclohexadienyl}]^+$ intermediate (**XXV)** followed by the C-C bond activation event, resulting in the desired aromatic ring **XXVII** with the concomitant elimination of methane.

[59] Crabtree, R. H.; Dion, R. P.; Gibboni, D. J.; McGrath, D. V.; Holt, E. M. *J. Am. Chem. Soc*. **1986**, *108*, 7222-7227.

[60] Halcrow, M. A.; Urbanos, F.; Chaudret, B. *Organometallics* **1993**, *12*, 955-957.

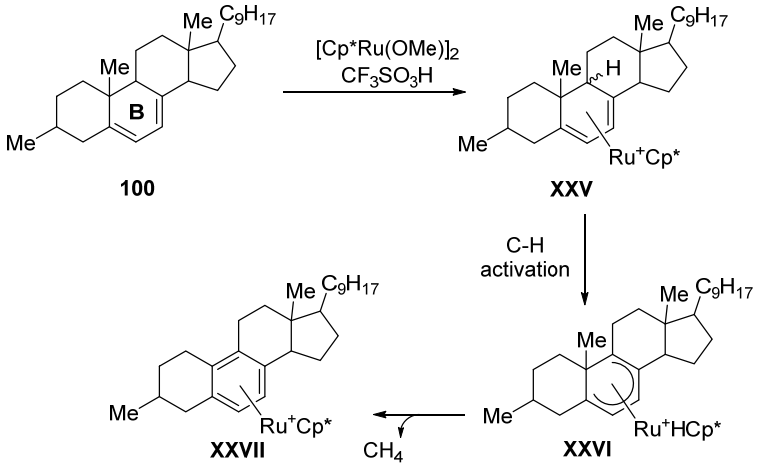

Figure 3.9

Chelation assisted activation of C-C bonds was first reported by Suggs[61] and co-workers. They used a Rh(I)-complex to promote the C-C bond activation of quinolone derivatives (**101**) under mild reaction conditions (Figure 3.10). The authors showed by deuterated experiments that in this case the C-H activation of the alkyl substituent does not take place prior to the C-C activation event.

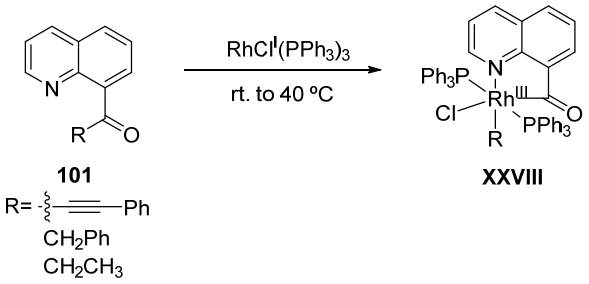

Figure 3.10

Following the same methodology, a set of chiral rhodium complexes were synthesized by incorporating a chiral substituent at α-position to the ketone (Figure 3.11).[62]

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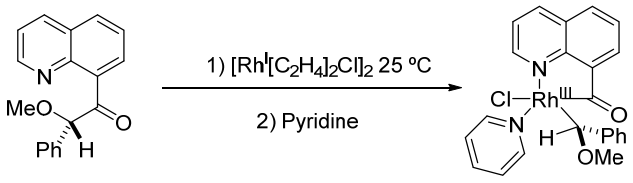
[61] Suggs, J. W.; Cox, S. D. *J. Organometall. Chem*. **1981**, *221*, 199-201

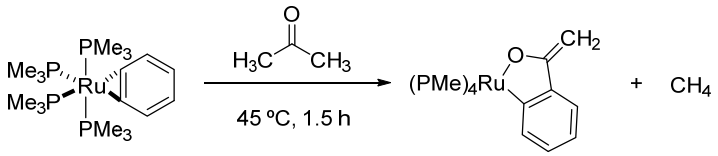
[62] Suggs, J. W.; Jun, C-H. *J. Am. Chem. Soc*. **1986**, *108*, 4679-4681.



102 **XXIX**

Figure 3.11

In 1989, the group of Bergman [63] synthesized two different Ru complexes (**XXX** and **XXXI**) for the activation of ketones (Figure 3.12). When the former **XXX** was used in acetone at 45 ºC for 1.5 days, it was isolated a complex **XXXII** with the formal incorporation of acetone while releasing methane.



XXX **XXXII**, 28%

Figure 3.12

When using **XXXI**, the authors employed hexafluoroacetone to promote the targeted C-C bond activation. The authors proposed a mechanism based on an initial hydroxyl dissociation (**XXXIII)** that allows the coordination of the hexafluoroacetone (**XXXIV**). Next the hydroxy ion attack to the carbonyl group, giving the complex **XXXV** that triggers a C-C activation to yield **XXXVI** while releasing fluoroform (Figue 3.13).

[63] Hartwig, J. F.; Andersen, R. A.; Bergman, R. G. *J. Am. Chem. Soc*. **1989**, *111*, 2717-2719.

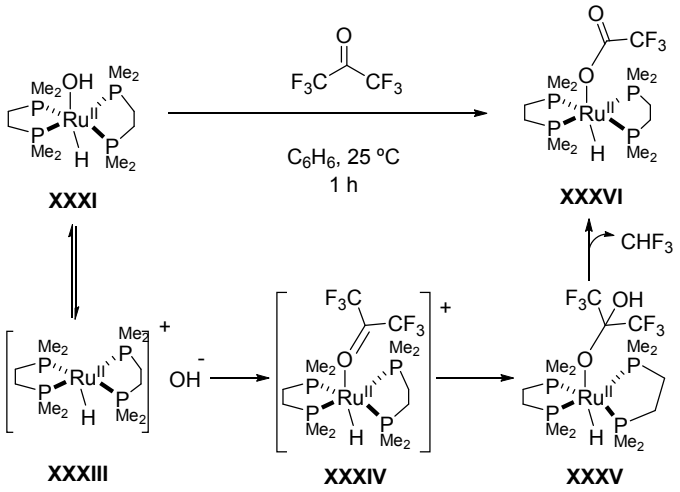


Figure 3.13

In 1993, the group of Milstein[64] demonstrated that the activation of rather inert C-C bonds is also possible using pincer ligands (Figure 3.14). The use of diphosphine ligand **103** with $HRh(PPh_3)_4$ in THF at room temperature produces **XXXVII** in good yields via C-H activation. After heating this complex **XXXVII** at 90 ºC under H_2 atmospheres, the C-C bond activation takes place in quantitative yield (**104)** while forming methane. The authors proposed a reversible C-H activation followed by C-C bond activation in the presence of H_2 atmospheres. These results also show the thermodynamic preference for C-C bond activation over the C-H activation.

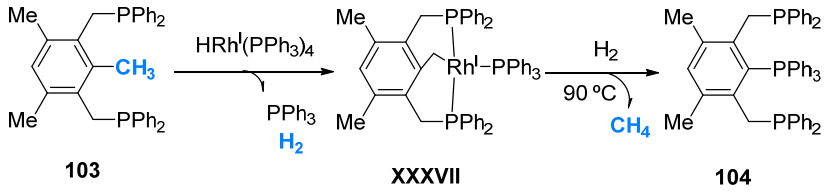
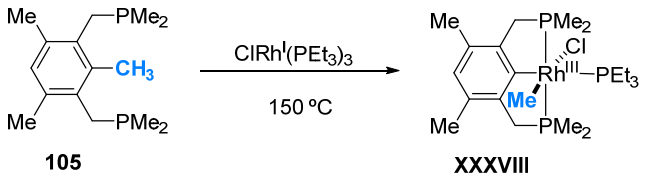


Figure 3.14

Only two years later, the same group reported the first direct oxidative addition of a C-C bond to a metal center (Figure 3.15). They showed that

[64] Gozin, M.; Welsman, A.; Ben-David, Y.; Milstein, D. *Nature* **1993**, *364*, 699-701.

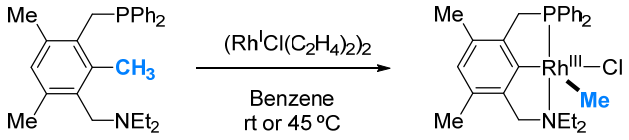
this oxidative addition is highly dependent on the electron density of the metal center and that can be thermodynamically more favorable than the C-H activation process.[65]



105 **XXXVIII**

Figure 3.15

Milstein also described the study of a non symmetric pincer ligand bearing a phosphine and an amine as chelating motifs (**106**) (Figure 3.16).[66] In this case, C-C bond activation was also selective over the C-H bond activation under mild reaction conditions, affording complex **XXXIX**.



106 **XXXIX**

Figure 3.16

In 1994, Ito and co-workers[67] reported that Rh(I) can promote the C-C bond activation of cycloalkanones to promote a formal ring-contraction event (Figure 3.17). For example, ketone **107** was decarbonylated using Wilkinson complex to deliver the more strained cyclobutane **108** in 57% yield after 8 days in refluxing toluene.

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[65] Liou, S-Y.; Gozin, M.; Milstein, D. *J. Am. Chem. Soc*. **1995**, *117*, 9774-9775.

[66] Gandelman, M.; Vigalok, A.; Shimon, L. J. W.; Milstein, D. *Organometallics* **1997**, *16*, 3981-3986.

[67] Murakami, M.; Amili, H.; Ito, Y. *Nature* **1994**, *370*, 540-541.

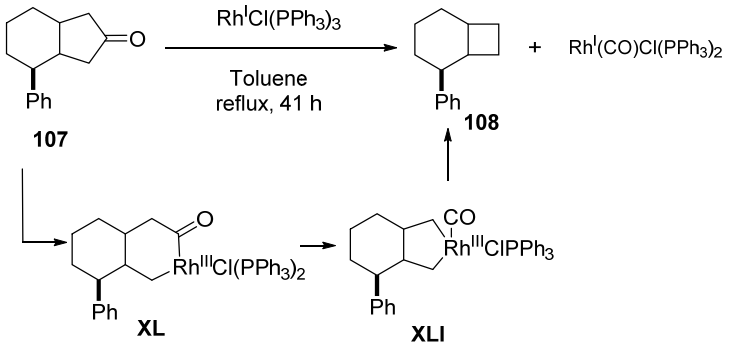


Figure 3.17

More recently, Jones [68] and co-workers developed a transformation where platinum can carry out the activation of sp^2-sp C-C bond of diphenyl acetylene (**XLII**) under photochemical conditions (**XLIII**) (Figure 3.18).

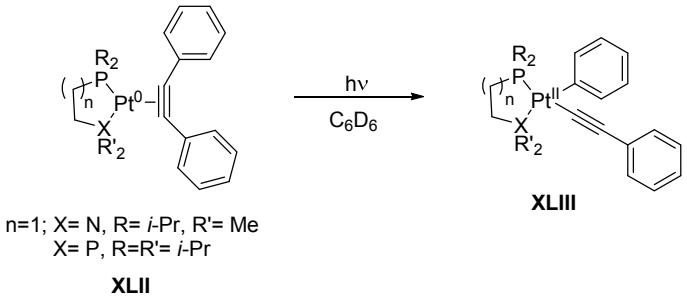


Figure 3.18

In 2004, Daugulis and Brookhart [69] reported the synthesis of biaryl molecules (**110**) via decarbonylation of benzophenones (**109**) and acetophenones using $Cp^*Rh(C_2H_4)_2$ in refluxing toluene.

[68] Müller, C.; Iverson, C. N.; Lachicotte, R. J.; Jones, W. D. *J. Am. Chem. Soc*. **2001**, *123*, 9718-9719.

[69] Daugulis, O.; Brookhart, M. *Organometallics* **2004**, *23*, 527-534.

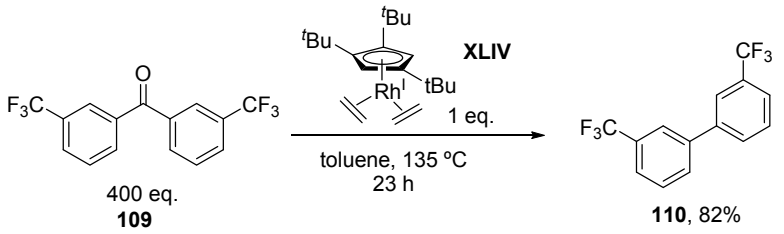


Figure 3.19

In 2008, Ruhland[70] and co-workers described another chelation-assisted strategy to promote the C-C bond activation event. They showed that it is possible to carry out the cleavage of sp^2-sp^2 C-C bond of biaryl molecules with a phosphonite directing group (Figure 3.20). When **111** was mixed with $Ni(PPh_3)_2(CO)_2$, phosphine atoms coordinated to the Ni center and two equivalents of PPh_3 were released (**XLV**). After increasing the temperature up to 95 ºC under CO atmospheres (5 bars), the corresponding benzophenone Ni-complex **XLVI** was isolated in 20% yield, that formally derives from a Csp^2-Csp^2 activation followed by CO insertion.

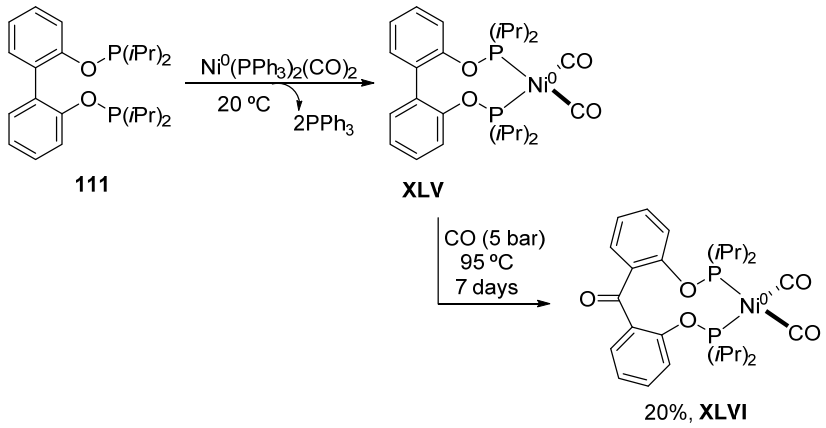


Figure 3.20

[70] Ruhland, K.; Obenhuber, A.; Hoffmann, S. D. *Organometallics* **2008**, *27*, 3482-3495.

3.3 Catalytic approaches for the activation of unstrained C-C single bonds

3.3.1 Chelation assisted transformations

The catalytic activation of unstrained C-C single bonds has received comparatively less attention, an observation that goes in line with the inherent difficulties associated to such transformation when compared with strained motifs. In 1998, the Milstein group[71] reported a catalytic version of their bidentate phosphine pincer ligand under H_2 pressure or excess of $HSi(OEt)_3$ (Figure 3.21).

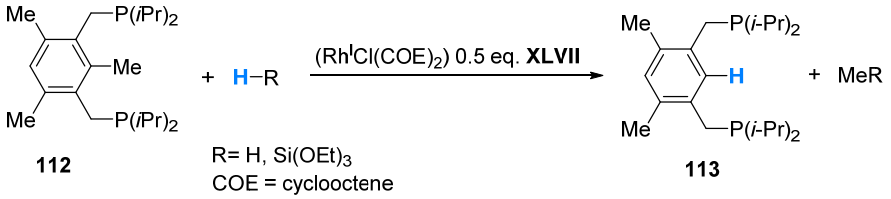


Figure 3.21

It was proposed that the first step in the catalytic cycle consisted of the hydrogenation of the cyclooctene ligand (COE) prior substrate complexation to the Rh(I) catalyst **XLVII** to form **XLVIII**. In this manner, the targeted C-C bond is proximal to the Rh^I center, thus triggering an oxidative addition, furnishing the corresponding Rh(III)-complex **XLIX**. Under H_2 atmospheres, methane is released by hydrogenolysis of the methyl-Rh^{III} bond and complex **L** evolved via a subsequent reductive elimination to form Rh(I) complex **LI** that undergoes an exchange with another molecule of substrate (**112**) to produce the desired product (**113**) and regenerate the active Rh(I) species (Figure 3.22).

[71] Liou, S-Y.; Van der Boom, M. E.; Milstein, D. *Chem. Commun*. **1998**, 687-688.

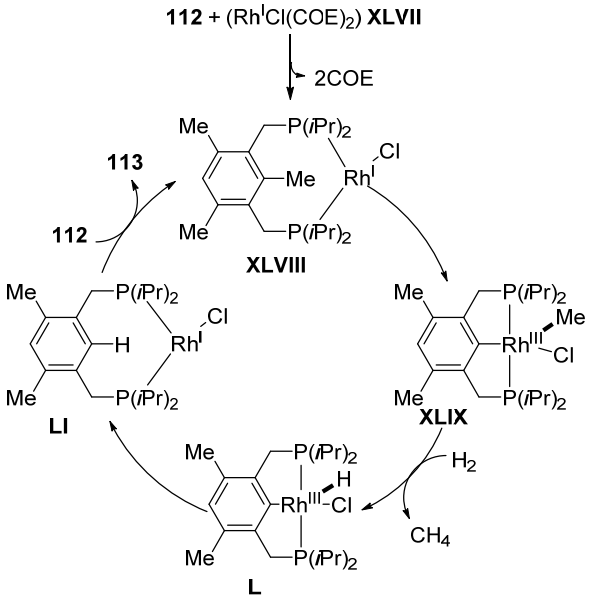


Figure 3.22

Subsequently, Murai [72] and co-workers described a chelation-assisted decarbonylation of allyl phenyl ketones via activation of unstrained C-C bonds, using an oxazoline motif as a directing group for the decarbonylation of alkyl phenyl ketones **114** with $Ru_3(CO)_{12}$ (5 mol%) as catalyst under 5 atm of CO (Figure 3.23).

[72] Chatani, N.; Le, Y.; Kakiuchi, F.; Murai, S. *J. Am. Chem. Soc*. **1999**, *121*, 8645-8646.

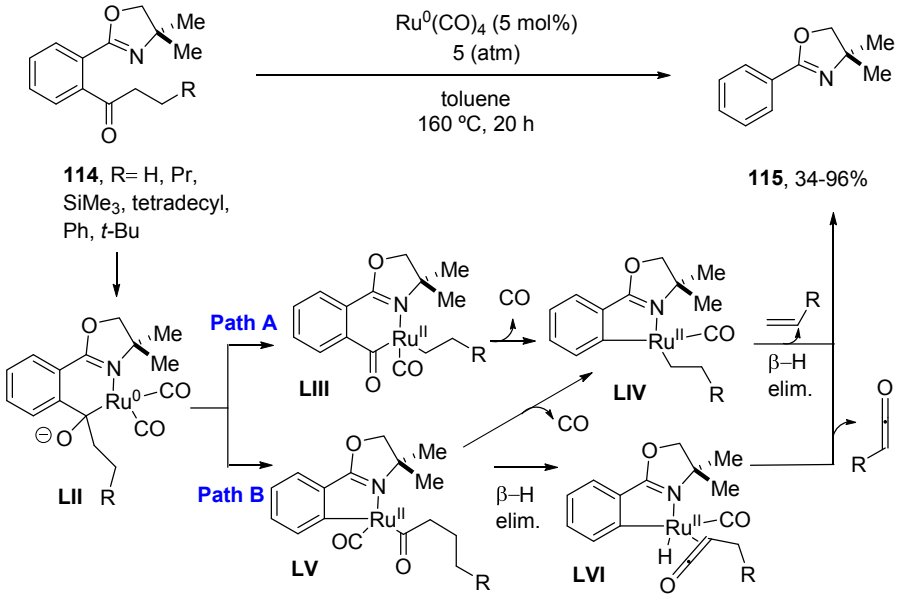


Figure 3.23

The authors proposed two different mechanistic routes that are initiated via coordination of the Ru-complex to **114** followed by addition across the carbonyl bond to deliver **LII**. At this point, two different C-C single bonds can be activated. The cleavage of the Csp^3-Csp^3 C-C bond (**Path A**) would render a six-membered metalacycle **LIII** that after decarbonylation will afford the complex **LIV**. Final β-hydride elimination followed by reductive elimination would take place to provide the final product **115**. Alternatively, the activation of the Csp^2-Csp^3 C-C bond gives acces to the five-membered metalacycle **LV** that can extrude CO to afford the same intermediate **LIV** or can undergo β-hydride elimination to provide complex **LVI** and a molecule of ketene (**Path B**). A final reductive elimination would occur to obtain the desired product **115**.

In 2002, the Jun group [73] reported a C-C activation for the decarbonylation of unstrained ketones **116** using Wilkinson catalyst and 2-amino-3-picoline (**117**) as a directing group (Figure 3.24).

[73] Jun, Ch.; Lee, H. *J. Am. Chem. Soc*. **1999**, *121*, 880-881.

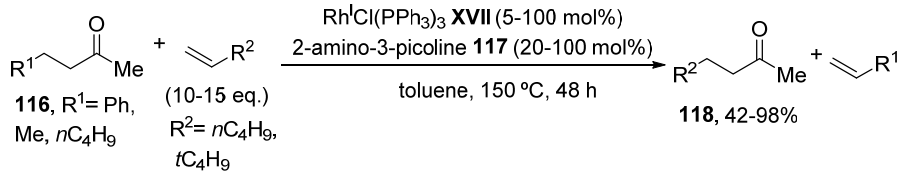


Figure 3.24

Figure 3.25 illustrates the proposed catalytic cycle consisting of an initial condensation of ketone (**116**) with 2-amino-3-picoline (**117**) to provide the imine **LVII**. Coordination of the Rh(I)-catalyst (**XVII**) to the pyridine motif promotes a C-C bond activation en route to rhodacycle **LVIII** which can undergo β-hydride elimination to give rise to the corresponding alkene and complex **LIX**. Migratory insertion into 1-hexene delivers intermediate **LX**, that subsequently triggers a reductive elimination, forming the imine **LXI** while regenerating the Rh(I) catalyst (**XVII**). The corresponding hydrolysis of **LXI** provides the desired product **118** and regenerates the 2-amino-3-picoline (**117**).

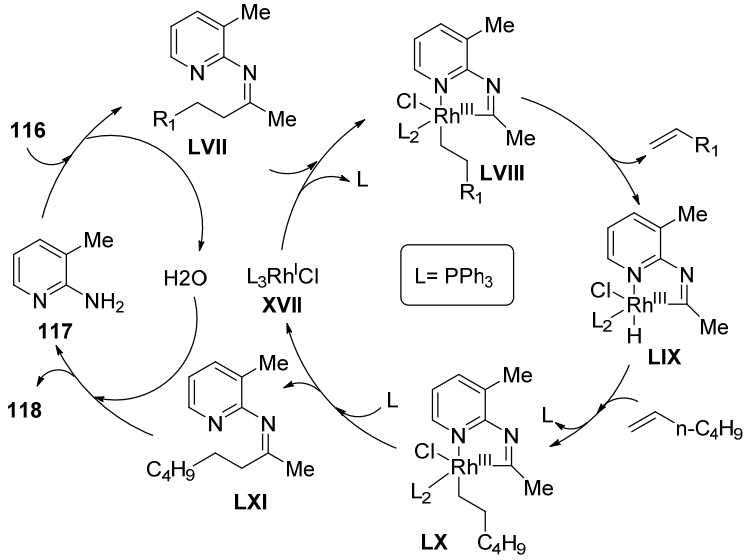


Figure 3.25

Prompted by the use of 2-amino-3-picoline (**117**) in C-C bond cleavage, Jun[74] and co-workers described an assisted C-C activation strategy for ring-opening of different cycloalkanones. Interestingly, cyclohexanone **120** and cyclopentanone **121** were obtained in a combined 82% yield (76:24 ratio) when the reaction was carried out with cycloheptane imine **119** without 1-hexene (Figure 3.26).[75] The authors propose a mechanism similar to the one outlined in Figure 3.25. In absence of 1-hexene however, the intermediate **LIX** reinserts into the appended olefin in a 6-exo fashion. A final reductive elimination and hydrolysis provides the corresponding cyclohexanone **120**. As for product **121**, β-hydride elimination after reinsertion of the olefin takes place, followed by 5-exo-trig insertion and a final reductive elimination/hydrolysis event.

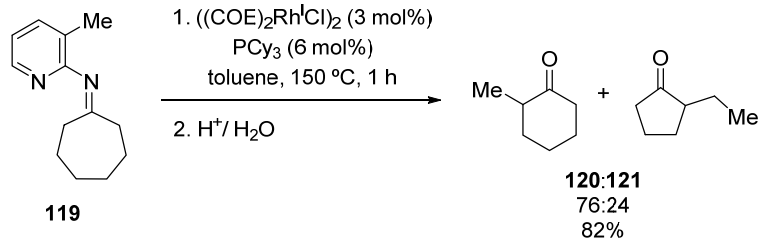


Figure 3.26

In 2009, Douglas and Dreis[76] discovered an intramolecular quinoline-directed alkene carboacylation reaction via C-C bond activation. The use of substrate **122** in refluxing toluene with $(RhCl(C_2H_4)_2)_2$ (**LXII**) (5 mol%) provides the formation of the desired product **123** containing a quaternary stereogenic center (Figure 3.27).

[74] Jun, Ch-H.; Lee, H.; Lim, S-G. *J. Am. Chem. Soc*. **2001**, *123*, 751-752.

[75] Jun, Ch-H.; Moon, Ch. W.; Lee, H.; Lee, D-Y. *J. Mol. Catal. A* **2002**, *189*, 145-156.

[76] Dreis, A. M.; Douglas, Ch. J. *J. Am. Chem. Soc*. **2009**, *131*, 412-413.

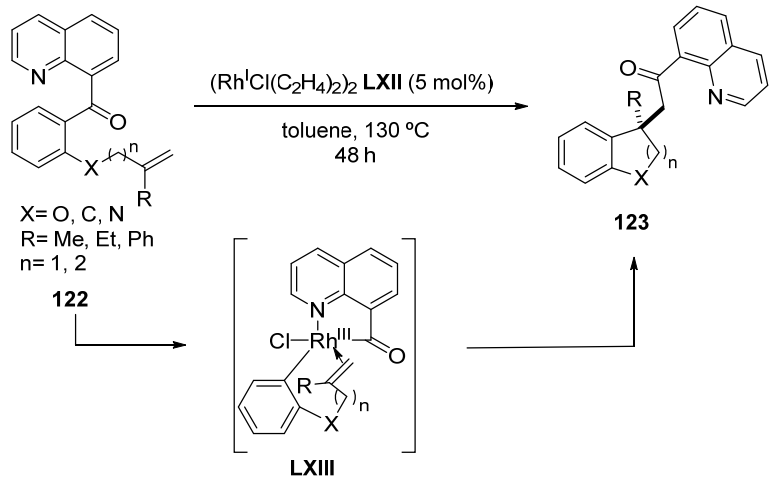


Figure 3.27

A few years later, Johnson and co-workers[77] studied the mechanism for this transformation (Figure 3.28). They proposed that the reaction is first-order in substrate, first-order in catalyst and the C-C bond activation was the rate-limiting step. The proposed mechanism starts with the coordination of the Rh(I)-catalyst **XVII** to the substrate **122** to get the complex **LXIV**. Then, C-C activation occurs affording complex **LXV**, followed by a rearrangement to provide **LXVI**; further reductive elimination (**LXVII)** and a final exchange with **122** gives rise to **123** with concomitant regeneration of Rh(I) catalyst **LXII**.

[77] Johnson, J. B.; Rathbun, C. *J. Am. Chem. Soc*. **2011**, *133*, 2031-2033.

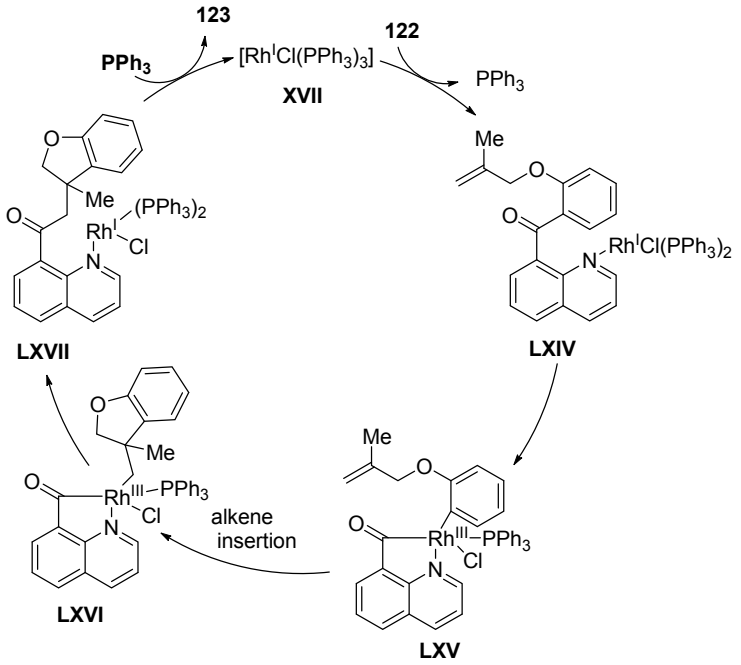


Figure 3.28

In 2012, Shi[78] and co-workers published a pyridine-assisted C-C bond activation for the decarbonylation of aryl/alkenyl/alkyl aryl ketones (**124**) (Figure 3.29). The transformation begins with the coordination of the Rh(I) catalyst **LXVIII** followed by C-C bond activation (**LXIX**) and decarbonylation (**LXX)** thus setting the stage for obtaining **125** via reductive elimination.

[78] Lei, Z-Q.; Li, H.; Li, Y.; Zhang, X-S.; Chen, K.; Wang, X.; Sun, J.; Shi, Z. *Angew. Chem. Int. Ed*. **2012**, *51*, 2690-2694.

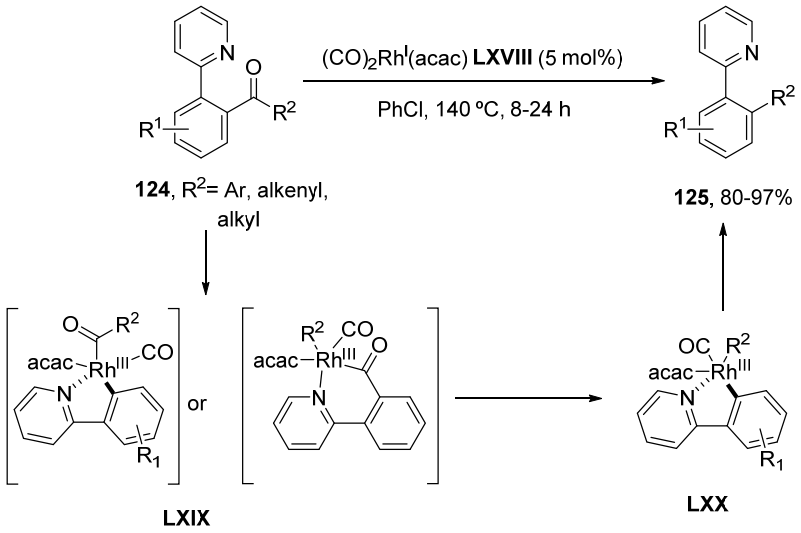


Figure 3.29

3.3.2 Polarized C-C single bonds

In 2012, Fillion [79] and co-workers reported the selective reductive cleavage of unstrained benzylic C-C bonds in benzylated Meldrum acids derivatives (**126**) (Figure 3.30). They exposed **126** to 15 mol% of Pd/C in the presence of 1 atm of H_2 for 24 h in MeOH at room temperature to induce the C-C bond scission, which delivered the corresponding benzylic products **127** and Meldrum acid. The authors observed significant electronic effects in the transformation: while high yields were obtained (65-96%) for *ortho*- and *para*-substituted compounds, no reaction occurred with *meta*-substituted substrates. The steric hindrance at the benzylic position also plays an important role in this transformation. Specifically, while high yields were obtained with a methyl groups located at the benzylic position, the presence of an isopropyl group shuts down the reactivity.

[79] Wilsily, A.; Nguyen, Y.; Fillion, E. *J. Am. Chem. Soc.* **2009**, *131*, 15606-15607.

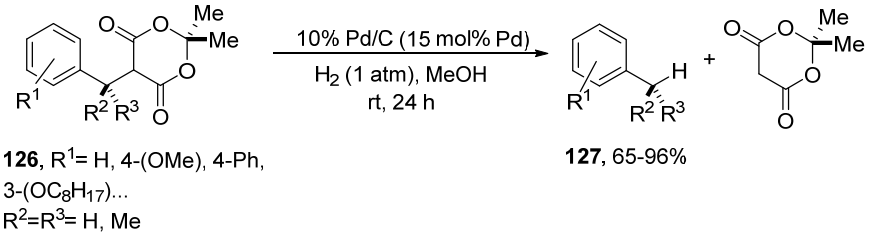


Figure 3.30

Arisawa, Yamaguchi [80] and co-workers showed a Rh-acyl transfer without the assistance of a directing group (Figure 3.31). A variety of unsymmetrical ketones were prepared from benzyl ketones **128** and thioesters **129** using $RhH(CO)(PPh_3)_3$ (**LXXI**) and 1,2-bis(diphenylphosphino)benzene (dppbz) in *N*,*N*'-dimethylimidazolidinone (DMI) at 150 ºC for 12 h. The authors suggested that the C-C activation event should be triggered by a Rh(I)-complex to deliver a $R^1C(O)$-Rh-C_{benzyl} intermediate, which can exchange with the thioester $R^2C(O)$-SMe by forming a $R^2C(O)$-Rh-C_{benzyl} intermediate that ultimately forms **130** after reductive elimination (Figure 3.31).

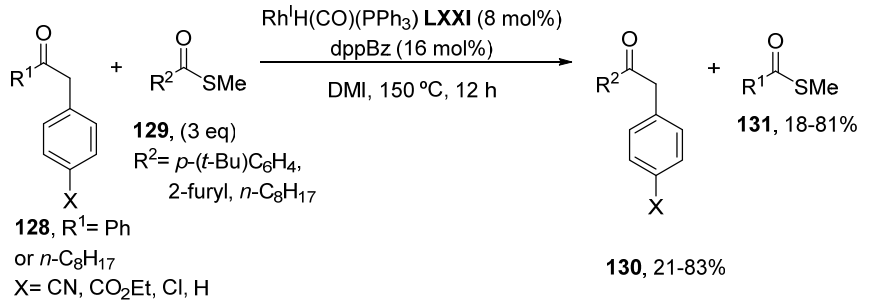


Figure 3.31

In 2013, Dong[81] and co-workers reported a catalytic version of the Rh-mediated decarbonylation of diynones previously described by Müller (Figure 3.32). The authors postulated that the key feature for success was

[80] Arisawa, M.; Kuwajima, M.; Toriyama, F.; Li, G.; Yamaguchi, M. *Org. Lett*. **2012**, *14*, 3804-3807.

[81] Dermenci, A.; Whittaker, R. E.; Dong, G. *Org. Lett*. **2013**, *15*, 2242-2245.

the use of a bidentate phosphine ligand that was believed to facilitate the elimination of the CO for catalyst regeneration. The wide scope of the reaction shows that there are no electronic or steric effects involved, obtaining good yields in almost all cases analyzed.

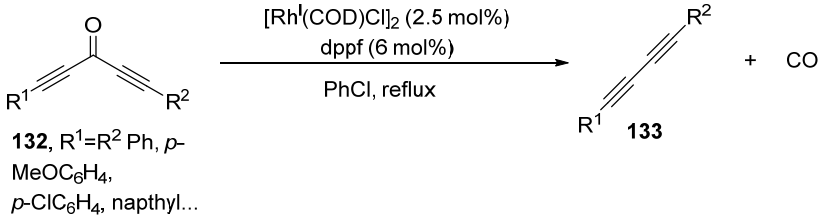


Figure 3.32

The proposed mechanism is depicted in Figure 3.33. Coordination of the Rh(I) species **LXXII** to the substrate **132** provides intermediate **LXXIII**. Then C-C activation gives Rh(III)-complex **LXXIV**, which, after decarbonylation affords intermediate **LXXV**. Finally, a reductive elimination provides the desired product **133** and the regeneration of the Rh(I)-active species (**LXXII**).

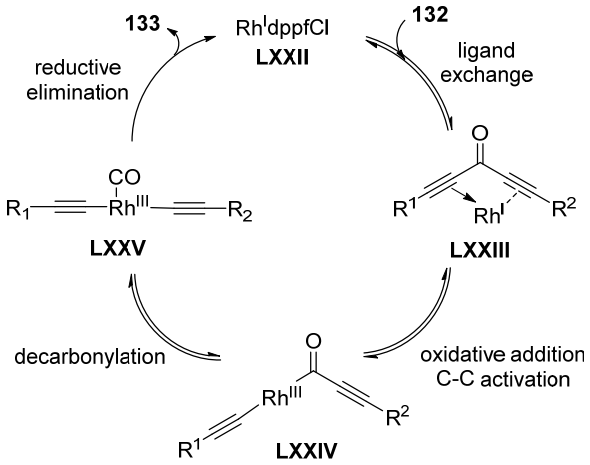
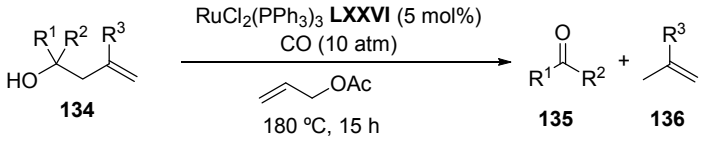


Figure 3.33

In 1998 Kondo and Mitsudo[82] developed the first activation of a C-C(OH) bond from tertiary homoallylic alcohols (**134**) (Figure 3.34). The selective catalytic C-C bond cleavage via β-carbon elimination was carried out using $RuCl_2(PPh_3)_3$ catalyst (**LXXVI**) and CO atmosphere (10 atm). Figure 3.35 shows a plausible mechanism based on the oxidative addition of the active Ru(II)-species into the hydroxy group to provide intermediate **LXXVII**. Then, the alkoxy ruthenium intermediate undergoes β-alkyl elimination (**LXXVIII**) with the release of the corresponding ketone **135**, which constitutes the driving force of the reaction. It is believed that the π-acidity of the CO plays an important role in the reductive elimination to afford the corresponding product **135** and the active catalyst **LXXVI** (Figure 3.35).



Entry	R^1	R^2	R^3	Yield (%)
136a	Ph	Me	H	94
136b	Ph	Ph	H	87
136c	Bu	Bu	H	71
136d	Ph	Me	Me	85

Figure 3.34

[82] Kodoi, K.; Nishinaga, E.; Okada, T.; Morizaki, Y.; Watanabe, Y.; Kondo, T.; Mitsudo, T-a. *J. Am. Chem. Soc*. **1998**, *120*, 5587-5588.

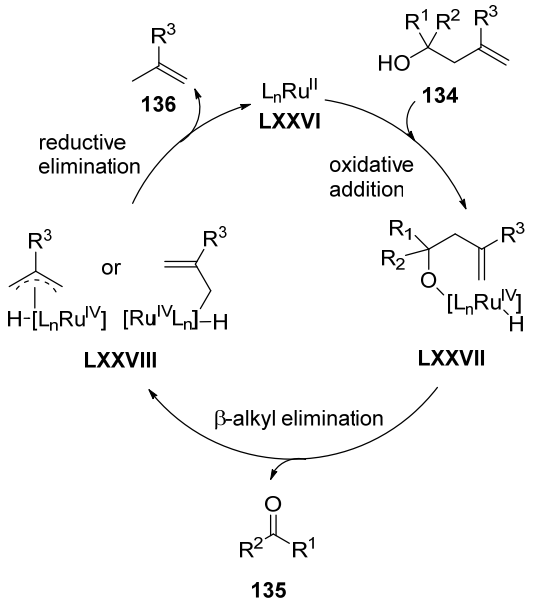
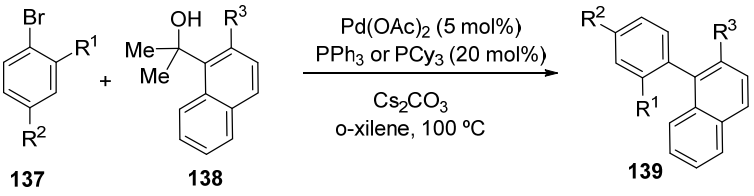


Figure 3.35

Miura[83] and co-workers reported that α,α-disubstituted aryl metanols could react with aryl bromides through palladium(0) catalyzed C-C bond activation to obtain biaryl products (Figure 3.36). They showed that the bulky phosphine ligand used plays an important role for the C-C cleavage.



Entry	R^1	R^2	R^3	Ligand	Yield 139 (%)
139a	H	H	H	PPh_3	94
139b	Me	H	H	PPh_3	72
139c	H	Me	H	PCy_3	82
139d	H	COOEt	H	PPh_3	91
139e	H	H	OMe	PPh_3	82

Figure 3.36

[83] Terao, Y.; Wakui, H.; Satoh, T.; Nomura, M.; Miura, M. *J. Am. Chem. Soc*. **2001**, *123*, 10407-10408.

In 2013, the Johnson[84] group studied the Miura C-C bond cleavage in more detail (Figure 3.37). They proposed a catalytic scenario based on oxidative addition of **137** to the Pd(0) species (**LXXIX**), followed by ligand exchange, triggering a β-aryl elimination that delivers benzophenone and final biaryl **139** via reductive elimination.

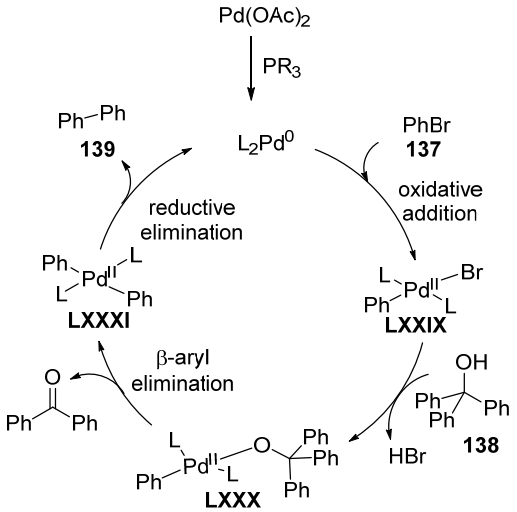


Figure 3.37

In 2006, Yorimitsu, Oshima et al.[85] disclosed a new and important palladium catalyzed allylation of aryl halides with homoallylic alcohols **140** as substrates (Figure 3.38). Their strategy was based on the retro-allylation reaction of **LXXXIII** via a six-membered transition state to afford σ-allyl(aryl)palladium complex **LXXXIV** that undergoes a final reductive elimination to provide the desired allylated product **142** (Figure 3.39).

[84] Bour, J. R.; Green, J. C.; Winton, V. J.; Johnson, J. B. *J. Org. Chem*. **2013**, *78*, 1665-1669.
[85] a) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc*. **2006**, *128*, 2210-2211. b) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc*. **2007**, *129*, 4463-4469.

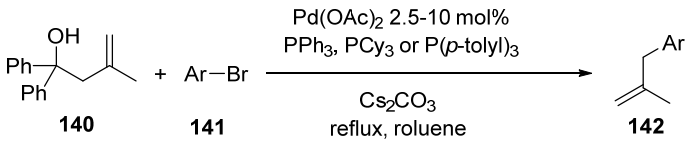


Figure 3.38

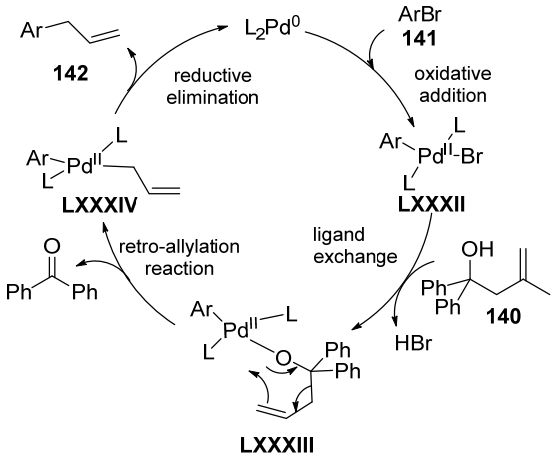


Figure 3.39

The same group [86] reported a Pd(TFA)-catalyzed 2-pyridylmethyl transfer to organic halides (Figure 3.40). 2-(2-pyridyl)ethanol derivatives **143** undergo β-alkyl elimination to generate **LXXXVIII** that triggers a reductive elimination to obtain the final product **145** and regenerate the catalyst (Figure 3.41). The authors demonstrated that the location of the nitrogen atom was crucial for the C_{sp3}-C_{sp3} cleavage. Indeed, no reaction occurs when 2-(4-pyridyl)ethanol derivatives are used instead of 2-(2-pyridyl)ethanol derivatives **143**.

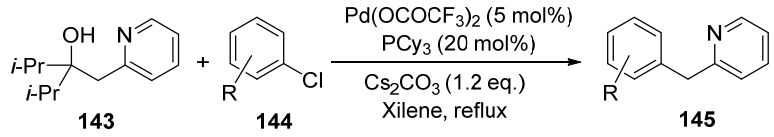


Figure 3.40

[86] Niwa, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2007**, *46*, 2643-22645.

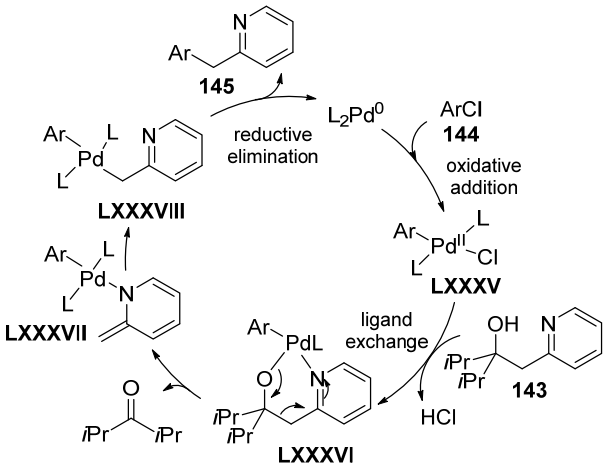


Figure 3.41

In 2009, Chiba[87] and co-workers published a Pd(II)-catalyzed ring-expansion reaction using cyclic 1,2-azidoalcohols (**146)** to provide pyridine and isoquinoline derivatives (**147**) via C-C bond activation followed by intramolecular C-N bond formation (Figure 3.42).

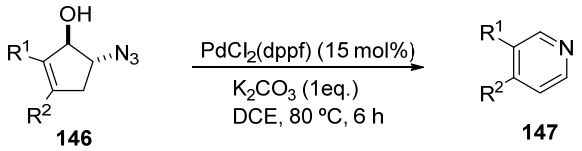


Figure 3.42

The proposed mechanism (Figure 3.43) was based on the formation of palladium (II) alkoxide **LXXXIX** from 1,2-azidoalcohol derivatives **146** with $PdCl_2$(dppf) and a base. The elimination of nitrogen gas gives rise to intermediate **XC**, setting the stage for an intramolecular nucleophilic attack of the iminyl moiety to the aldehyde motif **XCI**. A final protonation of **XCI** and subsequent dehydration provides the desired product **147**.

[87] Wang, Y-F.; Xu, Y-J.; Chiba, S.; *J. Am. Chem. Soc*. **2009**, *131*, 12886-12887.

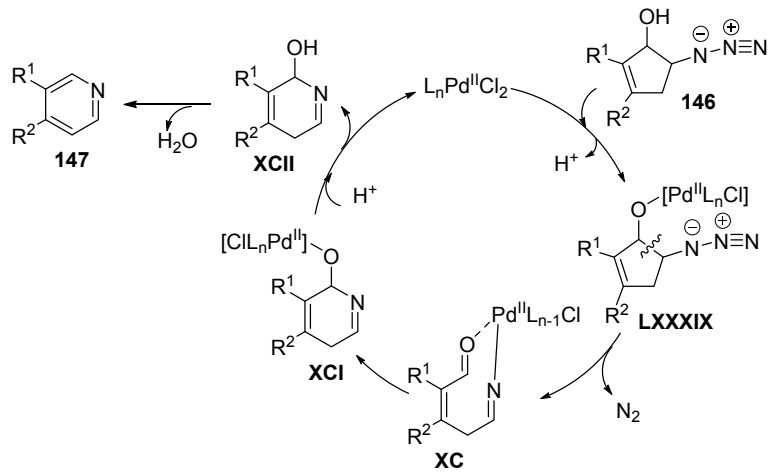


Figure 3.43

Prompted by the work of Oshima, Nishimura and Hayashi's[88] groups disclosed a Rh-catalyzed arylation of α,β-unsaturated carbonyl compounds with trisubstituted aryl methanols via C-C bond-cleavage (Figure 3.44).

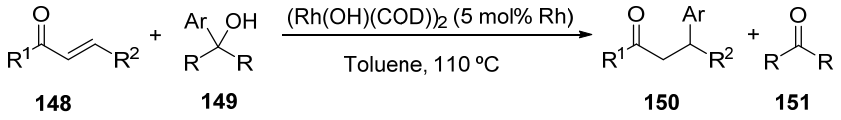


Figure 3.44

The reported catalytic cycle is depicted in Figure 3.45. β-aryl elimination was proposed to be the key step for generating the Ar-Rh species **XCIV** with the release of the corresponding ketone **151**. Insertion of the alkene moiety **148** into the Rh-Ar bond generates intermediate **XCV**, which promotes an exchange with **149**, delivering **150**.

[88] Katoh, T.; Nishimura, T.; Hayashi, T. *Angew. Chem. Int. Ed*. **2007**, *46*, 4937-4939.

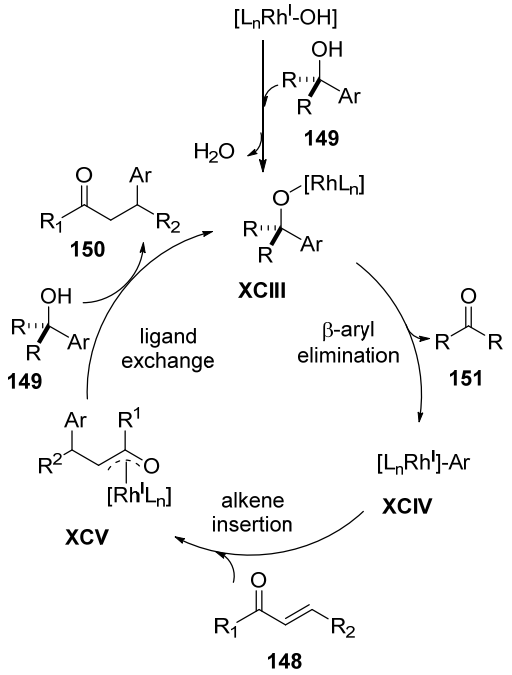


Figure 3.45

The chiral version of this transformation was also developed by the same authors using chiral ligands such as (*S*,*S*)-Bn-bod providing excellent yields and enantioselectivities (Figure 3.46).[88]

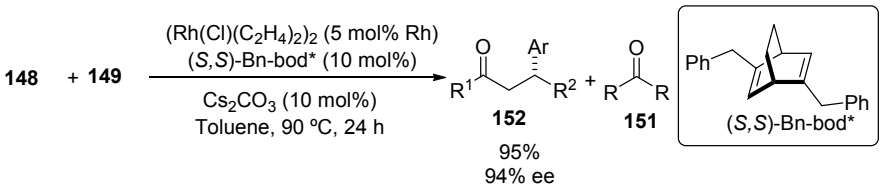


Figure 3.46

Chapter 4. Pd-catalyzed cross-coupling reaction of phenyl(piperidin-1-yl) carbanions with aryl halides

4.1 Objectives

The objectives for this chapter are the following:

1- To develop a new strategy to carry out the cross-coupling of in situ generated phenyl(piperidin-1-yl) carbanions with aryl halides via C-C single bond-cleavage of a 1,2-amino alcohol.

2- To develop a catalytic protocol capable of operating with high turnover numbers.

4.2 β-Amino alcohols as useful scaffolds for organic synthesis

1,2-Amino alcohols are an important class of compounds that are present in a large variety of biologically active compounds.[89] For example, (+)-Castanospermine is a polyhydroxilated alkaloid known to be a potent inhibitor of α- and β-glucosidases.[90,89d] Another abundant class is the cyclic amino alcohol family; for instance, quinine is a drug frequently used for malaria treatment.[91a] In general, it is common to find these entities in a wide number of compounds that display important biological properties. For example, Indinavir is an antiretroviral drug used in the HIV treatment whereas Amikacina is frequently used as antibiotic (Figure 4.1). [91b-c]

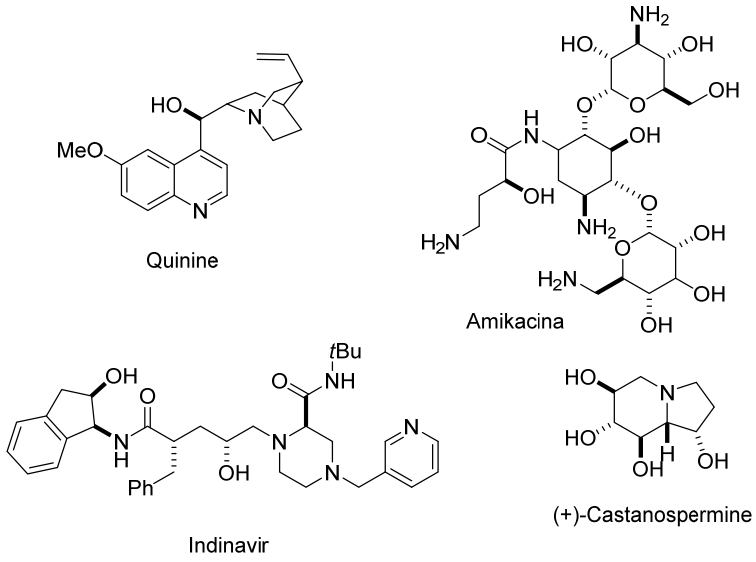


Figure 4.1

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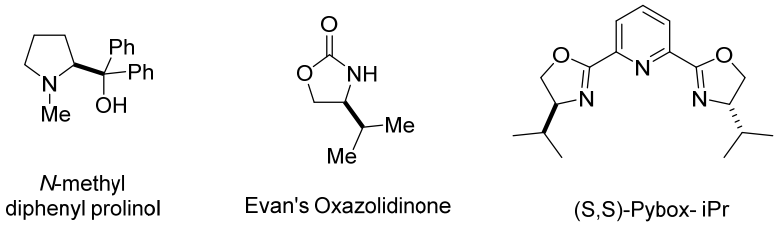
[89] (a) Bergmeier, S. C. *Tetrahedron*, **2000**, 2561-2576. (b) Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*, 835-875. (c) Kang, S. H.; Lee, H-S. Synlett **2004**, *10*, 1673-1685. (d) Michael, J. P. *Nat. Prod.Rep.* **1999**, *16*, 675-696.

[90] (a) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 520-542.

[91] (a) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc*. **1944**, *66*, 849 (b) Askin, d.; Eng, K. E.; Rossen, K.; Purick. R. M.; Wellis, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett*. **1994**, 35, 673-676. (c) Nicolaou, K. C.; Boddy, C. N. *J. Am. Chem. Soc.* **2002**, *124*, 10451-10455.

Apart from being ubiquitous in a number of pharmaceutical compounds, 1,2-amino alcohols are frequently used as ligands and chiral auxiliaries in asymmetric synthesis and catalysis (Figure 4.2). [89b, 92] Indeed, the ease for fine-tuning of the 1,2-amino alcohol core has contributed to the establishment of these motifs as chiral inductors in a myriad of catalytic transformations.[93]



N-methyl diphenyl prolinol | Evan's Oxazolidinone | (S,S)-Pybox- iPr

Figure 4.2

Our group has long been interested in the design of new families of easily-tuned β-amino alcohols for asymmetric catalytic reactions.[94] Among these, **153** was found to be among the most active ligands for promoting the enantioselective addition of dialkyl and diphenylzinc to aldehydes en route to highly enantioenriched alcohols.[94a] The ability to synthesize **153** at large scale, together with its excellent catalytic activity prompted our group to

---

[92] (b) Frantz, D. E.; Fässler, R.; Carriera, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 1806-1807.

[93] (a) Shibata, S.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc*. **1987**, *109*, 5551-5553. (b) Prakash, I.; Schaad, D. R.; Ager, D. J. *Chem. Rev***. 1998**, *96*, 835-875. (c) Lam, W-L.; Kitagawa, H.; Sugiura, M.; Koboyashi, S. *Chem. Rev*. **2002**, *102*, 2227-2302. (d) Kriening, S.; Evagelou, A.; Claasesn, B.; Baro, A.; Laschat, S. *Eur. J. Org. Chem*. **2014**, *30*, 6720-6733.

[94] (a) Alvarez-Larena, A.; Pinella, J-F.; Reddy, K. S.; Vidal-Ferran, A.; Solà, Ll.; Moyano, A.; Perciàs, M. A.; Riera, A. *J. Org. Chem*. **1998**, *63*, 7078-7082. (b) Reddy, K. S.; Solà, Ll.; Moyano, A.; Riera, A.; Pericas, M. A. *J. Org. Chem*. **1999**, *64*, 3969-3974. (c) Jimeno, C.; Vidal-Ferran, A.; Moyano, A.; Riera, A.; Pericas, M. A. *Tetrahedron Lett*. **1999**, *40*, 777-780. (d) Jimeno, C.; Reddy, K. S; Vidal-Ferran, A.; Moyano, A.; Riera, A.; Pericas, M. A. *Org. Lett*. **2000**, *2*, 3157-3159. (e) Pericàs, M. A.; Castellnou, D.; Rodríguez, I.; Riera, A.; Solà, Ll. *Adv. Synth. Catal*. **2003**, *345*, 1305-1313.

immobilize this ligand. To such end, a slightly modified immobilized version of the parent ligand was prepared (**155)** (Figure 4.3).[94e]

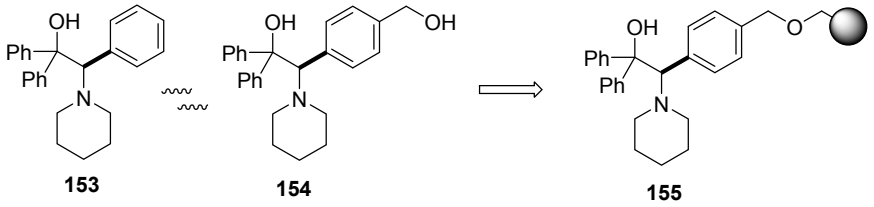
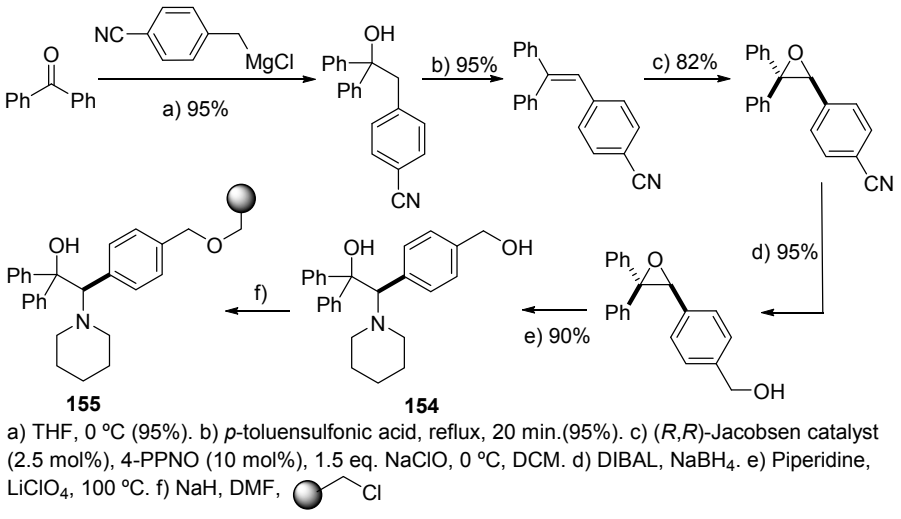


Figure 4.3

The synthesis of **155** consisted of an addition of the Grignard reagent to the benzophenone followed by dehydration to deliver a triphenyl ethylene derivative (Figure 4.4).[95] Enantioselective epoxidation under Jacobsen's conditions and a subsequent reduction of the nitrile provided the corresponding alcohol, setting the stage for a ring-opening of the epoxide with piperidine and $LiClO_4$. The amino alcohol **154** was finally supported on a Merrifield resin via the ether linkage by a simple nucleophile attack to the chloromethylene group of the resin **155** (Figure 4.4).



a) THF, 0 ºC (95%). b) *p*-toluensulfonic acid, reflux, 20 min.(95%). c) (*R*,*R*)-Jacobsen catalyst (2.5 mol%), 4-PPNO (10 mol%), 1.5 eq. NaClO, 0 ºC, DCM. d) DIBAL, $NaBH_4$. e) Piperidine, $LiClO_4$, 100 ºC. f) NaH, DMF,

Figure 4.4

[95] Vidal-Ferran, A.; Bampos, N.; Moyano, A.; Pericàs, M. A.; Riera, A.; Sanders, J. A. M. *J. Org. Chem*. **1998**, *63*, 6309-6318.

Although counterintuitive, the final treatment with the chloromethyl group of the resin turned out to be particularly problematic, as **156** was observed in significant amounts (Figure 4.5). Such compound can be visualized as the fragmentation of the β-amino alcohol core via C-C cleavage promoted by strong bases (NaH) (Figure 4.5).

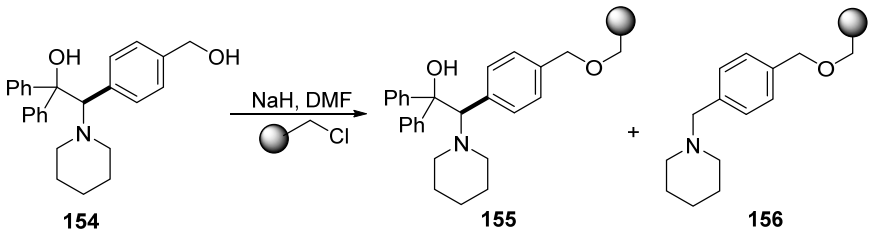


Figure 4.5

The fragmentation observed, is somewhat reminiscent from the Grobb fragmentation (Figure 4.6).[96a,b] For example, *N*-halo α-amino acids are known to produce ketones via a base-promoted decarboxylation followed by a hydrolysis event. A related fragmentation was observed by Risch when using γ-amino alcohols in which an ammonium salt served as a leaving group (Figure 4.6).[96c] Unlike these precedents, the fragmentation of **155** did not possess a good leaving group, an intriguing observation that makes this transformation rather unique. [96]

[96] (a) Grob, C. A.; Baumann. W. *Helv. Chim. Acta* **1955**, *38*, 594-610. (b) Grob, C. A.; Kiefer, H. R.; Lutz, H. J.; Wilkens, H. J. *Helv. Chim. Acta* **1967**, *60*, 416-431. (c) Mölm, D.; Flörke, U.; Risch, N. *Eur. J. Org. Chem*. **1998**, 2185-2192. (d) Santaballana, J. A.; Armesto, X. L.; L. Canle. M.; García, M. V. *Chem. Soc. Rev*. **1998**, *27*, 453-460.

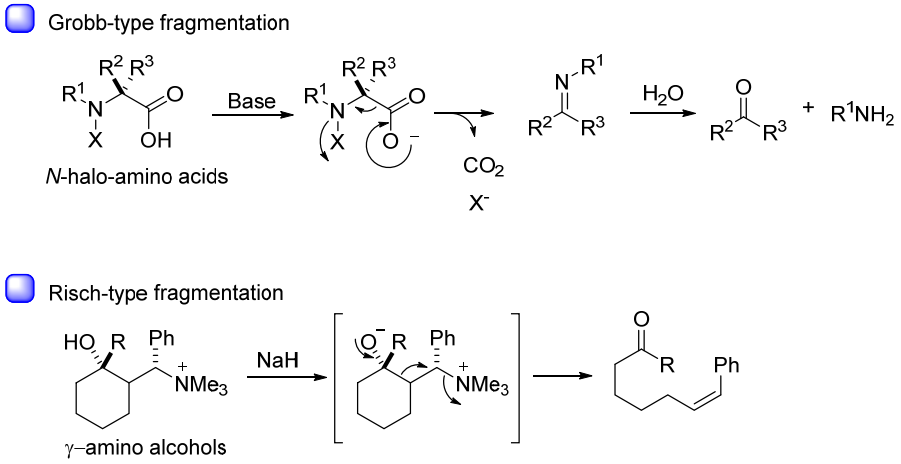


Figure 4.6

Intrigued about these results, experimental and theoretical studies were conducted to study the fragmentation of different β-amino alcohols and to shed light into the targeted C-C bond cleavage. [97] After some experimentation, it was concluded that the thermal C-C bond-cleavage is directed basically by the structure of the substrate. Specifically, the fragmentation is controlled by the nature of the substituents located at the β-carbon; the more aromatic substituents located at the α-position of the amino moiety, the easier the cleavage will be. Such a finding can be correlated from the stabilization of the α-amino carbanions resulting from the fragmentation (Figure 4.7).

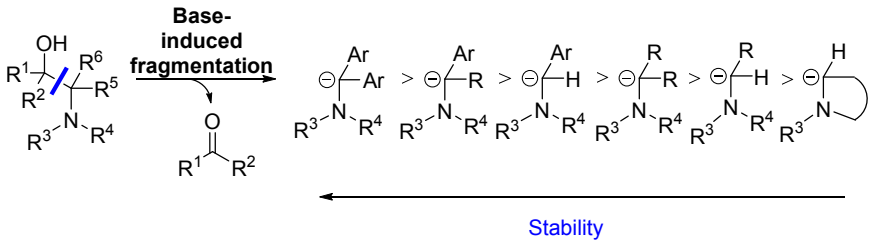


Figure 4.7

[97] Dani Font PhD manuscript (page 99).

4.3 General overview for the obtention of α-amino carbanions

A close look into the literature data indicates that there are a number of procedures for generating α-carbanions from primary and secondary amines. [98] Indeed the generation of α-carbanions from primary and secondary amines is facilitated by the presence of an activating group covalently attached to the nitrogen atom. Different functional groups such us nitrosamines, amides, formamidines or carbamates are useful activating agents for the α-deprotonation of the primary and secondary amines (Figure 4.8).

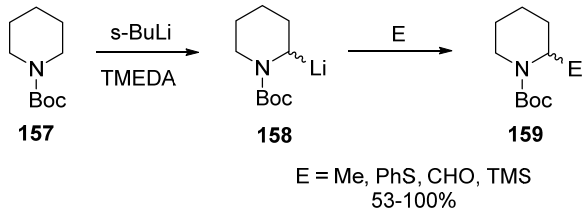


Figure 4.8

In sharp contrast, the generation of α-carbanions of tertiary amines has been less explored. [99] Unlike the utilization of primary or secondary amines, the absence of N-H bond does not allow the introduction of a directing group that would facilitate the deprotonation event. In general, the utilization of non-stabilized α-amino carbanions as synthons in organic synthesis is virtually absent due to the lack of reliable methods for their generation. The main strategies developed to such purposes are the following. (1) Direct deprotonation, (2) Formation of amine-Lewis acid complexes, (3) Metal-lithium exchange and (4) Reductive cleavage scenarios.

---

[98] (a) Zajdel, J. W.; Beak, P. *Chem. Rev.* **1984**, *84*, 471-523. (b) Thayumanavan, S.; Park, Y. S.; Gallagher, D. J.; Basu, A.; Beak. P. *Acc. Chem.Res.* **1996**, *29*, 552-560.

[99] (a) Singh, P.; Kessar, V. S.; *Chem. Rev.* **1997**, *97*, 721-737. (b) Qi, M.; Katritzky, A. R. *Tetrahedron* **1998**, *54*, 2647-2668.

(1) Direct deprotonation. As expected, the utilization of strong bases limit the applicability of these processes. Additionally, low yields are generally achieved using this strategy. Kinetic measurements of the acidity of the hydrogen located at the α-carbon demonstrated that the C-H abstraction is several orders of magnitude lower that those possessing sulfur or a phosphine atoms. Nonetheless, in 1965, Lepley[100] and Giumanini obtained 33% of **162** from the *N*,*N*-dimethylaniline (**160**), by using 1-iodobutane (**161**) and *n*-BuLi in hexanes (Figure 4.9).

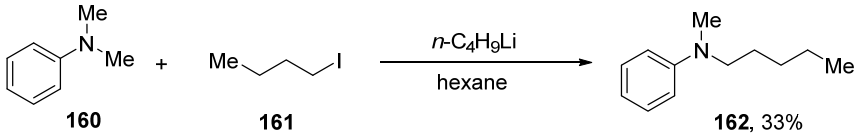


Figure 4.9

In 1974, Smith reported the lithiation of *N*-methylpyrrolidine, *N*-methylpiperidine, triethylamine and trimethylamine in refluxing hexane followed by treatment with an appropriate electrophilic component (Figure 4.10).[101]

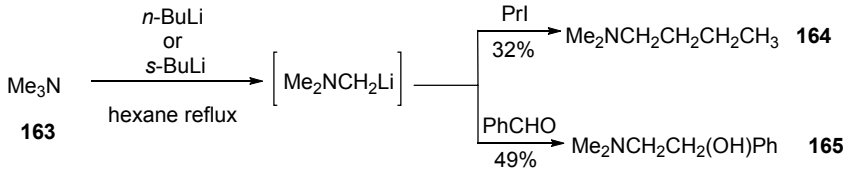


Figure 4.10

In 1984, Ahlbrecht and Dollinger observed the corresponding α-metalated piperidine using superbases such as *s*-BuLi/*t*-BuOK (Figure

[100] (a) Giumanini, A. G.; Lepley, A. R. *Chem. Ind*. (London) **1965**, 1035-1036. (b) Giumanini, A. G.; Lepley, A. R. *J. Org. Chem*.**1966**, *31*, 2055-2060. (c) Lepley, A. R.; Khan, W. A. *J. Org. Chem*.**1966**, *31*, 2061-2064. (d) Lepley, A. R.; Khan, W. A. *J. Chem. Soc., Chem. Commun*. **1967**, 1198-1199.

[101] Smith, W. N. *Adv. Chem*. Ser. **1974**, *130*, 23-55.

4.11).[102] As expected, the reaction was regioselective and the less acidic methylene units did not get deprotonated. Final treatment with either octyl bromide or PhCHO delivered **169** and **171** in 70 and 73% yield, respectively.

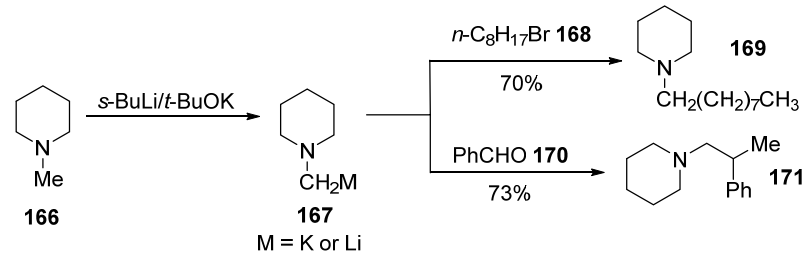


Figure 4.11

In line with lower pka of benzylic C-H bonds, it was found that a cocktail based on *n*BuLi/KO^{t}Bu results in **174** when using **172** as starting precursor followed by benzophenone treatment. Interstingly, the use of *n*BuLi results in a directed ortho metalation pathway **173** (Figure 4.12). [103]

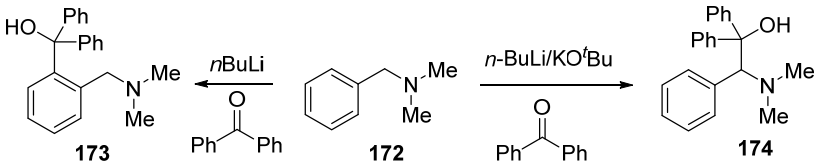


Figure 4.12

(2) Formation of amine-Lewis acid complexes. In 1991, Kassar reported the deprotonation of preformed amine-BF_3 complexes. [104] Thus, *N*-methylpiperidine (**166**) was treated with boron trifluoride etherate to forn the complex **175**, which can be deprotonated at low temperatures followed by subsequent reaction with different electrophiles. As expected, the

[102] Ahlbrecht, H.; Dollinger, H. *Tetrahedron Lett*. **1984**, *25*, 1353-1356.

[103] (a) Ahlbrecht, H.; Harbach, J.; Hauck, T.; Kalinowski, H.-O. *Chem. Ber.* **1992**, *125*, 1753. (b) Puterbaugh, W. H.; Hauser, C. R. *J. Am. Chem. Soc.* **1963**, *85*, 2467-2470. (c) Snieckus, V. *Chem. Rev*. **1990**, *90*, 879-933.

[104] Kessar, S. V.; Singh, P.; Vohra, R.; Kaur, N. P.; Singh, K. N. *J. Chem. Soc., Chem. Commun*. **1991**, 567-570.

presence of an ammonium salt allowed for significantly lower down the pka of the primary C-H bond, thus facilitating the deprotonation reaction (Figure 4.13).

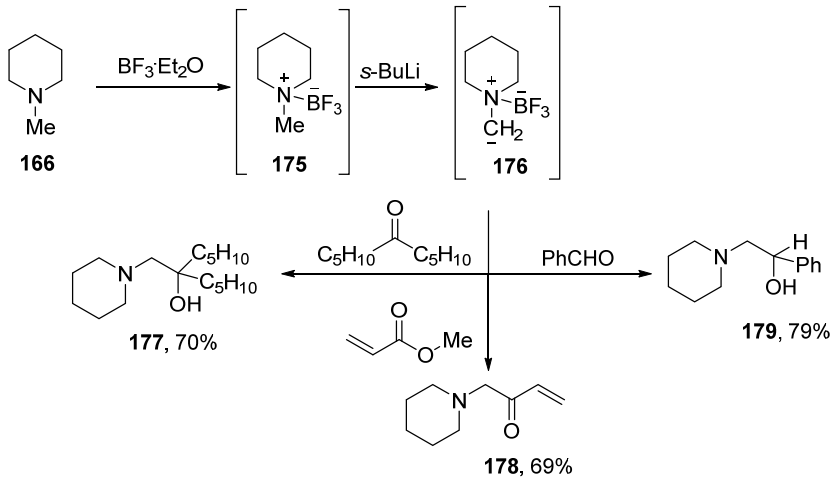


Figure 4.13

(3) Metal-lithium exchange. In 1970, Peterson reported a Sn-Li exchange as alternative for obtaining transient α-amino carbanions that could be treated with RCHO to deliver the corresponding 1,2-amino alcohols in good overall yield (Figure 4.14).[105]

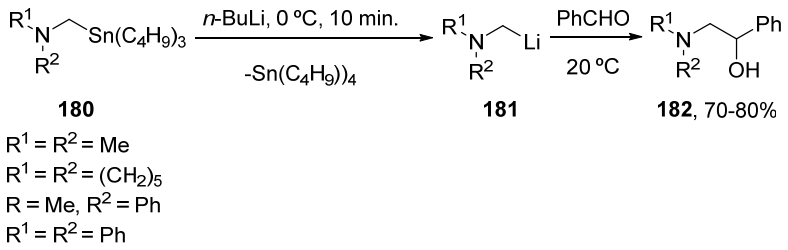


Figure 4.14

(4) Reductive cleavage. It has been demonstrated that α-aminosulfides could be used as platforms for generating α-amino carbanion via C-S bond-

[105] (a) Peterson, D. J. *J. Organomet. Chem*. **1970**, *21*, 63-64. (b) Peterson, D. J. *J.Am. Chem. Soc.* **1971***, 93*, 4027-4031.

cleavage using lithium 4,4-di-*t*-butylbiphenylide (LDBB) as reducing agent (Figure 4.15).[106]

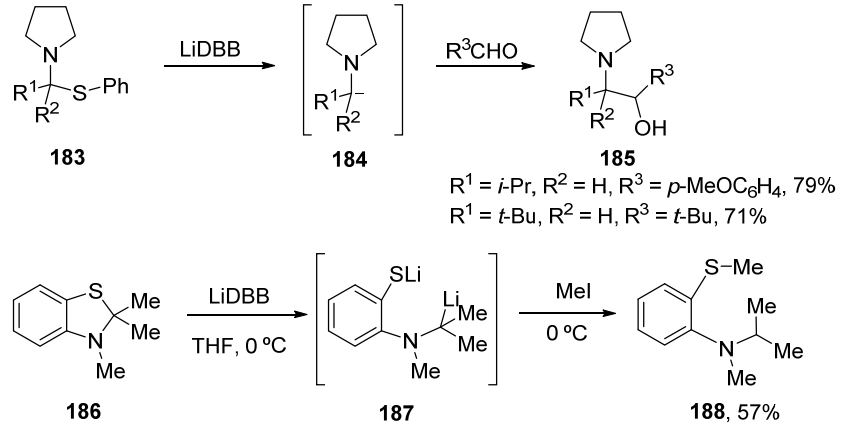


Figure 4.15

Apart from the corresponding sulfide derivatives, the utilization of sulphones can be used for similar purposes. For example, tosylmethylamines (**189**) were found to be particularly suited for generating α-carbanions via either $Li(Sm)_2$ or SmI_2 treatment (Figure 4.16).[107]

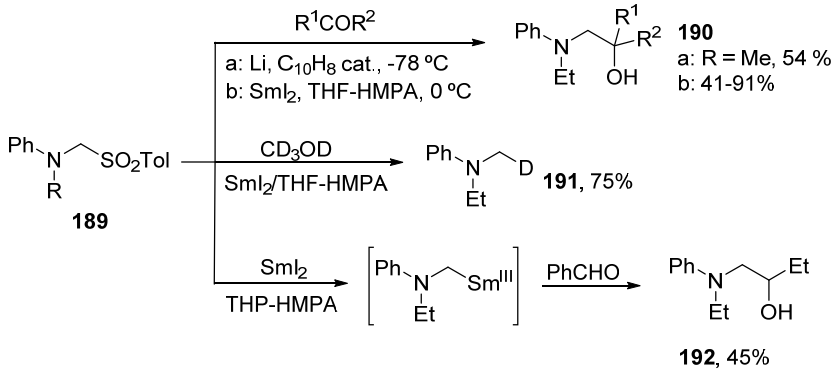


Figure 4.16

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[106](a) Broka, C. A.; Shen, T. *J. Am. Chem. Soc*. **1989**, *111*, 2981-2984. (b) Florio, S.; Capriati, V.; Gallo, A.; Cohen, T. *Tetrahedron Lett*. **1995**, *36*, 4463-4466.

[107] (a)Alonso, D. A.; Alonso, E.; Nájera, C.; Ramón, D. J.; Yus, M. Tetrahedron 1997, 53, 4835-4856. (b) Katritzky, A. R.; Feng, D.; Qi, M. J. Org. Chem. 1997, 62, 6222-6225.

4.4 Results and discussions

Although the fragmentation of β-amino alcohols is visualized as a parasitic and therefore to be avoided parasitic reaction, we decided to turn this observation into a strategic advantage for generating α-amino carbanions under mild reaction conditions and study their reactivity. Among the different alternatives, we wondered whether in situ generated α-amino carbanions could serve as cross-coupling partners en route to dibenzylamine derivatives, molecules of relevance in industrial settings (Figure 4.17).[108]

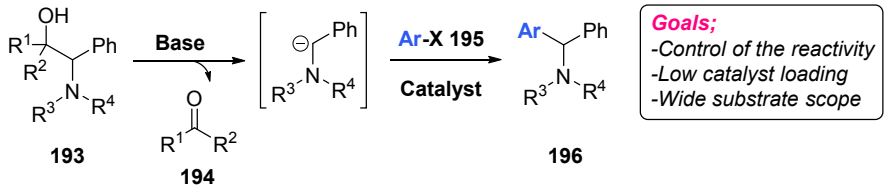

Figure 4.17

We hypothesized that the utilization of Pd catalysts and aryl halides will trigger an oxidative addition that will likely participate in a ligand exchange with the β-amino alcohol (**193**).[85] Subsequent β-carbon elimination with the extrusion of a ketone **194** followed by a reductive elimination will deliver the targeted product **196** while recovering the active Pd(0) catalyst (Figure 4.18). If successful, such a route could set the standards for the design of an enantioselective route using racemic 1,2-amino alcohols and chiral ligands.

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[108] (a) Sakai, N.; Hori, H.; Yoshida, Y.; Konakahara, T.; Orgiwara, Y. *Tetrahedron* **2015**, *71*, 4722-4729. (b) Tomashenko, O.; Sokolov, V.; Tomashevskiy, A.; Chaplisnki, V.; Meijere, A. *Eur. J. Org. Chem*. **2008**, 5107-5111. (c) Nédélec, J-Y.; Troupel, M.; Gall, E. *Tetrahedron*, **2006**, *62*, 9953-9965.

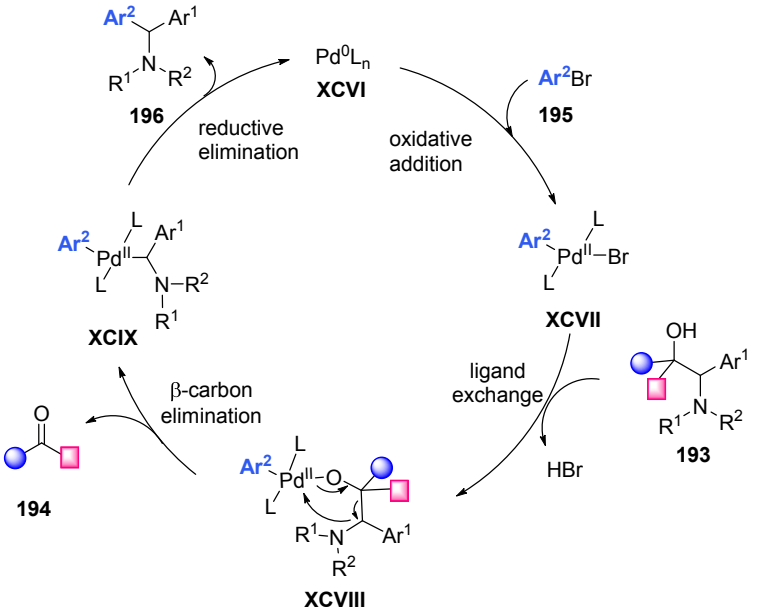


Figure 4.18

4.4.1 Synthesis of 1,2-amino alcohols

As model substrates, we chose **197** and **153** (Figure 4.19). The choice of the piperidine motif was primary due to the previous fragmentation observed when anchoring β-amino alcohols to Merrifield resins (Figure 4.19).[94]

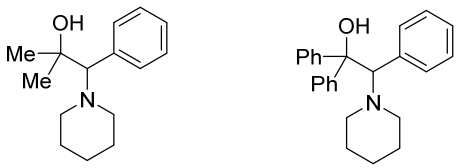


Figure 4.19

Specifically, **197** and **153** could be synthesized in large scale from commercially available precursors (Figure 4.20 and Figure 4.21). As for **197**, the dehydration of commercially available 2-methyl-1-phenylpropan-2-ol (**198**) with *p*-toluenesulfonic acid in benzene afforded the corresponding styrene in 80% yield. Epoxidation with *m*-chloroperbenzoic

acid and a final ring opening with piperidine afforded a 90:10 regioisomeric mixture of two regioisomers (**197**:**199**) that could be easily separated by column chromatography (Figure 4.20).

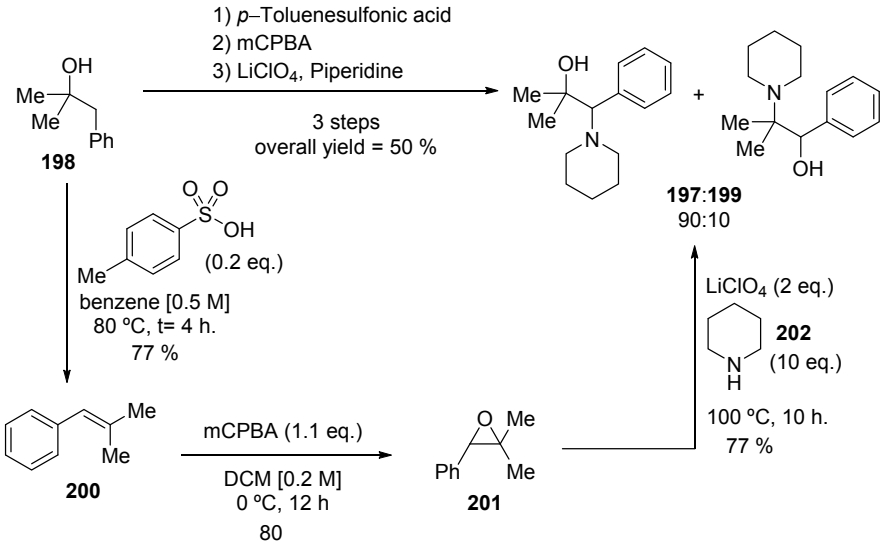


Figure 4.20

The synthesis of **153** follows an otherwise identical route to that shown for **197**, the difference being that triphenyl ethylene is commercial available. In this case the epoxidation worked better with $NaClO_2$ as oxidizing agent and only one regioisomer **153** was obtained in the ring opening of the epoxidation with piperidine mediated by $LiClO_4$ (Figure 4.21).

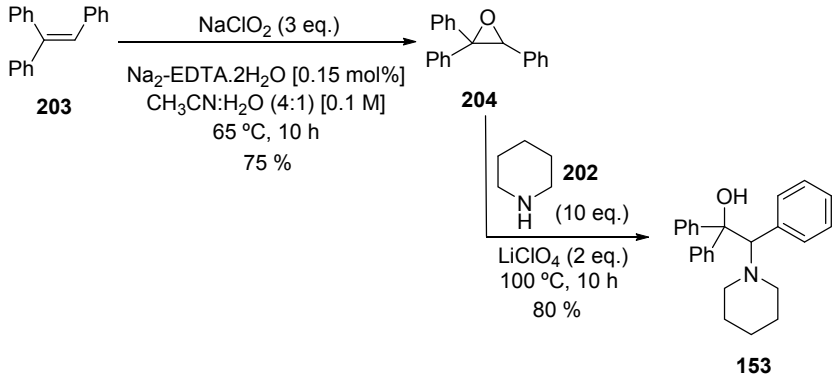


Figure 4.21

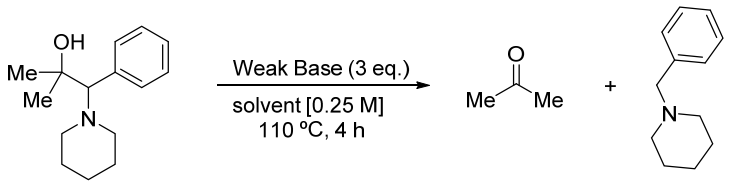
4.4.2 Study of the fragmentation of 1,2-amino alcohols

With substantial amounts of **153** and **197** in hand, we focused our attention on studying the fragmentation of the β-amino alcohol motif. Despite the preliminary results of our research group,[97] little knowledge was acquired regarding the variables that exert an influence on the C-C bond-cleavage event. Therefore, we turned our attention to systematically examine this fragmentation in detail.

4.4.2.1 Fragmentation of 197

We initiated our optimization by studying the ability of different weak bases to promote the targeted C-C bond-cleavage. As shown in the Table 1, K_2CO_3, K_3PO_4 and Cs_2CO_3 in aprotic solvents resulted in no conversion, recovering **197** unaltered.

Table 1. Screening with weak bases in different solvents[a, b]



197 **205** **206**

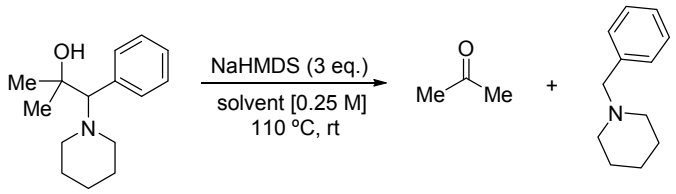
Solvent	K_2CO_3	K_3PO_4	Cs_2CO_3
DMF	0	0	0
Diglyme	0	0	0
Dioxane	0	0	0

Reaction conditions: (a) **197**; 0.13 mmol, base (3 eq.), solvent [0.25 M], 110 ºC for 4 h. (b) Reactions were followed by GC-FID using dodecane as internal standard.

In light of these results, we anticipated that a stronger base could be necessary to effect the fragmentation of **197**.[97] Among the bases analyzed, we decided to use highly basic but poorly nucleophilic NaHMDS in aprotic solvents. As evident from the results compiled in Table 2, the nature of the

solvent was critical for success. While a no general trend can be extrapolated from the results using apolar aprotic solvents, the employment of DMF resulted in full conversion to **206**, even after just 1 h.

Table 2. Screening with NaHMDS in different solvents[a, b]



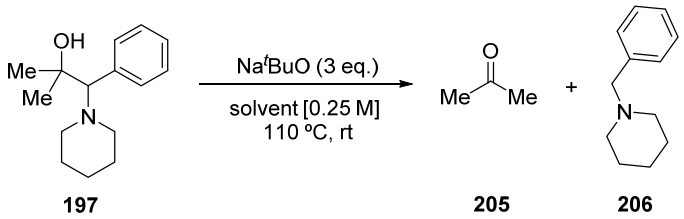
197 **205** **206**

Solvent	1h	2h	4h
Dioxane	31 (31)	46 (49)	60 (64)
THF	26 (26)	43 (43)	61 (61)
CH_3CN	5 (14)	16 (16)	20 (20)
Diglyme	52 (66)	81 (82)	93 (93)
DMF	97 (97)	98 (98)	100 (100)

Reaction conditions: (a) **197**; 0.13 mmol, NaHMDS (3 eq.), Solvent [0.25 M], 110 ºC for 1-4 h. (b) Yields (conversions) were determined by GC-FID using dodecane as internal standard.

As shown in Table 3, NaO^{t}Bu followed an identical pattern to that shown for NaHMDS, with apolar aprotic solvents providing low yields of **206** whereas DMF resulted in full conversion to the targeted fragmentation product. It is worth noting that the reactions based on NaO^{t}Bu turned out to be more sluggish than those with NaHMDS, an observation that is attributed to solubility issues (Table 3).

Table 3. Screening with Na^{t}BuO in different solvents[a, b]



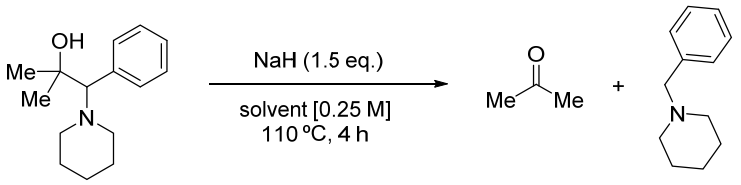
197 **205** **206**

Solvent	1h	2h	4h
Dioxane	8 (13)	12 (20)	18 (18)
THF	15 (15)	20 (22)	25 (32)
CH_3CN	5 (5)	7 (10)	10 (15)
Diglyme	0	0	0
DMF	99 (99)	100 (100)	-

Reaction conditions: (a) **197**; 0.13 mmol, Na^{t}BuO (3 eq.), Solvent [0.25 M], 110 ºC for 1-4 h. (b) Yield (conversion) were determined by GC-FID using dodecane as internal standard.

Interestingly, the use of NaH followed a different pattern, as THF, diglyme and dioxane provided significant amount of **206**. Once again, DMF proved to be a superior solvent for effecting the C-C bond-cleavage (Table 4).

Table 4. Screening with NaH in different solvents at 80 or 110 ºC[a, e]



197 205 206

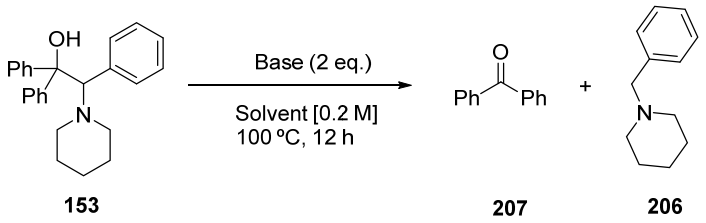
Entry	Solvent	Conversion (%)	Yield 206 (%)
1	DMF	100[b], 100[c], 100[d]	96[b], 97[c], 100[d]
2	THF	18[b], 81[c], 100[d]	15[b], 68[c], 100[d]
3	Diglyme	74[b], 89[c], 100[d]	60[b], 75[c], 100[d]
4	Dioxane	78[c], 100[d]	68[c], 81[c]
5	Hexane	0[c], 5[d]	0[c], 0[d]
6	Toluene	0[c], 5[d]	4[d]
7	CF_3-toluene	0[c], 8[d]	6[d]

Reaction conditions: (a) **197**; 0.13 mmol, NaH (1.5 eq.), Solvent [0.25 M]. (b) Reactions at 80 ºC for 4 h. (c) Reactions 110 ºC for 4 h. (d) Reactions at 110 ºC for 12 h. (e) Conversion and yield were determined by GC-FID using dodecane as internal standard.

4.4.2.2 Fragmentation of 153

In line with these results shown for **197**, the β-amino alcohol **153** did not trigger a fragmentation event using weak bases such as K_2CO_3, K_3PO_4 and Cs_2CO_3 in THF or Dioxane. Thus, we focused our attention on the utilization of NaH as the base in apolar aprotic solvents such as dioxane or THF. As expected, around 80% yield was obtained when using NaH after 12 h reaction time (Table 5).

Table 5. Screening with different solvents with NaH[a, b, c]



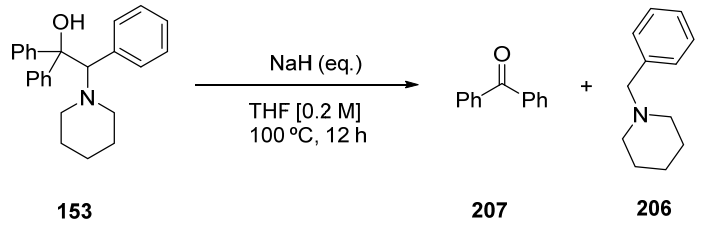
153 207 206

Solvent	206 (yield(conversion))
Dioxane	77 (99)
THF	80 (100)

Reaction conditions: (a) **153**; 0.13 mmol, base NaH (2 eq.), solvent [0.2 M], 100 ºC for 12 h. (b) Yield and conversion were determined by HPLC-DAD (210 nm) using naphthalene as internal standard. (c) Different amounts of diphenylmethanol were observed.

As shown in Table 6, the reaction could be conducted either with an excess, or using the base as limiting reagent. The latter result indicates that the in situ formed α-amino carbanion is a stronger base than NaH, thus effectively promoting the fragmentation reaction. While at first sight desired, it is important to highlight that such a finding might be limiting the application profile of using transient α-amino carbanions generated after a corresponding fragmentation reaction in future catalytic endeavors.

Table 6. Screening with different equivalents of base[a, b, c]



153 207 206

Entry	NaH (eq.)	Conversion (%)	Yield 206 (%)
1	2	100	80
2	1.2	100	75
3	0.9	100	73

Reaction conditions: (a) **153**; 0.13 mmol, NaH (eq.), THF [0.2 M], 100 ºC for 12 h. (b) Conversions and yields were determined by ^{1}H NMR using 1,4-dioxane as internal standard (c) Different amount of diphenylmethanol were observed.

The fragmentation of **153** merits further discussion: (A) a rather characteristic blue-green color was generated at early stages upon treatment with the base; (B) diphenylmethanol was obtained in variable amounts. These observations point towards the intermediacy of radical species, as the radical anion of the benzophenone could be generated in the presence of strong electron reductants.[109] Two different mechanisms might account for the former: (1) heterolytic C-C bond-cleavage mediated by base, generating high concentrations of α-amino carbanions and triggering a single-electron transfer (SET), that generates **209** and **210** (Figure 4.22 (a)); (2) homolytic C-C bond-cleavage, producing directly **211** and **210** (Figure 4.22 (b)).

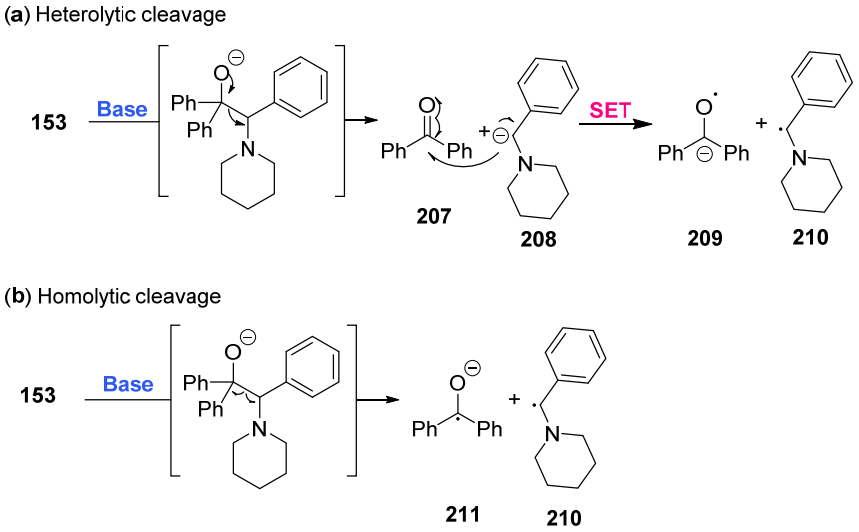


Figure 4.22

Regardless of how exactly the C-C bond-cleavage occurs, **210** might be promoting a hydrogen atom abstraction (HAT) en route to **206** (Figure

[109] Hug, G. L.; Bartoszewicz, J.; Kozubek, H.; Pietrzak, M.; Marciniak, B. *J. Photo. and Photobiol A: Chemistry* **2008**, *198*, 250-255.

4.23). Base on the tabulated bond dissociation energies of the corresponding C-H bond of THF (BDE = 92 Kcal/mol) and the tertiary amino alcohol (BDE = 106 Kcal/mol) it seems plausible that a HAT process takes place effectively with THF (Figure 4.23).

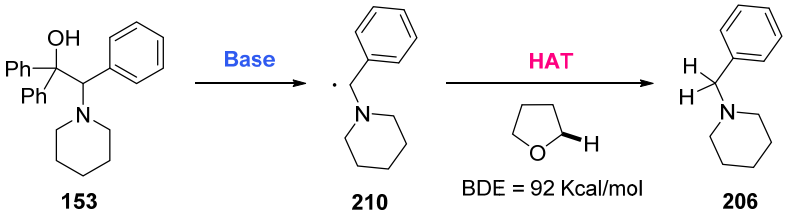


Figure 4.23

4.4.3 Alkylation of α-amino carbanion with benzyl bromide

With the optimal conditions in hand for effecting the C-C bond-cleavage event, we focused our attention on the alkylation of the resultant carbanion with an appropriate electrophile (Figure 4.24).

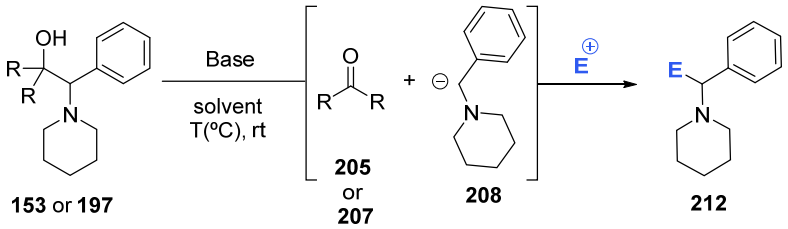


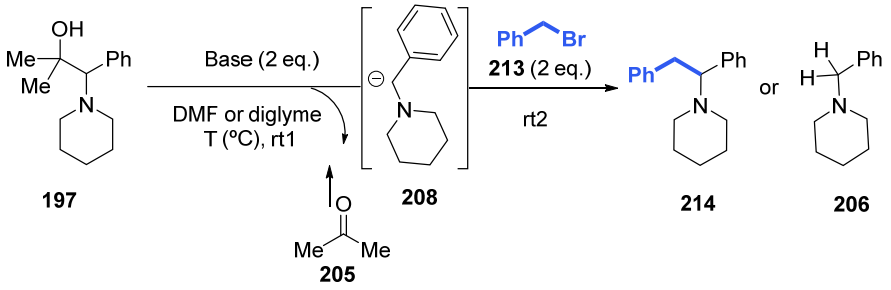
Figure 4.24

4.4.3.1 Alkylation of amino alcohol 197

To such end, we selected benzyl bromide as electrophilic partner hoping to explore the extent of this reaction while setting the basis for a future catalytic event. We first evaluated the reaction of amino alcohol **197** with benzyl bromide (**213**) taking into consideration the efficiency observed when fragmenting such β-amino alcohol. In line with our fragmentation experiments, we observed full conversion in either DMF or diglyme at temperatures above 80 ºC. While DMF proved to be particularly suited for

the fragmentation event, no traces of **214** were observed in the crude of reaction mixtures. Additionally, the observed **206** did not account for the mass balance, indicating that a non-negligible radical parasitic pathway must be taking place. The best results were accomplished with NaH at 140 ºC, but still low yields were obtained (22%) with significant amounts of **206** being generated (64%) (Table 7).

Table 7. Alkylation of 197 in DMF or diglyme with different bases[a, b]



Base	T (ºC)	Reaction time	Conversion (%)	206 (%)	214 (%)
NaHMDS[c, e]	110	1 h/ 1.5 h	100	57	0
NaH[c, e]	110	1 h/ 1.5 h	100	4	0
NaHMDS[d, e]	80	1 h/1.5 h	100	13	2
NaHMDS[d,e]	100	1 h/1.5 h	100	37	5
NaH[d, e]	80	1 h/1.5 h	27	3	4
NaH[d, e]	100	1 h/1.5 h	95	15	17
NaH[d, e]	140	20 min/0.5 h	100	64	22
NaH[d, e]	140	20 min/1 h	100	64	22
NaH[d, f]	140	1h	99	28	2

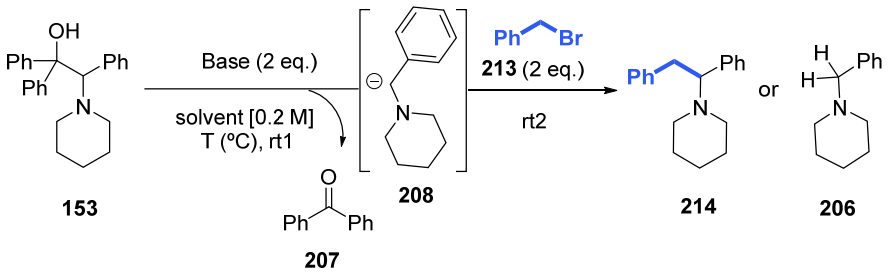
Reaction conditions: (a) **197**; 0.13 mmol, base (2 eq.), solvent [0.2 M], T = 80, 100, 110 or 140 ºC. (b) Conversion and yield were determined by GC-FID using dodecane as internal standard. (c) DMF as solvent. (d) Diglyme as solvent. (e) rt1/rt2 (fragmentation time/reaction time). (f) All reagents together.

Although tentative, the poor results associated to the use of **197** might indicate that the α-amino carbanion might be deprotonating either the starting β-amino alcohol or the α-protons of the generated acetone.

4.4.3.2 Alkylation of amino alcohol 153

To avoid this acid-base side reaction related with the α-acidic protons of the generated acetone and with the aim of obtaining more valuable information for our future purpose, we turned our attention to the employment of **153**, as the residual benzophenone (**207**) does not possess α-acidic protons. We started our investigations with NaH as the base, as it showed to be the most efficient base for promoting the C-C bond cleavage of **197** (Table 8).

Table 8. Different solvents with NaH[a, b, c]



Entry	Solvent [M]	T (ºC)	Reaction time	(206) (%)	(214) (%)	(207) (%)
1	Diglyme [0.2]	140	20 min/1 h	72	9	3
2	Diglyme [0.2]	140	20 min/5 h	60	16	0
3	Diglyme [0.2]	110	1 h	15	45	92
4	Diglyme [0.2]	140	1 h	9	46	86
5	Diglyme [0.2]	140	5 h	17	45	83
6	Diglyme [0.4]	140	1 h	13	44	71
7	Dioxane [0.2]	110	1 h	12	46	60
8	Dioxane [0.2]	140	1 h	21	44	87

9	THF [0.2]	110	1 h	16	38	68
10	THF [0.2]	140	1 h	17	45	54

Reaction conditions: (a) **153**; 0.13 mmol, NaH (2 eq.), solvent, T = 110 or 140 ºC for rt1/rt2 or one step. (b) Conversions and yields were determined by GC-FID using dodecane as internal standard. (c) Different amounts of diphenyl methanol (**215**) were detected.

Although high conversions were observed the desired product **214** was only obtained in moderated yield (45%) together with substantial amounts of **206** (9-21%) and diphenylmethanol (**215**).

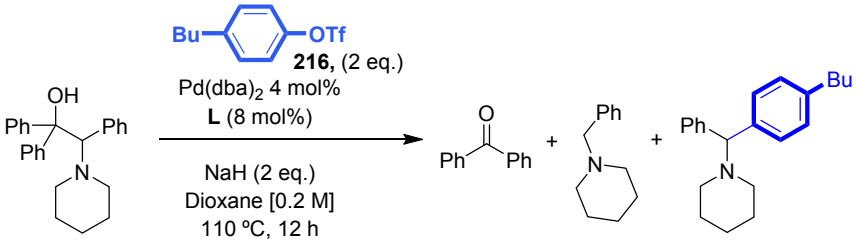
4.4.4 Palladium catalyzed cross-coupling reaction with 153.

After acquiring some knowledge about the cleavage of the C-C bond of β-amino alcohols as well as the behavior of α-amino carbanion with benzyl bromide, we set out to study the viability of promoting a catalytic scenario using aryl halides counterparts and palladium catalysts. Although we anticipated that such an approach would not be trivial taking into account the inherent reactivity of α-amino carbanions, their propensity to SET and the perception that an optimal balance of all experimental variables should be critical for success, we were attracted to the challenge.

We started our optimization using **153**, with NaH as the base and $Pd(dba)_2$ as the precatalyst at 110 ºC in dioxane. As for the aryl halide, we decided to strart our study with 4-butylphenyl trifluoromethanesulfonate (**216**), as we expected that a fast oxidative addition would be required in order to intercept the in situ generated α-amino carbanion and avoid parasitic pathways. As shown in Table 9, we systematically examined the role of monodentate phosphines, as we anticipated that these ligands might be critical for promoting a fast transmetalation with the α-amino carbanion, as monodentate phosphines are known to trigger fast dissociation, thus opening up coordination sides at the metal center. A quick look at the crude reaction mixture revealed that the fragmentation occurred in all cases analyzed, as judged by the high yield obtained of **207**. However, not even

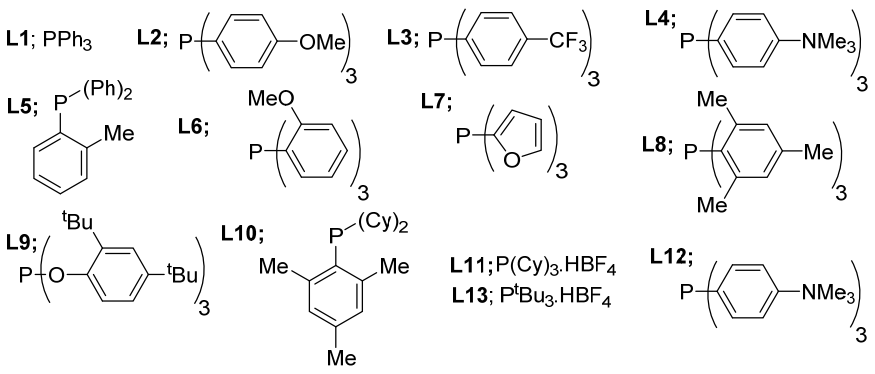
traces of **217** were obtained, indicating that these conditions did not allow us to intercept the α-amino carbanion effectively. Intriguingly, however, the amount of **206** did not correlate with **207** being generated, an issue that can be interpreted to parasitic SET-type processes.

Table 9. Screening of different monodentate phosphine ligands[a, b, c]



153 **207** **206** **217**

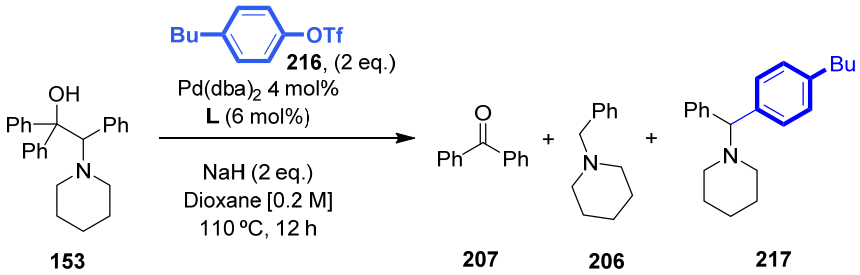
Entry	Ligand	Yield 207 (%)	Yield 206 (%)	Yield 217 (%)
1	**L1**	88	17	2
2	**L2**	97	37	0
3	**L3**	98	32	0
4	**L4**	45	33	0
5	**L5**	76	36	0
6	**L6**	33	18	0
7	**L7**	73	37	0
8	**L8**	31	14	0
9	**L9**	50	35	0
10	**L10**	92	12	0
11	**L11**	86	22	3
12	**L12**	86	10	0
13	**L13**	77	18	0



Reaction conditions; (a) **153** (0.21 mmol), $Pd(dba)_2$ (4 mol%), ligand (8 mol%), NaH (2 eq.), dioxane [0.2 M], 110 ºC for 14-16 h. (b) Yields were determined by GC-FID using dodecane as internal standard. (c) Buthylphenol, buthylbenzene and homocoupling product were detected.

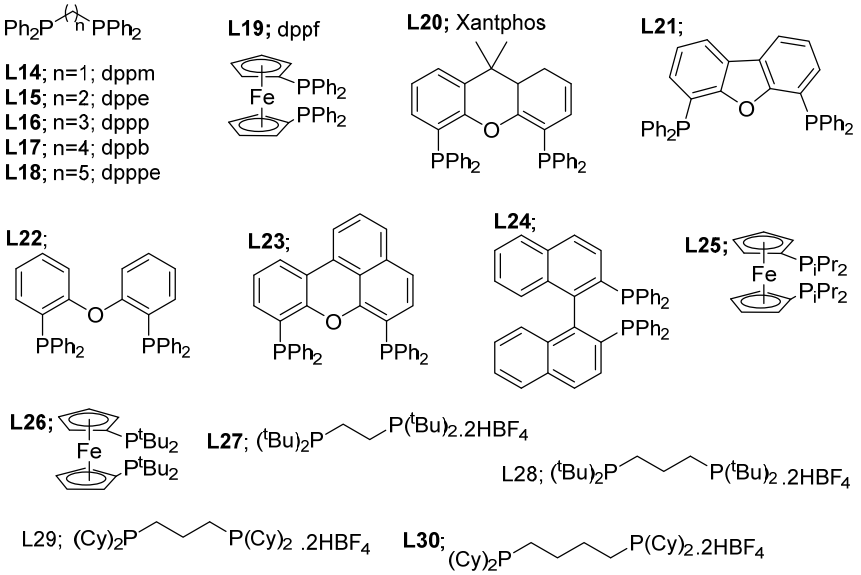
Subsequently, we focused our attention on the use of bidentate phosphine ligands (Table 10). Although in low yields, it is particularly noteworthy that **217** was obtained in variable amounts, thus demonstrating the viability of our catalytic approach. While one might argue that the flexibility of the ligand was critical for success, the results in Table 10, did not allow us to extract a definitive conclusion in terms of structure-reactivity relationships. Indeed, variable results were obtained with ligands with similar electronic, steric effects or bite-angles. Among all ligands examined, the best results were found when employing dppf (entry 6). Once again, however, the **207** generated did not correlate well with the amount of **206** and **217** combined.

Table 10. Screening of different bidentate phosphine ligands[a, b, c]



153 207 206 217

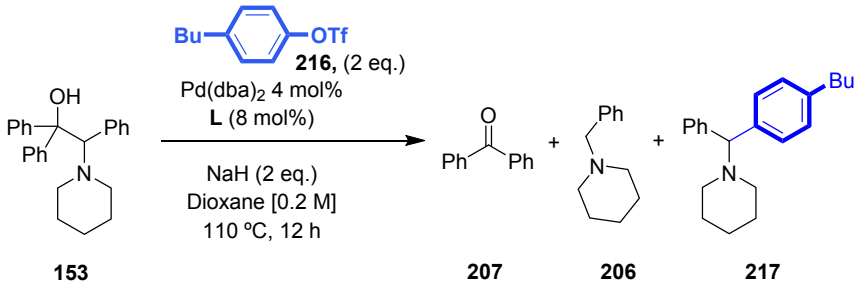
Entry	Ligand	Yield 207 (%)	Yield 206 (%)	Yield 217 (%)
1	**L14**	71	11	0
2	**L15**	86	6	10
3	**L16**	83	6	22
4	**L17**	95	7	18
5	**L18**	83	8	0
6	**L19**	87	6	33
7	**L20**	49	15	20
8	**L21**	75	7	2
9	**L22**	89	5	19
10	**L23**	41	13	25
11	**L24**	92	4	11
12	**L25**	95	28	25
13	**L26**	23	17	8
14	**L27**	78	16	15
15	**L28**	49	11	6
16	**L29**	73	18	18
17	**L30**	65	22	4



Reaction conditions; (a) **153** (0.21 mmol), $Pd(dba)_2$ (4 mol%), ligand (6 mol%), NaH (2 eq.), dioxane [0.2 M], 110 ºC for 14-16 h. (b) Yields were determined by GC-FID using dodecane as internal standard. (c) Buthylphenol, buthylbenzene and homocoupling product were detected.

In order to suppress the parasitic SET-processes, we turned our attention to particularly electron-rich and bulky ligands, as we expected an irreversible and fast oxidative addition while accessing to low coordinated Pd(II) intermediates that could facilitate the transmetalation with the corresponding α-amino carbanion. To such end, we systematically analyzed the role of *N*-heterocyclic carbenes (NHC), as these ligands are exceptional σ-donors and modular enough to accommodate different steric environments. Unfortunately, none of the ligands analyzed, regardless of the different electronic or steric environments, provided even traces of **217** (Table 11).

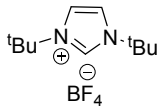
Table 11. Screening of different NHC ligands[a, b, c]



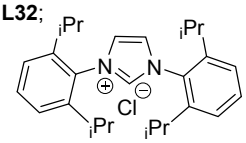
153 **207** **206** **217**

Entry	Ligand	Yield 207 (%)	Yield 206 (%)	Yield 217 (%)
1	**L31**	51	25	0
2	**L32**	70	26	0
3	**L33**	94	4	0
4	**L34**	74	24	0
5	**L35**	90	11	0
6	**L36**	79	5	0

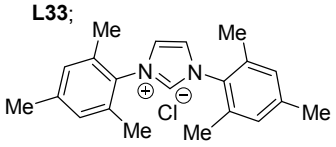
L31;



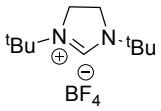
L32;



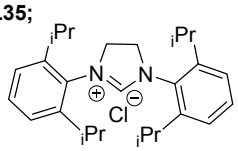
L33;



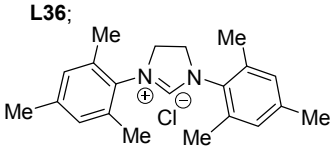
L34;



L35;



L36;

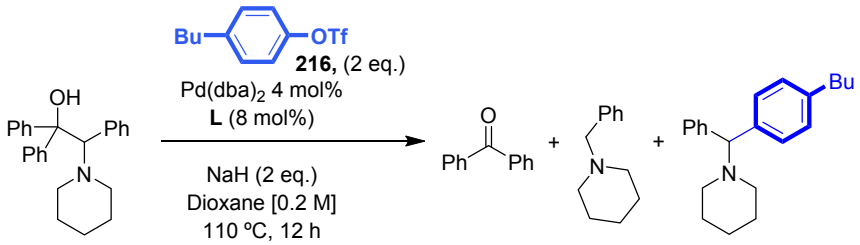


Reaction conditions; (a) **153** (0.21 mmol), $Pd(dba)_2$ (4 mol%), ligand (8 mol%), NaH (2 eq.), dioxane [0.2 M], 110 ºC for 14-16 h. (b) Yields were determined by GC-FID using dodecane as internal standard. (c) Buthylphenol was detected.

In view of the promising results associated with phosphine ligands, we decided to look at the ability of biarylphosphine ligands popularized by Buchwald. These ligands have shown to be particularly efficient for a myriad of cross-coupling reactions. As shown in Table 12, these ligands were found to be particularly suited for our purposes, obtaining

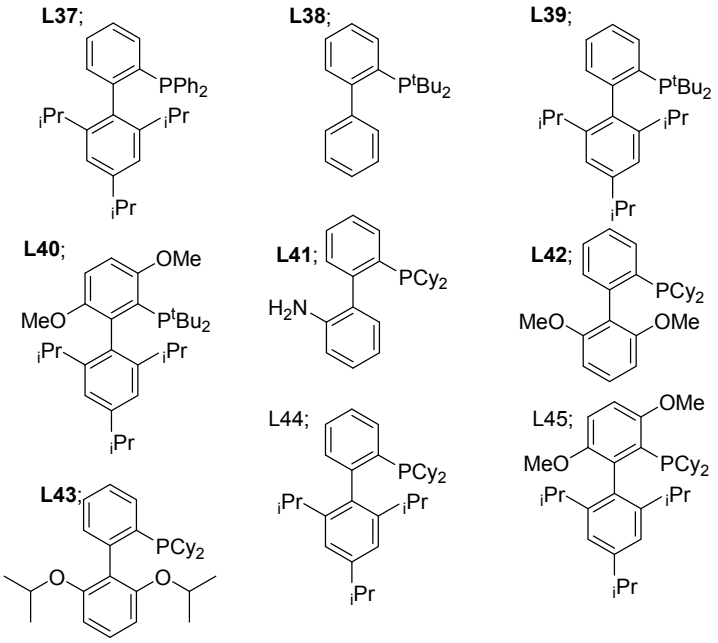
considerable amounts of **217** with a number of biarylphosphine ligands. Among these, the use of Brettphos (**L45**) delivered 40% yield of **217**.

Table 12. Screening of different Buchwald type ligands[a, b, c]



153 **207** **206** **217**

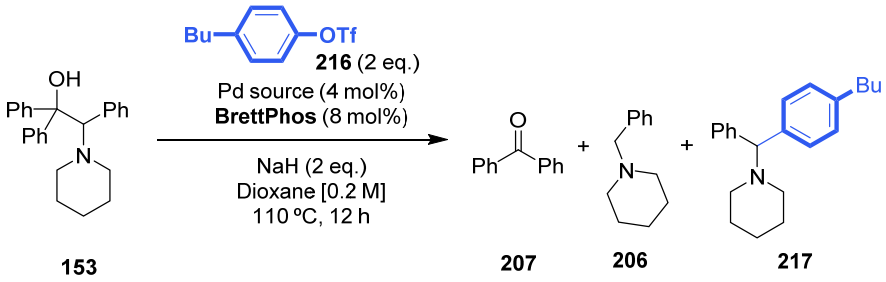
Entry	Ligand	Yield 207 (%)	Yield 206 (%)	Yield 217 (%)
1	**L37**	22	16	0
2	**L38**	99	5	13
3	**L39**	93	8	6
4	**L40**	92	8	4
5	**L41**	76	15	30
6	**L42**	60	10	25
7	**L43**	62	15	27
8	**L44**	95	16	5
9[d]	**L45**	87	11	40



Reaction conditions; (a) **153** (0.21 mmol), $Pd(dba)_2$ (4 mol%), ligand (8 mol%), NaH (2 eq.), dioxane [0.2 M], 110 ºC for 14-16 h. (b) Yields were determined by GC-FID using dodecane as internal standard. (c) Buthylphenol, buthylbenzene and homocoupling product were detected. (d) Isolated yield.

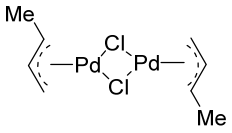
Encouraged by the results using Brettphos (**L45**), we decided to look at the activity of different Pd(II) precatalysts as the corresponding α-amino carbanion or the **206** could reduce Pd(II) to the active Pd(0) species. Unfortunately, none of the Pd(II) catalysts analyzed allowed for obtaining higher amounts of **217**. Intriguingly, the utilization of Pd_2dba_3 proved inferior than $Pd(dba)_2$, thus showing the subtleties of our catalytic protocol (Table 13).

Table 13. Screening of different Palladium catalysts[a, b, c]



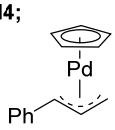
153 207 206 217

Entry	Pd source	Yield 207 (%)	Yield 206 (%)	Yield 217 (%)
1	**Pd1**	87	20	16
2	**Pd2**	81	7	4
3	**Pd3**	82	8	26
4	**Pd4**	67	11	0
5	**Pd5**	88	14	4
6	**Pd6**	79	8	0
7	**Pd7**	72	9	0
8	**Pd8**	80	7	10
9	**Pd9**	82	4	24
10	**Pd10**	90	7	0

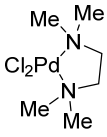
Pd1;


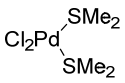
Pd2; $PdCl_2$

Pd3; $(COD)PdCl_2$

Pd4;


Pd5; $PdBr_2$

Pd6;


Pd7;


Pd8; $Cl_2Pd(PPh_3)_2$

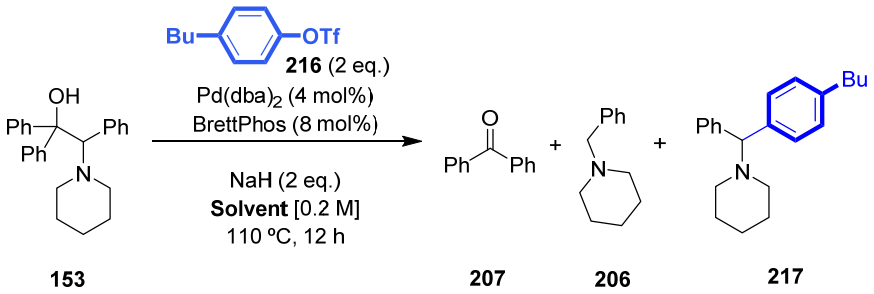
Pd9; $Pd_2(dba)_3$

Pd10; $Pd(OAc)_2$

Reaction conditions; (a) **153** (0.21 mmol), Pd source (4 mol%), BrettPhos (8 mol%), NaH (2 eq.), dioxane [0.2 M], 110 ºC for 14-16 h. (b) Yields were determined by GC-FID using dodecane as internal standard. (c) Buthylphenol, buthylbenzene and homocoupling product were detected.

As a number of solvents promoted efficiently the fragmentation of **153**, we decided to look at different alternatives to dioxane. Unfortunately, no significant improvement was made when using THF, diglyme and DMF. While THF provided similar yields to that shown for dioxane, little reactivity was shown for diglyme whereas DMF resulted in nearly quantitative formation of **206** (Table 14).

Table 14. Screening of different solvents[a, b, c]



153 **207** **206** **217**

Entry	Solvent	Yield 207 (%)	Yield 206 (%)	Yield 217 (%)
1	**Dioxane**[d]	87	11	40
2	**THF**	86	15	40
3	**Diglyme**	26	8	0
4	**DMF**[e]	99	88	0
5	**Dioxane**[f]	92	56	4
6	**Dioxane**[g]	83	7	32
7	**THF**[h]	62	7	22
8	**THF**[i]	72	8	28

Reaction conditions; (a) **153** (0.21 mmol), $Pd(dba)_2$ (4 mol%), BrettPhos (8 mol%), NaH (2 eq.), solvent [0.2 M], 110 ºC for 14-16 h. (b) Yields were determined by GC-FID using dodecane as internal standard. (c) Butylphenol, butylbenzene and homocoupling product were detected. (d) Isolated yield. (e) Dppf was used as ligand. (f) With 50 µL of DMF at 65 ºC. (g) Reaction time = 48 h. (h) 1.1 eq. of NaH. (i) 1.5 eq. of NaH.

Taken together our study suggested that α-amino carbanions might indeed serve as coupling partners. However, low yields have been found, an

observation that is likely attributed to the exceptional reactivity of α-amino carbanions, ending up in SET-processes. Alternatively, we can't rule out the possibility of homolytic cleavage of the C-C bond of β-amino alcohol.

4.5 Conclusions

-The study of the fragmentation reaction of 1,2-amino alcohols has been carried out with good yields.

-A fragmentation of β-amino alcohols followed by an alkylation event with benzyl bromide has been conducted in moderate yields.

-A catalytic fragmentation of β-amino alcohols/arylation event has been conducted with aryl triflates and Pd catalysts.

4.6 Experimental section

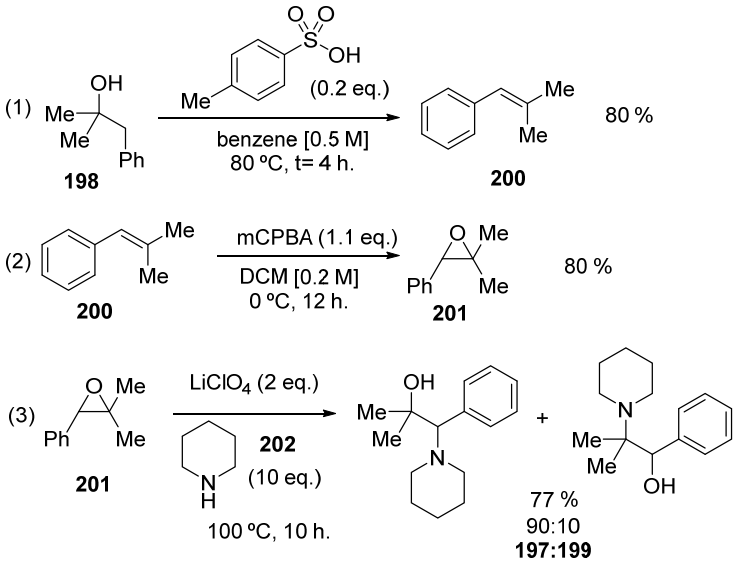
4.6.1. General considerations

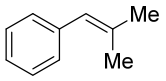
Reagents. Reagents were weighted in open air, and only for some sensitive ligands during the screening process the glovebox was used. Reactions were set up under argon atmosphere in Schlenk tubes. All reagents were purchased and directly used from commercial sources. Some dry solvents (CH_3CN and toluene) were used from the SPS system (Inovative technology, Newburyport, MA) and the rest were also purchased from commercial sources. Flash column chromatography was carried out with ultra pure silica gel flash 60 (230-240 mesh)

Analytical methods. ^{1}H NMR, ^{13}C NMR and melting point, where applicable, are attached for all compounds. ^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz and 400 MHz Bruker apparatus at 20 ºC. All NMR spectra are presented in part per million (ppm) and were measured relative to the signal of $CHCl_3$ (7.27 ppm in the case of ^{1}H NMR and 77.0 ppm for the ^{13}C NMR). All ^{13}C NMR were obtained with ^{1}H decoupling. Coupling constants (*J*), are reported in hertz. Melting points were measured using open glass capillaries in a Mettler Toledo MP70 apparatus. Mass spectra were recorded on a Waters LCT Premier spectrometer. Gas chromatographic analyses were performed on Hewlett-Packard 6890 gas chromatography instrument with FID detector using 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase.

4.6.2 Synthesis of *β*-amino alcohols

4.6.2.1 Synthetic pathway for 197

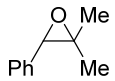




200

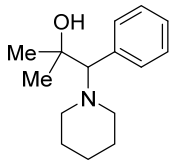
(2-Methylprop-1-en-1-yl)benzene (**200**).[110] To a solution of 2-methyl-1-phenylpropane-2-ol (46.6 mmol) in benzene (90.0 mL) under argon atmosphere, was added *p*-toluenesulfonic acid (9.31 mmol). The reaction mixture was heated under reflux for 3 h and poured into aqueous $NaHCO_3$ solution (150 mL). The organic layer was washed with brine (2 x 150 mL), water (2x150 mL), dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude mixture was purified by flash column chromatography on silica gel (Hexane 100%) affording 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.33-7.28 (m, 2H), 7.24-7.20 (m, 2H), 7.19-7.15 (m, 1H), 6.27 (s, 1H), 1.9 (s, 3H), 1.86 (s, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.7, 135.4, 128.7, 127.9, 125.7, 125.1, 26.85, 19.36.

[110] Stavber, G.; Zupan, M.; Stavber, S. *Tetrahedron Lett.* **2006**, *47*, 8463-8466.



201

2,2-Dimethyl-3-phenyloxirane (201).[111] To a solution of (2-methylprop-1-en-1-yl)benzene (**201**, 40 mmol) in DCM (200 mL) at 0 ºC, was added mCPBA (44 mmol). The reaction mixture was stirred at room temperature for 12 h. DCM was added and the organic phase was washed with $NaHCO_3$ (2 x 200mL), with brine (250 mL), dried with anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (Hexane 100%) affording 80% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.39 (m, 5H), 3.87 (s, 1H), 1.49 (s, 3H), 1.08 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.8, 128.3, 127.6, 126.6, 64.8, 61.3, 25.0, 18.2.



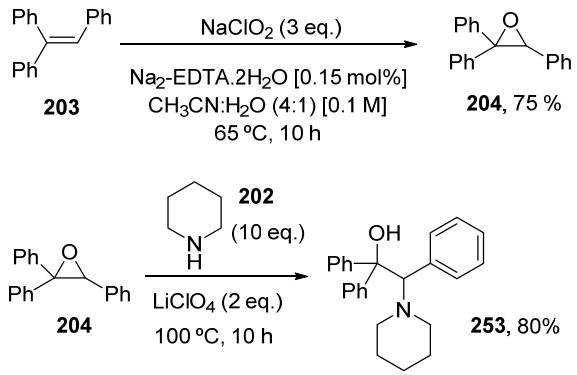
197

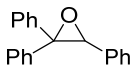
2-Methyl-1-phenyl-1-(piperidin-1-yl)propan-2-ol (197). To a solution of 2,2-dimethyl-3-phenyloxirane (**201**, 66 mmol) in piperidine (65.4 mL) $LiClO_4$ (132 mmol) was added portionwise. The reaction was heated at 100 ºC for 12 h. Water (50 mL) and toluene (50 mL) were added to the reaction mixture. The aqueous phase was extracted with toluene (2 x 50 mL) and the organic solvent was removed under reduced pressure. The crude was purified by flash column chromatography on silica gel (hexanes/EtOAc 95:5) affording 77% yield in a mixture of isomers (9:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.25 (m, 5H), 3.34 (s, 1H), 2.72 (m, 2H), 2.26 (m,

[111] Fristrup, P.; Dideriksen, B. D.; Tanner, D.; Norrby, P-O. *J. Am. Chem. Soc*. **2005**, *127*, 13672-13679.

*2*H), 1.70-1.50 (m, 4H), 1.31 (m, 5H), 1.17 (2, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 135.9, 130.8, 127.7, 127.2, 79.8, 72.7, 53.9, 29.2, 26.9, 26.7, 24.2. MS (ESI+) *m/z* (%) 604 (M+H). HRMS *calcd*. for ($C_{15}H_{24}NO$): 234.1858, *found* 234.1855.

4.6.2.2 Synthetic pathway for 153



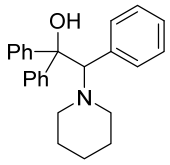


204

2,2,3-Triphenyloxirane (204). [112] To a solution of ethane-1,1,2-triethylbenzene (31 mmol) in CH_3CN (355 mL) and aqueous Na_2·EDTA solution ($5x10^{-4}$ M, 1.5 µmol) was added sodium chlorite (93 mmol). The mixture was heated at 65 ºC for 48 h. The reaction was quenched by saturated solution of $Na_2S_2O_3$ and the mixture was extracted with DCM (3x 300 mL). The organic phase was washed with water and brine and dried with Na_2SO_4. The organic solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (Hexanes/EtOAc 95:5) affording 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45-7.05 (m, 15H), 4.38 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ

[112] a) Brandes, B. D.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378. b) Geng, X-G.; Wang, Z.; Li, X-Q.; Zhang, Ch. *J. Org. Chem*. **2005**, *70*, 9610-9613.

141.5, 136.5, 136.0, 129.7, 128.9, 128.4, 128.3, 128.2, 128.2, 128.1, 127.3, 126.9, 69.0, 68.6.

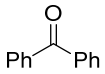


153

1,1,2-Triphenyl-2-(piperidin-1-yl)ethan-1-ol (153).[94a] To a solution of 2,2,3-triphenyloxirane **(204**, 29.4 mmol) in piperidine (29.2 mL) $LiClO_4$ (58.8 mmol) was added portionwise. The reaction was heated at 100 ºC for 12 h. Water (50 mL) and toluene (50 mL) were added to the reaction mixture. The aqueous phase was extracted with toluene (2 x 50 mL). The organic solvent was removed under reduced pressure. The crude was crystallized with ethanol affording the desired compound in 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67-7.63 (m, 2H), 7.33-7.24 (m, 4H), 7.20-7.08 (m, 6H), 7.06-7.01 (m, 2H), 6.98-6.93 (m, 1H) 4.52 (s, 1H), 2.43-2.38 (m, 2H), 2.04-1.95 (m, 2H), 1.45-1.37 (m, 4H), 1.31-1.23 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 149.3, 145.8, 137.4, 131.3, 127.9, 127.4, 127.2, 126.9, 126.1, 125.6, 78.6, 77.7, 54.4, 26.8, 24.1.

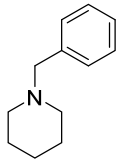
4.6.3 Fragmentation reaction

General procedure IV. An oven-dried Schlenk tube containing a stirring bar was charged with the corresponding β-amino alcohol (1.0 eq.). Subsequently, inside the glove box, the base was added. Under argon atmosphere solvent was added by syringe and the solution was warmed up to 110 ºC and stirred for 12-16 h. The mixture was then allowed to warm to room temperature. EtOAc (10 mL) was added and the mixture was filtered through a small path of Celite. The filtrate was evaporated and the resulting oil was purified by flash column chromatography (hexanes/EtOAc 9:1).



207

Benzophenone (207).[97] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84-7.76 (m, 4H), 7.62-7.59 (m, 2H), 7.51-7.42 (m, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 196.5, 137.5, 132.3, 129.9, 128.1.

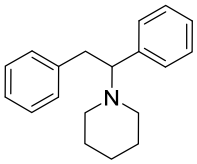


206

***N*-Benzyl bromide (206).**[97] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.22 (m, 5H), 3.47 (s, 2H), 2.44-2.33 (m, 4H), 1.61-1.54 (m, 4H), 1.48-1.39 (m, 2H), ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 129.2, 128.1, 126.8, 63.9, 54.5, 25.9, 24.4.

4.6.4 Alkylation reaction with benzyl bromide

General procedure V.[97] An oven-dried Schlenk tube containing a stirring bar was charged with the corresponding β-amino alcohol (1.0 eq.). Subsequently, inside the glove box, the base was added. Under argon atmosphere, solvent and benzyl bromide were subsequently added by syringe and the solution was warmed up to 110 ºC and stirred for 12-16 h. The mixture was then allowed to warm to room temperature. EtOAc (10 mL) was added and the mixture was filtered though a small path of Celite. The filtrate was evaporated and the resulting oil was purified by flash column chromatography (hexanes/EtOAc 95:5).

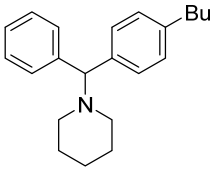


214

1-(1,2-Diphenylethyl)piperidine (214).[97] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.15 (m, 3H), 7.14-7.04 (m, 5H), 7.01-6.96 (m, 2 H), 3.58 (dd, J = 9.4, 5.2 Hz, 1H) 3.30 (dd, J = 13.3, 5.2 Hz, 1H), 2.99 (dd, J = 13.3, 9.5 Hz, 1H), 2.49-2.35 (m, 4H), 1.62-1.47 (m, 4H), 1.39-1.30 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.9, 139.4, 129.3, 128.9, 127.8, 127.6, 126.8, 125.6, 72.3, 51.4, 39.2, 26.4, 24.7.

4.6.5 Pd-catalyzed cross-coupling reaction of phenyl(piperidin-1-yl) carbanions with aryl halides

General Procedure VI. An oven-dried Schlenk tube containing a stirring bar was charged with the corresponding 1,2-amino alcohol (1.0 eq.), Pd source (4 mol%) and the corresponding ligand (6 or 8 mol%). Inside the glove box, the base was added. Next, under nitrogen atmosphere, the solvent and the electrophile were added. The solution was warmed up to 110 ºC and stirred for 12-16 h. The mixture was then allowed to warm to room temperature, EtOAc (10 mL) was added and the mixture was filtered though a short pad of Celite. The filtrated was evaporated and the resulting oil was purified by flash column chromatography to isolate **217**.



217

1-((4-Butylphenyl)(phenyl)methyl)piperidine (217). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42-7.36 (m, 2H), 7.30-7.21 (m, 5H), 7.18-7.12 (m, 1H), 7.09-7.03 (m, 2H), 4.18 (s, 1H), 2.57-2.50 (m, 2H), 2.37-2.24 (m, 4H), 1.62-1.50 (m, 7H), 1.46-1.38 (m, 2H), 1.37-1.28 (m, 2H), 0.9 (t, J = 7.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 143.5, 141.2, 140.3, 128.3, 128.2, 127.9, 127.8, 126.5, 76.5, 53.2, 35.3, 33.6, 26.2, 24.7, 22.4, 13.9.

UNIVERSITAT ROVIRA I VIRGILI
FROM CLICK CHEMISTRY TO CATALYTIC CLEAVAGE OF UNSTRAINED C-C BONDS
Míriam Sau Roca

5. Formal β-arylation of aldehydes via Pd-catalyzed C-C bond cleavage of 1,2-amino alcohols

5.1 Objectives

The objectives for this chapter are the following:

1- To develop a new strategy to carry out a formal β-arylation of aldehydes via catalytic C-C bond cleavage of *N*-allyl amino alcohols with aryl bromides.

2- To identify a catalyst able to mediate this transformation with high turnover numbers and good chemoselectivity profile.

3- To carry out the enantioselective version of the formal β-arylation of aldehydes via catalytic C-C bond cleavage of *N*-allyl amino alcohols with aryl bromides.

5.2 Retroallylation in C-C bond cleavage strategies

Allylation reactions are useful transformations in organic chemistry.[113] While a myriad of stoichiometric allylation techniques have been described,[113] the means to promote metal-catalyzed allylation reactions is particularly attractive, allowing for rapidly building up molecular complexity from simple precursors. Despite the recent advances realized,[113] an exquisite regio and stereocontrol in allylation processes still remains rather problematic. For example, the crotylation of organic substrates typically ends up in α- or γ-substituted compounds, the former commonly possessing (*E*), (*Z*)-selectivity issues (Figure 5.1).[114]

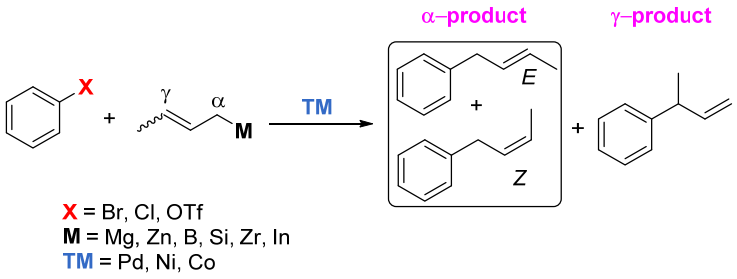


Figure 5.1

Indeed, typical mixtures of α/γ-regioisomers are observed via transmetalation or σ-π-σ interconversion. In this case, such a pathway

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[113] a) Asao, N.; Yamamoto, Y. *Chem. Rev.* **1993**, *93*, 2207-2293. b) Fu, J.; Denmark, S. E. *Chem. Rev.* **2003**, *103*, 2763-2793.

[114] a) Tsuji, T.; Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2002**, *41*, 4137-4140. b) Ohmiya, H.; Tsuji, T.; Yorimitsu, H.; Oshima, K. *Chem. Eur. J.* **2004**, *10*, 5640-5649. c) Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem.* **2001**, *66*, 2459-2465. d) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075-7076. e) Mori, A.; Shimizu, M.; Hirabayashi, K.; Tanaka, M.; Fujita, A.; Matsuhashi, H.; Hiyama, T. *Organometallics*, **1996**, *15*, 5762-5765. f) Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486. g) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9587. h) Obora, Y.; Tsuji, Y. *J. Org. Chem.* **1995**, *60*, 4647-4649. i) Hirano, K.; Yorimitsu, H.; Oshima, K. Synlett 2005, 1787-1788. j) Lee, P. H.; Lee, J.; Lee, K. *J. Org. Chem.* **2002**, *67*, 8265-8268.

occurs when the final reductive elimination is not particularly fast (Figure 5.2).

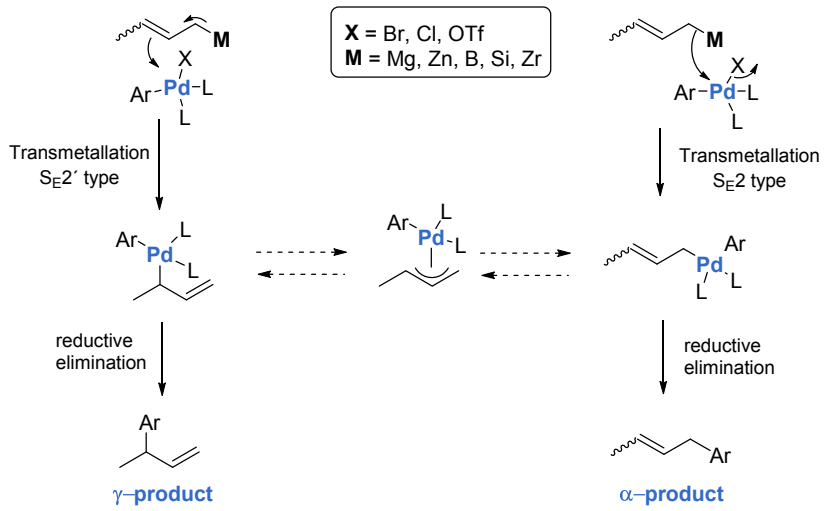

Figure 5.2

On the other hand, excluding boron-allyl species and those that come from the group fourteen in the periodic table, allyl-metal species have a fluxional character. Indeed, σ-π isomerization can take place before transmetalation at mild temperature, thus giving mixtures of α/γ-regioisomers (Figure 5.3).

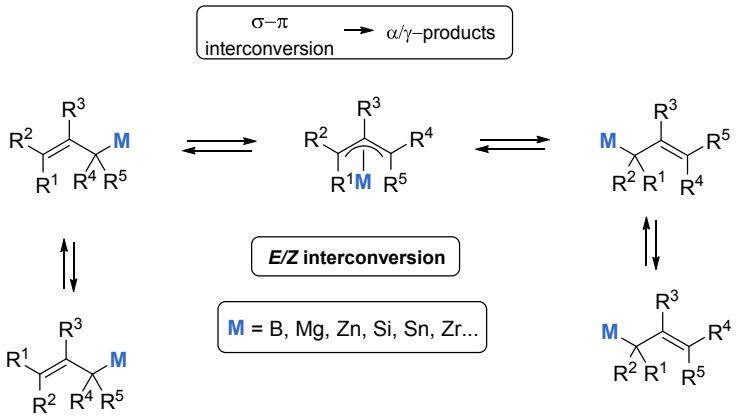

Figure 5.3

Although few examples for the preparation of well-defined allyl metal species have been described,[114d-e,h, 115] their utilization in cross-coupling reactions is still rather problematic taking into consideration that high temperatures are typically required. To such end, chemists have design alternative pathways for promoting allylation reactions. Among these, the means to promote retro-allylation has been essential to implement these techniques in the cross-coupling arena.[116]

5.2.1 Catalytic transformations using retro-allylation techniques

As already mentioned in the introduction (Chapter 3, **section 3.3.2**), a catalytic deallylation reaction of tertiary homoallylic alcohols via selective cleavage of C-C single bond was first reported by Mitsudo and Kondo (Figure 5.4 (a)).[82] Unfortunately, high temperatures, CO pressures and the presence of allyl acetate were required for the reaction to occur (Figure 5.4 (a)). A significant step-forward in this field was carried out by the group of Koichiro Oshima using Pd-catalysts (Figure 5.4 (b)), resulting in the synthesis of well defined σ-allyl(aryl) metal intermediates via selective C-C bond cleavage.[85] Unlike classical approaches for preparing allyl metal species, the utilization of simple and readily available homoallylic alcohols is particularly attractive, both from a practical and synthetic standpoint.

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[115] a) Hatanaka, Y.; Hiyama, T. *Pure Appl. Chem*. **1994**, *66*, 1471-1478. b) Sebeliu, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc*. **2006**, *128*, 8150-8151. c) Ikeda, I. J.; Kakiuchi, K.; Hirako, K.; Shiba, K.; Kurosawa, H. *J. Chem. Soc., Chem. Commun.* **1994**, 1099-1100. d) Ikeda, I. J.; Hirako, K.; Shiba, K.; Kurosawa, H. *Inorg. Chim. Acta* **1996**, *250*, 149-154. e) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett*. **2006**, *35*, 1368-1369. f) Yamamoto, Y.; Takada, S.; Miyaura, N.; Iyama, T. Tachikawa. H. *Organometallics* **2009**, *28*, 152-160.

[116] a) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *Org. Lett.* **2005**, *16*, 3577-3579. b) Fujita, K.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2004**, *69*, 3302-3307. c) Jones, P.; Knochel, P. *J. Org. Chem*. **1999**, *64*, 186-195.

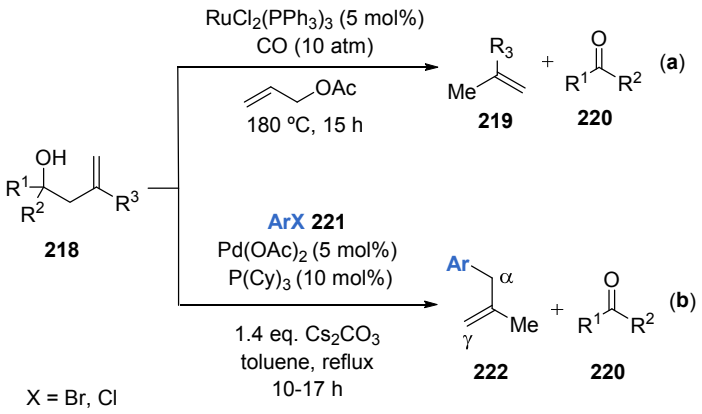


Figure 5.4

The proposed mechanism for Oshima's findings goes via initial oxidative addition followed by ligand exchange, generating an oxypalladium intermediate that would easily trigger a retroallylation via a six-membered transition state (Figure 5.5). A final reductive elimination would deliver the allylation product with concomitant recovery of the $Pd(0)L_n$ species.

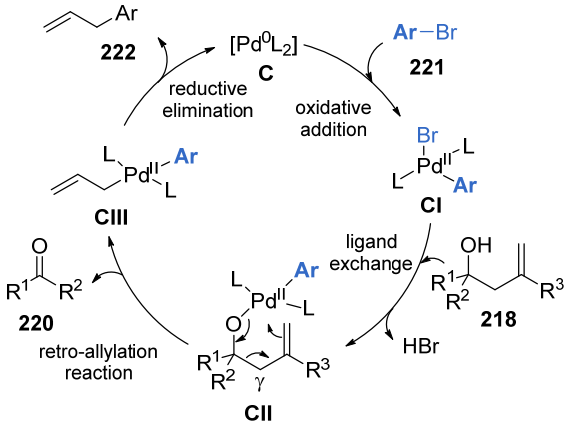
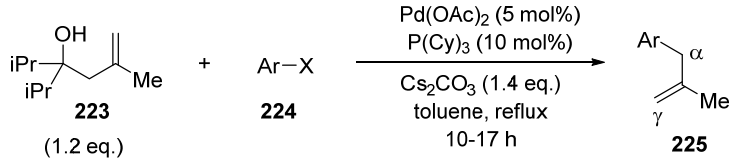


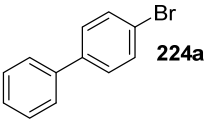
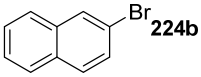
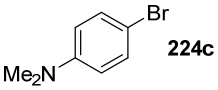
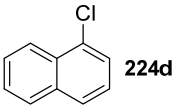
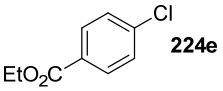
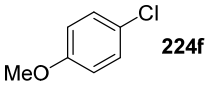
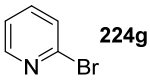
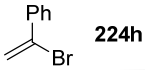
Figure 5.5

The scope of the reaction was limited to rather specific homoallylic alcohols and aryl halides (Figure 5.6).[117] As shown, aryl bromides as well as

[117] Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4463-4469.

aryl chlorides were well tolerated providing good yields and excellent regioselectivities, favoring the α-isomer. Unfortunately, substrates containing sensitive functional groups were rarely tolerated.



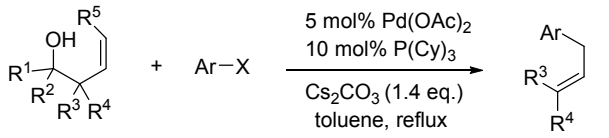
Entry	Ar-X	Yield 225 (%)
1	 **224a**	83
2	 **224b**	86
3	 **224c**	80
4	 **224d**	79[a]
5	 **224e**	79, 72[b,c]
6	 **224f**	70, 98[b,c]
7	 **224g**	56
8	 **224h**	5

[a] 2-methallynaphthalene as byproduct (8%) [b] Under Microwave irradiation 250 ºC for 15 min. [c] 30 mol% of ligand

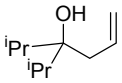
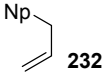
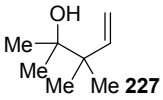
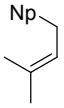
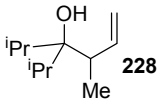
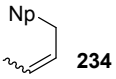
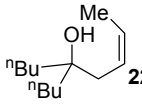
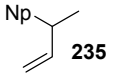
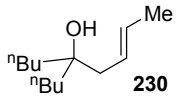
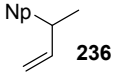
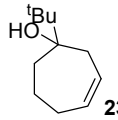
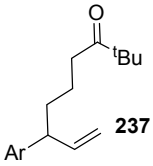
Figure 5.6

As for the homoallylic alcohol, a variety of substituents could be introduced. As expected, an erosion of the stereoselectivity was found with homoallylic alcohols possessing substituents at the allyl terminus (Figure 5.7, entry 3). The authors found that (Z)-alkenes reacted several orders of

magnitude faster than (*E*)-alkenes. Particularly noteworthy was the observation that cyclic homoallylic alcohols (**231**) could be utilized, thus delivering the final product in a more atom-economical manner (Figure 5.7, entry 6).



226-231 (1.2 eq.) | **224** | **232-237**

Entry	Alcohol	Ar-X 224	Product	Yield (%) (E/Z ratio)
1	 **226**	**224i**	 **232**	83
2	 **227**	**224i**	 **233**	92
3	 **228**	**224i**	 **234**	80[a] (*E*/*Z*= 63:37)
4	 **229**	**224i**	 **235**	48[b]
5	 **230**	**224i**	 **236**	11
6	 **231**	**224j** 80, 88[c] **224k** 68 **224l** 70 **224m** 65 **224n** 64 **224o** 46	 **237**	

a) 2-5% of branched product. b) 72% with P(p-tol)$_3$ as ligand. c) Under microwave irradiation 250 ºC, 15 min. d) 2.5 mol% Pd(OAc)$_2$, 7.5 mol% PCy$_3$ in Xylene reflux.

Figure 5.7

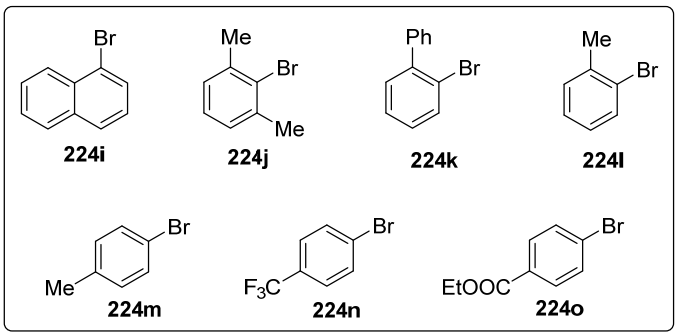


Figure 5.8

Intrigued about the different reactivity of **229** and **230**, they rationalized these results on the basis of steric hindrance between the palladium center and the *trans*-substituent of the homoallylic alcohol, preventing the retroallylation from occurring (Figure 5.9).

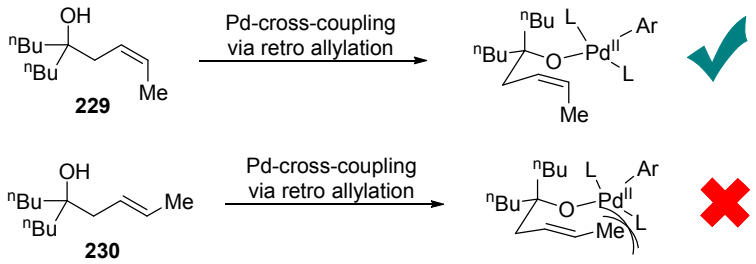
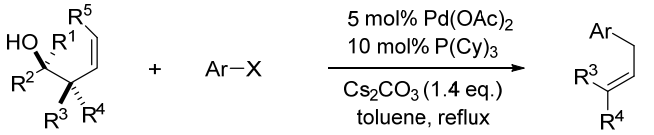
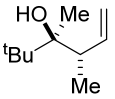
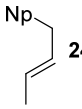
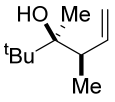
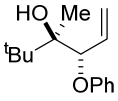
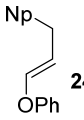
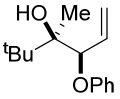
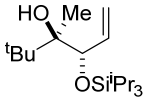
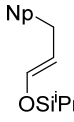
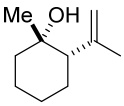
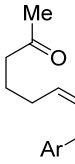
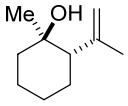
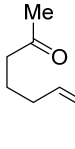


Figure 5.9

As previously mentioned, no stereocontrol was possible with the homoallylic alcohol **228** which led to a mixture of *E/Z*-isomers (63:37). Consequently, the authors synthesized different diastereomerically pure starting materials (entry 1-7 Figure 5.10) to demonstrate that the reaction can be carried out in a stereoselective manner. These diastereomerically pure homoallylic alcohols were submitted under the optimized reaction conditions, affording in all cases the allylated arenes with very high regio- and stereocontrol (Figure 5.10).



238-244 (1.2 eq.) + **224** → **245-251**

Entry	Alcohol	Ar-X	Product	Yield (%) (E/Z ratio)
1	 **238**	**224i** **224e** **224f**	 **245**	95[a] (*E*/*Z*=97:3) 78[a] (*E*/*Z*=95:5) 67[a] (*E*/*Z*=96:4)
2	 **239**	**224i** **224e** **224f**	 **246**	70[a] (*E*/*Z*=0:100) 73[a] (*E*/*Z*=0:100) 77[a] (*E*/*Z*=0:100)
3	 **240**	**224i**	 **247**	88 (*E*/*Z*=99:1) 93[b] (*E*/*Z*=95:5)
4	 **241**	**224i**	 **248**	67 (*E*/*Z*=1:99) 92[b] (*E*/*Z*=1:99)
5	 **242**	**224i**	 **249**	87 (*E*/*Z*=97:3)
6	 **243**	**224f** **224j** **224l** **224m** **224n** **224o**	 **250**	76 (*E*/*Z*= 1:99) 54 (*E*/*Z*= 1:99) 81 (*E*/*Z*= 1:99) 61[c] (*E*/*Z*= 1:99) 64 (*E*/*Z*= 5:95) 84 (*E*/*Z*= 5:95)
7	 **244**	**224j** **224m**	 **251**	86 (*E*/*Z*= 99:1) 71 (*E*/*Z*= 95:5)

a) 2-5% of branched product. b) Results under microwave irradiation. c) Performed for 22h.

Figure 5.10

To explain the high level of stereoselective transfer control, the authors proposed the mechanistic scenario depicted in Figure 5.11, in which the bulkiest substituents are located at the equatorial position. Starting from **238**, the most stable reaction intermediate will be the one possessing the ^{t}Bu and the vicinal Me group at the equatorial position, favoring the formation of the *trans* σ-allyl(aryl)palladium complex (**CIV**) that ultimately will deliver the corresponding *trans*-allylated arene **245**. Following an analogous rationale, **239** will likely end up in the *cis*-palladium intermediate **CV** that, upon reductive elimination, will provide the *Z*-allyl arylated product **246**.

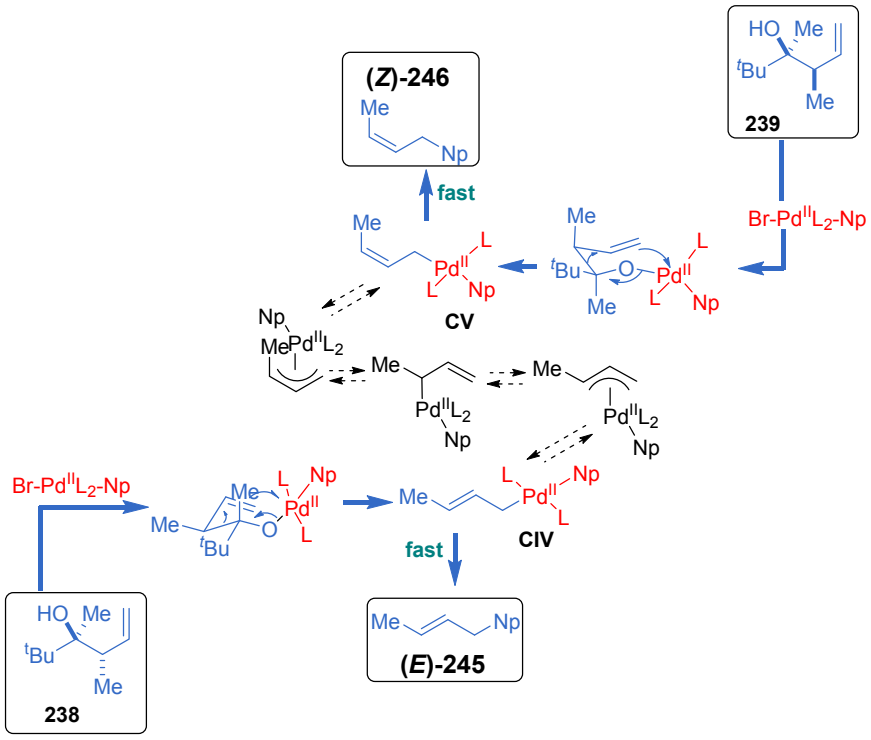
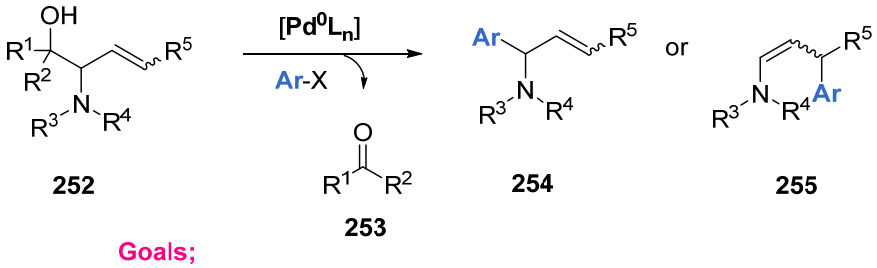


Figure 5.11

5.3 Results and discussions

Although no doubt a significant step forward, particularly from both regio- and stereoselectivity stand point, the retroallylation reaction developed by Oshima[85] presented a limited substrate scope. Prompted by the always-growing interest in amino alcohols for building up molecular complexity, we wondered whether appropriately substituted amino alcohol derivatives with an allylic terminus could be employed in retroallylation processes. If successful, such a methodology could ultimately end up in either allylic amines or well-defined enamine motifs, important synthons in organic synthesis, thus providing an additional handle for the further derivatization. Such a transformation, however, would only be practical if we could secure an excellent regioselectivity and chemoselectivity profile (Figure 5.12).



Goals;
- *Control the reactivity and regioselectivity (**254**) vs (**255**)*
- *Low catalyst loading*
- *Wide substrate scope*

Figure 5.12

We hypothesized that this reaction would be initiated by an oxidative addition of an aryl halide (**256**) to in situ generated Pd(0)L_n species **CVI** (Figure 5.13). Subsequent amino alcohol-halogen exchange assisted by a base would take place to afford intermediate **CVIII**, setting the stage for a retroallylation reaction via six-membered transition state, providing **CIX** intermediate. If reductive elimination is rapid enough, no σ-π-σ interconversion will take place en route to **CIX**, thus delivering **258**

exclusively. Hydrolysis of this enamine under acidic workup would give the corresponding β-arylated aldehyde (**259**) (Figure 5.13).

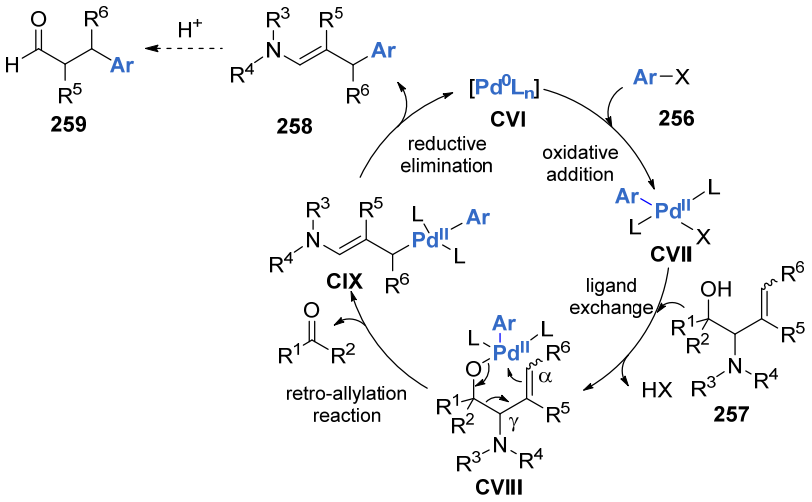


Figure 5.13

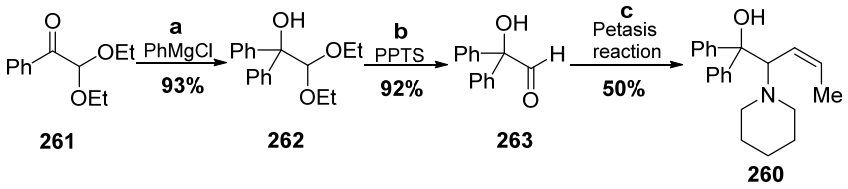
If successful, such a methodology will constitute a rare example of a formal β-arylation of α,β-unsaturated aldehydes. Indeed, such a transformation has eluded chemists for many years and only few precedents exist. Among these, the β-arylation described by Mac Millan is particularly noteworthy, combining both photoredox and organocatalysis.[118]

5.3.1 Optimization of the reaction conditions

We chose **260** (Figure 5.14) as our model substrate due to its ease of synthesis from simple precursors in essentially 2 steps (Figure 5.14). The synthetic pathway involves a simple addition of PhMgCl to commercially available 2,2-diethoxy-1-phenylethan-1-one (**261**) in THF at room temperature. Then, mild acidic catalytic cleavage of acetal **262** with pyridinium *p*-toluenesulfonate in water/acetone at reflux generated **263** that

[118] a) Pirnot, M. T.; Rankic, D. A.; Martin, D. B. C.; MacMillan, D. W. C. *Science* **2013**, *339*, 1593-1596. b) Terrett, J. A.; Clift, M. D.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2014**, *136*, 6858-6861.

was immediately exposed under Petasis conditions with piperidine and commercially available *cis*-propenylboronic acid in hexafluoroisopropanol (HFIP) under microwave irradiation. This reaction proceeds via iminium ion formation (from the condensation of an aldehyde and a secondary amine) followed by nucleophilic addition of the corresponding boronic acid.[119]



Conditions; a) PhMgCl (1.2 eq.) in THF 0 ºC to room Tº, 2 h. **b)** PPTS (0.4 eq.) in H_2O/Acetone (7:3), reflux for 2 days. **c**) Piperidine (1.0 eq.), cis-propenylboronic acid (1.2 eq.), HFIP (0.5 mL), under microwave irradiation (50 min, 80 ºC)

Figure 5.14

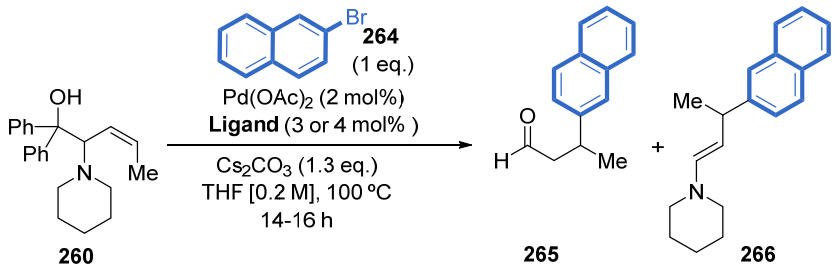
5.3.1.1 Optimization of the reaction conditions for the formal β-arylation of aldehydes via C-C bond cleavage of an amino alcohol (260)

With significant amounts of **260** in hand, a systematic evaluation of the different experimental parameters (catalyst, ligand, metal, base, solvent and reaction conditions) was carried out. Among the catalyst used, it came as no surprise that Pd(II) sources proved to be particularly suited for our purposes, as shown initially by Oshima.[85] We started our optimization using **260** (1 eq.) as model substrate, $Pd(OAc)_2$ (2 mol%) as catalyst, Cs_2CO_3 (1.3 eq.) as base and 2-bromo-naphthalene (**264**) as coupling partner in THF at 100 ºC. In line with other cross-coupling reactions, we expected that the nature of the ligand would be critical for success. That being set, we decided to exhaustively analyze the role of the ligand in the reaction outcome. A representative number of these ligands are highlighted in Table 1.

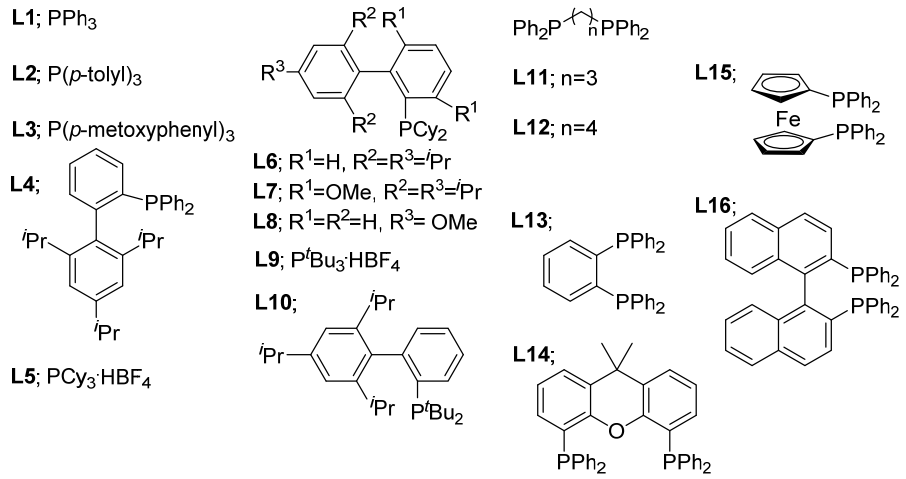
---

[119] a) Gois, P. M. P.; Cal, P. M. S. D.; Montalbano, F.; Candelais, N. R. *Chem. Rev*. **2010**, *110*, 6169-6193. b) Ayaz, M.; Dietrich, J.; Hulme, C. *Tetrahedron Lett*. **2011**, *52*, 4821-4823

Table 1. Screening of different ligands



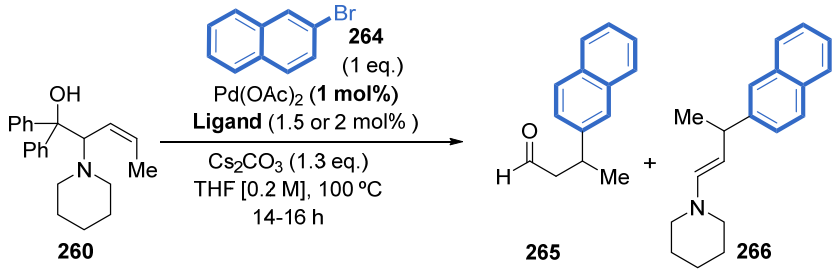
Entry	Ligand	Conversion (%)	Yield (%) (265 + 266)
1	**L1**	100	75
2	**L2**	100	73
3	**L3**	100	74
4	**L4**	90	50
5	**L5**	70	49
6	**L6**	100	76
7	**L7**	60	35
8	**L8**	92	60
9	**L9**	86	55
10	**L10**	30	0
11	**L11**	90	69
12	**L12**	84	50
13	**L13**	38	17
14	**L14**	42	22
15	**L15**	90	66
16	**L16**	100	80



Reaction conditions: (a) **260** ($8 \cdot 10^{-2}$ mmol), $Pd(OAc)_2$ (2 mol%), Ligand (3 mol% bidentate ligand or 4 mol% monodentate ligand), Cs_2CO_3 (1.3 eq.), THF [0.2 M], 100 ºC for 14-16 h. (b) Conversions and yields were determined by ^1H NMR using 1,4-dioxane as internal standard.

As shown in Table 1, we found that a number of different ligands resulted in good conversion to products after the workup. Interestingly, (*E*)-enamine (**266**) was exclusively formed, with no traces of (*Z*)-**266** being detected in the crude mixtures. While simple aryl monophosphine ligands (**L1**-**L3**) provided good yields, the steric bulk posed by **L4** resulted in low yields. Indeed, electron-rich and bulky alkyl monophosphine ligands consistently caused an erosion in yield of (**265**+**266**). An otherwise similar outcome was found when employing bidentate phosphines, although Binap resulted in a remarkable 69% yield of (**265**+**266**). Taking these results into account, we decided to continue our screening with the best five ligand backbones (**L1**, **L2**, **L3**, **L6** and **L16**) by evaluating their performance at 1 mol% $Pd(OAc)_2$. As shown in Table 2, although the yields and conversions were somewhat comparable, we decided to keep a 2 mol% Pd loading for a reliability and experimental ease standpoint.

Table 2. Screening of ligands with 1 mol% $Pd(OAc)_2$

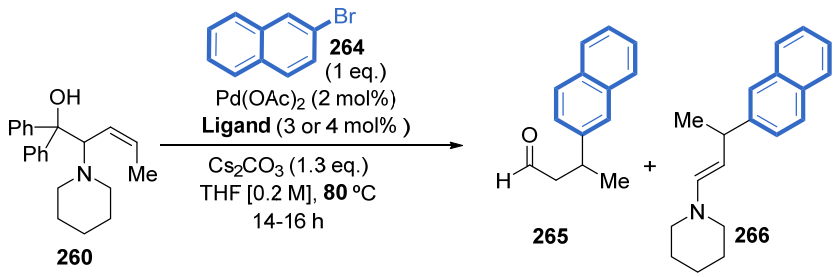


Entry	Ligand	Conversion (%)	Yield 265+266 (%)
1	**L1**	90	68
2	**L2**	85	62
3	**L3**	88	65
4	**L6**	88	64
5	**L16**	77	49
6	**L1**	76	60[c]

Reaction conditions: (a) **260** ($8 \cdot 10^{-2}$ mmol), $Pd(OAc)_2$ (1 mol%), Ligand (1.5 mol% bidentate L and 2 mol% monodentate L), Cs_2CO_3 (1.3 equiv.), THF [0.2 M], 100 ºC for 14-16 h. (b) Conversions and yields were determined by ^1H NMR using 1,4-dioxane as internal standard. (c) T = 90 ºC.

Next, we set out to test the effect of temperature on the reaction outcome. To such end, the reaction was carried out at 80 ºC with the five best ligands previously mentioned above (**L1**, **L2**, **L3**, **L6** and **L16**).

Table 3. Screening of ligands at 80 ºC

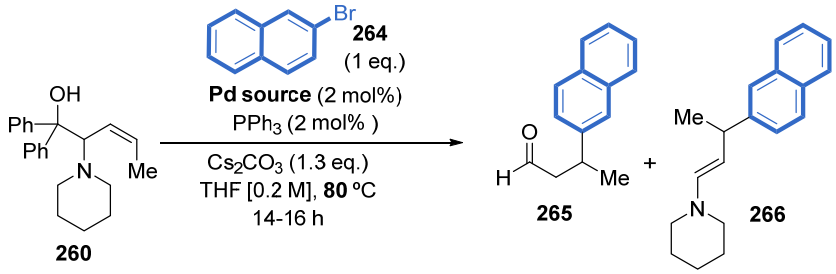


Entry	Ligand	Conversion (%)	Yield 265+266 (%)
1	**L1**	66	57
2	**L2**	62	51
3	**L3**	56	50
4	**L6**	64	51
5	**L16**	27	18

Reaction conditions: (a) **260** ($8 \cdot 10^{-2}$ mmol), $Pd(OAc)_2$ (2 mol%), Ligand (3 mol% bidentate L and 4 mol% monodentate L), Cs_2CO_3 (1.3 eq.), THF [0.2 M], 80 ºC for 14-16 h. (b) Conversions and yields were determined by ^1H NMR using 1,4-dioxane as internal standard.

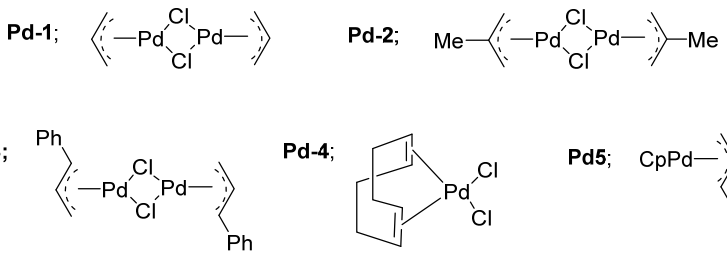
As becomes evident from the results compiled in Table 3, both yields and conversions dropped significantly at 80 ºC. With these results in hand, we next focused our attention on the screening with different Pd(II) sources using PPh_3 as ligand (Table 4).

Table 4. Screening of different palladium sources



Entry	Pd source	Conversion (%)	Yield (%) (265)+(266)
1	$Pd(OAc)_2$	66	57
2	Pd-1	69	67
3	Pd-2	61	50
4	Pd-3	71	57
5	Pd-4	51	41
6	Pd-5	26	20
7	$PdCl_2$	9	0
8	$PdCl_2(SMe)_2$	59	51

Pd sources;

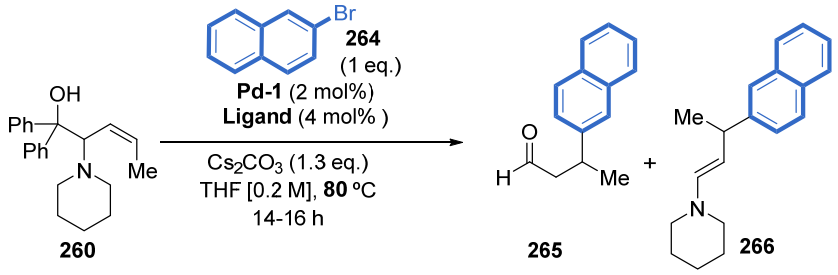


Reaction conditions: (a) **260** ($8 \cdot 10^{-2}$ mmol), Pd source (2 mol% of Pd), Ligand (3 mol% bidentate L and 4 mol% monodentate L), Cs_2CO_3 (1.3 eq.), THF [0.2 M], 80 ºC for 14-16 h. (b) Conversions and yields were determined by ^1H NMR using 1,4-dioxane as internal standard.

Specifically, different allylpalladium (II) chloride dimer species (**Pd-1**, **Pd-2**, **Pd-3**) as well as monomeric palladium (II) species (**$Pd(OAc)_2$**), **Pd-4**, **Pd-5** and **PdCl2**) were tested. Interestingly, the reaction worked equally

well with allyl Pd(II) dimeric species when compared with the result employing $Pd(OAc)_2$. As shown in Table 5, the utilization of **Pd-1** with a different set of ligands revealed that **L6** could also be used with similar yields to that shown for **L1**. Taking these results into consideration, we next decided to find out the best combination when using either $Pd(OAc)_2$ or **Pd-1** with both **L1** and **L6** (Table 6).

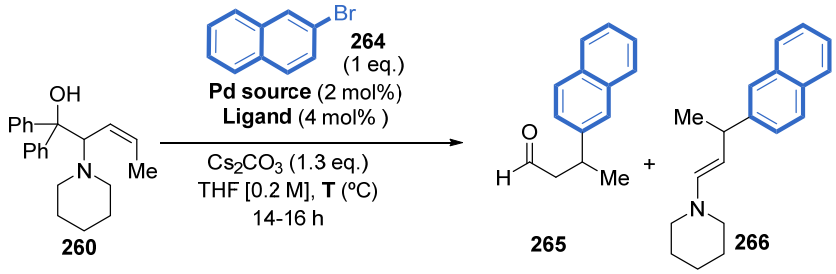
Table 5. Screening of different ligands with Pd-1 source



Entry	Ligand	Conversion (%)	Yield (%) (265) + (266)
1	**L1**	69	67
2	**L2**	69	59
3	**L3**	61	55
4	**L6**	88	73
5	**L16**	64	49

Reaction conditions: (a) **260** ($8 \cdot 10^{-2}$ mmol), **Pd1** source (2 mol% of Pd), Ligand (3 mol% bidentate ligand and 4 mol% monodentate ligand), Cs_2CO_3 (1.3 eq.), THF [0.2 M], 80 ºC for 14-16 h. (b) Conversions and yields were determined by ^1H NMR using 1,4-dioxane as internal standard.

Table 6. Screening of other conditions



Entry	Other tests	Conversion (%)	Yield 265 (%)
1	**Pd1, 100ºC, L1**	98	52[b]
2	**Pd1, 90ºC, L1**	100	85[c]
3	**Pd1, 90ºC, L6**	100	77[c]
4	**$Pd(OAc)_2$, 90ºC, L1**	100	85[c]
5	**$Pd(OAc)_2$, 90ºC, L6**	100	60[c]

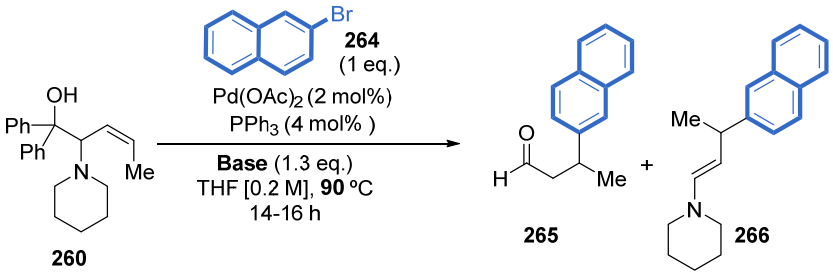
Reaction conditions: (a) **260** ($7.8x10^{-2}$ mmol), **Pd1** or $Pd(OAc)_2$ (2 mol% of Pd), **L1** or **L6** (4 mol%), Cs_2CO_3 (1.3 eq.), THF [0.2 M], 90 or 100 ºC for 14-16 h. (b) Conversions and yields were determined by ^1H NMR using 1,4-dioxane as internal standard. (c) Isolated yields.

As shown in Table 6, all reagent combinations evaluated provided similar results. Among these, we decided to fix the reaction conditions based on the **$Pd(OAc)_2$/L1** as the **Pd-1/L1** combination was considerably more expensive and more complicated to handle.

Next, we focused our attention on the role of the base as it might have a significant influence on the deprotonation event prior to the retroallylation step. Consequently, we set out to screen different bases at 2 mol% of $Pd(OAc)_2$ using PPh_3 as ligand. As shown in Table 7, we observed a dramatic drop in conversions and yields with strong bases (NaH or NaO^{t}Bu) or with similar basicity to that shown for Cs_2CO_3 (K_2CO_3 or H_3PO_4). Although tentative, these results might be attributed to the peculiar role exerted by the Cs^{2+} cation. This cation possesses a big radius that it is translated in a low charge density and large polarizability, causing a lower

degree of solvatation compared to other alkali metal salts. In fact, it is known that its solubility in aprotic solvents is, in general, higher than the other alkali metal salts.

Table 7. Screening of different bases

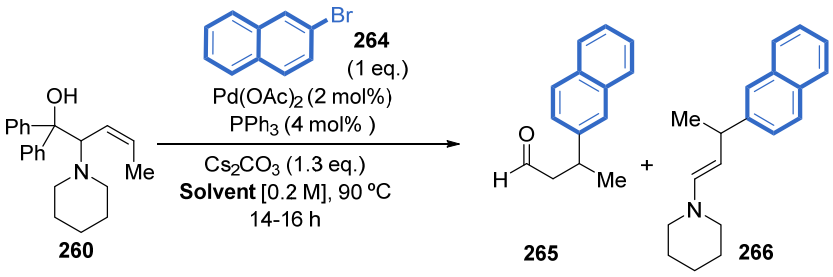


Entry	Base	Conversion (%)	Yield (%) (265) + (266)
1	**Cs_2CO_3**	100	85[c]
2	**K_2CO_3**	44	19
3	**K_3PO_4**	52	33
4	**Na^{t}BuO**	47	25
5	**NaH**	100	0

Reaction conditions: (a) **260** ($8\cdot10^{-2}$ mmol), $Pd(OAc)_2$ (2 mol%), **L1** (4 mol%), Base (1.3 eq.), THF [0.2 M], 90 ºC for 14-16 h. (b) Conversions and yields were determined by ^{1}H NMR using 1,4-dioxane as internal standard. (c) Isolated Yield.

The last reaction parameter optimized was the solvent (Table 8). In line with other cross-coupling reaction, the use of aprotic apolar solvents such as toluene, DME and dioxane gave the best results, but slightly worse than THF. In contrast, more polar solvents like DMF or *tert*-butanol, resulted in a significant erosion in yield.

Table 8. Screening of different solvents



Entry	Solvent	Conversion (%)	Yield (%) (265) + (266)
1	**THF**	100	85[c]
2	**Toluene**	89	72
3	***tert*-Butanol**	79	46
4	**Ph-CF_3**	71	51
5	**DME**	87	68
6	**DMF**	80	46
7	**Dioxane**	90	67

Reaction conditions: (a) **260** ($8 \cdot 10^{-2}$ mmol), $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), Cs_2CO_3 (1.3 eq.), **Solvent** [0.2 M], 90 ºC for 14-16 h. (b) Conversions and yields were determined by ^1H NMR using 1,4-dioxane as internal standard. (c) Isolated yields.

5.3.2 Scope of the reaction

After establishing the optimal reaction conditions for the formal β-arylation of aldehydes via C-C bond cleavage of amino alcohol **260** with 2-bromonaphthalene (**264**), we decided to explore the scope of this transformation. A wide range of *N*-allyl 1,2-amino alcohol were prepared, some of them according to the procedure shown in Figure 5.14 and others with slight modifications as shown below.

5.3.2.1 Synthesis of other *N*-allyl 1,2-amino alcohols

As mentioned previously in Figure 5.14, the synthesis of the starting material is based on a three-step sequence terminated with a Petasis

reaction. Therefore, we synthesized additional α-hydroxy aldehydes (**267-269)** by a two step procedure with high yields and in multigram scale according to Figure 5.14 (Figure 5.15).

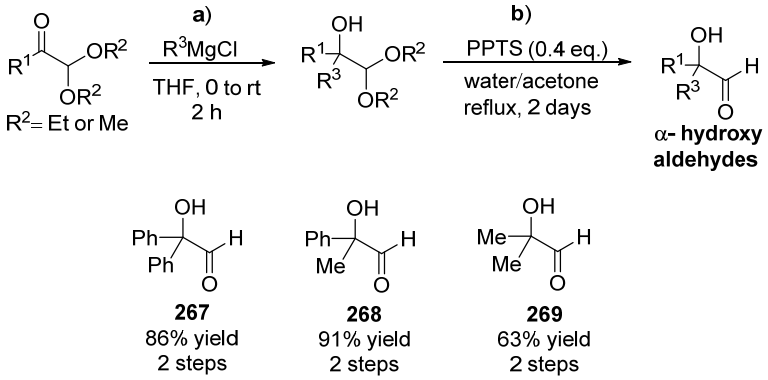
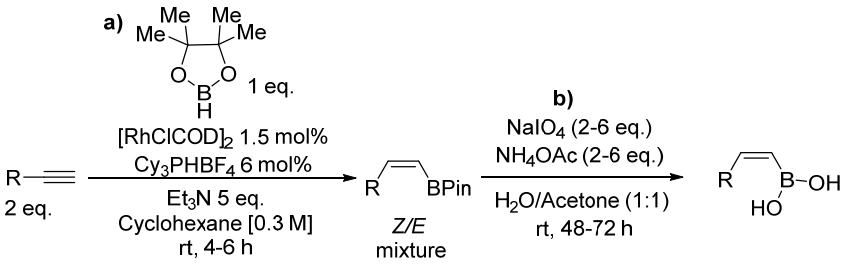


Figure 5.15

As the portfolio of commercially available vinyl boronic acids is rather limited, we also set out to synthesize a wide variety of *cis*-vinyl boronic acids. Two different general procedures (**A** and **B**) were utilized to prepare these reagents (Figure 5.16). In procedure **A**,[120] a Rh-catalyzed addition of pinacolborane to the corresponding alkyne provided as the major product the corresponding *cis*-pinacol ester that was subsequently treated with $NaIO_4/NH_4OAc$ to afford the desired *cis*-vinylboronic acid. In procedure **B**, *cis*-vinylboronic acids were obtained via lithium-halogen exchange followed by $B(OiPr)_3$ quench and a final hydrolytic workup. In all cases, these boronic acids were used in the Petasis reaction without further purification.

[120] Shimizu, H.; Igarashi, T.; Miura, T. Murakami, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 11465-11469

General procedure A



General procedure B

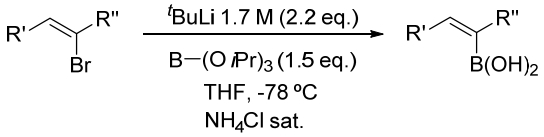


Figure 5.16

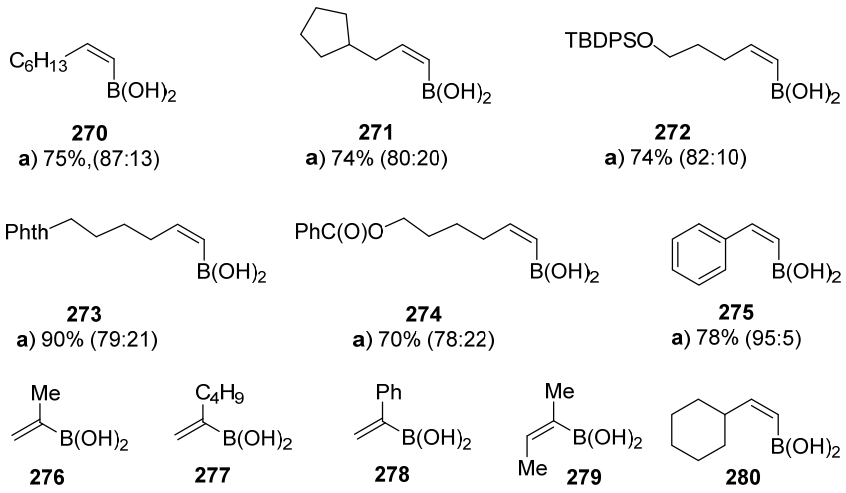


Figure 5.17

With a vast array of vinyl boronic acids (**270-280**) (Figure 5.17) and α-hydroxy aldehydes in hand (**267-269**) (Figure 5.15), we conducted the Petasis reaction with different set of amines under microwave irradiation (Figures 5.18).

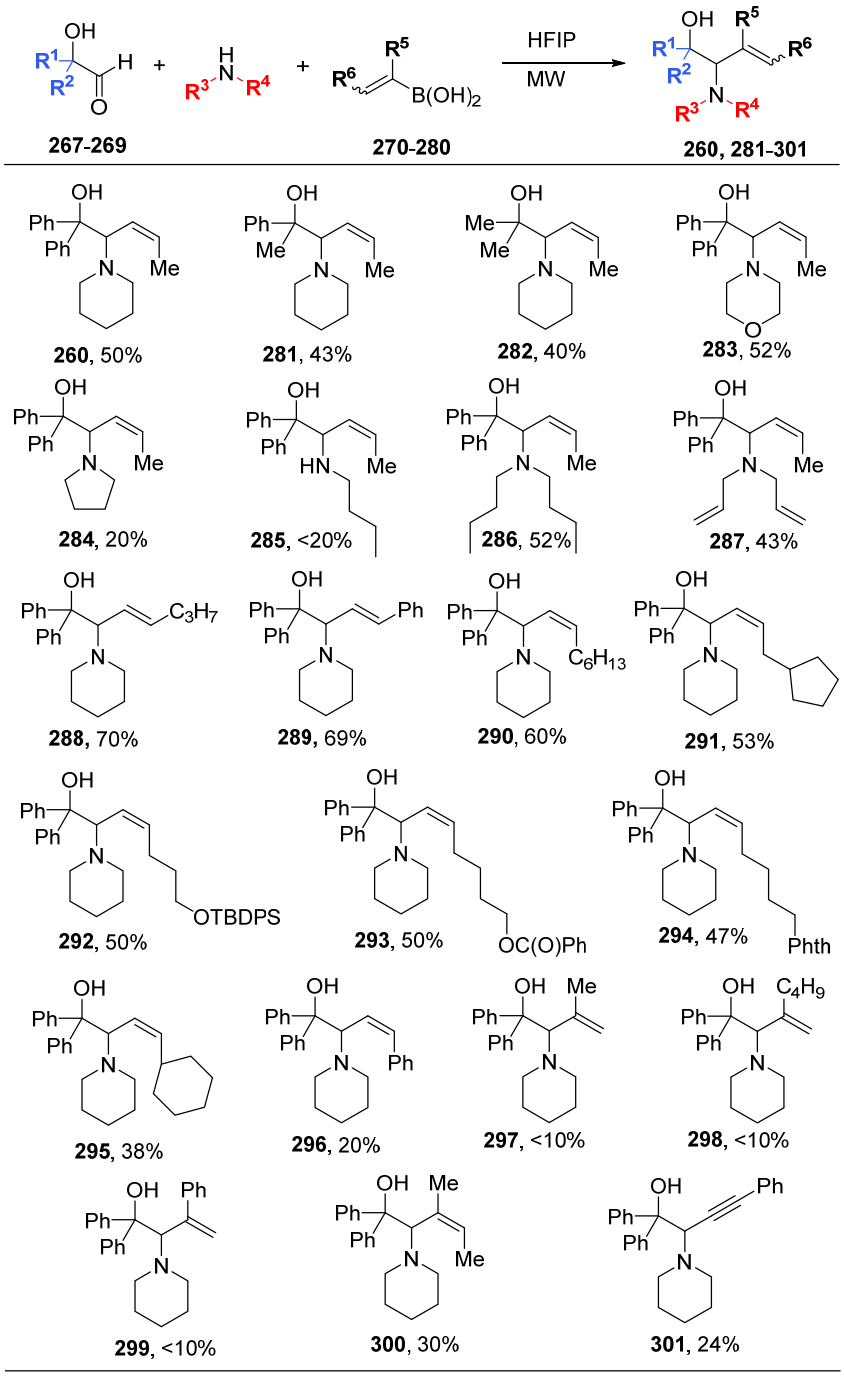

HFIP
MW
267-269
270-280
260, 281-301
260, 50%
281, 43%
282, 40%
283, 52%
284, 20%
285, <20%
286, 52%
287, 43%
288, 70%
289, 69%
290, 60%
291, 53%
292, 50%
293, 50%
294, 47%
295, 38%
296, 20%
297, <10%
298, <10%
299, <10%
300, 30%
301, 24%

Figure 5.18

As shown in the Figure 5.18, a wide range of different substituted *N*-allyl 1,2-amino alcohols (**260**, **281-301**) could be synthesized, either varying the amine, the vinyl or the tertiary alcohol motif. It is worth noting that the Petasis reaction turned out to be highly capricious and not as high yielding as expected; indeed, many substrates were obtained in low yields. At present we do not have any rationale for these results.

5.3.2.2 Formal Pd-catalyzed β-arylation of aldehydes via retroallylation of 1,2- amino alcohols (260) with different aryl bromides

With a diverse set of amino alcohols (**260**, **281-301**) in hand, we focused our attention on the generality of the Pd-catalyzed β-arylation of aldehydes using different substituted aryl bromides and **260** as the model amino alcohol. As illustrated in Figure 5.19, the reaction was rather general regardless of both the steric and electronic effects on the aryl halide utilized. Although one might have anticipated problems with ortho-substituted aryl halides, this was not the case, and **303-305** were all obtained in good yields. More importantly, the reaction was found to be particularly compatible with a variety of sensitive functional groups such us esters (**308**), aldehydes (**309**), acetals (**310**), nitro groups (**311**), nitriles (**312**) or ketones possessing relatively acidic α-hydrogens (**313**). As shown for **314**, the presence of nitrogen-containing heteroaromatic rings do not interfere; similarly, benzothiophene derivatives could also be obtained, albeit in lower yields (**315**).

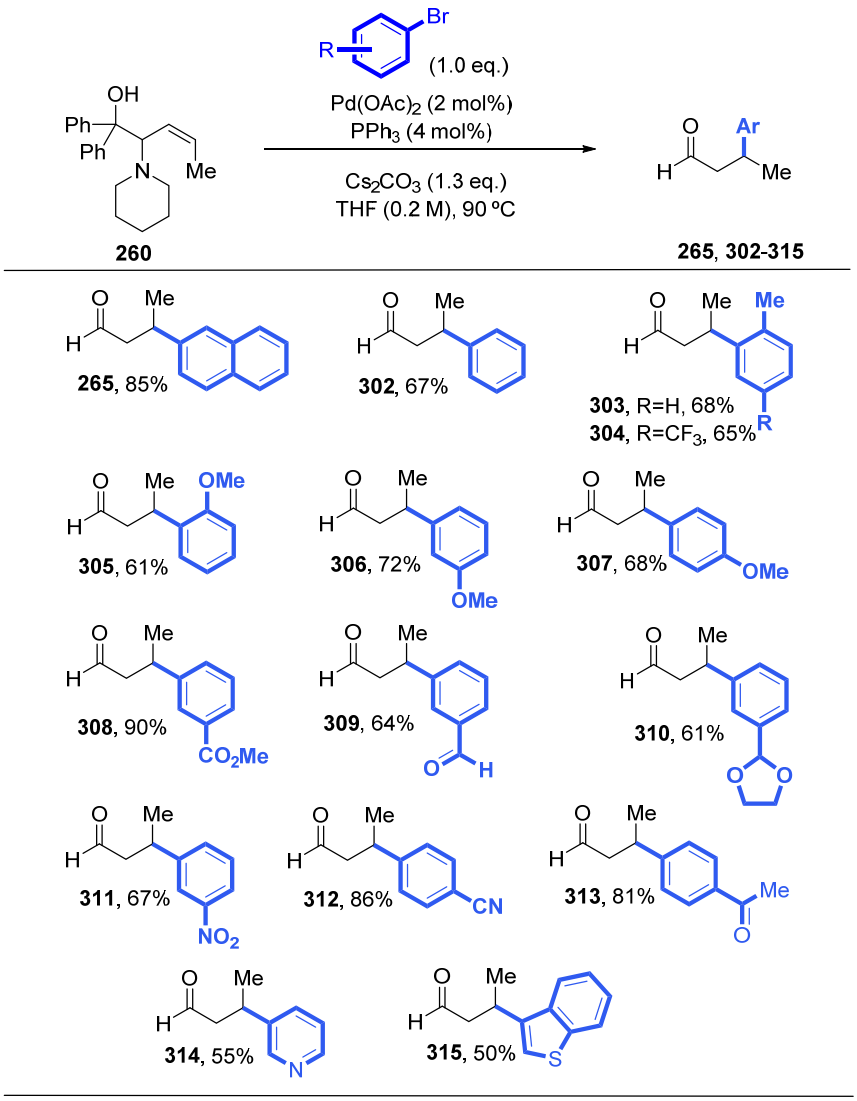


Figure 5.19

Unfortunately, the use of aryl triflates **316** or aryl chlorides **317** as coupling partner did not result in the desired β-arylated aldehyde in useful yields (Figure 5.20). While in the case of phenyl trifluoromethanesulfonate (**316**) only 30% yield was observed, no product was detected with 2-chloro naphthalene (**317**) under the optimized reaction conditions. This was probably due to the high energy required for effecting C-Cl bond cleavage using relatively electron poor phosphine ligands. Although speculative, we

believe that particularly electron-rich ligands would be capable of promoting the reaction with the more challenging aryl chlorides and aryl triflates. It is worth mentioning that no product formation was observed with **318-321**. While the presence of a proximal aldehyde might block the subsequent coordination to the alkene terminus (**318**), the presence of the acid motif was not tolerated, probably due to solubility issues (**319**). At present we do not have an explanation for the lack of reactivity of 1-bromo-2-methylpropene (**320**) or β-bromostyrene (**321**), as vinyl halides generally provide similar, if not better, yields in classical cross-coupling processes (Figure 5.20).

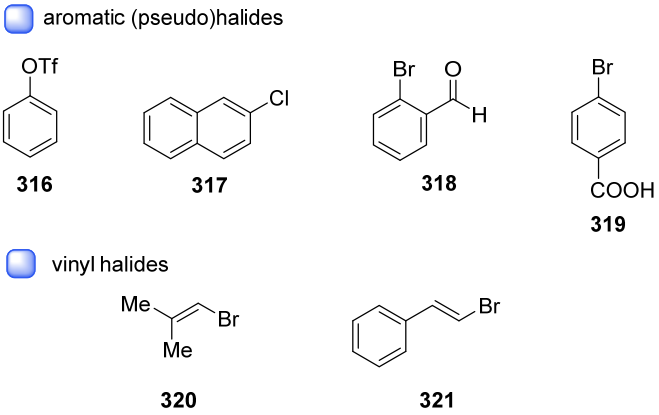


Figure 5.20

5.3.2.3 Formal Pd-catalyzed β-arylation of aldehydes via retroallylation of other 1,2- amino alcohols with 2-bromonaphthalene

Next, we decided to look at the preparative scope regarding the amino alcohol counterpart. Without further optimization, we found that a wide variety of substrates could be utilized with equal ease, delivering the targeted β-arylated aldehydes in good yields. The reaction proceeded with amino alcohols bearing a combination of aryl/alkyl (**281**) or alkyl/alkyl (**282**) moieties in the tertiary alcohol motif, with full conversion observed in all cases (Figure 5.21). Amino alcohols bearing different amine backbones could also be utilized; while dibutyl (**286**), diallyl (**287**) and morpholino

(**283**) derivatives posed no problems, a pyrrolidine **284** unit was not tolerated (Figure 5.21).

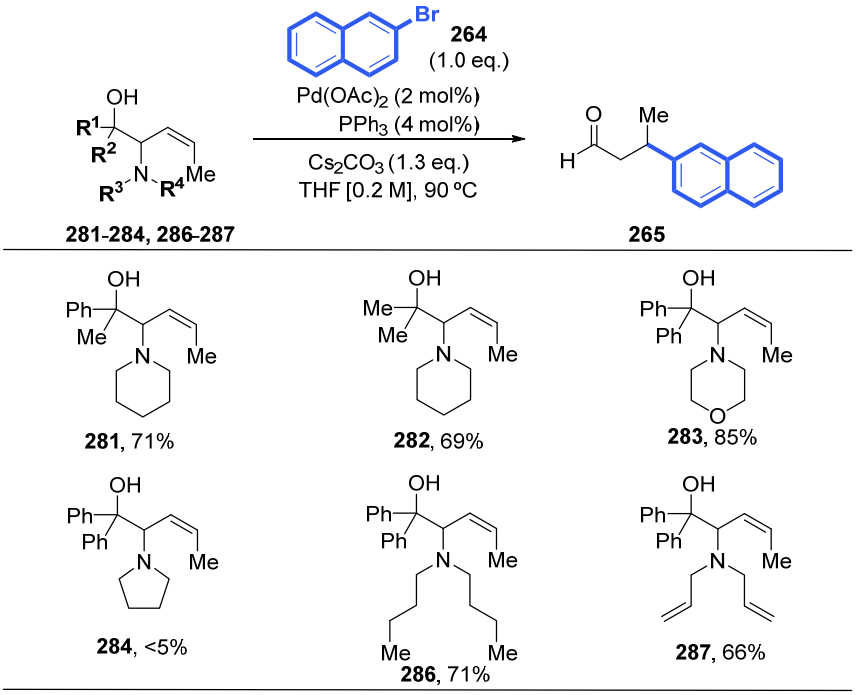


Figure 5.21

Regarding the amino alcohols bearing different *N*-allyl residues (Figure 5.22), those with alkylic moieties were perfectly tolerated, regardless of whether bulky groups were utilized **290** and **291**, indicating that these groups do not interfere for alkene binding into the Pd center. Different functional groups such us silyl ethers (**292**), esters (**293**) or amides (**294**) were also well accommodated. The reaction also proceeded with amino alcohol possessing a trisubstituted olefin (**300**), thus resulting in a densely functionalized aldehyde at α and β-positions. Unfortunately, amino alcohols bearing bulkier groups on the alkene terminus provided low yields of the targeted compounds (**327**). Although further fine-tuning of reaction conditions was carried out with **295**, yields were never higher than 30%. A blank experiment where **295** was dissolved in THF at 70 ºC for 12 h demonstrated that this particular amino alcohol was not stable under the

reaction conditions, recovering 70% of the corresponding starting material as for **296** and **301**, we found that decomposition pathways dominate, resulting in low yields of the corresponding aldehydic compounds.

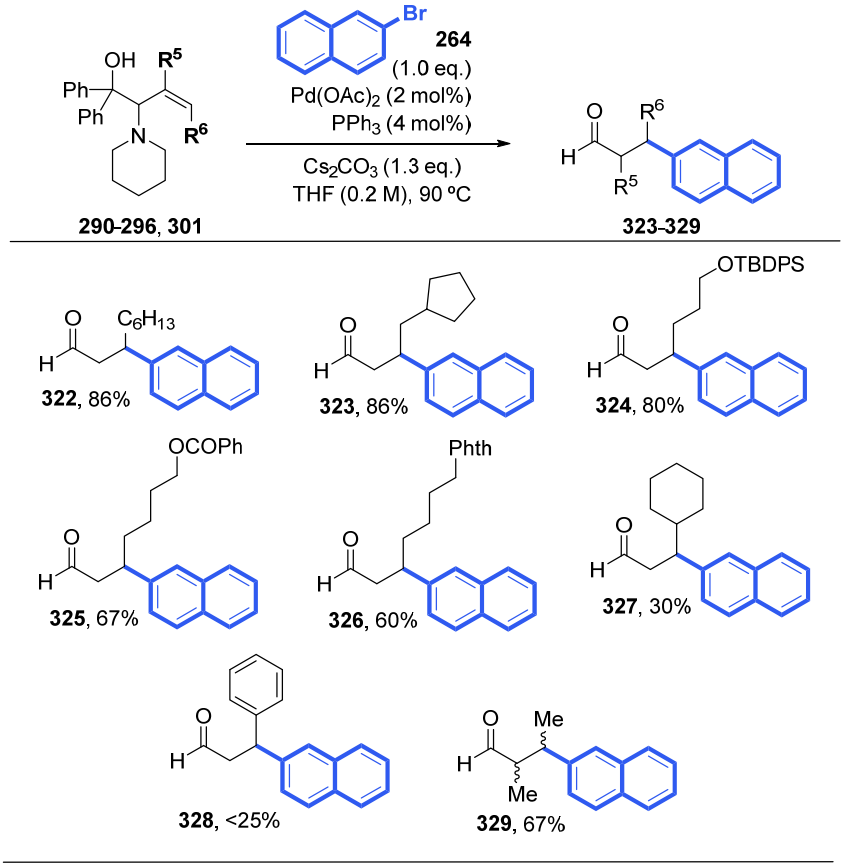


Figure 5.22

Unfortunately, our arylative method could not be applied to amino alcohols bearing *trans*-alkenes, regardless whether aromatic (**289**) or aliphatic (**288**) substituents were present on the vinyl entity. In all cases, low conversions were achieved, even at higher temperatures, using different palladium sources or bases. These results can be interpreted on the basis of a non favorable coordination of the alkene to the Pd centre (Figure 5.23).

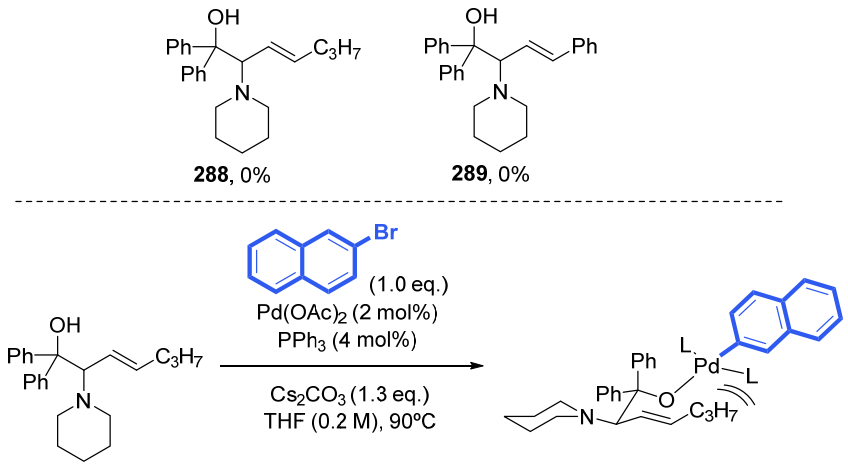


Figure 5.23

5.3.3 Formal obtention of α,β-functionalized aldehydes via Pd-cat. C-C bond cleavage of 260 followed by enamine alkylation

Taking into consideration that the crude reaction mixtures contained essentially the pure *E*-enamine intermediate (**266**), we wondered whether an in situ exposure of the crude material to a proper electrophile would result in densely functionalized aldehydes at α and β-position (**330**) (Figure 5.24).

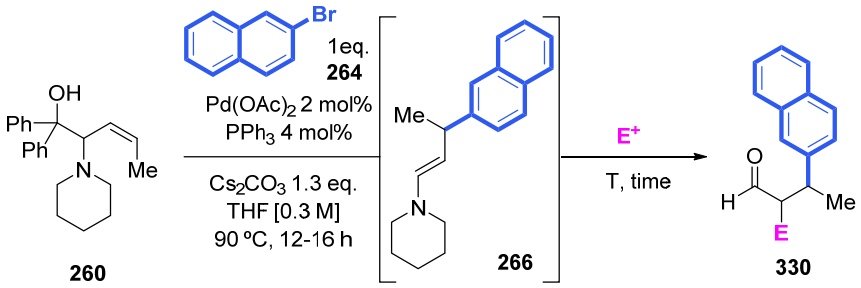


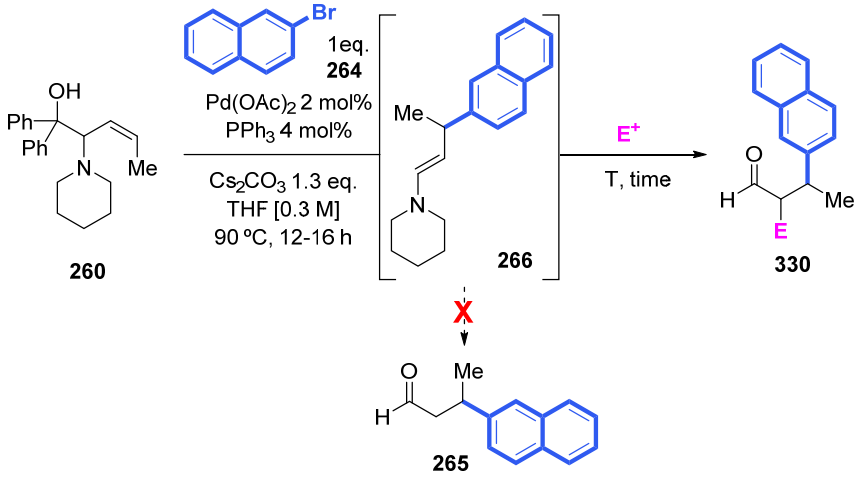
Figure 5.24

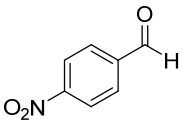
To our surprise, a close survey into the literature data revealed that the alkylation of well-defined enamines was far from trivial.[121] Indeed, few

[121] a) Hodgson, D. M.; Bray,C. D.; Kindon, N. D. *J. Am. Chem. Soc*. **2004**, *126*, 6870-6871. b) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77-80. c) Zoli, L.; Benfatti, F.;

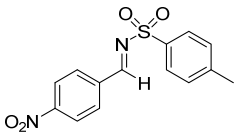
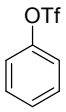
precedents exist for this a priori seemingly simple reaction. Prompted by this observation, we initiated an optimization for promoting a tandem retroallylation/functionalization via in situ generated enamines with an appropriate electrophile. Although we tested a myriad of different electrophiles, ranging from MeI to carbonyl-type compounds, almost in all cases we obtained predominantly the undesired β-arylated aldehyde (**265**) (Table 9).

Table 9. Alkylation with different electrophile



Entry	Electrophile[a]	Conditions	Results (dr)
1	CH_3I	90 ºC/12 h	**265**
2	$PhCH_2Br$	90 ºC/12 h	**265**
3	PhCHO	110 ºC/24 h	**265**
4		90 ºC/7 h	Traces of **330**
5	PhCOCl	90 ºC/15 h	**265**
6	MeOC(O)Cl	90 ºC/7 h	**265**

Cozzi, P. G. *Angew. Chem.* **2009**, *121*, 1339-1342. d) Arceo, E.; Jurberg, I. D.; Álvarez-Fernandez, A.; Melchiorre, P. *Nature Chem.* **2013**, *5*,750-756.

7		90 ºC/7 h	Decomposition
8		90 ºC/7 h	**265**
9		90 ºC/7 h or 90 ºC/12 h	43% of **265**[b] + 30% of **330**[b] (1.3:1)
10		90 ºC/7 h	**57% 330**[c] (1.3:1)

a) 3 equivalents of electrophile were used. b) Yield determined by ^{1}H NMR. c) Isolated yield.

Although many discouraging results were obtained, we found that allyl iodide and methyl vinyl ketone (**entries 9** and **10** Table 9) provided decent amounts of the expected product, particularly when using methyl vinyl ketone (**entry 10**, Table 9). In both cases, diastereomeric ratios around 1.3:1 were obtained. This observation is probably related to the lack of bulky groups around the enamine backbone that facilitate the selective differentiation between the two faces of the enamine. Although no good results were obtained in terms of dr, this example showed that it was feasible to carry out the formal α and β-functionalization of an aldehyde via C-C bond cleavage of amino alcohols followed by the alkylation of the resultant enamine in a one pot procedure (Figure 5.25).

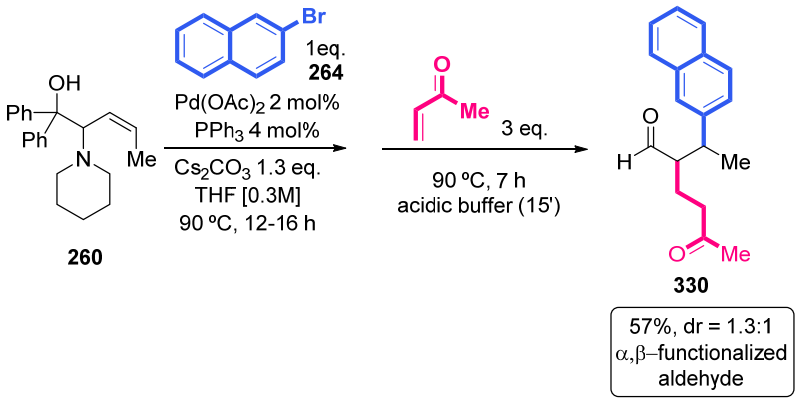


Figure 5.25

5.3.4 Enantioselective β-arylation of aldehydes via C-C bond cleavage of *N*-allyl amino alcohols

Encouraged by the results shown in **section 5.3.2**, we wondered whether it would be possible to develop a procedure to carry out this reaction in an enantioselective manner.

5.3.4.1 Optimization of the reaction conditions

Taking into consideration the excellent results found when employing PPh_3 and BINAP in the racemic version, we first decided to look at the ability of (*S*)-BINAP (**331**) and chiral phosphine derivative **332** to promote the targeted asymmetric event. Unfortunately, racemic product was obtained in both cases (Figure 5.26).

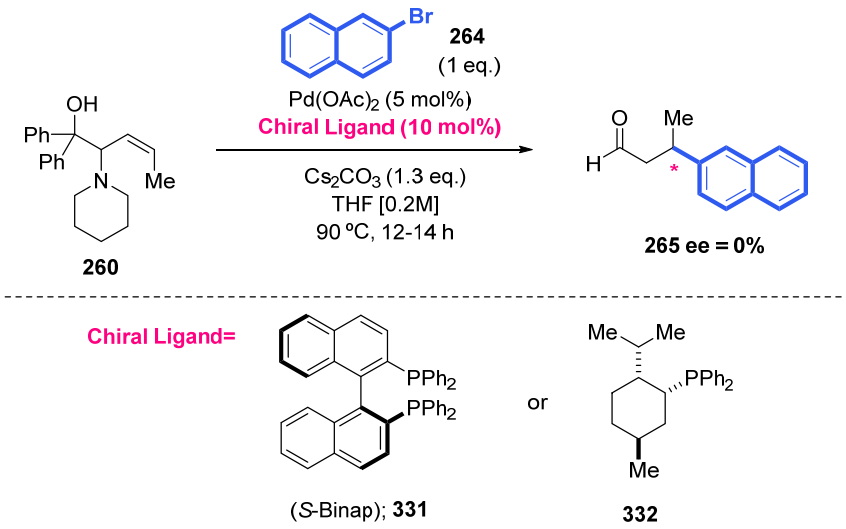
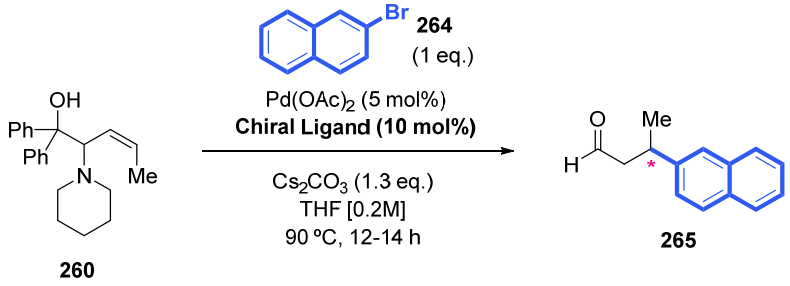


Figure 5.26

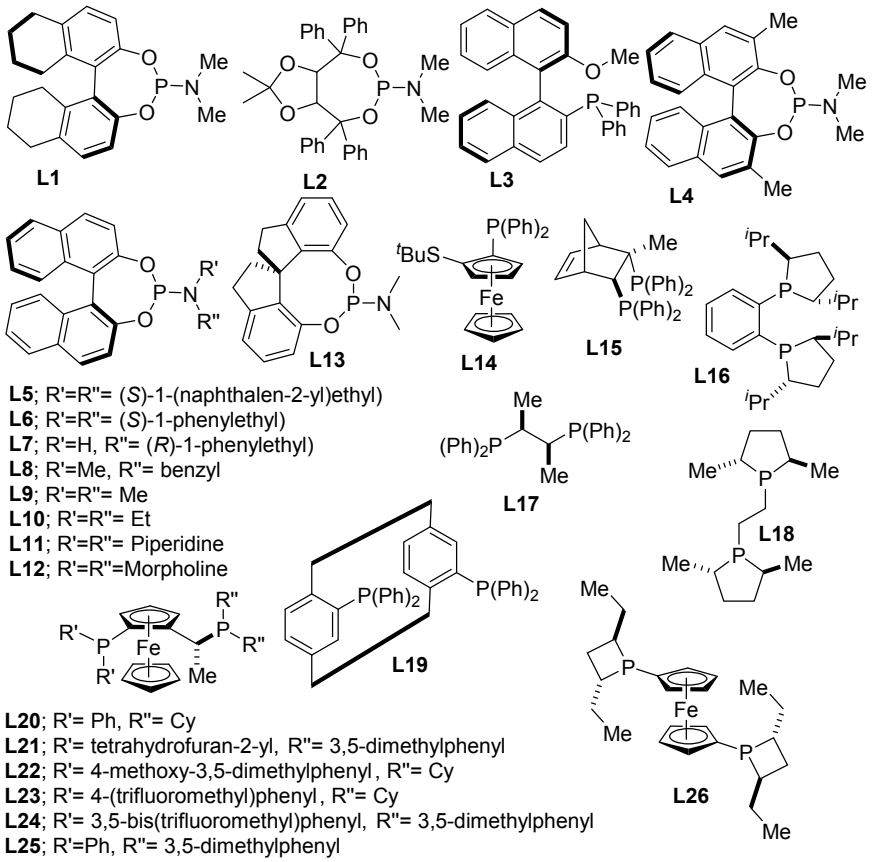
While certainly discouraging results, we decided to carry out an extensively screening of chiral ligands, hoping to get an insight into the features that might lead us to an asymmetric event. To such end, we decided to use The High Throughput Experimentation (HTE) laboratory from ICIQ, that allows setting up a large number of reactions at the same time while analyzing the results in a short period of time (Table 10).

Table 10. Screening of different chiral ligands[a, b]



Entry	Ligand	Yield 265 (%)	ee (%)
1	**L1**	29	29
2	**L2**	60	56
3	**L3**	54	4

4	**L4**	43	11
5	**L5**	18	-
6	**L6**	8	-
7	**L7**	7	-
8	**L8**	10	-
9	**L9**	10	-
10	**L10**	18	49
11	**L11**	12	-
12	**L12**	11	-
13	**L13**	55	rac
14	**L14**	8	-
15	**L15**	26	26
16	**L16**	34	32
17	**L17**	72	rac
18	**L18**	32	19
19	**L19**	32	rac
20	**L20**	32	rac
21	**L21**	43	19
22	**L22**	42	9
23	**L23**	30	rac
24	**L24**	52	20
25	**L25**	27	rac
26	**L26**	46	13



L5; R'=R"= (*S*)-1-(naphthalen-2-yl)ethyl)
L6; R'=R"= (*S*)-1-phenylethyl)
L7; R'=H, R"= (*R*)-1-phenylethyl)
L8; R'=Me, R"= benzyl
L9; R'=R"= Me
L10; R'=R"= Et
L11; R'=R"= Piperidine
L12; R'=R"=Morpholine

L20; R'= Ph, R"= Cy
L21; R'= tetrahydrofuran-2-yl, R"= 3,5-dimethylphenyl
L22; R'= 4-methoxy-3,5-dimethylphenyl, R"= Cy
L23; R'= 4-(trifluoromethyl)phenyl, R"= Cy
L24; R'= 3,5-bis(trifluoromethyl)phenyl, R"= 3,5-dimethylphenyl
L25; R'=Ph, R"= 3,5-dimethylphenyl

Reaction conditions: (a) Experiments carried out in HTE laboratory; **260** (20 μmol), $Pd(OAc)_2$ (5 mol%), chiral ligand (10 mol%), Cs_2CO_3 (1.3 eq.), THF [0.2 M] at 90 ºC for 12-14 h. (b) Conversions and yields were determined by HPLC analysis using biphenyl as internal standard.

Among all the ligands tested, we did not observe a clear trend on structure-reactivity relationships. Still, we concluded that the best compromise in terms of yield and enantioselectivity corresponded to phosphoramidite-type ligands, with **L2** holding great promise for the implementation of an asymmetric event. Indeed, the utilization of **L2** resulted in 60% yield and 56% ee. Unfortunately, analogues of **L2** were not commercially available. Therefore, we set out to synthesize a family of related phosphoramidites following the route depicted in Figure 5.27. Based

on the addition of an in situ generated Grignard reagent to a bis-ester followed by treatment with PCl_3 and HNR'R''.

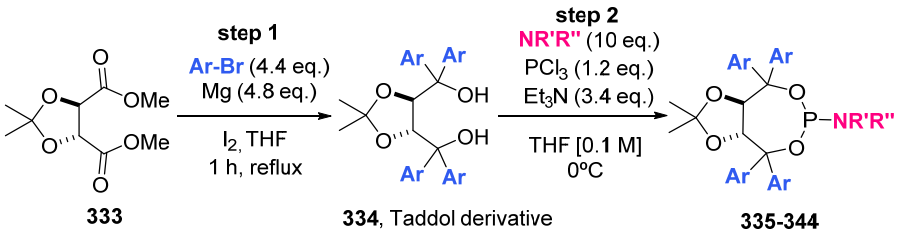


Figure 5.27

As shown in Figure 5.28, a variety of different phosphoramidites (**335-344**) were synthesized by varying the Taddol skeleton as well as the amine counterpart. In all cases, good overall yields could be obtained for preparing the corresponding phosphoramidites. With this set of phosphoramidites in hand, the next step was to test their behaviour under the reaction conditions.

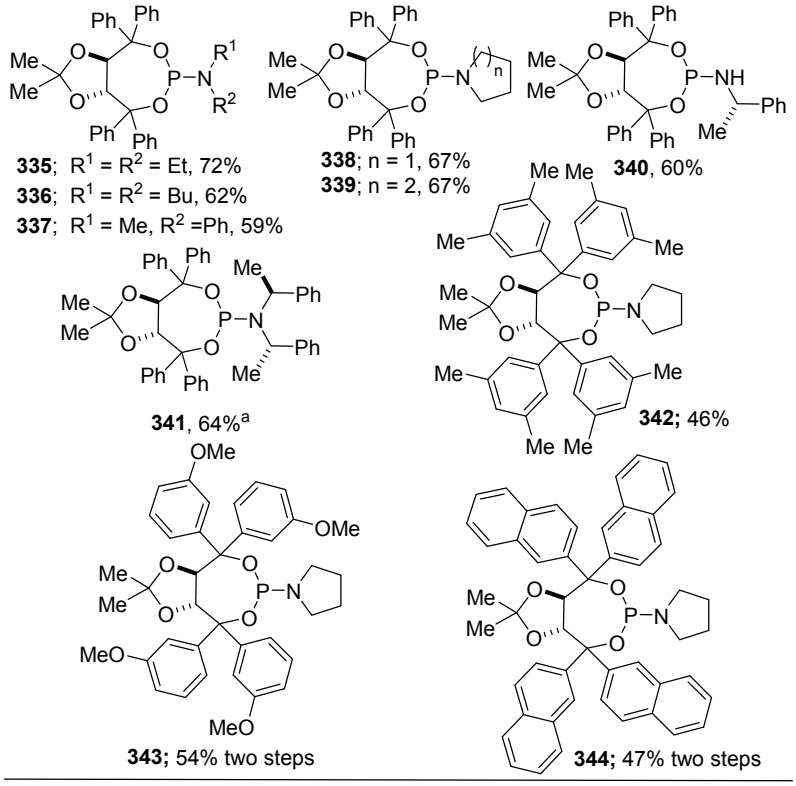
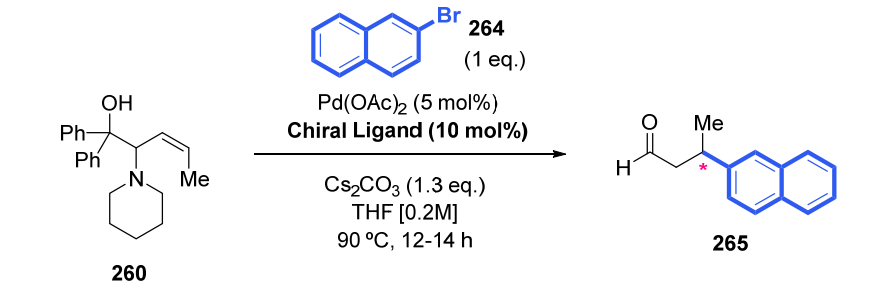
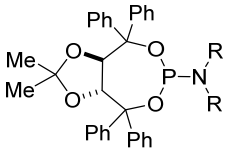


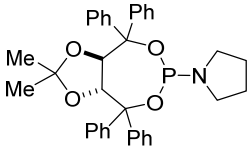
Figure 5.28

Table 11. Screening of different phosphoramidites ligands[a, b, c, d]

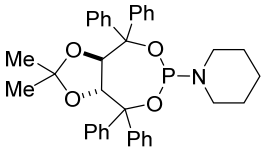




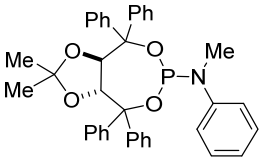
L2;R = Me; Conv:-/ **Yield**: 60%/ **ee**: 56%
335;R = Et; Conv:60%/ **Yield**: 32%/ **ee**: 62%
336;R = Bu; Conv:65%/ **Yield**: 40%/ **ee**: 54%



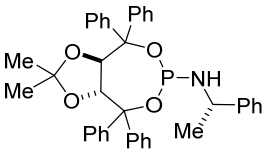
338; Conv: 53%
Yield: 45%
ee: 61%



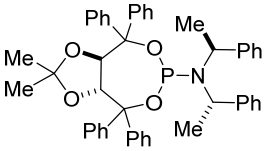
339; Conv: 67%
Yield: 44%
ee: 56%



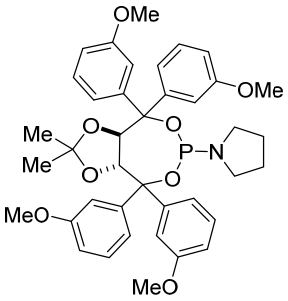
337, Conv: 60%
Yield: 33%
ee: 59%



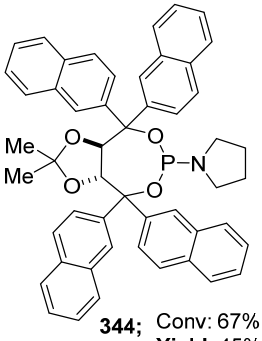
340; Conv: 68%
Yield: 17%
ee: -



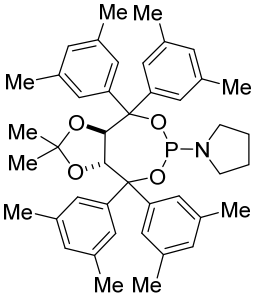
341; Conv: 40%
Yield: 5%
ee: -



343; Conv: 65%
Yield: <20%
ee: -



344; Conv: 67%
Yield: 45%
ee: 50%

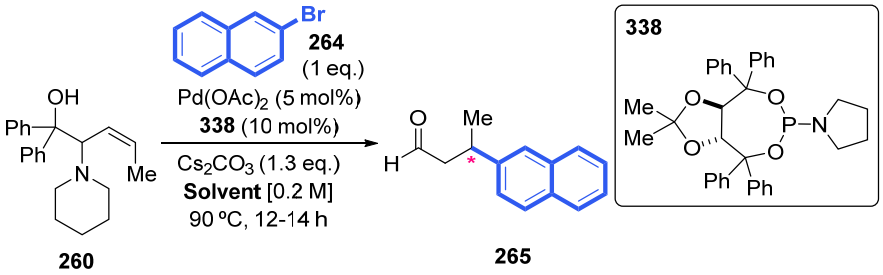


342; Conv: 70%
Yield: <20%
ee: -

Reaction conditions; a) **260** (0.23 mmol), $Pd(OAc)_2$ (5 mol%), chiral ligand (10 mol%), Cs_2CO_3 (1.3 eq.), THF [0.2 M)], 90 ºC for 12-14 h. b) Conversions were determined by ^1H NMR c) Isolated yields. d) Enantioselectivities (ee) were determined by HPLC using biphenyl as internal standard.

As shown in Table 11, low to moderate yields and enantioselectivities were obtained in all cases. Among all ligands examined, **338** gave a promising 61% ee with 45% yield, showing the feasibility of this transformation. Encouraged by these results, we decided to evaluate the influence of the solvent on enantioselectivity (Table 12).

Table 12. Solvent Screening[a, b, c, d]



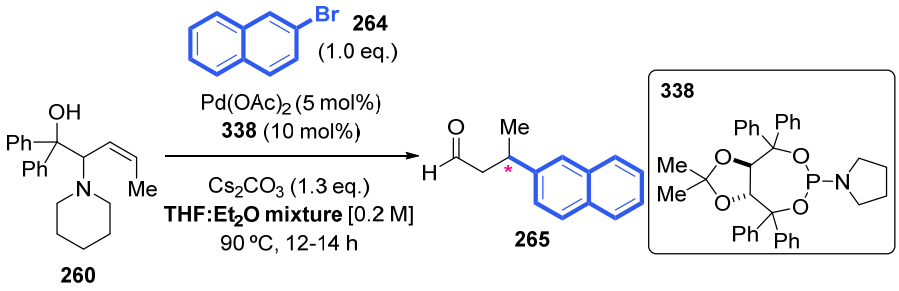
Entry	Solvent	Conversion (%)	Yield 265 (%)	ee (%)
1	**THF**	-	45	61
2	**Toluene**	78	54	37
3	**Et_2O**	33	20	77
4	**Dioxane**	69	52	51
5	***Tert*-Butanol**	88	20	65
6	**$PhCF_3$**	69	44	56
7	**DME**	63	42	65
8	**DMF**	71	20	61

Reaction conditions; a) **260** (0.23 mmol), 5 mol% $Pd(OAc)_2$ (5 mol%), **338** (10 mol%), Cs_2CO_3 (1.3 eq.), Solvent [0.2 M], 90 ºC for 12-14 h. b) Conversions were determined by ^1H NMR c) Isolated yields. d) Enantioselectivities (ee) were determined by HPLC using biphenyl as internal standard.

Interestingly, the use of ethereal solvents like DME or particularly Et_2O resulted in an increase of enantioselectivity, with the latter obtaining a promising 77% ee, albeit in lower yields (20%). In light of these results, we wondered whether a mixture of THF and Et_2O could improve both

reactivity (THF) and enantioselectivity (Et_2O). Unfortunately, all solvent combinations analyzed did not result an improved yield or enantiomeric excess (Table 13).

Table 13. Screening of different mixtures of THF/Et_2O[a, b, c, d]

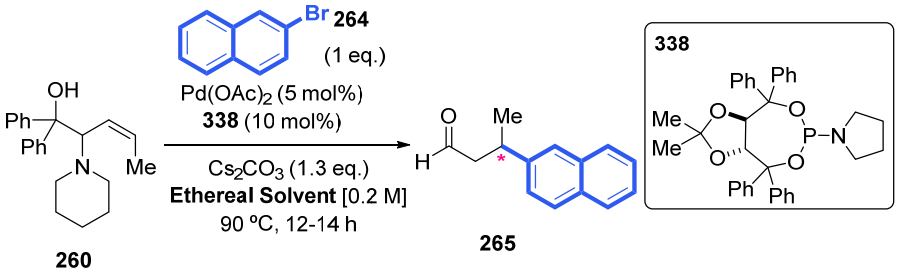


Entry	Mixture (THF:Et_2O)	Conversion (%)	Yield 265 (%)	ee (%)
1	**1:1**	71	55	47
2	**1:3**	56	44	62
3	**2:8**	52	40	64

Reaction conditions; a) **260** (0.23 mmol), $Pd(OAc)_2$ (5 mol%), **338** (10 mol%), Cs_2CO_3 (1.3 eq.), Solvent mixture [0.2 M], at 90 ºC for 12-14 h. b) Conversions were determined by ^1H NMR c) Isolated yields. d) Enantioselectivities (ee) were determined by HPLC using biphenyl as internal standard.

Prompted by the significant better enantioselectivity observed with ethereal solvents, we focused our attention on the utilization of related solvents (Table 14). Among these tested, *tert*-butyl methyl ether (TBME) turned out to be better that Et_2O in terms of yield.

Table 14. Screening of different ethereal solvents[a, b, c, d]

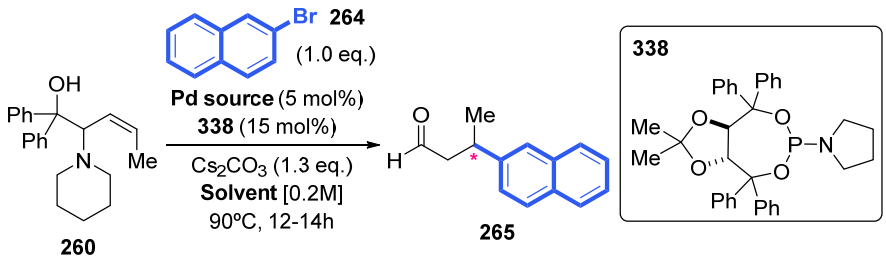


Entry	Solvent	Conversion (%)	Yield 265 (%)	ee (%)
1	**Et_2O**	33	20	78
2	**PhOMe**	62	41	58
3	**TBME**	43	33	71
4	**Butyl vinyl ether**	19	7	-
5	**Cyclopentyl methyl ether**	70	49	52
6	**Diisopropyl ether**	72	53	46
7	**2-Methyltetrahydrofuran**	68	50	52

Reaction conditions; a) **260** (0.23 mmol), $Pd(OAc)_2$ (5 mol%), **338** (10 mol%), Cs_2CO_3 (1.3 eq.), ethereal solvent [0.2 M], 90 ºC for 12-14 h. b) Conversions were determined by ^1H NMR c) Isolated yields. d) Enantioselectivities (ee) were determined by HPLC using biphenyl as internal standard.

Interestingly, we found similar levels of reactivity and enantioselectivity when utilizing $Pd(OAc)_2$, $Pd(dba)_2$ or $Pd(P\text{-}o\text{-}tolyl_3)_2$ as pre-catalyst. Taking this into consideration we turned our attention to exploring the catalyst:ligand ratio using either $Pd(OAc)_2$, $Pd(dba)_2$ or $Pd(P\text{-}o\text{-}tolyl_3)_2$, either in Et_2O or TBME. While in low yields (29%), we found that $Pd(OAc)_2$:L ratio of 1:3 in Et_2O provided **265** in 81% ee (entry 3, Table 15).

Table 15. Screening of other conditions[a, b, c, d]



Entry	Pd/L ratio	Solvent	Conversion (%)	Yield 265 (%)	ee (%)
1	$Pd(OAc)_2$ (1:2)	Et_2O	33	20	78
2	$Pd(OAc)_2$ (1:2)	TBME	43	33	71
3	$Pd(OAc)_2$ (1:3)	Et_2O	35	29	81
4	$Pd(OAc)_2$ (1:3)	TBME	42	41	75
5	$Pd(P(o\text{-tolyl})_3)_2$ (1:3)	Et_2O	40	33	75
6	$Pd(P(o\text{-tolyl})_3)_2$ (1:3)	TBME	50	40	70
7	$Pd(dba)_2$ (1:3)	Et_2O	58	40	60
8	$Pd(dba)_2$ (1:3)	TBME	44	33	70

Reaction conditions; a) **260** (0.23 mmol), Pd source (5 mol%), **338** (10 or 15 mol%), Cs_2CO_3 (1.3 eq.), Solvent [0.2 M], 90 ºC for 12-14 h. b) Conversions were determined by ^1H NMR c) Isolated yields. d) Enantioselectivities (ee) were determined by HPLC using biphenyl as internal standard.

Although certainly other experiments will need to be conducted to improve these results even further, particularly in terms of yield, we conclude that we were able to perform the formal enantioselective palladium-catalyzed β-arylation of aldehydes via C-C bond cleavage in good enantioselectivity.

5.4 Conclusions

- A formal β-arylation of aldehydes via Pd-catalyzed C-C bond cleavage of *N*-allyl-amino alcohols has been developed. The procedure tolerates a wide variety of amino alcohols and aryl bromide counterparts.

- The alkylation of in situ generated enamine intermediate could be performed with α,β-unsaturated systems to afford α,β-substituted aldehydes in a one pot procedure.

- Good enantioselectivities (81% ee) could be obtained for the formal β-arylation of aldehydes using phosphoramidite ligands derived from Taddol.

5.5 Experimental section

5.5.1 General considerations

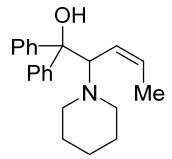
Reagents. Reactants were weighted in open air, only for the use of some sensitive ligand during the screening process the glovebox was used. Reactions were set up under argon atmosphere in Schlenk tubes. All reagents were purchased and directly used from commercial sources. Some dry solvents (Et_2O and toluene) were used from the SPS system (Innovative technology, Newburyport, MA) and the rest were purchased from commercial sources. Flash column chromatography was carried out with ultra pure silica gel flash 60 (230-240 mesh)

Analytical methods. ^{1}H NMR, ^{13}C NMR and melting point, where is applicable, are attached for all compounds. ^{1}H NMR and ^{13}C NMR were recorded on a 300 MHz, 400 MHz and 500 MHz Bruker apparatus at 20 ºC. All NMR spectra are presented in part per million (ppm) and were measured relative to the signal of $CHCl_3$ (7.27 ppm in the case of ^{1}H NMR and 77.0 ppm for the ^{13}C NMR). All ^{13}C NMR were obtained with ^{1}H decoupling. Coupling constants (*J*), are reported in hertz. Melting points were measured using open glass capillaries in a Mettler Toledo MP70 apparatus. Infrared spectra were carried out on a Bruker Tensor 27. Mass spectra were recorded on a Waters LCT Premier spectrometer. Liquid chromatography analyses were carried out on UPLC and UPC2 instruments.

5.5.2 Synthesis of *N*-allyl 1,2-amino alcohols

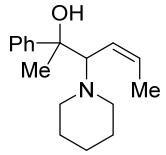
General procedure VII. A microwave glass tube (10 mL) containing a stirring bar was charged with the corresponding α-hydroxy aldehyde, the corresponding boronic acid and dissolved in the corresponding solvent. The amine was subsequently added dropwise by syringe at room temperature. The mixture was then heated and stirred under MW irradiation. The

reaction was then diluted in CH_2Cl_2 and washed twice with brine. The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc). The preparation of starting material was carried out with a microwave apparatus equipped with an autosampler fitted with a carrousel.



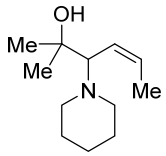
260

(*Z*)-1,1-Diphenyl-2-(piperidin-1-yl)pent-3-en-1-ol (**260**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-prop-1-en-1-ylboronic acid (103 mg, 1.2 mmol) and piperidine (95 μL, 1.0 mmol.) in HFIP (0.6 mL) at 80 ºC for 50 min. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.55). White solid, yield = 50% (160.0 mg). mp = 77-80 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57-7.52 (m, 2H), 7.47-7.42 (m, 2H), 7.29-7.21 (m, 4H), 7.20-7.13 (m, 2H), 5.86 (dqd, *J*= 11.1, 7.0, 0.8 Hz, 1H), 5.54 (tq, *J* = 11.1, 1,8, 1H), 4.01 (d, *J* = 11.1, 1H), 2.37-2.20 (m, 4H), 1.77 (dd, *J* = 7.0, 1.8 Hz, 3H), 1.56-1.46 (m, 4H), 1.40-1.30 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8, 145.1, 128.5, 127.9, 127.6, 127.3, 126.6, 126.4, 126.3, 76.4, 68.4, 52.6, 26.6, 24.2, 14.1 ppm. IR (neat, cm^{-1}): 3026, 2932, 2838, 1444, 1021, 756, 743, 698. MS (ESI+) *m/z* (%) 322 (M+H). HRMS *calcd*. for ($C_{22}H_{28}NO$): 322.2165, *found* 322.2170.



281

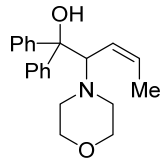
(*Z*)-2-Phenyl-3-(piperidin-1-yl)hex-4-en-2-ol (281). Following general procedure **VII**, using 2-hydroxy-2-phenylpropanal (150 mg, 1.0 mmol), (*Z*)-prop-1-en-1-ylboronic acid (172 mg, 2.0 mmol) and piperidine (109 µL, 1.1 mmol) in HFIP (0.5 mL) at 80 ºC for 50 min. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.41). Colorless oil, yield = 43% (111.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44-7.40 (m, 2H), 7.31-7.25 (m, 2H), 7.22-7.17 (m, 1H), 5.95-5.73 (m, 2H), 5.29 (tq, *J* = 11.2, 1.9 Hz, 1H), 3.38 (d, *J* = 11.0 Hz, 1H), 2.28-2.07 (m, 4H), 1.76 (dd, *J* = 6.9, 1.9 Hz, 3H), 1.52-1.41 (m, 7H), 1.38-1.27 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 145.9, 129.3, 127.4, 126.3, 126.2, 124.8, 73.3, 70.7, 52.4, 27.9, 26.5, 24.3, 13.6 ppm. IR (neat, cm^{-1}): 2975, 2931, 2808, 1493, 1443, 995, 743, 700. MS (ESI+) *m/z* (%) 260 (M+H). HRMS *calcd*. for ($C_{17}H_{26}NO$): 260.2009, *found* 260.2001.



282

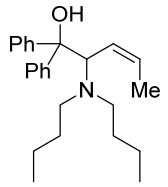
(*Z*)-2-Methyl-3-(piperidin-1-yl)hex-4-en-2-ol (**282**). Following general procedure **VII**, using 2-hydroxy-2-methylpropanal (88 mg, 1.0 mmol), (*Z*)-prop-1-en-1-ylboronic acid (129 mg, 1.5 mmol) and piperidine (119 µL, 1.2 mmol) in HFIP (0.5 mL) at 80 ºC for 50 min. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 70:30, R_f = 0.41). Colourless oil, yield = 40% (79.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.85 (dqd, *J* = 11.1, 6.9, 0.8 Hz, 1H), 5.45 (tq, *J* = 11.1, 1.8 Hz, 1H), 3.15-3.08 (m, 1H), 2.73-2.61 (m, 2H), 2.50-2.37 (m, 2H), 1.68 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.63-

1.50 (m, 4H), 1.45-1.33 (m, 2H), 1.13 (s, 3H), 1.07 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 129.4, 124.9, 71.2, 69.7, 53.4, 27.9, 26.8, 25.2, 24.4, 13.6 ppm. IR (neat, cm^{-1}): 2971, 2930, 2804, 1442, 1374, 1172, 961, 718. MS (ESI+) m/z (%) 198 (M+H). HRMS *calcd*. for ($C_{12}H_{24}NO$): 198.1852, *found* 198.1845.



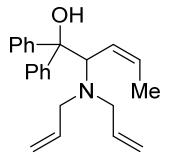
283

(*Z*)-2-Morpholino-1,1-diphenylpent-3-en-1-ol (**283**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-prop-1-en-1-ylboronic acid (103 mg, 1.2 mmol) and morpholine (82 μL, 1.0 mmol.) in HFIP (0.5 mL) at 80 ºC for 50 min. with 100 W. Column chromatography: silica gel (DCM, R_f = 0.29). White solid, yield = 52% (167.0 mg). mp = 84-89 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.51 (m, 2H), 7.47-7.40 (m, 2H), 7.24-7.10 (m, 6H), 5.91 (dq, *J* = 11.0, 6.9 Hz, 1H), 5.43 (tq, *J* = 11.0, 1.8 Hz, 1H), 4.13-4.02 (m, 1H), 3.53 (t, *J* = 4.6 Hz, 4H), 2.39-2.19 (m, 4H), 1.68 (dd, *J* = 7.0, 1.8 Hz, 3H) ppm.^{13}C NMR (75 MHz, $CDCl_3$): δ 147.1, 144.8, 129.2, 128.0, 127.5, 127.2, 126.8, 126.5, 126.3, 125.8, 77.0, 68.2, 67.3, 51.9, 14.0 ppm. IR (neat, cm^{-1}): 2962, 2850, 1493, 1448, 1116, 997, 747, 699. MS (ESI+) *m/z* (%) 324 (M+H). HRMS *calcd*. for ($C_{21}H_{26}NO$): 324.1958, *found* 324.1961.



286

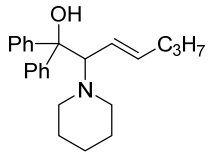
(*Z*)-2-(Dibutylamino)-1,1-diphenylpent-3-en-1-ol (**286**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-prop-1-en-1-ylboronic acid (121 mg, 1.5 mmol) and dibutylamine (240 µL, 1.5 mmol.) in DCM/HFIP (9:1) (0.6 mL) at 90 ºC for 30 min. with 50 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.70). Pale yellow oil, yield = 52% (190.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63-7.56 (m, 4H), 7.33-7.24 (m, 4H), 7.24-7.16 (m, 2H), 6.81 (bs, 1H), 5.89 (dq, *J* = 11.0, 6.9 Hz, 1H), 5.6 (tq, *J* = 11.0, 1.8 Hz, 1H), 4.15-4.07 (m, 1H), 2.20-2.03 (m, 4H), 1.67 (dd, *J* = 6.9, 1.8 Hz, 3H), 1.53-1.36 (m, 4H), 1.26-1.11(m, 4H), 0.86 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 145.0, 128.8, 127.8, 127.6, 127.2, 126.6, 126.5, 126.3, 125.9, 76.1, 64.8, 51.4, 30.8, 20.4, 14.0, 13.95 ppm. IR (neat, cm^{-1}): 2957, 2928, 2859, 1447, 1377, 1031, 740, 697. MS (ESI+) *m/z* (%) 366 (M+H). HRMS *calcd*. for ($C_{25}H_{36}NO$): 366.2791, *found* 366.2787.



287

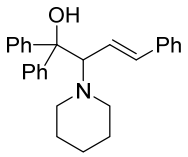
(*Z*)-2-(Diallylamino)-1,1-diphenylpent-3-en-1-ol (**287**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-prop-1-en-1-ylboronic acid (121 mg, 1.5 mmol) and diallylamine (123 µL, 1.0 mmol.) in DCM/HFIP (9:1) (0.6 mL) at 100 ºC for 60 min. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.68). Pale Yellow oil, yield = 43% (143.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57-7.49 (m, 4H), 7.32-7.14 (m, 6H), 6.35 (bs, 1H), 5.92-5.70 (m, 3H), 5.50 (tq, *J* = 11.1, 1.8 Hz, 1H), 5.16-5.12 (m, 2H), 5.12-5.09 (m, 1H),5.09-5.06 (m, 1H), 4.27-4.20 (m, 1H), 2.98 (ddt, *J* = 14.3, 4.1, 1.9 Hz, 2H), 2.65 (ddt, *J* = 14.3, 8.3, 1.0 Hz, 2H), 1.65 (dd, *J*

= 6.9, 1.8 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 146.8, 144.6, 136.1, 129.5, 127.8, 127.6, 127.3, 126.8, 126.7, 126.6, 125.0, 117.5, 63.0, 54.1, 14.1 ppm. IR (neat, cm^{-1}): 2978, 2822, 1447, 1376, 992, 918, 742, 697. MS (ESI+) *m/z* (%) 334 (M+H). HRMS *calcd*. for ($C_{23}H_{28}NO$): 334.2165, *found* 334.2158.



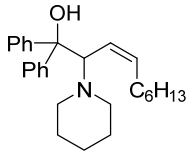
288

(*E*)-1,1-Diphenyl-2-(piperidin-1-yl)hept-3-en-1-ol (**288**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (270 mg, 1.27 mmol), (*E*)-pent-1-en-1-ylboronic acid (145 mg, 1.12 mmol) and piperidine (126 µL, 1.28 mmol.) in DCM (0.6 mL) at 100 ºC for 85 min. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 95:5, R_f = 0.50). White solid, yield = 68% (750.0 mg). mp = 65-69 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.58 (m, 2H), 7.49-7.45 (m, 2H), 7.31-7.25 (m, 4H), 7.23-7.17 (m, 2H), 5.77 (dt, *J* = 15.5, 6.8 Hz, 1H), 5.41 (ddt, *J* = 15.5, 10.0, 1.4 Hz, 1H), 3.62 (d, *J* = 10.0 Hz, 1H), 2.38-2.29 (m, 2H), 2.29-2.18 (m, 2H), 2.15-2.10 (m, 2H), 1.58-1.50 (m, 4H), 1.49-1.42 (m, 2H), 1.41-1.33 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 148.0, 145.5, 136.7, 127.7, 127.7, 127.2, 126.8, 126.6, 126.2, 125.7, 75.9, 75.4, 52.4, 34.8, 26.5, 24.2, 22.5, 13.7 ppm. IR (neat, cm^{-1}): 3052, 2924, 2847, 1490, 1444, 995, 753, 700. MS (ESI+) *m/z* (%) 350 (M+H). HRMS *calcd*. for ($C_{24}H_{32}NO$): 350.2478, *found* 350.2486.



289

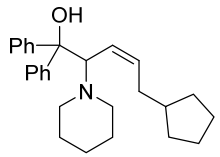
(*E*)-1,1,4-Triphenyl-2-(piperidin-1-yl)but-3-en-1-ol (**289**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (270 mg, 1.27 mmol), (*E*)-styrylboronic acid (188 mg, 1.27 mmol) and piperidine (126 μL, 1.72 mmol.) in DCM (0.6 mL) at 100 ºC for 80 min. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.40). White solid, yield = 69% (367.0 mg). mp = 108-112 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54-7.50 (m, 2H), 7.44-7.39 (m, 2H), 7.30-7.06 (m, 11H), 6.57 (d, J = 16.0 Hz, 1H), 6.11 (dd, J = 16.0, 10.2 Hz, 1H), 3.70 (d, J = 10.2 Hz, 1H), 2.39-2.29 (m, 2H), 2.27-2.15 (m, 2H), 1.51-1.40 (m, 4H), 1.33-1.21 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.8, 145.3, 136.7, 134.6, 128.7, 127.9, 127.8, 127.6, 127.4, 126.7, 126.6, 126.5, 126.4, 126.0, 76.2, 75.4, 52.4, 26.5, 24.1 ppm. IR (neat, cm^{-1}): 2933, 2851, 1493, 1470, 1447, 907, 729, 693. MS (ESI+) *m/z* (%) 384 (M+H). HRMS *calcd*. for ($C_{27}H_{30}NO$): 384.2322, *found* 384.2317.



290

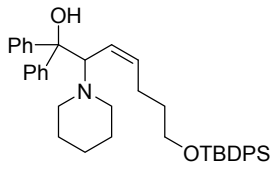
(*Z*)-1,1-Diphenyl-2-(piperidin-1-yl)dec-3-en-1-ol (**290**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-oct-1-en-1-ylboronic acid (234 mg, 1.5 mmol) and piperidine (109 μL, 1.1 mmol) in HFIP (0.6 mL) at 90 ºC for 2 h. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.53). Pale yellow oil, yield = 60% (244.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64-7.59 (m, 2H), 7.54-7.49 (m, 2H), 7.32-7.26 (m, 4H), 7.24-7.17 (m, 2H), 6.89 (bs, 1H), 5.78 (dt, *J* = 11.0, 7.2 Hz, 1H), 5.43 (tt, *J* = 11.0, 1.8 Hz, 1H), 4.06-3.98 (m, 1H), 2.43-2.11 (m, 6H), 1.61-1.49 (m, 4H), 1.49-1.28 (m, 10H), 0.95 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.6, 145.0, 134.8, 127.8, 127.5, 127.2, 126.5, 126.4, 126.3, 124.9, 76.4,

69.1, 52.4, 31.8, 29.5, 29.2, 28.5, 26.6, 24.1, 22.6, 14.1 ppm. IR (neat, cm^{-1}): 2926, 2653, 1447, 1033, 746, 697. MS (ESI+) *m/z* (%) 392 (M+H). HRMS *calcd*. for ($C_{27}H_{38}NO$): 392.2948, *found* 392.2952.



291

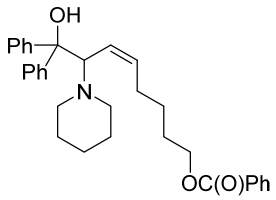
(*Z*)-5-Cyclopentyl-1,1-diphenyl-2-(piperidin-1-yl)pent-3-en-1-ol (**291**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-(3-cyclopentylprop-1-en-1-yl)boronic acid (231 mg, 1.5 mmol) and piperidine (109 μL, 1.1 mmol.) in HFIP (0.6 mL) at 90 ºC for 2 h with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.59). Pale yellow oil, yield = 53% (206.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62-7.54 (m, 2H), 7.52-7.44 (m, 2H), 7.32-7.13 (m, 6H), 6.84 (bs, 1H), 5.78 (dt, *J* = 11.1, 6.9 Hz, 1H), 5.42 (tt, *J* = 11.1, 1.8 Hz, 1H), 4.02-3.93 (m, 1H), 2.38-2.13 (m, 6H), 1.95-1.73 (m, 3H), 1.71-1.45 (m, 8H), 1.42-1.29 (m, 2H), 1.26-1.09 (m, 2H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 145.0, 134.1, 127.8, 127.6, 127.2, 126.6, 126.6, 126.3, 125.4, 76.5, 69.2, 52.7, 40.3, 34.4, 32.6, 32.5, 26.7, 25.1, 25.0, 24.3 ppm. IR (neat, cm^{-1}): 2933, 2855, 1447, 1033, 743, 697. MS (ESI+) *m/z* (%) 390 (M+H). HRMS *calcd*. for ($C_{27}H_{36}NO$): 390.2791, *found* 390.2792.



292

(*Z*)-7-((tert-butyldiphenylsilyl)oxy)-1,1-diphenyl-2-(piperidin-1-yl)hept-3-en-1-ol (**292**). Following general procedure **VII**, using 2-hydroxy-2,2-

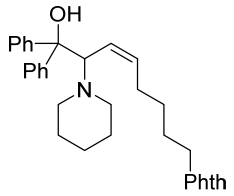
diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-(5-((tert-butyldiphenylsilyl)-oxy)pent-1-en-1-yl)boronic acid (552 mg, 1.5 mmol) and piperidine (119 µL, 1.2 mmol.) in HFIP (0.6 mL) at 90 ºC for 2 h. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.36). Pale yellow oil, yield = 50% (302.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73-7.68 (m, 4H), 7.61-7.56 (m, 2H), 7.52-7.48 (m, 2H), 7.47-7.38 (m, 6H), 7.29-7.15 (m, 6H), 5.73 (dt, *J* = 11.0, 8.0 Hz, 1H), 5.42 (tt, *J* = 11.0, 1.7 Hz, 1H), 4.06-3.96 (m, 1H), 3.74 (t, *J* = 6.3 Hz, 2H), 2.39-2.20 (m, 6H), 1.74-1.64 (m, 2H), 1.57-1.46 (m, 4H), 1.43-1.32 (m, 2H), 1.1 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 147.6, 145.0, 135.6, 134.0, 134.0, 133.9, 129.6, 127.9, 127.7, 127.6, 127.5, 127.3, 126.6, 126.4, 126.3, 125.4, 76.5, 69.1, 63.6, 52.5, 32.6, 26.9, 26.6, 25.0, 24.2, 19.3 ppm. IR (neat, cm^{-1}): 2931, 2855, 1427, 1106, 734, 698. MS (ESI+) *m/z* (%) 604 (M+H). HRMS *calcd*. for ($C_{40}H_{50}NO_2Si$): 604.3605, *found* 604.3612.



293

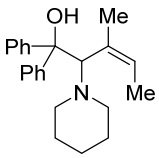
(*Z*)-8-Hydroxy-8,8-diphenyl-7-(piperidin-1-yl)oct-5-en-1-yl benzoate (**293**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-(6-(benzoyloxy)hex-1-en-1-yl)boronic acid (372 mg, 1.5 mmol) and piperidine (119 µL, 1.2 mmol) in HFIP (0.6 mL) at 90 ºC for 2 h. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.51). Colourless oil, yield = 50% (242.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.11-8.02 (m, 2H), 7.61-7.41 (m, 7H), 7.30-7.12 (m, 6H), 5.75 (dt, *J* = 11.1, 7.2 Hz, 1H), 5.46 (tt, *J* = 11.1, 1.7 Hz, 1H), 4.36 (t, *J* = 6.5 Hz, 2H), 4.01-3.92 (m, 1H), 2.39-2.14 (m, 6H), 1.91-1.75 (m, 2H), 1.63-1.42 (m, 6H), 1.40-1.29 (m, 2H) ppm. ^{13}C

NMR (75 MHz, $CDCl_3$): δ 166.6, 147.5, 144.9, 133.9, 132.9, 130.4, 129.5, 128.4, 127.8, 127.6, 127.3, 126.6, 126.5, 126.3, 125.6, 76.5, 69.4, 64.8, 52.6, 28.7, 28.1, 26.6, 26.2, 24.2 ppm. IR (neat, cm^{-1}): 2932, 2852, 1716, 1270, 1111, 748, 700. MS (ESI+) *m/z* (%) 484 (M+H). HRMS *calcd*. for ($C_{32}H_{38}NO_3$): 484.2846, *found* 484.2847.



294

(*Z*)-2-(8-Hydroxy-8,8-diphenyl-7-(piperidin-1-yl)oct-5-en-1-yl)-isoindoline-1,3-dione (**294**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*Z*)-(6-(1,3-dioxoisoindolin-2-yl)hex-1-en-1-yl)boronic acid (468 mg, 1.5 mmol) and piperidine (119 μL, 1.2 mmol) in HFIP (0.6 mL) at 90 ºC for 2 h. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.27). Colourless oil, yield = 47% (239.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89-7.83 (m, 2H), 7.76-7.70 (m, 2H), 7.60-7.55 (m, 2H), 7.51-7.46 (m, 2H), 7.29-7.11 (m, 6H), 5.71 (dt, *J* = 11.1, 7.2 Hz, 1H), 5.44 (tt, *J* = 11.1, 1.7 Hz, 1H), 4.01-3.94 (m, 1H), 3.75-3.69 (dd, *J* = 7.6, 6.6 Hz, 2H), 2.38-2.23 (m, 4H), 2.23-2.11 (m, 2H), 1.79-1.67 (m, 2H), 1.56-1.29 (m, 8H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 147.3, 144.8, 133.9, 132.1, 127.8, 127.5, 127.3, 126.6, 126.5, 126.3, 125.4, 123.2, 76.6, 69.4, 52.6, 37.8, 28.5, 27.9, 26.8, 26.5, 24.2 ppm. IR (neat, cm^{-1}): 2934, 2854, 1707, 1395, 1034, 749, 718, 700. MS (ESI+) *m/z* (%) 509 (M+H). HRMS *calcd*. for ($C_{33}H_{37}N_2O_3$): 509.2799, *found* 509.2806.

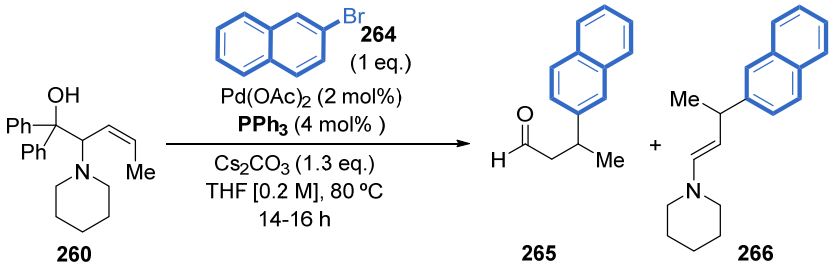


300

(*Z*)-3-Methyl-1,1-diphenyl-2-(piperidin-1-yl)pent-3-en-1-ol (**300**). Following general procedure **VII**, using 2-hydroxy-2,2-diphenylacetaldehyde (212 mg, 1.0 mmol), (*E*)-but-2-en-2-ylboronic acid (150 mg, 1.5 mmol) and piperidine (119 µL, 1.2 mmol) in HFIP (0.6 mL) at 90 ºC for 2 h. with 100 W. Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_{fM} = 0.45, R_{fm} = 0.35). White solid, yield = 30% (101.0 mg). mp = 74-78 ºC. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71-7.66 (m, 2H), 7.52-7.45 (m, 2H), 7.29-7.21 (m, 2H), 7.19-7.01 (m, 4H), 5.34-5.20 (m, 1H), 4.51 (s, 1H), 2.41-2.29 (m, 2H), 2.29-2.18 (m, 2H), 1.84 (dq, *J* = 6.9, 1.5 Hz, 3H), 1.50-1.28 (m, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 150.9, 146.9, 134.2, 128.1, 127.1, 126.2, 125.9, 125.7, 125.4, 124.8, 76.6, 69.6, 53.4, 26.7, 24.4, 21.6, 14.5 ppm. IR (neat, cm^{-1}): 2922, 2845, 1448, 1032, 743, 704, 693. MS (ESI+) *m/z* (%) 336 (M+H). HRMS *calcd*. for ($C_{23}H_{30}NO$): 336.2322, *found* 336.2328.

5.5.3 Blank experiments

The corresponding blank experiments were also carried out to visualize that palladium acetate and PPh_3 are necessary for the success of the reaction.



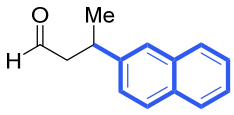
260 **265** **266**

Entry	$Pd(OAc)_2$	PPh_3	Conversion 258 (%)	Yield[b] (%) (265)+(266)
1	√	√	66	57
2	**x**	√	0	0
3	√	**x**	0	0

Reaction conditios: (a) **260** ($8 \cdot 10^{-2}$ mmol), $Pd(OAc)_2$ (2 mol%), PPh_3 (4 mol%), Cs_2CO_3 (1.3 eq.), THF [0.2 M], 80 ºC for 14-16 h. (b) Conversions and yields were determined by ^1H NMR using 1,4-dioxane as internal standard.

5.5.4 Synthesis of β-arylated aldehydes

General Procedure VIII. An oven-dried Schlenk tube containing a stirring bar was charged with the corresponding 1,2-amino alcohol (1.0 eq.), Cs_2CO_3 (1.3 eq.) and the aryl bromide (1.0 eq.). The schlenk tube was then evacuated and back-filled with argon (this sequence was repeted three times) and finally an atmospheric pressure of argon was established. THF, $Pd(OAc)_2$ (2 mol%) and PPh_3 (4 mol%) were subsequently added by syringe from stock solutions. The solution was warmed up to 90 ºC and stirred for 12-16 h. The mixture was then allowed to warm to room temperature. EtOAc (10 mL) was added and the mixture was filtered though a path of Celite. The filtrated was evaporated and the resulting oil was purified by conventional flash column chromatography.

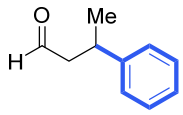


265

3-(Naphthalen-2-yl)butanal (**265**).[122] Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 2-

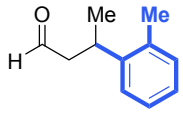
[122] Akagawa, K.; Akabane, H.; Sakamoto. S.; Kudo. K. *Org. Lett*. **2008**, *10*, 2035-2037.

bromonaphthalene (48 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.55). Colourless oil, yield = 85% (39.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (t, J = 2.0 Hz, 1H), 7.84-7.78 (m, 3H), 7.67-7.64 (m, 1H), 7.50-7.41 (m, 2H), 7.40-7.35 (m, 1H), 3.54 (h, J = 7.0 Hz, 1H), 2.86 (ddd, J = 16.7, 7.0, 2.0 Hz, 1H), 2.75 (ddd, J = 16.7, 7.0, 2.0 Hz, 1H), 1.42 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.7, 142.8, 133.5, 132.3, 128.4, 127.6, 126.1, 125.5, 125.4, 124.9, 51.6, 34.3, 22.1 ppm.



302

3-Phenylbutanal (**302**).[123] Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and bromobenzene (25µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.65). Colourless oil, yield = 67% (23.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.73 (t, J = 2.0 Hz, 1H), 7.37-7.18 (m, 5H), 3.38 (h, J = 7.0 Hz, 1H), 2.78 (ddd, J = 16.6, 7.0, 2.0 Hz, 1H), 2.68 (ddd, J = 16.6, 7.0, 2.0 Hz, 1H), 1.34 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ 200.0, 145.8, 128.6, 127.9, 127.7, 126.8, 126.4, 51.4, 34.0, 21.8 ppm.



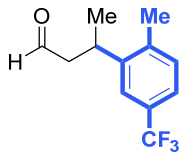
303

3-(*o*-Tolyl)butanal (**303**).[124] Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 1-bromo-2-methylbenzene

[123] Nicolaou, K. C.; Mathison, C. J. N.; Montagon, T. *J. Am. Chem. Soc*. **2004**, *126*, 5192-5201.

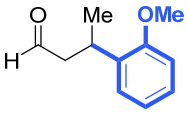
[124] Mantilli, L.; Mazet, C. *Tetrahedron Letters* **2009**, *50*, 4141-4144

(28 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.5). Colourless oil, yield = 68% (26.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (t, J = 2.0 Hz, 1H), 7.21-7.10 (m, 4H), 3.61 (h, J = 7.0 Hz, 1H), 2.77 (ddd, J = 16.7, 6.3, 2.0 Hz, 1H), 2.67 (ddd, J = 16.7, 7.0, 2.0 Hz, 1H), 2.36 (s, 3H), 1.28 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.8, 143.5, 135.0, 130.6, 126.4, 126.2, 125.2, 51.2, 29.2, 21.5, 19.4 ppm.



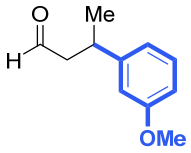
304

3-(2-Methyl-5-(trifluoromethyl)phenyl)butanal (**304**). Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 1-bromo-2-methyl-4-(trifluoromethyl)benzene (37 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.47). Colourless oil, yield = 65% (35.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.74 (t, J = 1.5 Hz, 1H), 7.41-7.32 (m, 2H), 7.28-7.23 (m, 1H), 3.65 (h, J = 6.9 Hz, 1H), 2.86-2.66 (m, 2H), 2.43 (s, 3H), 1.29 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.7, 144.6, 139.4, 130.9, 128.8 (q), 125.7, 122.9 (q), 121.9 (q), 51.1, 29.0, 21.4, 19.5 ppm. IR (neat, cm^{-1}): 2966, 1724, 1327, 1160, 1115, 1096. MS (ESI+) *m/z* (%) 253 (M+Na). HRMS *calcd*. for ($C_{12}H_{13}F_3NaO$): 253.0811, *found* 253.0803.



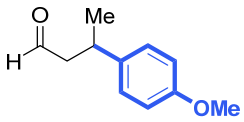
305

3-(2-Methoxyphenyl)butanal (**305**).[125] Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 1-bromo-2-methoxybenzene (30 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.3). Colourless oil, yield = 61% (27.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (t, J = 2.4 Hz, 1H), 7.25-7.17 (m, 2H), 6.98-6.91 (m, 1H), 6.90-6.86 (m, 1H), 3.84 (s, 3H), 3.76 (h, J = 7.0 Hz, 1H), 2.74 (ddd, J = 16.1, 7.0, 2.4 Hz, 1H), 2.62 (ddd, J = 16.1, 7.0, 2.4 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 202.6, 156.6, 133.2, 127.4, 126.8, 120.7, 110.5, 55.2, 50.6, 27.7, 20.3 ppm.



306

3-(3-Methoxyphenyl)butanal (**306**).[126] Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 1-bromo-3-methoxy- benzene (30 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.29). Colourless oil, yield = 72% (30.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, J = 2.0 Hz, 1H), 7.28-7.22 (m, 1H), 6.86-6.75 (m, 3H), 3.81 (s, 3H), 3.35 (h, J = 7.1 Hz, 1H), 2.76 (ddd, J = 16.6, 6.7, 1.8 Hz, 1H), 2.66 (ddd, J = 16.6, 7.6, 2.0 Hz, 1H), 1.33 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.8, 159.8, 147.1, 129.7, 119.1, 112.9, 111.5, 55.2, 51.7, 34.3, 22.1 ppm.

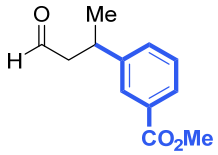


307

[125] Samizu, K.; Ogasawara, K. *Tetrahedron Letters* **1994**, *35*, 7989-7992.

[126] Cong, X.; Huarong, T.; Xiaoming, Z. *J. Am. Chem. Soc*. **2015**, *137*, 14367-14372.

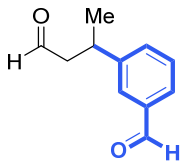
3-(4-Methoxyphenyl)butanal (**307**).[127] Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 1-bromo-4-methoxybenzene (30 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.26). Colourless oil, yield = 68% (28.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (m, 1H), 7.17-7.10 (m, 2H), 6.88-6.81 (m, 2H), 3.78 (s, 3H), 3.32 (h, J = 7.1 Hz, 1H), 2.71 (ddd, J = 16.4, 7.1, 1.6 Hz, 1H), 2.62 (ddd, J = 16.4, 7.1, 1.6 Hz, 1H), 1.30 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9, 158.1, 137.5, 127.6, 114.0, 55.2, 51.9, 33.5, 22.3 ppm.



308

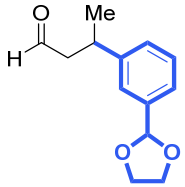
Methyl 3-(4-oxobutan-2-yl)benzoate (**308**). Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and methyl 3-bromobenzoate (51 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.26). Colourless oil, yield = 90% (43.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (t, J = 1.8 Hz, 1H), 7.93-7.86 (m, 2H), 7.44-7.34 (m, 2H), 3.91 (s, 3H), 3.42 (h, J = 7.1 Hz, 1H), 2.78 (ddd, J = 16.9, 7.1, 1.8 Hz, 1H), 2.70 (ddd, J = 16.9, 7.1, 1.8 Hz, 1H), 1.33 (d, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.1, 167.0, 145.8, 131.5, 130.5, 128.7, 127.8, 127.7, 52.1, 51.5, 34.0, 22.0 ppm. IR (neat, cm^{-1}): 2957, 1716, 1281, 1196, 1069, 754, 697. MS (ESI+) *m/z* (%) 229 (M+Na). HRMS *calcd*. for ($C_{12}H_{14}NaO_3$): 229.0835, *found* 229.0840.

[127] Itooka, R.; Iguchi, Y.; Miyaura, N. *J. Org. Chem*. **2003**, *68*, 6000-6004.



309

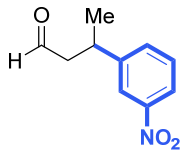
3-(4-Oxobutan-2-yl)benzaldehyde (**309**). Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 3-bromobenzaldehyde (28 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.41). Colourless oil, yield = 64% (27.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.00 (s, 1H), 9.72 (t, J = 1.8 Hz, 1H), 7.79-7.69 (m, 2H), 7.55-7.44 (m, 2H), 3.47 (h, J = 7.0 Hz, 1H), 2.88-2.66 (m, 2H), 1.35 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.8, 192.3, 146.7, 136.8, 133.2, 129.3, 128.5, 127.3, 51.5, 33.9, 22.0 ppm. IR (neat, cm^{-1}): 2964, 1721, 1694, 1585, 1152, 797, 698. MS (ESI+) *m/z* (%) 199 (M+Na). HRMS *calcd*. for ($C_{11}H_{12}NaO_2$): 199.0730, *found* 199.0731.



310

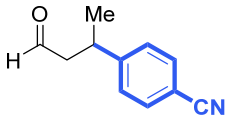
3-(3-(1,3-Dioxolan-2-yl)phenyl)butanal (**310**). Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 2-(3-bromophenyl)-1,3-dioxolane (36 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.27). Colourless oil, yield = 61% (31.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (t, J = 2.0 Hz, 1H), 7.35-7.31 (m, 3H), 7.25-7.20 (m, 1H), 5.79 (s, 1H), 4.16-4.09 (m, 2H), 4.08-4.00 (m, 2H), 3.39 (h, J = 7.0 Hz, 1H), 2.76 (ddd, J = 16.7, 7.0, 2.0 Hz, 1H), 2.66 (ddd, J = 16.7, 7.0, 2.0 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.6, 145.7, 138.2, 128.7, 127.7,

124.7, 103.6, 65.3, 51.7, 34.2, 22.0 ppm. IR (neat, cm^{-1}): 2961, 1721, 1259, 1074, 1024, 795, 702. MS (ESI+) *m/z* (%) 221 (M+H). HRMS *calcd*. for ($C_{13}H_{17}O_3$): 221.1172, *found* 221.1166.



311

3-(3-Nitrophenyl)butanal (**311**). Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 1-bromo-3-nitrobenzene (16 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.21). Colourless oil, yield = 67% (30.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.73 (t, *J* = 1.5 Hz, 1H), 8.11-8.05 (m, 2H), 7.59-7.55 (m, 1H), 7.50-7.44 (m, 1H), 3.51 (h, *J* = 7.0 Hz, 1H), 2.83 (ddd, *J* = 17.4, 7.0, 1.5 Hz, 1H), 2.76 (ddd, *J* = 17.4, 7.0, 1.5 Hz, 1H), 1.35 (d, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.2, 148.5, 147.6, 133.4, 129.5, 121.6, 121.6, 51.4, 33.7, 21.9 ppm. IR (neat, cm^{-1}): 2966, 1721, 1524, 1347, 807, 738, 686. MS (ESI-) *m/z* (%) 192 (M-H). HRMS *calcd*. for ($C_{10}H_{10}NO_3$): 192.0666, *found* 192.0662.

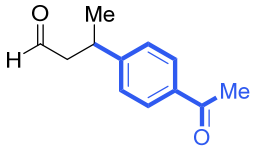


312

4-(4-Oxobutan-2-yl)benzonitrile (**312**).[128] Following general procedure **VIII**,_using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 4-bromobenzonitrile (44 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.25). Colourless oil, yield = 86% (35.0

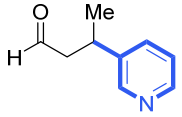
[128] Yang, J. W.; Hechavarria, M. T.; Vignola, N.; List. B. *Angew. Chem. Int. Ed*. **2005**, *44*, 108-110.

mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (t, J = 1.6 Hz, 1H), 7.62-7.57 (m, 2H), 7.36-7.30 (m, 2H), 3.43 (h, J = 7.2 Hz, 1H), 2.78 (ddd, J = 17.6, 7.2, 1.6 Hz, 1H), 2.71 (ddd, J = 17.6, 7.2, 1.6 Hz, 1H), 1.31 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.1, 151.0, 132.5, 127.7, 118.8, 110.4, 51.2, 34.1, 21.7 ppm.



313

3-(4-Acetylphenyl)butanal (**313**).[129] Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 1-(3-bromophenyl)ethan-1-one (47 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.24). Colourless oil, yield = 81% (36.0 mg). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (t, J = 1.8 Hz, 1H), 7.93-7.85 (m, 2H), 7.34-7.28 (m, 2H), 3.42 (h, J = 7.0 Hz, 1H), 2.78 (ddd, J = 17.3, 7.0, 1.8 Hz, 1H), 2.69 (ddd, J = 17.3, 7.0, 1.8 Hz, 1H), 2.56 (s, 3H), 1.32 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.9, 197.6, 151.1, 135.6, 128.8, 126.9, 51.3, 34.1, 26.5, 21.8 ppm.



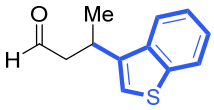
314

3-(Pyridin-3-yl)butanal (**314**).[130] Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 3-bromopyridine (23 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.18). Colourless oil, yield = 55% (19.5 mg). ^{1}H NMR (500 MHz,

[129] Caló. V.; Nacci, A.; Monopoli. A.; Spinelli, M. *Eur, J. Org. Chem*. **2003**, 1382-1385.

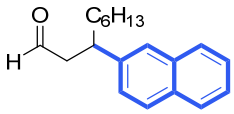
[130] Weerasinghe. D. K.; Sainsburg. M. *J. Chem. Soc. Chem. Commun*. **1981**, *13*, 630-631.

$CDCl_3$): δ 9.71 (t, J = 1.7 Hz, 1H), 8.50-8.49 (m, 1H), 8.49-8.43 (m, 1H), 7.54-7.50 (m, 1H), 7.25-7.20 (m, 1H), 3.39 (h, J = 7.0 Hz, 1H), 2.77 (ddd, J = 17.1, 7.0, 1.7 Hz, 1H), 2.71 (ddd, J = 17.1, 7.0, 1.7 Hz, 1H), 1.32 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.6, 148.7, 147.9, 140.7, 134.2, 123.5, 51.3, 31.6, 21.8 ppm.



315

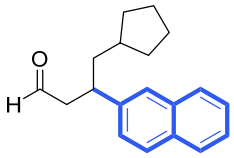
3-(Benzo[b]thiophen-3-yl)butanal (**315**). Following general procedure **VIII**, using 1,2-amino alcohol (**260**) (75 mg, 0.234 mmol) and 3-bromobenzo[b]thiophene (31 µL, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 90:10, R_f = 0.22). Colourless oil, yield = 50% (24.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.81 (t, J = 1.9 Hz, 1H), 7.91-7.86 (m, 1H), 7.82-7.79 (m, 1H), 7.45-7.35 (m, 2H), 7.15 (bs, 1H), 3.88-3.76 (m, 1H), 2.94 (ddd, J = 16.9, 5.7, 1.9 Hz, 1H), 2.76 (ddd, J = 16.9, 8.2, 1.9 Hz, 1H), 1.46 (d, J = 6.9 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.5, 140.8, 140.2, 137.9, 124.4, 124.0, 123.1, 121.5, 120.6, 50.5, 27.7, 20.8 ppm. IR (neat, cm^{-1}): 2963, 1720, 1427, 761, 731. MS (ESI+) *m/z* (%) 227 (M+Na). HRMS *calcd*. for ($C_{12}H_{12}NaOS$): 227.0501, *found* 227.0495.



322

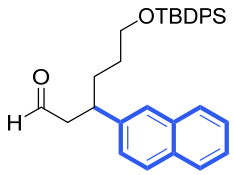
3-(Naphthalen-2-yl)nonanal (**322**). Following general procedure **VIII**, using 1,2-amino alcohol (**290**) (90 mg, 0.234 mmol) and 2-bromonaphthalene (48 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.67). Colourless oil, yield = 82% (54.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (t, J = 2.0 Hz, 1H), 7.85-7.77 (m,

3H), 7.65-7.61 (m, 1H), 7.50-7.41 (m, 2H), 7.37-7.32 (m, 1H), 3.35 (p, *J* =7.3 Hz, 1H), 2.82 (ddd, *J* = 16.4, 7.3, 2.0 Hz, 1H), 2.77 (ddd, *J* = 16.4, 7.3, 2.0 Hz, 1H), 1.78-1.69 (m, 2H), 1.37-1.08 (m, 8H), 0.85 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9, 141.3, 133.5, 132.4, 128.4, 127.6, 127.6, 126.1, 126.1, 125.5, 125.4, 50.6, 40.2, 36.5, 31.6, 29.2, 27.3, 22.6, 14.0 ppm. IR (neat, cm^{-1}): 2925, 2854, 1721, 1659, 1276, 818, 746, 702, 477. MS (ESI+) *m/z* (%) 291 (M+H). HRMS *calcd*. for ($C_{19}H_{24}NaO$): 291.1720, *found* 291.1719.



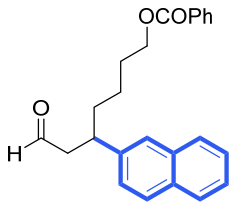
323

4-Cyclopentyl-3-(naphthalen-2-yl)butanal (**323**). Following general procedure **VIII**, using 1,2-amino alcohol (**291**) (89.5 mg, 0.234 mmol) and 2-bromonaphthalene (48 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.67). Colourless oil, yield = 86% (53.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (t, *J* = 2.0 Hz, 1H), 7.85-7.78 (m, 3H), 7.67-7.64 (m, 1H), 7.50-7.41 (m, 2H), 7.38-7.34 (m, 1H), 3.40 (m, 1H), 2.81 (ddd, *J* = 16.9, 7.6, 2.0 Hz, 1H), 2.76 (ddd, *J* = 16.9, 7.6, 2.0 Hz, 1H), 1.93-1.77 (m, 2H), 1.68-1.50 (m, 5H), 1.48-1.34 (m, 2H), 1.24-1.13 (m, 1H), 1.11-1.01 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.9, 141.4, 133.5, 132.4, 128.4, 127.6, 127.6, 126.2, 126.1, 125.5, 125.5, 50.9, 43.1, 39.4, 37.5, 33.2, 32.1, 25.1, 25.1 ppm. IR (neat, cm^{-1}): 2944, 2862, 1721, 817, 746, 477. MS (ESI+) *m/z* (%) 289 (M+Na). HRMS *calcd*. for ($C_{19}H_{22}NaO$): 289.1563, *found* 289.1568.



324

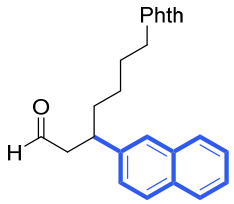
6-((*tert*-Butyldiphenylsilyl)oxy)-3-(naphthalen-2-yl)hexanal (**324**). Following general procedure **VIII**, using 1,2-amino alcohol (**292**) (139 mg, 0.234 mmol) and 2-bromonaphthalene (48 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.64). Colourless oil, yield = 80% (90.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (t, J = 2.0 Hz, 1H), 7.87-7.79 (m, 3H), 7.69-7.61 (m, 5H), 7.53-7.32 (m, 9H), 3.65 (t, J = 6.2 Hz, 2H), 3.35 (q, J = 6.8 Hz, 1H), 2.83 (ddd, J = 16.6, 6.8, 2.0 Hz, 1H), 2.76 (ddd, J = 16.6, 6.8, 2.0 Hz, 1H), 1.92-1.79 (m, 2H), 1.56-1.40 (m, 2H), 1.06 (s, 9H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.7, 140.9, 135.5, 135.5, 133.9, 133.9, 133.5, 132.4, 129.5, 129.5, 128.4, 127.6, 127.5, 127.5, 127.5, 126.2, 126.1, 125.5, 125.5, 63.5, 50.6, 39.9, 32.5, 30.1, 26.8, 19.2 ppm. IR (neat, cm^{-1}): 2930, 2857, 1723, 1107, 732, 700, 503. MS (ESI+) *m/z* (%) 503 (M+Na). HRMS *calcd*. for ($C_{32}H_{36}NaO_2Si$): 503.2370, *found* 503.2377.



325

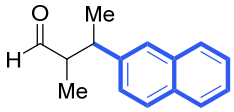
5-(Naphthalen-2-yl)-7-oxoheptyl benzoate (**325**). Following general procedure **VIII**, using 1,2-amino alcohol (**293**) (111.2 mg, 0.234 mmol) and 2-bromonaphthalene (48 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.38). Colourless oil, yield = 67% (57.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.70 (t, J = 2.0 Hz, 1H), 7.96-7.91 (m,

2H), 7.83-7.76 (m, 3H), 7.67-7.62 (m, 1H), 7.55-7.44 (m, 3H), 7.39-7.32 (m, 3H), 4.30-4.20 (m, 2H), 3.39 (p, J = 7.3 Hz, 1H), 2.85 (ddd, J = 16.8, 7.3, 2.0 Hz, 1H), 2.80 (ddd, J = 16.8, 7.3, 2.0 Hz, 1H), 1.88-1.66 (m, 4H), 1.45-1.25 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.5, 166.5, 140.8, 133.4, 132.7, 132.4, 130.3, 129.4, 128.5, 128.2, 127.6, 127.6, 126.2, 126.1, 125.5, 125.3, 64.5, 50.5, 39.9, 35.8, 28.4, 23.7 ppm. IR (neat, cm^{-1}): 2927, 1714, 1270, 1114, 710. MS (ESI+) *m/z* (%) 383 (M+Na). HRMS *calcd*. for ($C_{24}H_{24}NaO_3$): 383.1618, *found* 383.1607.



326

7-(1,3-Dioxoisoindolin-2-yl)-3-(naphthalen-2-yl)heptanal (**326**). Following general procedure **VIII**, using 1,2-amino alcohol (**294**) (117.0 mg, 0.234 mmol) and 2-bromonaphthalene (48 mg, 0.234 mmol). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.16). Colourless oil, yield = 60% (54.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (t, J = 2.0 Hz, 1H), 7.83-7.75 (m, 5H), 7.69-7.65 (m, 2H), 7.63-7.61 (m, 1H), 7.50-7.39 (m, 2H), 7.36-7.29 (m, 1H), 3.61 (t, J = 7.3 Hz, 2H), 3.36 (p, J = 7.3 Hz, 1H), 2.89-2.72 (m, 2H), 1.86-1.54 (m, 4H), 1.34-1.14 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.6, 168.2, 140.7, 133.7, 133.4, 132.3, 131.9, 128.4, 127.6, 127.5, 126.1, 126.0, 125.4, 125.4, 123.0, 50.4, 39.9, 37.5, 35.7, 28.2, 24.4 ppm. IR (neat, cm^{-1}): 2934, 1770, 1704, 1395, 718. MS (ESI-) *m/z* (%) 384 (M-H). HRMS *calcd*. for ($C_{25}H_{22}NO_3$): 384.1605, *found* 384.1622.



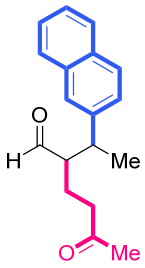
329

2-Methyl-3-(naphthalen-2-yl)butanal (**329**). Following general procedure **VIII**, using 1,2-amino alcohol (**300**) (78.0 mg, 0.234 mmol), 2-bromonaphthalene (48 mg, 0.234 mmol), 5 mol% $Pd(OAc)_2$ and 10 mol% PPh_3. Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.71). Colourless oil, yield = 62% (31.0 mg), in 1.25:1 dr. ^{1}H NMR (400 MHz, $CDCl_3$): Major product δ 9.76 (d, J = 3.1 Hz, 1H), 7.88-7.80 (m, 3H), 7.68-7.63 (m, 1H), 7.54-7.44 (m, 2H), 7.42-7.32 (m, 1H), 3.25-3.15 (m, 1H), 2.72-2.64 (m, 1H), 1.41 (d, J = 9.3 Hz, 3H), 0.95 (d, J = 7.0 Hz, 3H) ppm. Minor product δ 9.66 (d, J = 2.0 Hz, 1H), 7.88-7.80 (m, 3H), 7.68-7.63 (m, 1H), 7.54-7.44 (m, 2H), 7.42-7.32 (m, 1H), 3.41-3.32 (m, 1H), 2.81-2.72 (m, 1H), 1.43 (d, J = 7.3 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 204.8, 204.7, 141.6, 141.1 133.5, 132.4, 132.3, 128.3, 128.3, 127.7, 127.6, 127.5, 127.5, 126.3, 126.1, 125.9, 125.8, 125.6, 125.5, 125.5, 52.8, 52.4, 41.0, 40.3, 20.1, 17.4, 12.6, 10.4 ppm. IR (neat, cm^{-1}): 2966, 2930, 1721, 1453, 819, 746. MS (ESI+) *m/z* (%) 235 (M+Na). HRMS *calcd*. for ($C_{15}H_{16}NaO$): 235.1093, *found* 235.1097.

5.5.5 Enamine alkylation; Synthesis of α,β-functionalized aldehydes (one pot procedure)

General Procedure XIX. An oven-dried Schlenk tube containing a stirring bar was charged with the corresponding amino alcohol, Cs_2CO_3 (1.3 eq.) and 2-bromonaphthalene (1 eq.). The Schlenk tube was then evacuated and back-filled with argon (this sequence was repeated three times) and finally an atmospheric pressure of argon was established. THF [0.2 M], $Pd(OAc)_2$ (2 mol%, 0.05 M), and PPh_3 (4 mol%, 0.1 M) were subsequently added via syringe under argon and the solution was warmed up to 90 ºC and stirred for 12-16 h. The mixture was then allowed to warm to room temperature;

under argon, the vinyl methyl ketone (3 eq.) was added dropwise and the reaction mixture was warmed up again and stirred at 90 ºC for 6 h. The mixture was then allowed to reach room temperature and quenched with AcOH/NaAcO buffer and stirred at room temperature for 10 minutes. The reaction mixture was extracted with EtOAc (10 mL x 2) and the combined organic layers were washed with brine, dried with $MgSO_4$ and removed under reduced pressure. The residue was purified by conventional flash column chromatography (hexanes/ether).

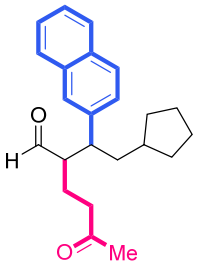


330

(*R*)-2-((*S*)-1-(Naphthalen-2-yl)ethyl)-5-oxohexanal (330)

Following general procedure **XIX**, using 1,2-amino alcohol (**260**) (150.0 mg, 0.470 mmol), Cs_2CO_3 (198 mg, 0.607 mmol), 2-bromonaphthalene (98 mg, 0.470 mmol), $Pd(OAc)_2$ (188 µL, 0.05 M) and PPh_3 (188 µL, 0.1 M). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.71). Colourless oil, yield = 57% (71.0 mg), in dr = 1.3:1. ^{1}H NMR (400 MHz, $CDCl_3$): Major product δ 9.65 (d, J = 3.9 Hz, 1H), 7.87-7.77 (m, 3H), 7.65 (m, 1H), 7.53-7.41 (m, 2H), 7.34 (m, 1H), 3.20 (dq, J = 9.3, 7.0 Hz, 1H), 2.65-2.52 (m, 2H), 2.40-2.27 (m, 2H), 2.02 (s, 3H), 1.95-1.70 (m, 1H), 1.37 (d, J = 7.0 Hz, 3H) ppm. Minor product δ 9.53 (d, J = 3.1 Hz, 1H), 7.87-7.77 (m, 3H), 7.65 (m, 1H), 7.53-7.41 (m, 2H), 7.34 (m, 1H), 3.35-3.26 (m, 1H), 2.53-2.42 (m, 2H), 2.53-2.42 (m, 2H), 2.33-2.21 (m, 2H), 2.08 (s, 3H), 1.63-1.53 (m, 1H), 1.44 (d, J = 7.1, 3H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ 207.8, 207.6, 204.6, 204.3, 140.9, 140.9, 133.5, 133.4, 132.4, 132.4, 128.5, 128.4, 127.7, 127.6, 127.6, 126.2, 126.2, 126.2, 126.0, 125.8, 125.7,

125.6, 125.5, 57.7, 57.1, 40.9, 40.7, 40.4, 40.1, 29.9, 29.9, 21.4, 20.1, 20.0, 18.3 ppm. IR (neat, cm^{-1}): 3054, 2962, 2930, 1714, 1436, 1366. MS (ESI+) *m/z* (%) 291 (M+Na). HRMS *calcd*. for ($C_{18}H_{20}NaO_2$): 291.1356, *found* 291.1351.

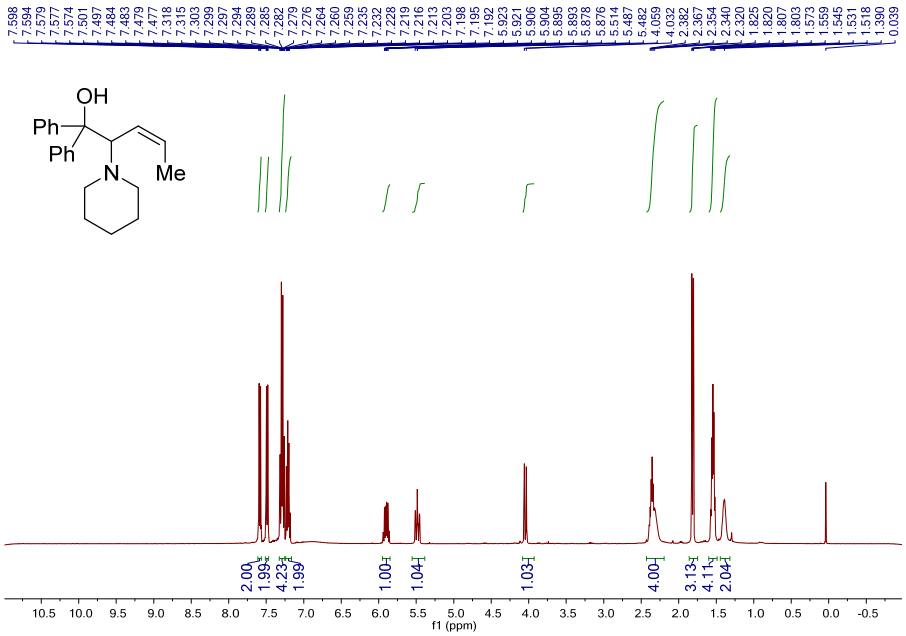


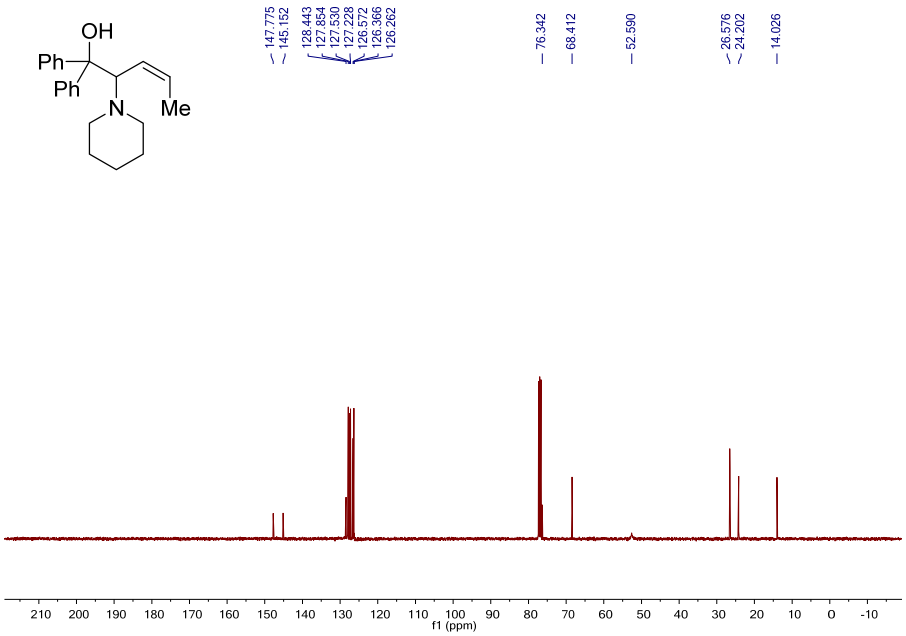
345

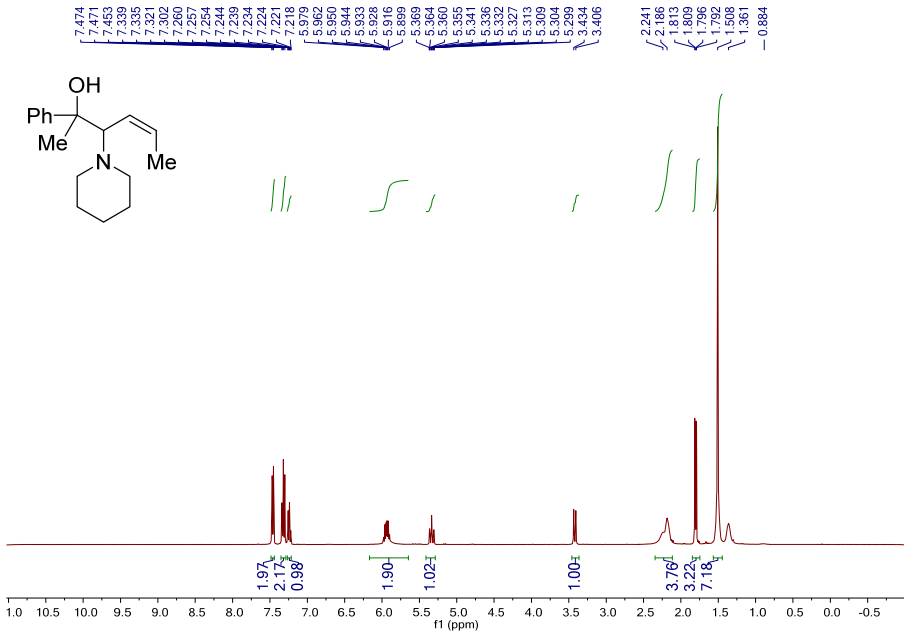
(*R*)-2-((*S*)-2-Cyclopentyl-1-(naphthalen-2-yl)ethyl)-5-oxohexanal (345)

Following general procedure **XIX**, using 1,2-amino alcohol (**291**) (89.5 mg, 0.230 mmol), Cs_2CO_3 (100 mg, 0.31 mmol), 2-bromonaphthalene (48 mg, 0.233 mmol), $Pd(OAc)_2$ (49 µL, 0.05 M) and PPh_3 (97 µL, 0.1 M). Column chromatography: silica gel (hexanes/EtOAc, 80:20, R_f = 0.55). Colourless oil, yield = 54% (41.7 mg), in dr = 1.25:1. ^1H NMR (300 MHz, $CDCl_3$): Major product δ 9.63 (d, J = 4.3 Hz, 1H), 7.87-7.76 (m, 3H), 7.63-7.59 (m, 1H), 7.52-7.42 (m, 2H), 7.34-7.28 (m, 1H), 3.15-3.03 (m, 1H), 2.65-2.39 (m, 2H), 2.35-2.19 (m, 1H), 2.00 (s, 3H), 1.86-0.92 (m, 13H) ppm. Minor product δ 9.47 (d, J = 3.5 Hz, 1H), 7.87-7.77 (m, 3H), 7.65 (m, 1H), 7.53-7.41 (m, 2H), 7.34 (m, 1H), 3.35-3.26 (m, 1H), 2.53-2.42 (m, 2H), 2.53-2.42 (m, 2H), 2.33-2.21 (m, 2H), 2.10 (s, 3H), 1.63-1.53 (m, 1H), 1.44 (d, J = 7.1, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 207.8, 207.5, 204.7, 204.4, 139.1, 138.8, 133.3, 132.5, 132.4, 128.4, 128.4, 127.6, 127.6, 127.4, 127.3, 126.3, 126.1, 125.7, 125.6, 125.6, 57.4, 56.9, 45.9, 45.4, 40.9, 40.9, 40.6, 38.4, 37.1, 33.4, 33.3, 31,7, 31.7, 30.0, 29.9, 25.0, 25.0, 25.0, 21.2, 20.9 ppm. IR (neat, cm^{-1}): 3053, 2944, 2863, 1714, 1508, 1367. MS (ESI+) *m/z* (%) 359 (M+Na). HRMS *calcd*. for ($C_{23}H_{28}NaO_2$): 359.1982, *found* 359.1966.

5.5.6 Selected NMR spectra



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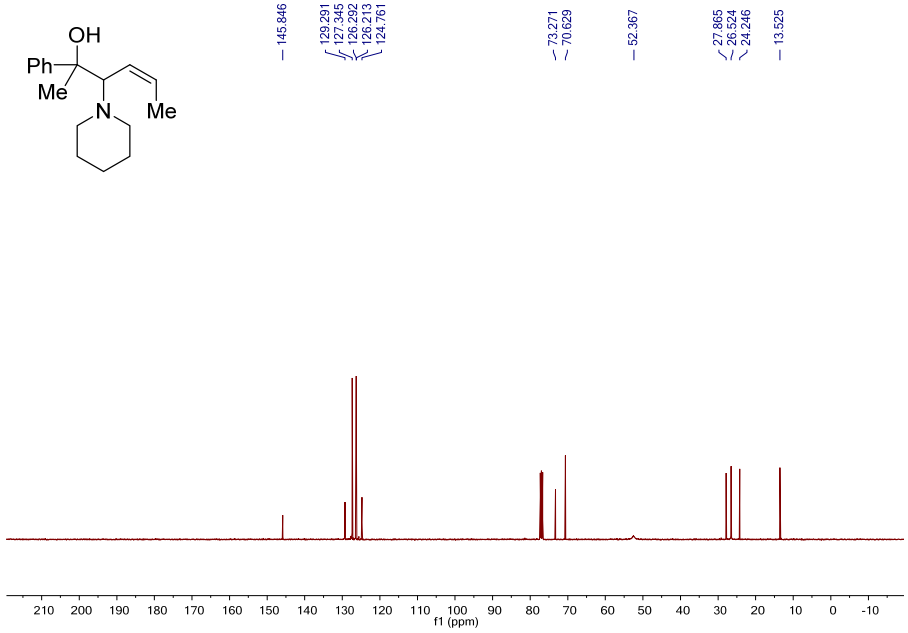
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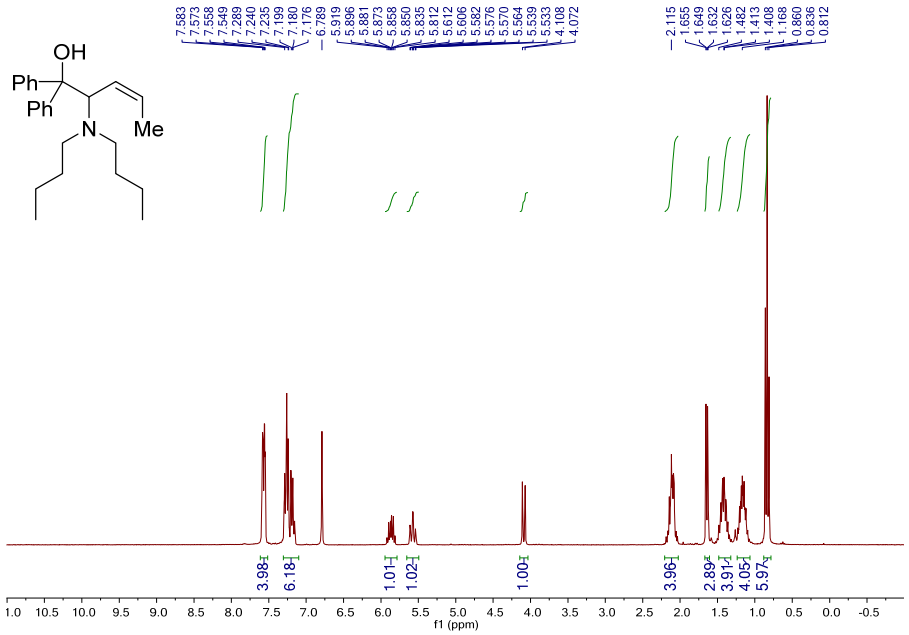
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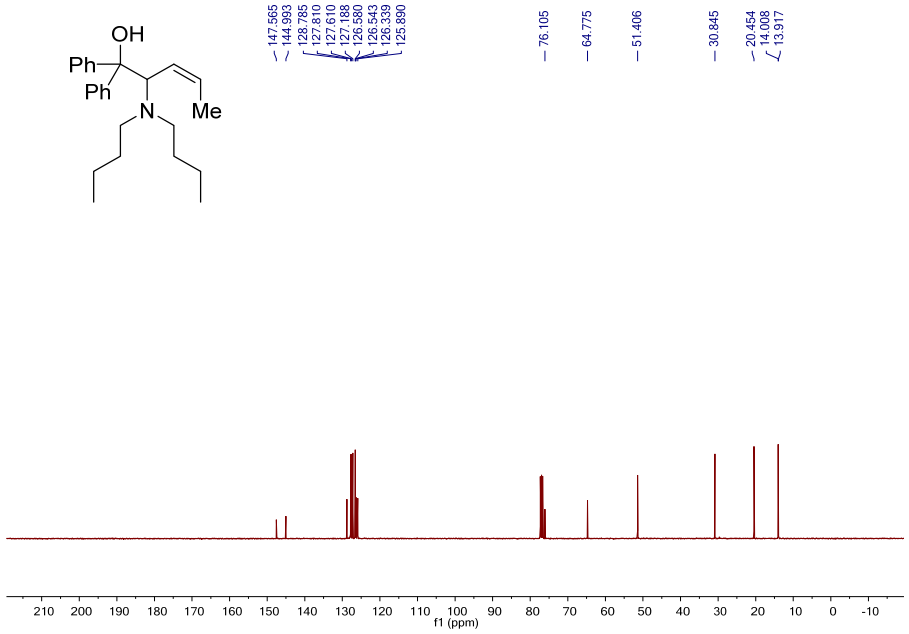
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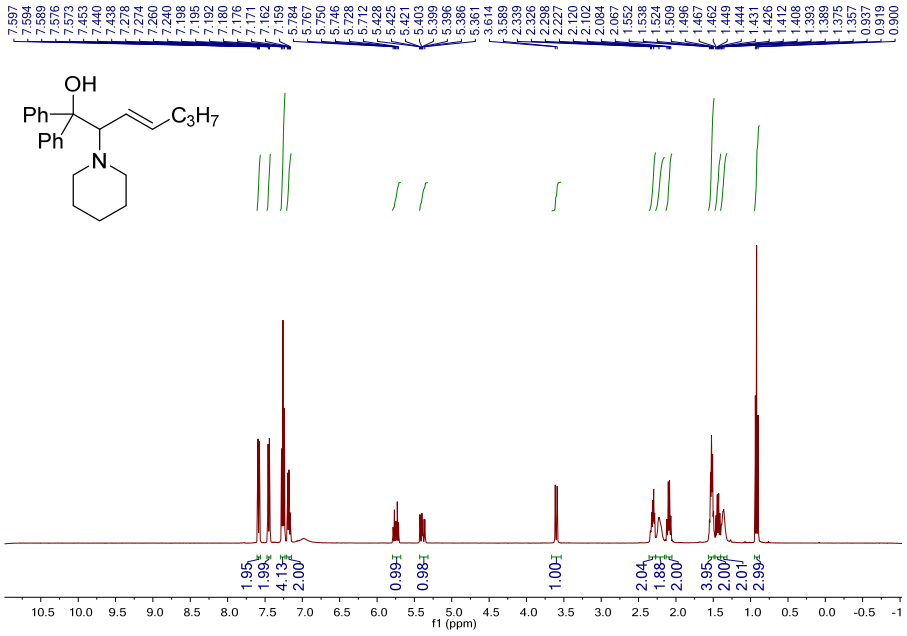
f1 (ppm)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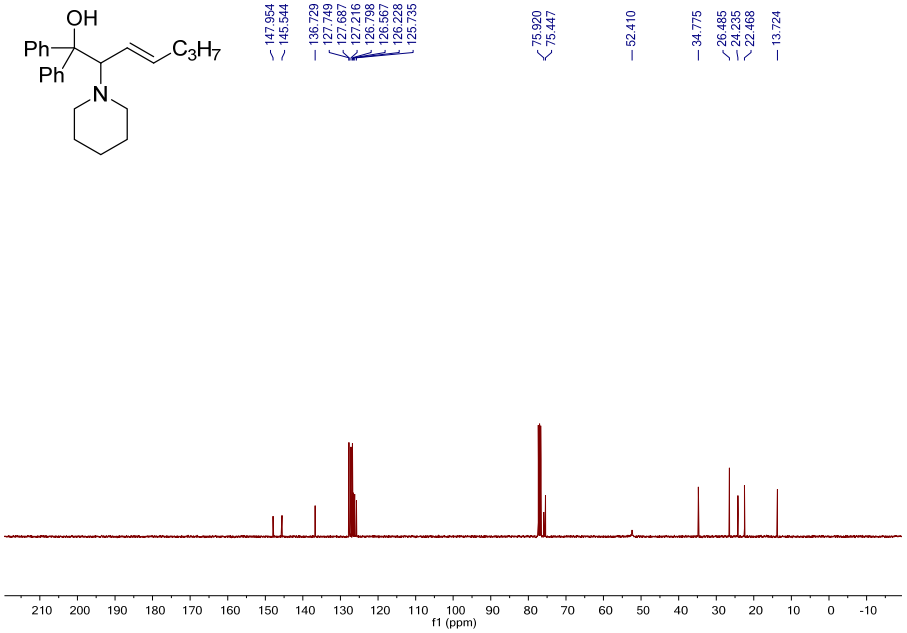
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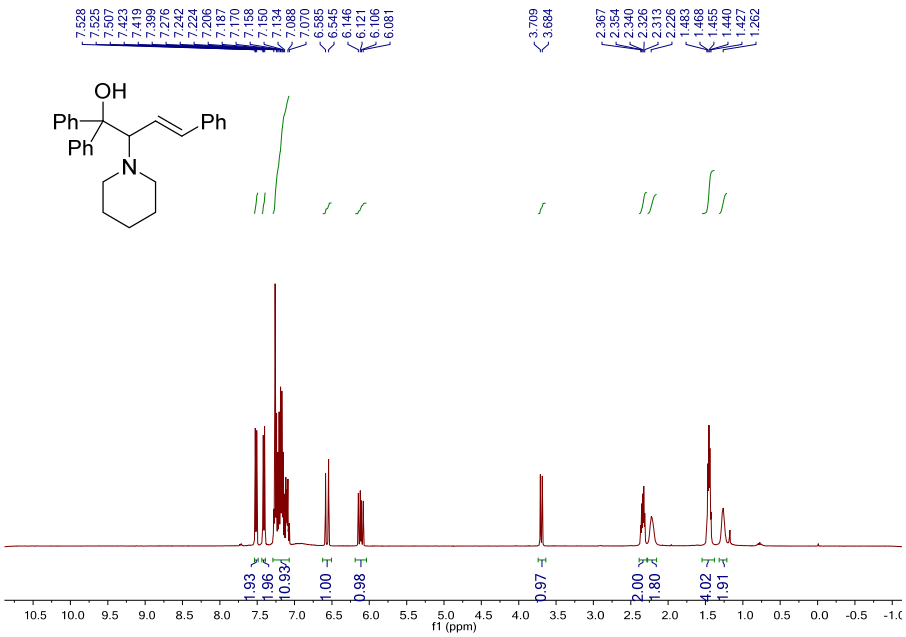
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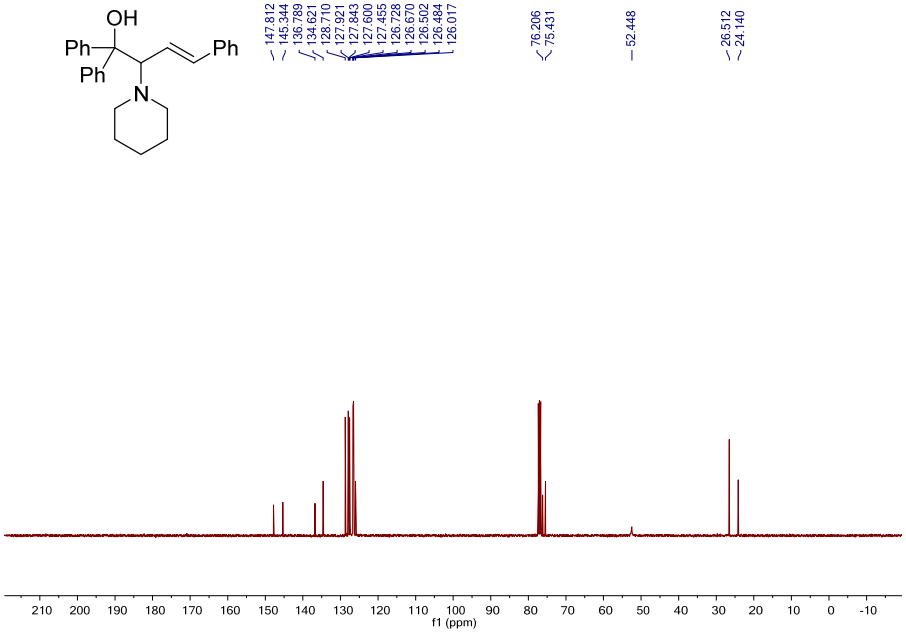
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Ph
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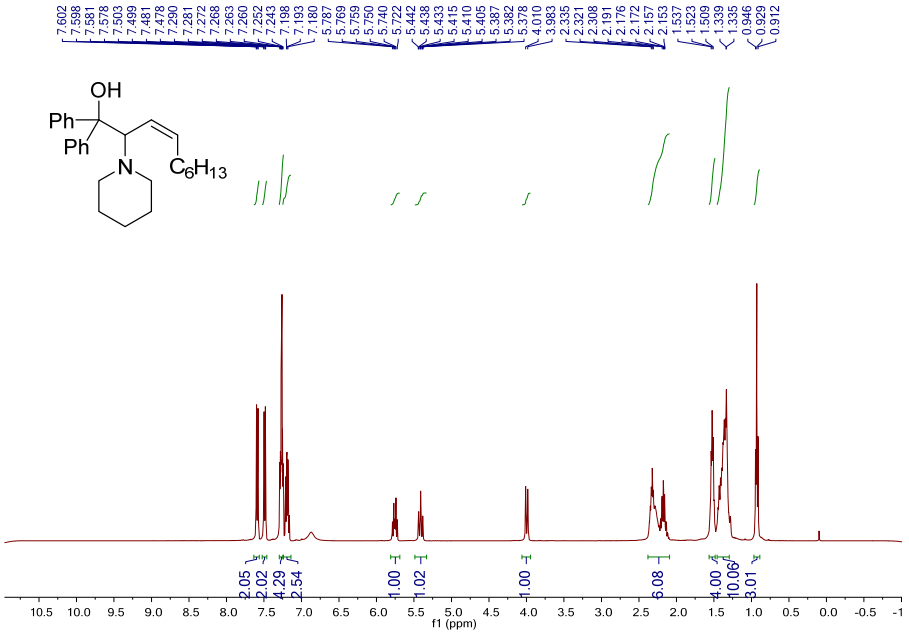
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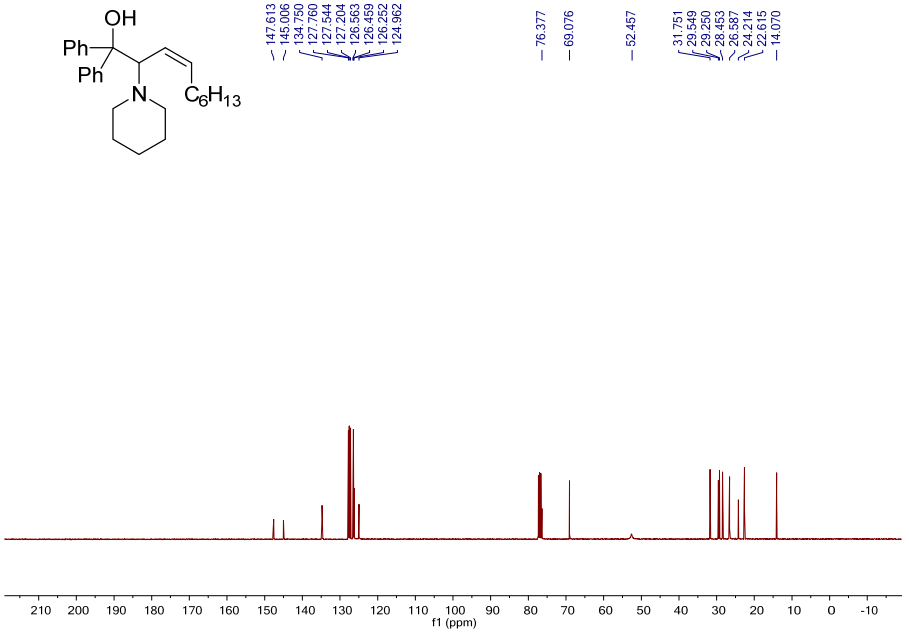
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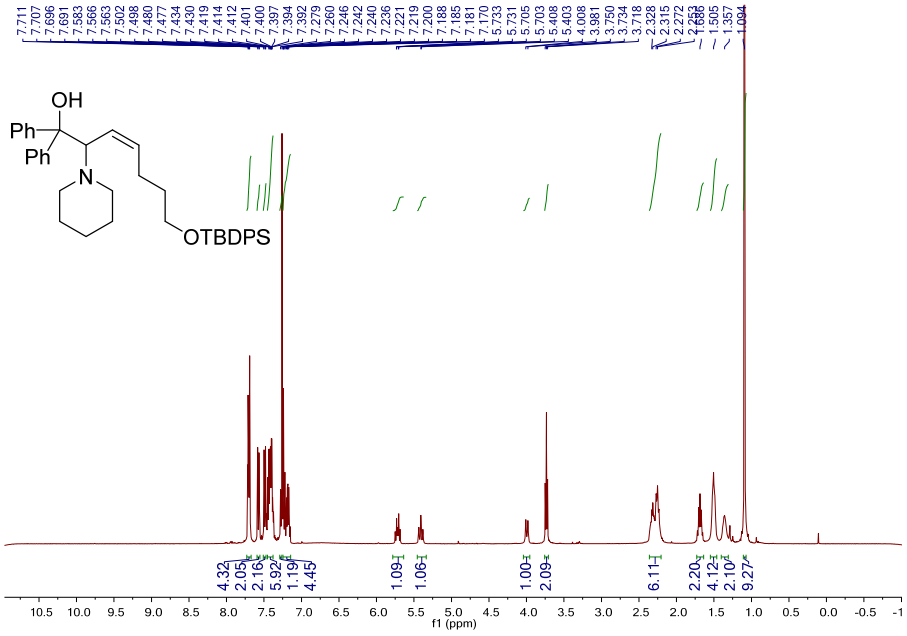
f1 (ppm)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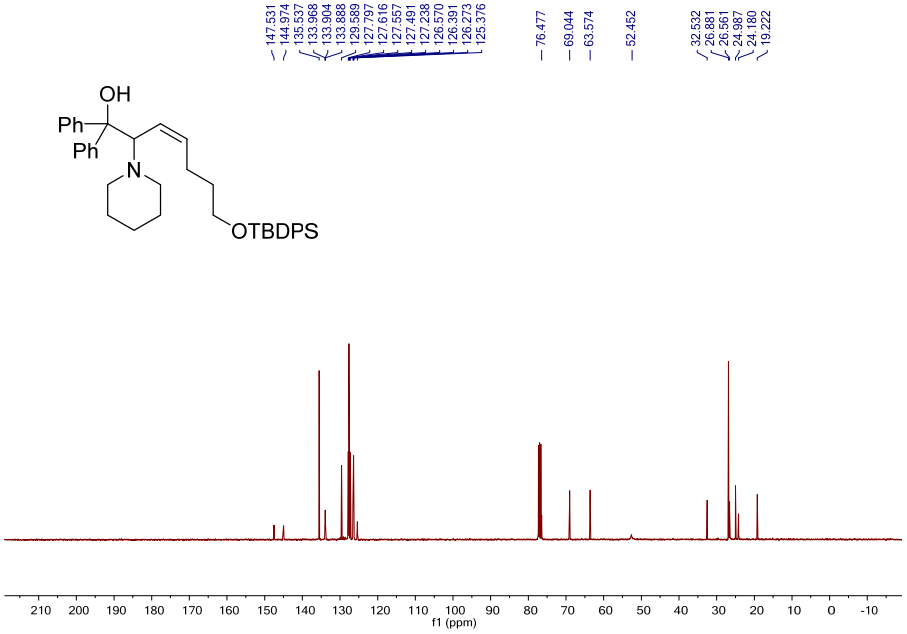
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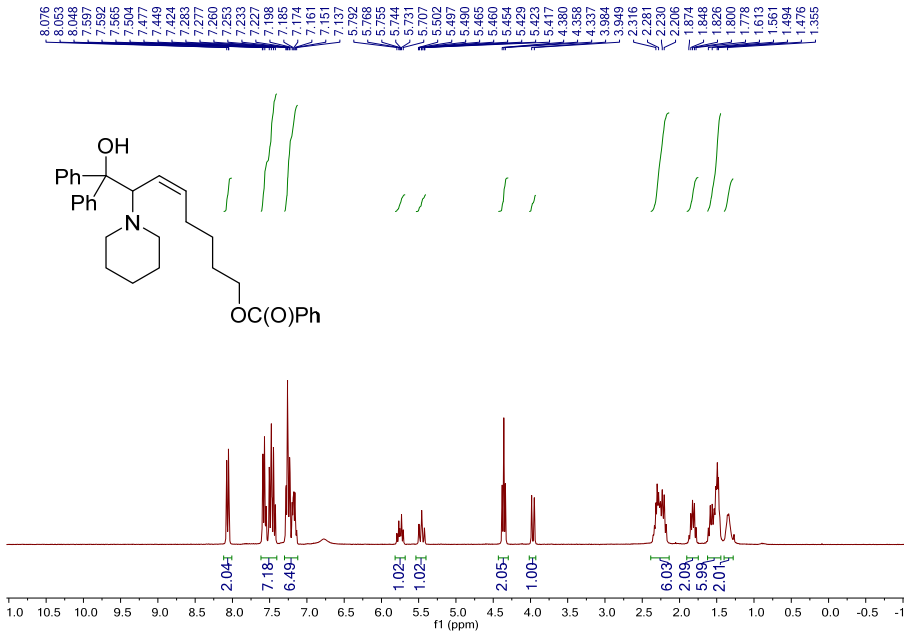
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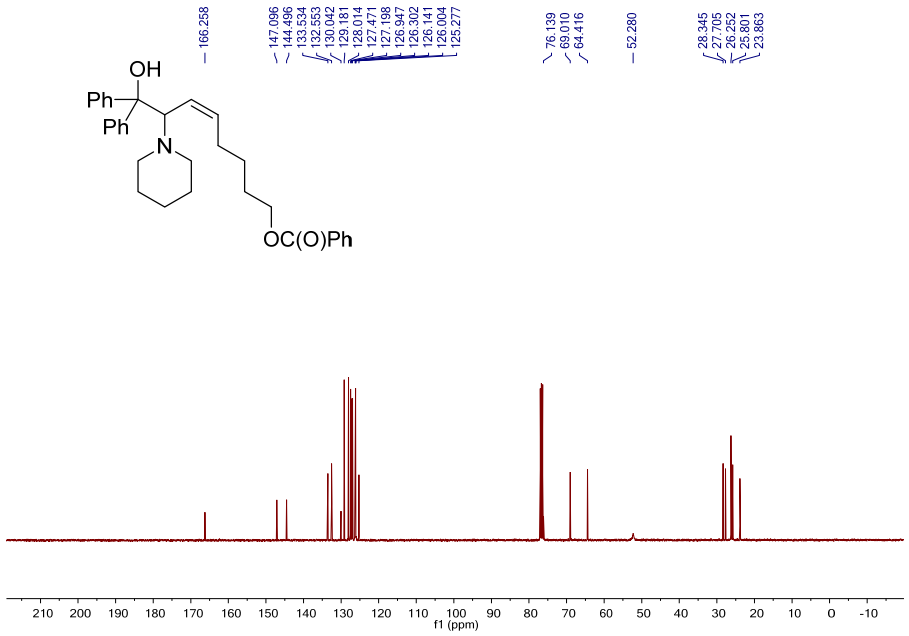
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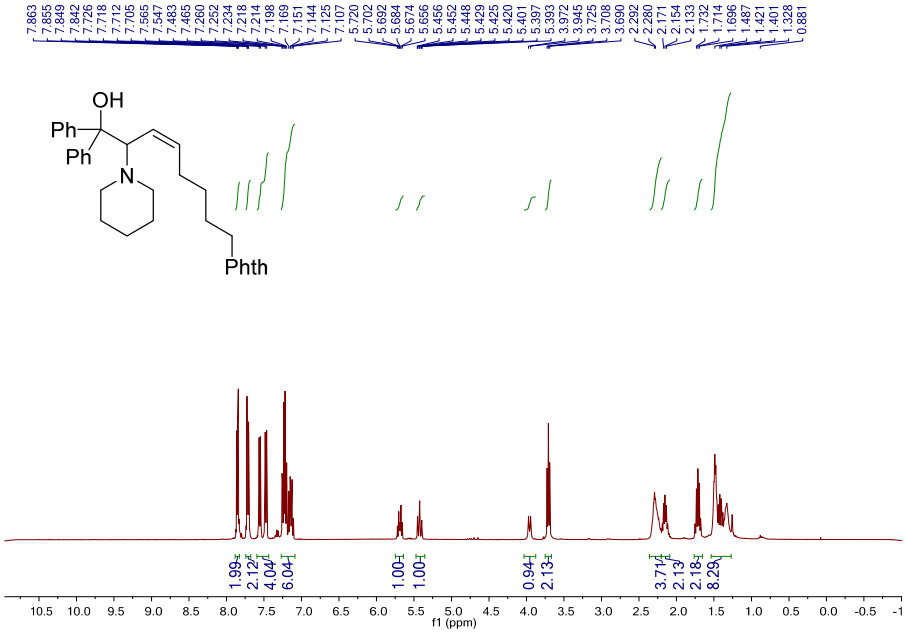
f1 (ppm)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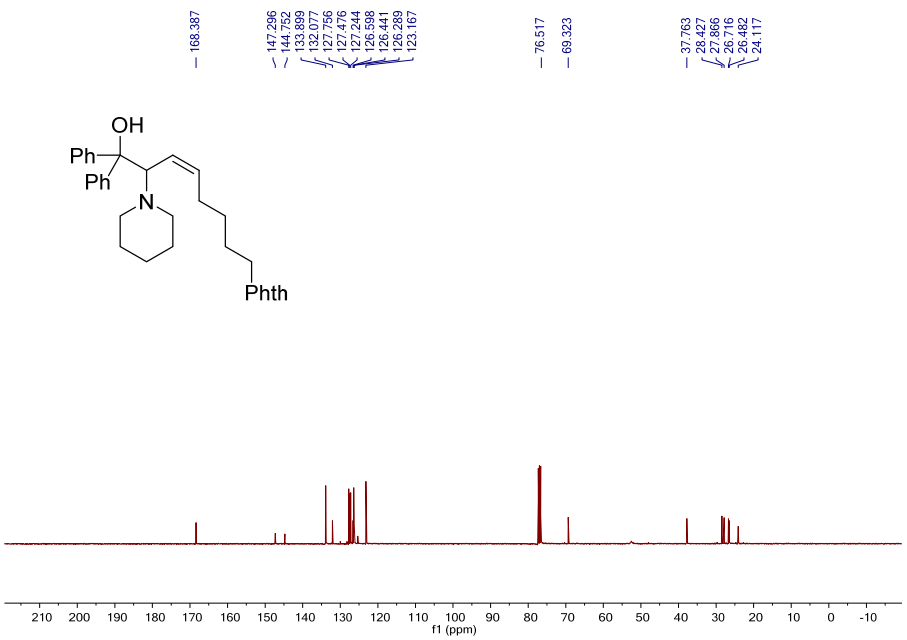
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Ph
Ph
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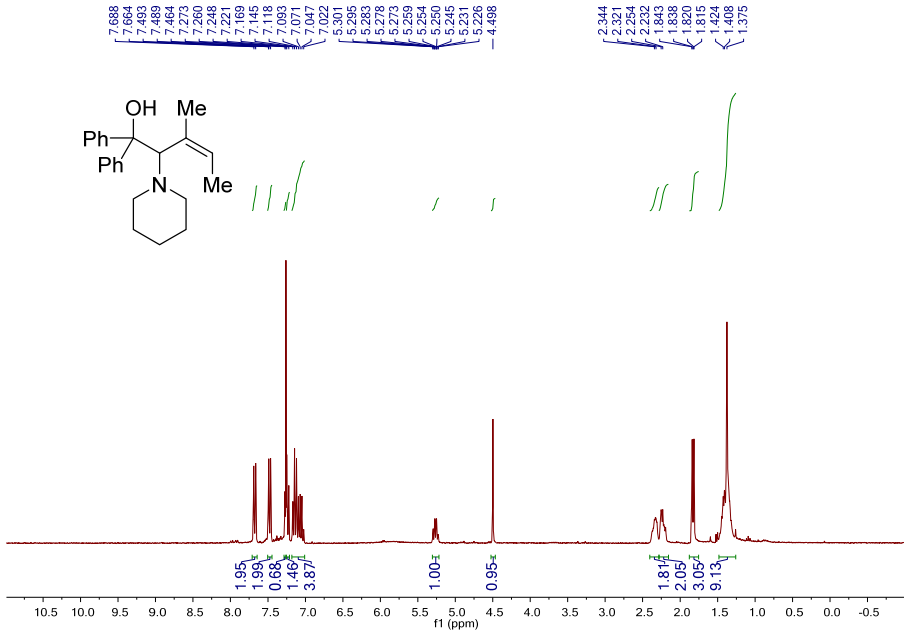
Phth
f1 (ppm)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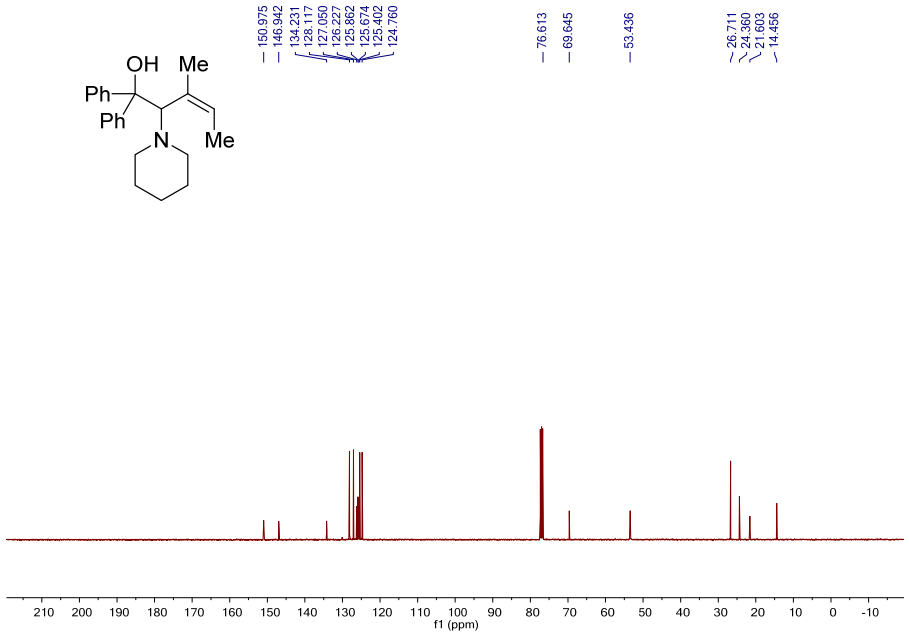
7.664
7.493
7.489
7.464
7.273
7.260
7.248
7.221
7.169
7.145
7.118
7.093
7.071
7.047
7.022
5.301
5.295
5.283
5.278
5.273
5.259
5.254
5.250
5.245
5.231
5.226
4.498
2.344
2.321
2.254
2.232
1.843
1.838
1.820
1.815
1.424
1.408
1.375
OH
Me
Ph
Ph
N
Me
1.95
1.99
0.68
1.46
3.87
1.00
0.95
1.81
2.05
3.05
9.13
f1 (ppm)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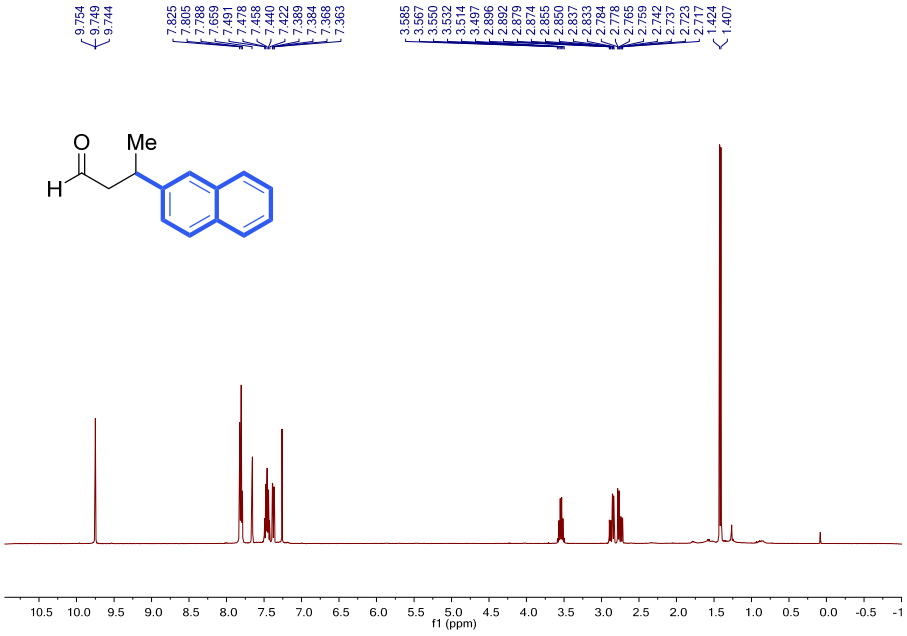
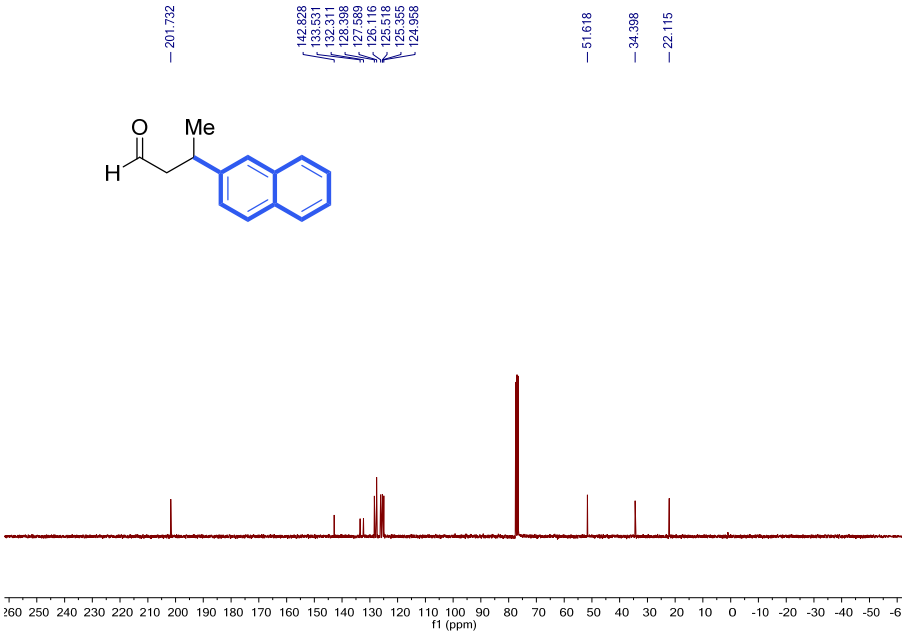
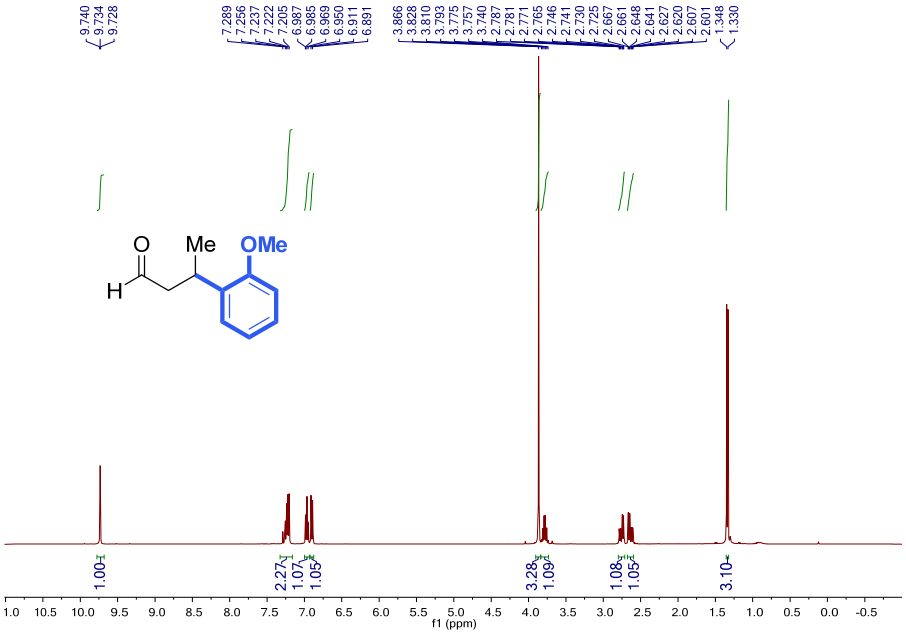
146.942
134.231
128.117
127.050
126.227
125.862
125.674
125.402
124.760
76.613
69.645
53.436
26.711
24.360
21.603
14.456
OH
Me
Ph
Ph
N
Me
f1 (ppm)


9.754
9.749
9.744
7.825
7.805
7.788
7.659
7.491
7.478
7.458
7.440
7.422
7.389
7.384
7.368
7.363
3.585
3.567
3.550
3.532
3.514
3.497
2.896
2.892
2.879
2.874
2.855
2.850
2.837
2.833
2.784
2.778
2.765
2.759
2.742
2.737
2.723
2.717
1.424
1.407
O
Me
H
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


201.732
142.828
133.531
132.311
128.398
127.589
126.116
125.518
125.355
124.958
51.618
34.398
22.115
O
Me
H
260 250 240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30 -40 -50 -6
f1 (ppm)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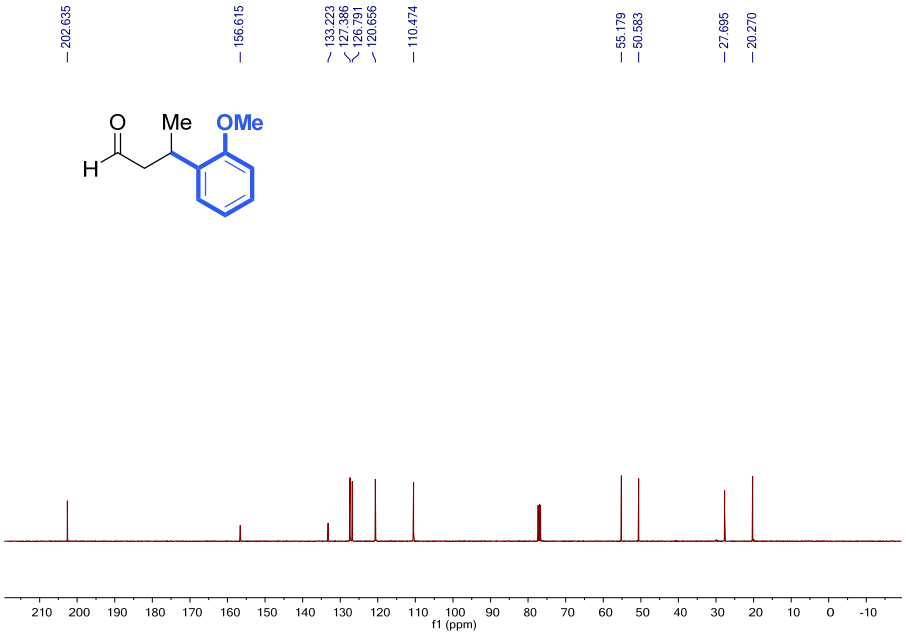
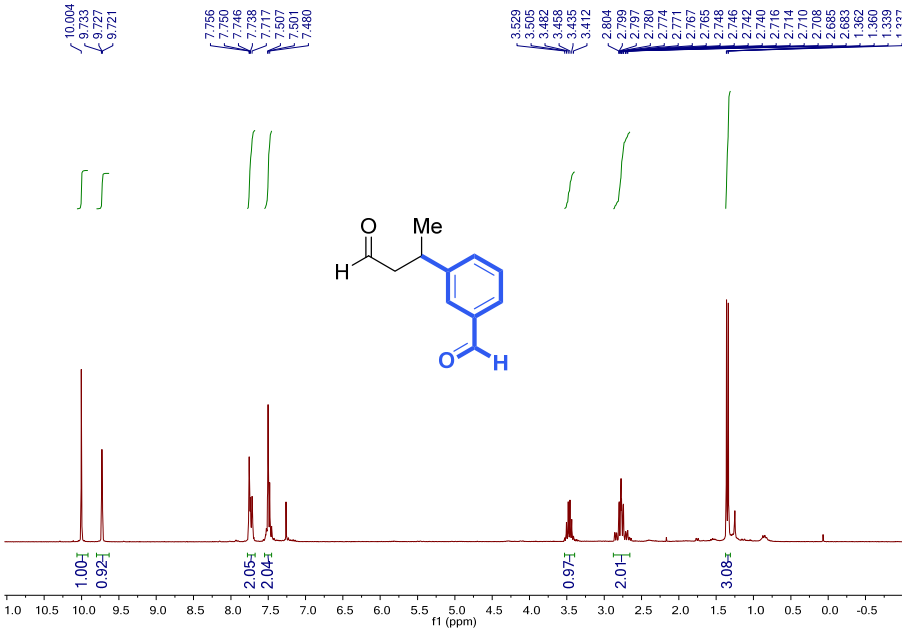
9.728
7.289
7.256
7.237
7.222
7.205
6.987
6.985
6.969
6.950
6.911
6.891
3.866
3.828
3.810
3.793
3.775
3.757
3.740
2.787
2.781
2.771
2.765
2.746
2.741
2.730
2.725
2.667
2.661
2.648
2.641
2.627
2.620
2.607
2.601
1.348
1.330
O
Me
OMe
H
1.00
2.27
1.07
1.05
3.28
1.09
1.08
1.05
3.10
f1 (ppm)


202.635
156.615
133.223
127.386
126.791
120.656
110.474
55.179
50.583
27.695
20.270
O
Me
OMe
H
f1 (ppm)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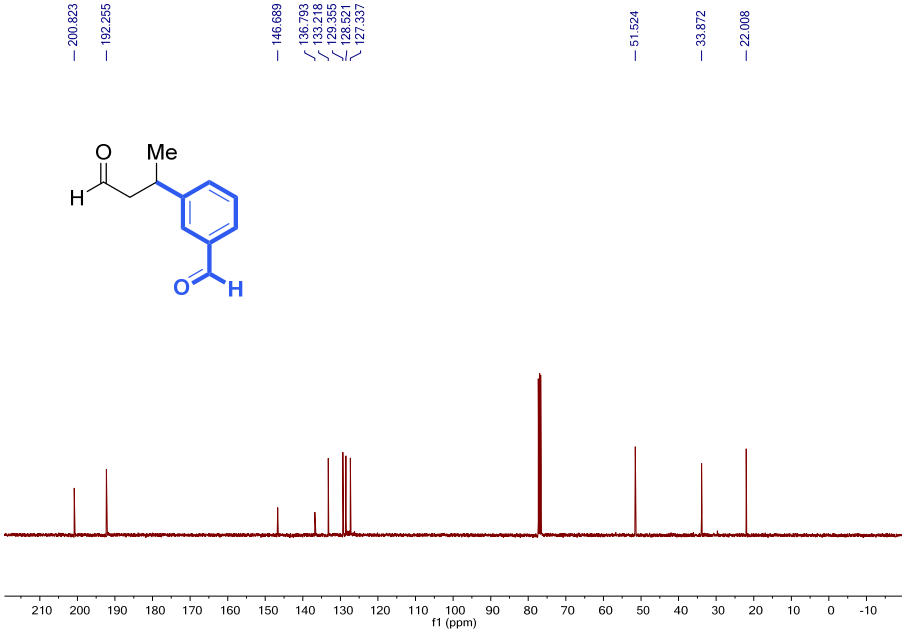
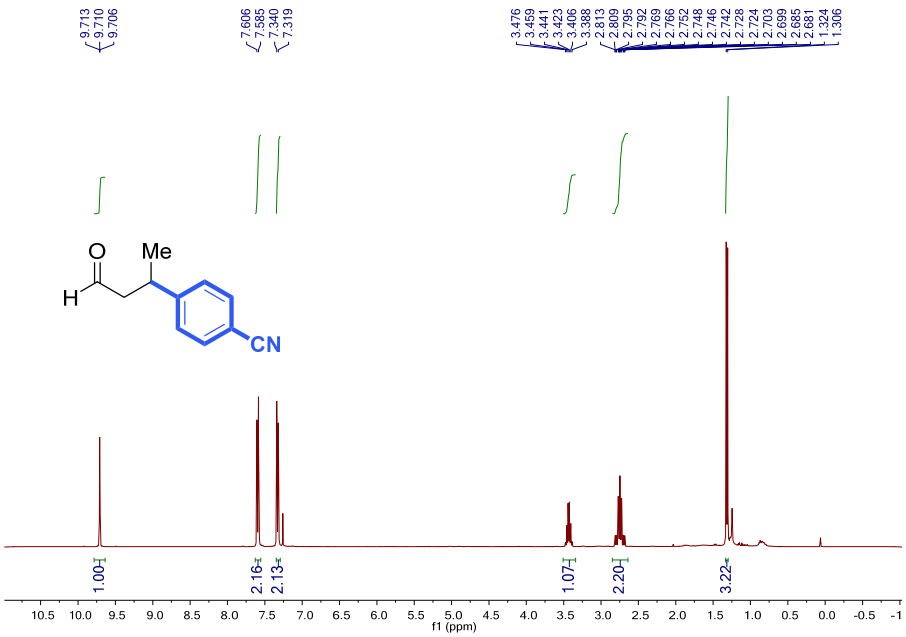
9.733
9.727
9.721
7.756
7.750
7.746
7.738
7.717
7.507
7.501
7.480
3.529
3.505
3.482
3.458
3.435
3.412
2.804
2.799
2.797
2.780
2.774
2.771
2.767
2.765
2.748
2.746
2.742
2.740
2.716
2.714
2.710
2.708
2.685
2.683
1.362
1.360
1.339
O
Me
H
O
H
1.00
0.92
2.05
2.04
0.97
2.01
3.08
f1 (ppm)


200.823
192.255
146.689
136.793
133.218
129.355
128.521
127.337
51.524
33.872
22.008
O
Me
H
O
H
f1 (ppm)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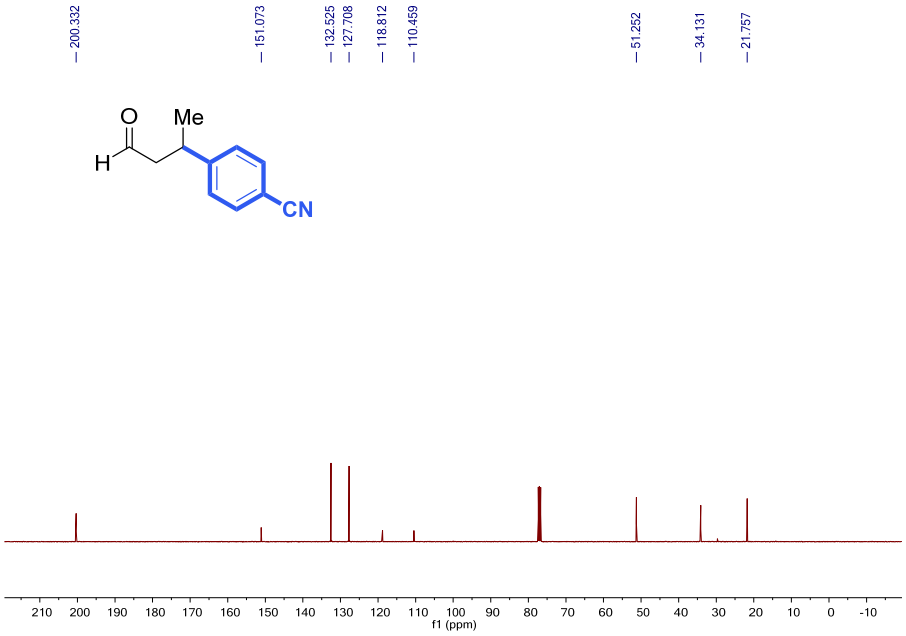
9.710
9.706
7.606
7.585
7.340
7.319
3.476
3.459
3.441
3.423
3.406
3.388
2.813
2.809
2.795
2.792
2.769
2.766
2.752
2.748
2.746
2.742
2.728
2.724
2.703
2.699
2.685
2.681
1.324
1.306
O
Me
H
CN
1.00
2.16
2.13
1.07
2.20
3.22
f1 (ppm)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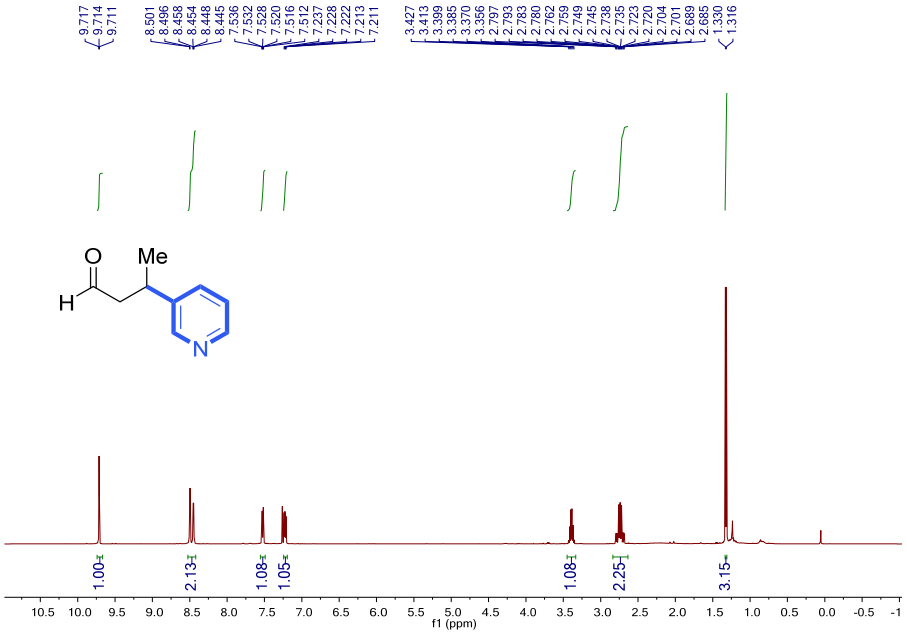
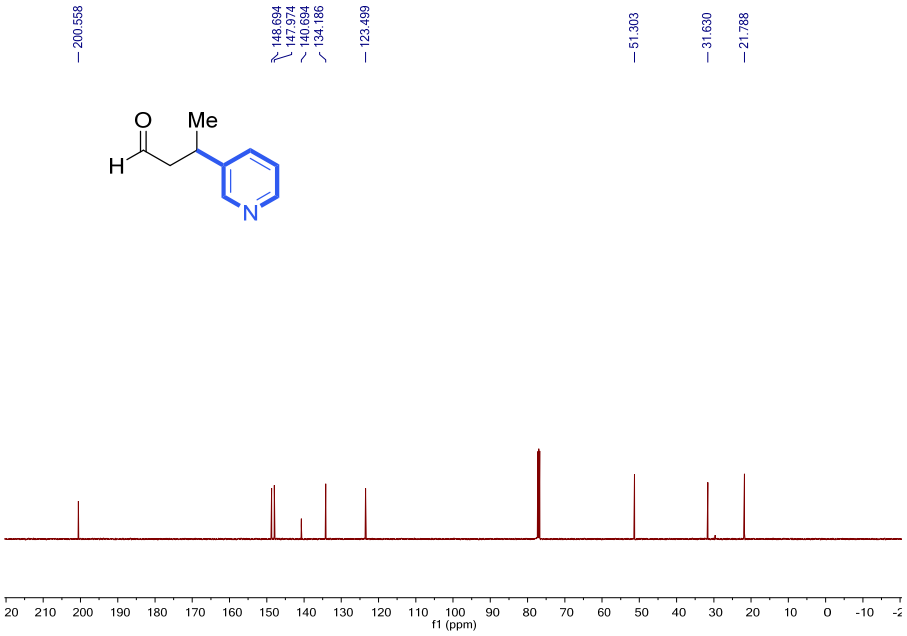
127.708
118.812
110.459
51.252
34.131
21.757
O
Me
H
CN
f1 (ppm)


9.717
9.714
9.711
8.501
8.496
8.458
8.454
8.448
8.445
7.536
7.532
7.528
7.520
7.516
7.512
7.237
7.228
7.222
7.213
7.211
3.427
3.413
3.399
3.385
3.370
3.356
2.797
2.793
2.783
2.780
2.762
2.759
2.749
2.745
2.738
2.735
2.723
2.720
2.704
2.701
2.689
2.685
1.330
1.316
O
Me
H
N
1.00
2.13
1.08
1.05
1.08
2.25
3.15
f1 (ppm)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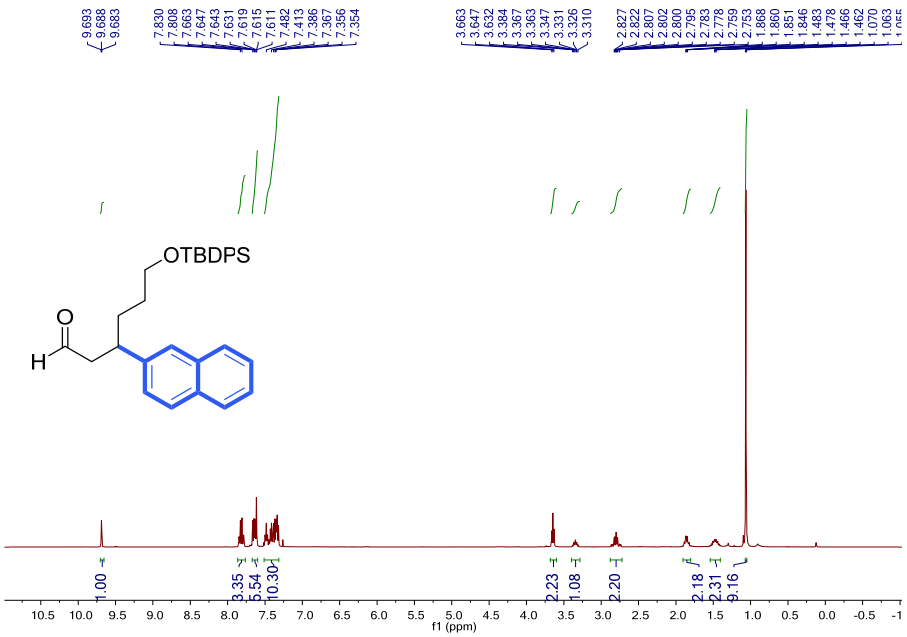
148.694
147.974
140.694
134.186
123.499
51.303
31.630
21.788
O
Me
H
N
f1 (ppm)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9.688
9.683
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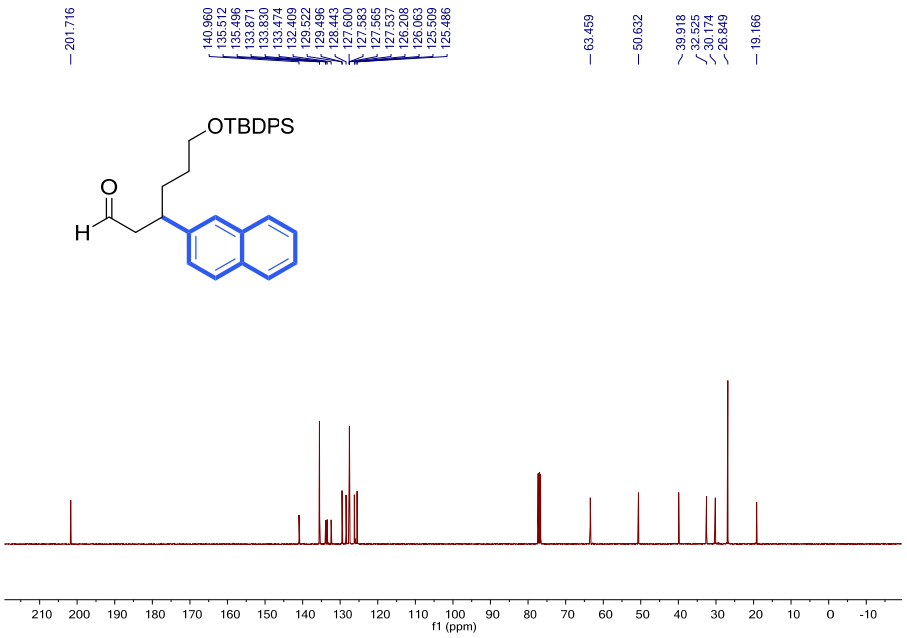
7.808
7.663
7.647
7.643
7.631
7.619
7.615
7.611
7.482
7.413
7.386
7.367
7.356
7.354
3.663
3.647
3.632
3.384
3.367
3.363
3.347
3.331
3.326
3.310
2.827
2.822
2.807
2.802
2.800
2.795
2.783
2.778
2.759
2.753
1.868
1.860
1.851
1.846
1.483
1.478
1.466
1.462
1.070
1.063
OTBDPS
O
H
1.00
3.35
5.54
10.30
2.23
1.08
2.20
2.18
2.31
9.16
f1 (ppm)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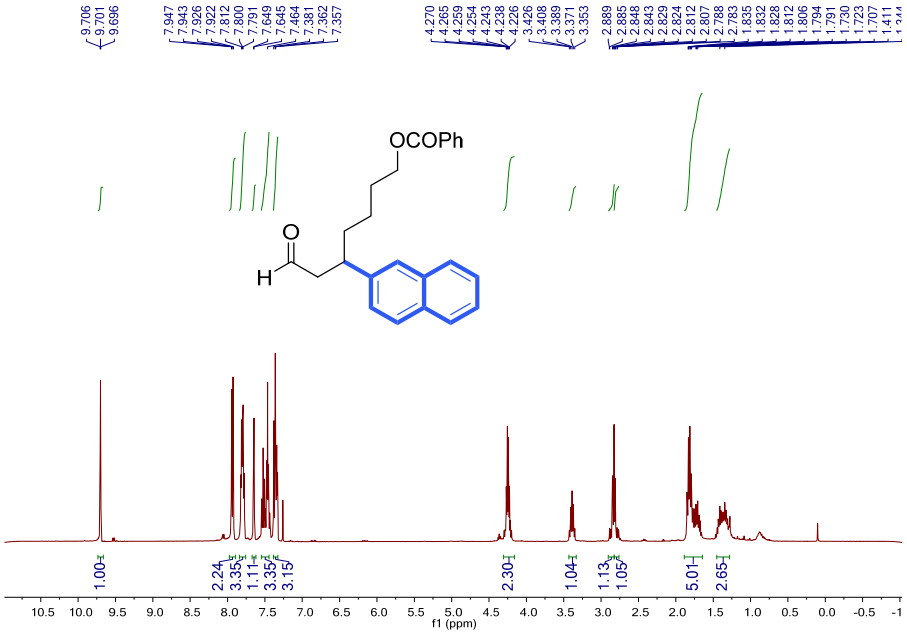
133.871
133.830
133.474
132.409
129.522
129.496
128.443
127.600
127.583
127.565
127.537
126.208
126.063
125.509
125.486
63.459
50.632
39.918
32.525
30.174
26.849
19.166
OTBDPS
O
H
f1 (ppm)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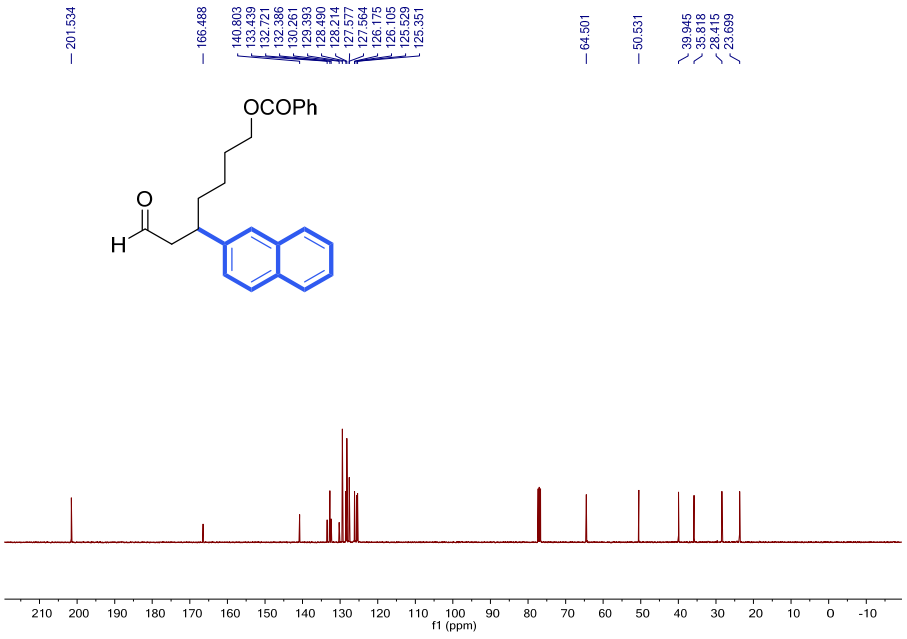
9.701
9.696
7.947
7.943
7.926
7.922
7.812
7.800
7.791
7.649
7.645
7.464
7.381
7.362
7.357
4.270
4.265
4.259
4.254
4.243
4.238
4.226
3.426
3.408
3.389
3.371
3.353
2.889
2.885
2.848
2.843
2.829
2.824
2.812
2.807
2.788
2.783
1.835
1.832
1.828
1.812
1.806
1.794
1.791
1.730
1.723
1.707
1.411
OCOPh
O
H
1.00
2.24
3.35
1.11
3.35
3.15
2.30
1.04
1.13
1.05
5.01
2.65
f1 (ppm)


201.534
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140.803
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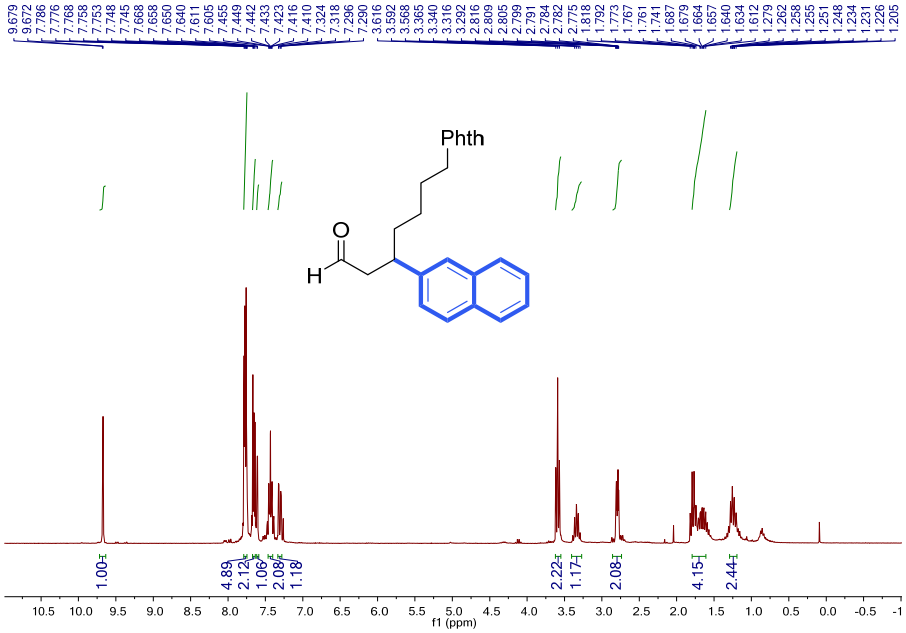
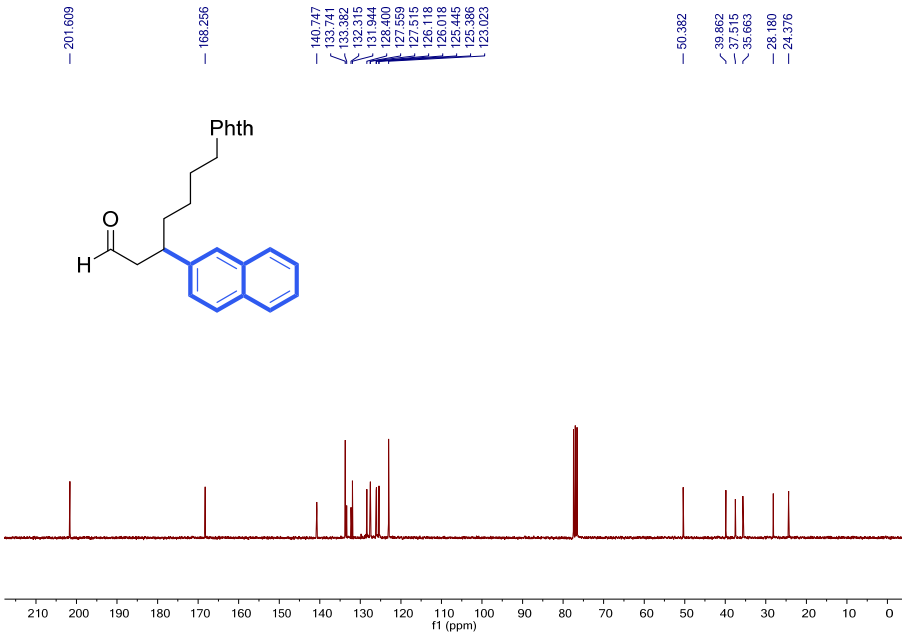
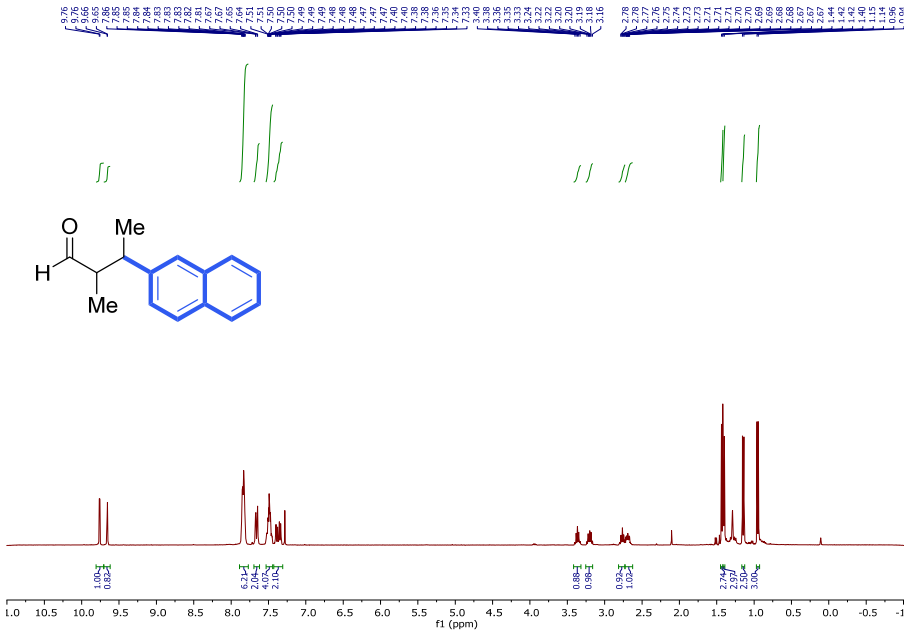
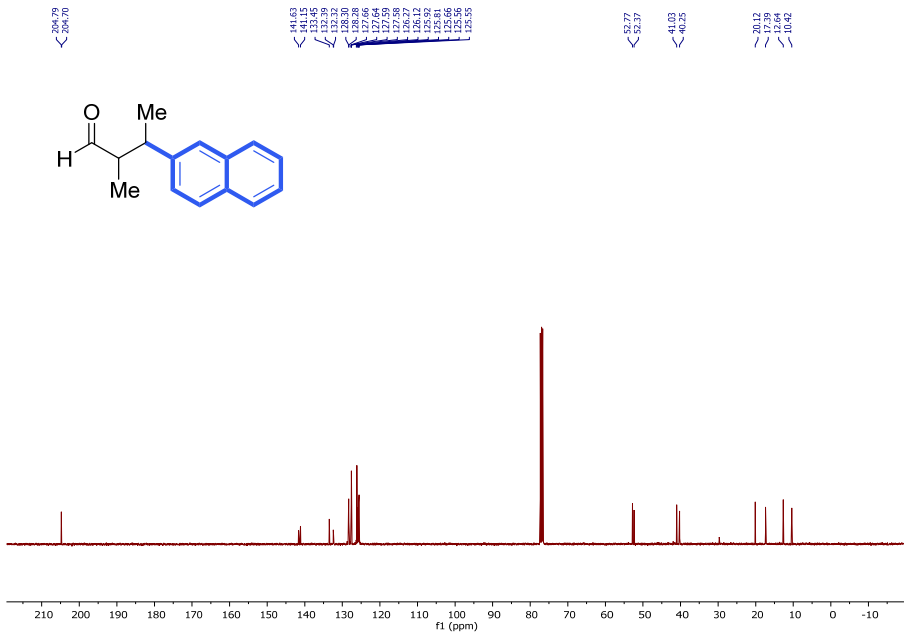
132.721
132.386
130.261
129.393
128.490
128.214
127.577
127.564
126.175
126.105
125.529
125.351
64.501
50.531
39.945
35.818
28.415
23.699
OCOPh
O
H
f1 (ppm)

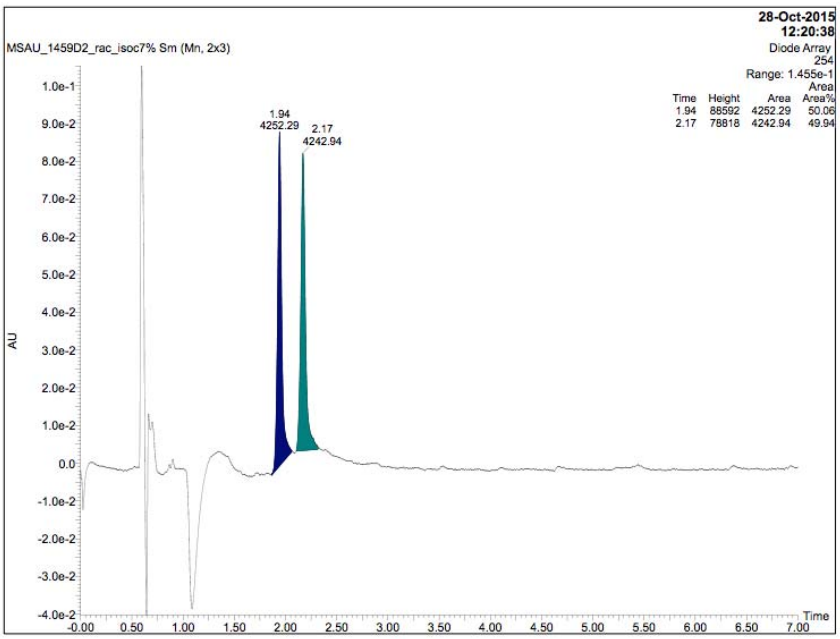

Phth
O
H
f1 (ppm)

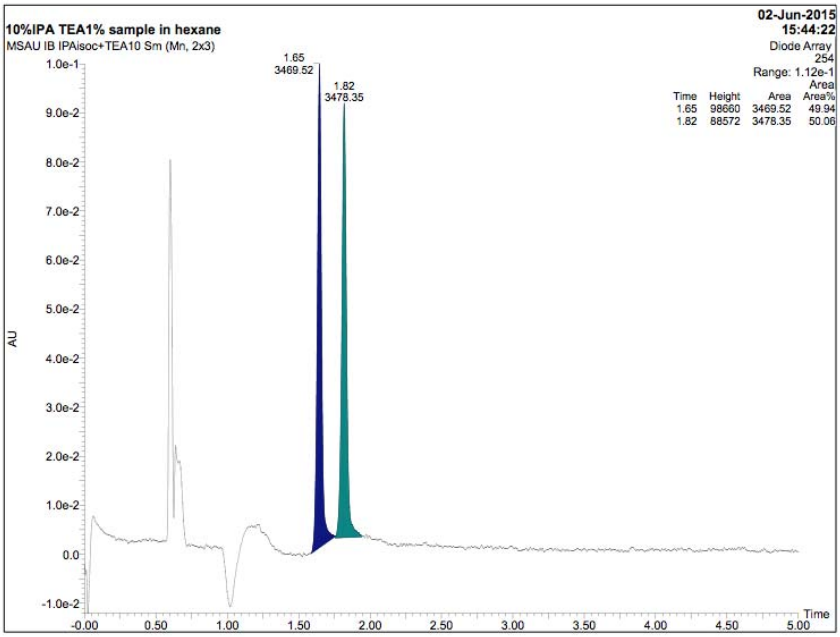

Phth
O
H
f1 (ppm)

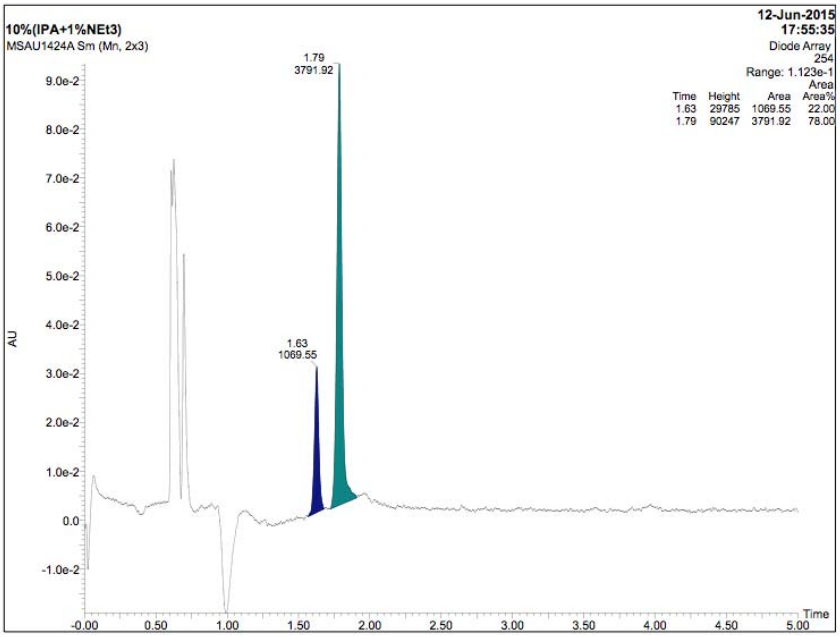

O
Me
H
Me
f1 (ppm)

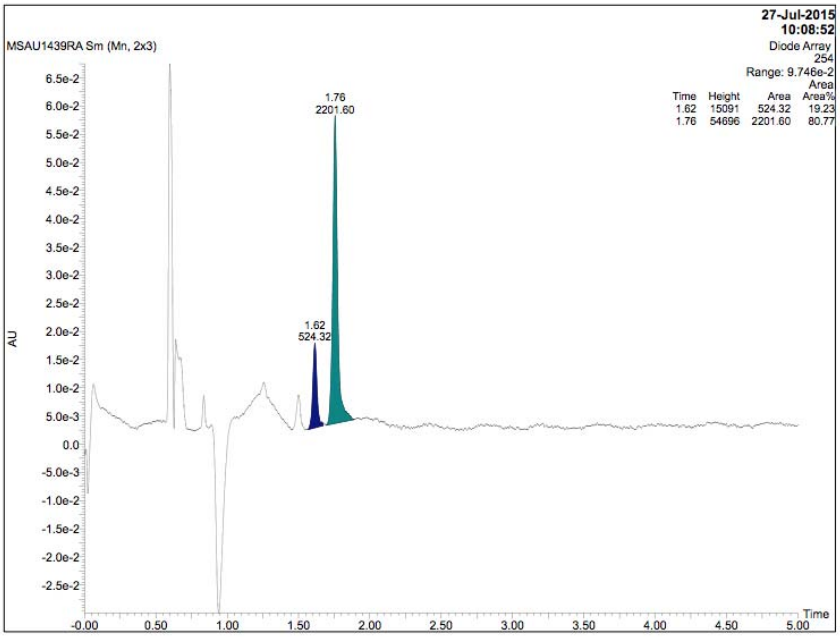

O
Me
H
Me
f1 (ppm)

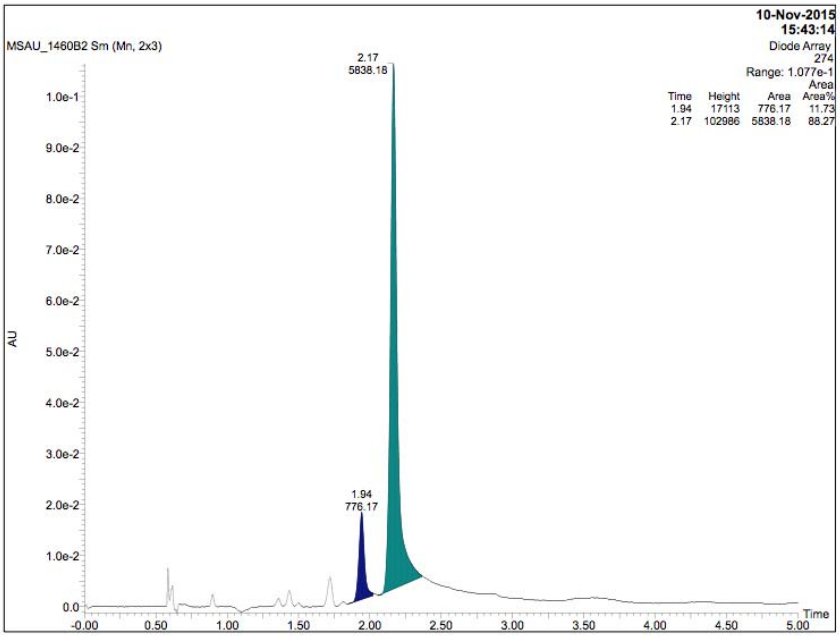
5.5.7 Selected HPLC analysis

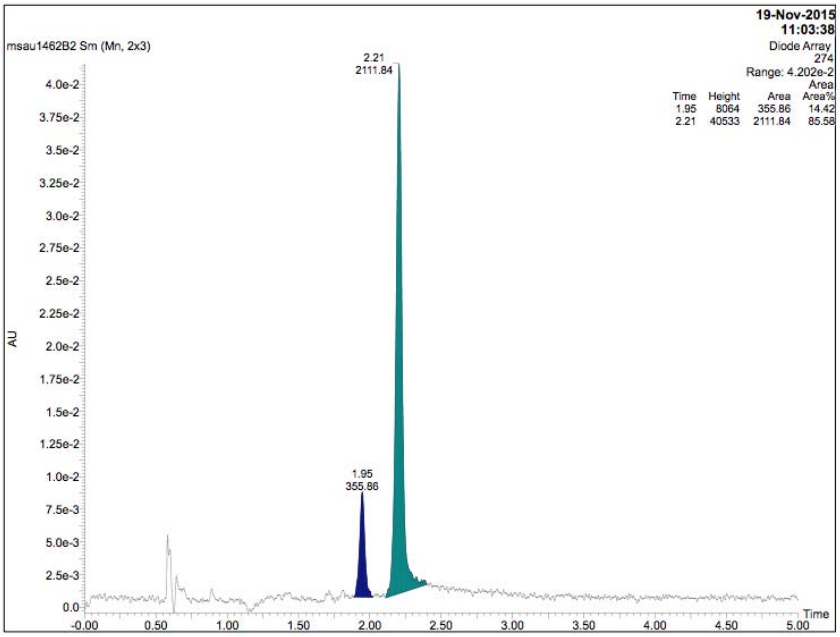





10%(IPA+1%NEt3)
MSAU1424A Sm (Mn, 2x3)
12-Jun-2015
17:55:35
Diode Array
254
Range: 1.123e-1
Area
Time Height Area Area%
1.63 29785 1069.55 22.00
1.79 90247 3791.92 78.00
1.79
3791.92
1.63
1069.55
AU
Time


MSAU1439RA Sm (Mn, 2x3)
27-Jul-2015
10:08:52
Diode Array
254
Range: 9.746e-2
Area
Time Height Area Area%
1.62 15091 524.32 19.23
1.76 54696 2201.60 80.77
1.76
2201.60
1.62
524.32
AU
Time


10-Nov-2015
15:43:14
MSAU_1460B2 Sm (Mn, 2x3)
Diode Array
274
Range: 1.077e-1
Area
Time Height Area Area%
1.94 17113 776.17 11.73
2.17 102986 5838.18 88.27
2.17
5838.18
1.94
776.17
AU
Time


19-Nov-2015
11:03:38
msau1462B2 Sm (Mn, 2x3)
Diode Array
274
Range: 4.202e-2
Area
Time Height Area Area%
1.95 8064 355.86 14.42
2.21 40533 2111.84 85.58
2.21
2111.84
1.95
355.86
AU
Time

UNIVERSITAT ROVIRA I VIRGILI
FROM CLICK CHEMISTRY TO CATALYTIC CLEAVAGE OF UNSTRAINED C-C BONDS
Míriam Sau Roca

General conclusions and outlook

In this PhD thesis we have carried out the synthesis of different molecules bearing interesting scaffolds for research. Different methodologies have been used to prepare such molecules, using either metal-free or metal-catalyzed procedures.

In **Chapter 2**, a family of propargyl ethers, thioethers or amines derived from phenylglycidol have been prepared via epoxide ring-opening with sodium azide followed by Cu-free 1,3-dipolar cycloaddition reaction. Both reactions could be carried out in one pot, being *t*-BuOH/H_2O (1:1) the best solvent at temperatures around 100 ºC for 3 h under microwave irradiation. The resulting seven membered-fused triazole motifs were obtained in good overall yields (Figure 6.1).

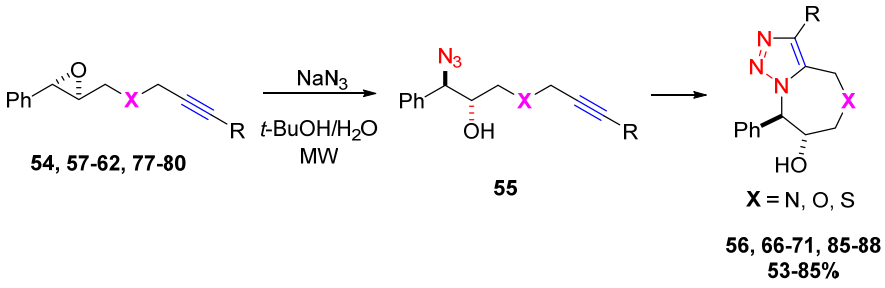


Figure 6.1

In the last decades the catalytic functionalization of C-C bonds has received considerable attention at the Community. At present, the vast majority of these catalytic events are based on the utilization of rather sophisticated strained motifs. During the present PhD thesis, we decided to tackle the challenge of providing the functionalization of unstrained C-C single bonds using 1,2-amino alcohols as starting materials. Specifically, in **Chapter 4**, we have studied the fragmentation of unstrained C-C bond of two different amino alcohols and the subsequent Pd-catalyzed arylation event (Figure 6.2).

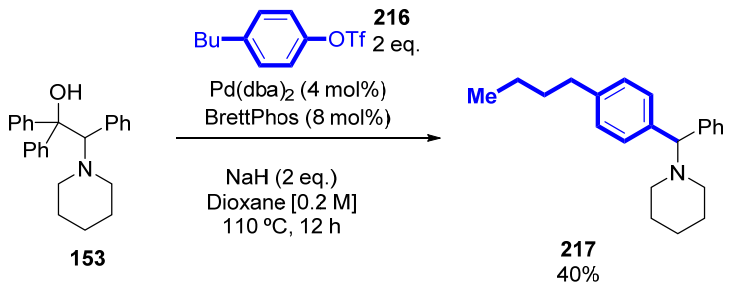


Figure 6.2

In **Chapter 5** we extended the applicability of the C-C bond cleavage of unstrained systems using simple *N*-allyl amino alcohols. Specifically, we have developed a Pd-catalyzed retroallylation reaction with *N*-allyl amino alcohols as a strategy for preparing β-arylated aldehydes. We were able to demonstrate the viability of this transformation with a wide substrate scope as well as carrying out the enantioselective version of such transformation using phosphoramidites as inductors of chirality (Figure 6.3).

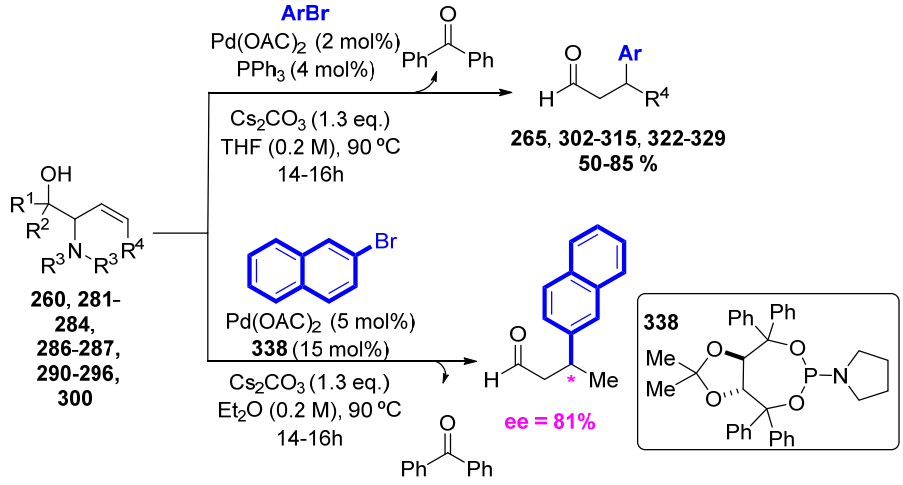


Figure 6.3

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Míriam Sau Roca

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Míriam Sau Roca

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FROM CLICK CHEMISTRY TO CATALYTIC CLEAVAGE OF UNSTRAINED C-C BONDS
Míriam Sau Roca