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École Doctorale de Chimie Moléculaire / Équipe ROCS

Ph.D. in Chemical and Natural Sciences XXIX Cycle

Transition Metal-Catalyzed Alkoxylation and Amination Reactions involving Propargyl or Allyl Derivatives

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La chimica è una cosa che serve a tutto. Serve a coltivarsi, serve a crescere, serve a inserirsi in qualche modo nelle cose concrete.

P. Levi

Dedicated to Anna,

my continuous inspiration.

Acknowledgements

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In the end, the bigger thanks goes to my friends of a life, Mary, Frenci, Ila, Ste and Marti for encouraging me every day. Last but not least, the two most important people in my life, Fabio and Anna.

Yours, Daria

Table of Contents

Abbreviations

AcOH: acetic acid

APT: attached proton test

Ar: aryl

B2A: but-2-enyl

B3A: but-3-enoic

BDE: bond dissociation energy

BINAP: 2,2'-bis(diphenylphosphyno)-1,1'-binaphtalene

Bn: benzyl

BQ: benzoquinone

$CDCl_3$: chloroform deuterated

DCE: dichloroethane

DCM: dichloromethane

DIPEA: *N,N*-diisopropylamine

DMA: *N,N*-dimethylacetamide

DMAP: 4-dimethylaminopyridine

DMF: *N,N*-dimethylformamide

DMSO: dimethylsulfoxide

dppe: 1,2-bis(diphenylphosphino)ethane

DPPF: 1,1'-ferrocenediyl-bis(diphenylphosphine)

ee: enantiomeric excess

Et_3N: triethylamine

HBQ: hydroquinone

HCl: hydrochloric acid

IR: infrared

MeCN: acetonitrile

MeOH: methanol

MnO_2: manganese dioxide

Mp: melting point

NBS: *N*-bromosuccinimide

NCS: *N*-chlorosuccinimide

NIS: *N*-iodosuccinimide

NMP: *N*-methyl-2-pyrrolidone

NMR: nuclear magnetic resonance

NQ: naphthoquinone

Ns: nosyl

Nu: nucleophile

NXS: *N*-halosuccinimide

OMe: methoxy

Phth: phthalimide

Piv: pivalate

ppm: parts per million

PTSA: *p*-toluenesulfonic acid

py: pyridine

r.t.: room temperature

TBME: methyl *tert*-butyl ether

THF: tetrahydrofuran

Tol: toluene

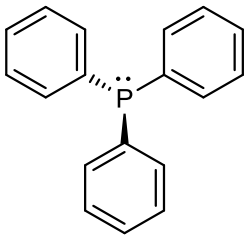
TOx: terminal oxidant

Ts: tosyl

Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Ligands Cited

Phosphorus Ligands



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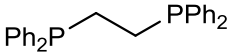

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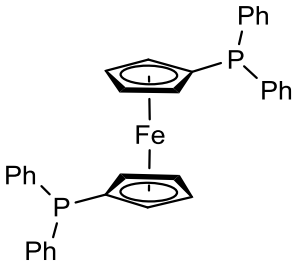

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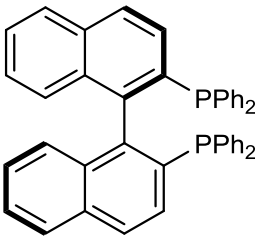

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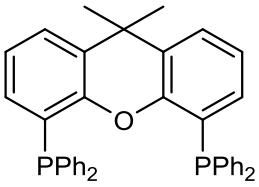
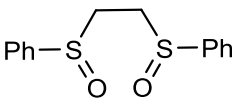


Xantphos

Nitrogen- and Sulfur-Containing Ligands



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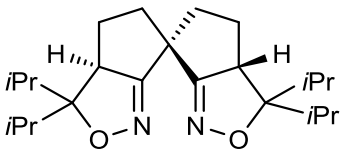
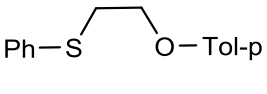


***i*Pr-SPRIX**



L1

L2

General Introduction

In the past few decades, transition metal-catalyzed reactions have gained a fundamental role in organic chemistry. This is undisputed and underlined by the list of Nobel prizes assigned to chemistry in the last century: Sabatier in 1912, Ziegler and Natta in 1963, Wilkinson and Fischer in 1973, Sharpless, Noyori and Knowles in 2001, Grubbs, Schrock and Chauvin in 2005 and, most recently, in 2010 Heck, Suzuki and Negishi for "palladium-catalyzed cross couplings in organic synthesis".

These three pioneering studies of palladium chemistry have developed independently a way to link organic molecules, which had previously been impossible, especially under mild reaction conditions and with the high degrees of selectivity and stereochemical control. These coupling reactions are now carried out routinely across the world, in research laboratories and industrial processes to assemble the building blocks of complex molecules.

Since these discoveries, many other couplings catalyzed by various transition metals have been reported the last years. In this thesis, we focused more particularly on reactions catalyzed by late transition metals in high oxidation states. These metals allow the formation of new bonds in mild conditions starting from easily accessible substrates, often not pre-functionalized, working selectively even in presence of high complex functional groups.

Among the most suitable starting material to perform these types of reactions with transition metals in high oxidation states, there are unactivated alkenes and alkynes that are extremely abundant chemical feedstocks, produced in large quantities from petrochemical sources. Consequently, they have been widely used for the synthesis of a vast range of organic chemical building blocks. A huge variety of synthetic transformations of multiple bonds is now achievable either at intermolecular or intramolecular level.

The oxidation of alkenes (or alkynes) to introduce carbon–oxygen and other carbon–heteroatom bonds is a highly important process, which enables higher polarity molecules to be prepared from these abundant hydrocarbons. Metal-catalyzed oxidation reactions are particularly notable in this respect and a palladium-catalyzed alkene oxidation, the Wacker oxidation, was one of the first transition metal-catalyzed industrial processes, permitting the efficient generation of acetaldehyde from ethylene.

These metal-catalyzed oxidation reactions involve the use of functional groups with similar electron properties, typically electron-rich groups, like C-C multiple bonds and alcohols or amines. The complexation of the metal to the multiple bonds generates an *umpolung* of reactivity, leading to a π-complexed species, which is susceptible to undergo a nucleophilic attack. This approach, which avoids

the need of leaving groups, offers many advantages in terms of atom economy of the process and environmental impact.

We can mechanistically differenciate these metal-catalyzed oxidations of C-C multiple bonds into different catalytic cycles based on the structure of isolated products. Two classes can imply catalytic cycles presented in Figure 1, allowing hydroamination or hydroalkoxylation reactions as well the alternative processes of amination or alkoxylation. In these catalytic cycles, the C-C multiple bond is activated by a complexation with an electron poor transition metal, allowing the nucleophilic attack.[1] The resulting σ-alkyl (or -vinyl complex) **I**, could undergo a demetallation process involving a hydrogen atom on the carbon in β position (β-H elimination – Wacker-type process – Figure 1 left) or by the participation of an electrophile species (protonation – Figure 1 right). The result is an aminated and alkoxylated product deriving by a process involving amination or hydroamination, and alkoxylation or hydroalkoxylation, respectively. In any case, by the elimination step the catalytic species is regenerated. The preferency towards to one of the two paths depends by the type of metal employed and by the structural characteristics of the intermediate **I**, in turn related to the starting material.

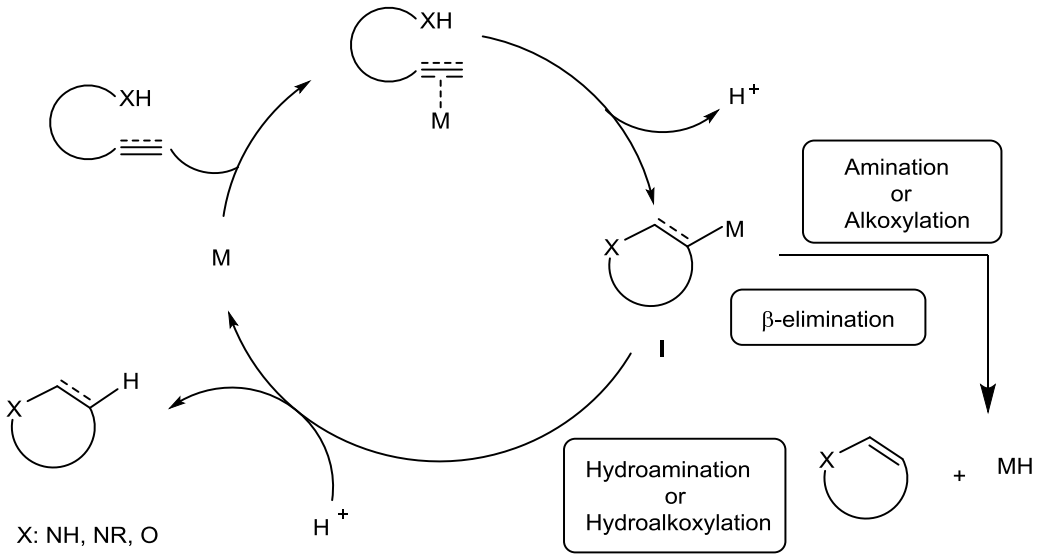
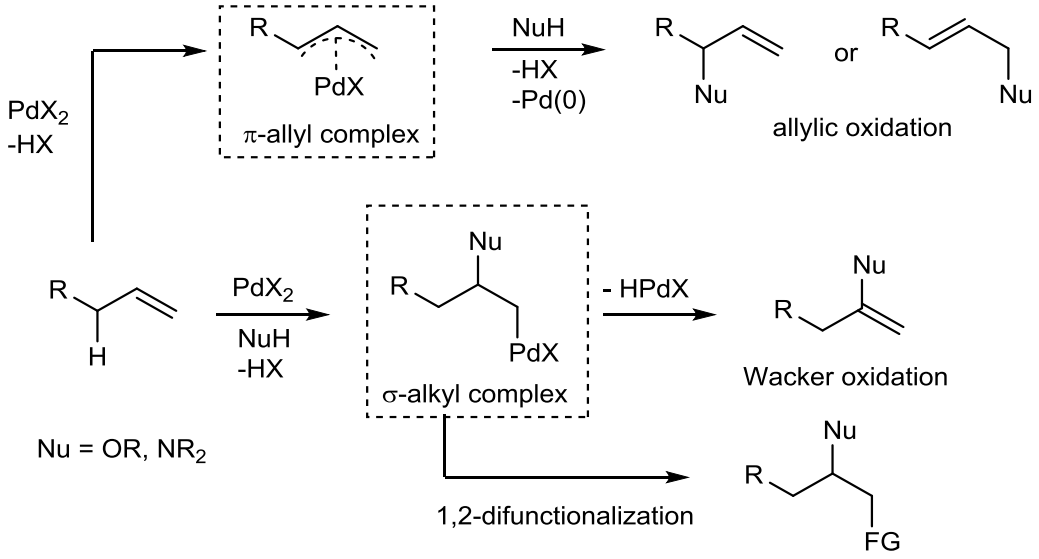


Figure 1: Possible Mechanism of Transition Metal-Catalyzed Reactions on Multiple Bonds.

The other class of mechanism occurs, more precisely, during palladium-catalyzed reactions. Since the pioneering Wacker process was developed, a wide range of palladium-catalyzed oxidation reactions are commonly used in synthetic laboratories (Scheme 1, bottom – nucleopalladation

[1] Collmann, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry,* University Science Books, Mill Valley, CA, **1987**.

mechanism). However, during these protocols and depending of the conditions used, an alternative mechanism to the Wacker-type catalytic cycle can take place if the substrate bears an allylic hydrogen atom in the α-position of the double bond. This latter can be removed and generate a η^3-allyl palladium complex, which can be *in situ* trapped by a nucleophilic species to deliver the final compound (Scheme 1, top – Allylic C-H activation process).



Scheme 1: Pathways for Palladium-Catalyzed Alkene Oxidation.

In this wide panorama of transition metals usable in catalysis, our attention has been directed towards the formation of carbon-nitrogen or carbon-oxygen bonds by palladium and copper complexes. In the first chapter, we will evoke the studies under intramolecular copper(II)- or palladium(II)-catalyzed alkoxylation of terminal triple and double bonds, and in the second chapter, new protocols of intermolecular palladium(II)-catalyzed allylic amination of β,γ-unsaturated compounds will be presented.

Chapter 1

Intramolecular Alkoxylation Reactions

Introduction

Since over the past few decades, one of the main challenges for an organic chemist is to find a way to produce synthetic or natural compounds in a more efficient and economical manner. Thus several highly regio- and stereo-selective procedures have been developed. Moreover, considering that one of the major problems in chemical production is the handling of waste, this drawback inescapably drives the chemists toward the search for environmental tolerable procedures since today there is not only the problem of what we can synthesize but also how we do it. In this panorama, the usefulness of reactions involving more than one bond formation in a single sequence without the isolation of the intermediates or without changing conditions is obvious.

Bearing in mind this target, we will focus on transition metal-catalyzed reactions involving more precisely an alkoxylation reaction as well a second functionalization step in a single procedure, performed at intramolecular level and allowing the construction of oxygenated heterocycles, which are important motifs in many biologically active compounds. This ubiquity continues to justify the development of new methods for their preparation.

In this chapter, we will present two methods for the construction of oxygen-containing heterocycles, such as a copper(II)-catalyzed intramolecular alkoxylation / halogenation of alkynyl ureas and secondary amides, and then a palladium(II)-catalyzed oxidative alkoxylation / arylation of alkenols.

1.1 Copper(II)-Catalyzed Intramolecular Alkoxyhalogenation Reactions of Alkynes

Abstract

A highly effective synthesis of haloalkylidene-substituted heterocycles by copper(II)-catalyzed cyclization of alkynyl ureas and secondary amides has been developed. The reaction, which involves catalytic $CuCl_2$ and stoichiometric amount of *N*-halosuccinimide, occurs selectively through an alkoxyhalogenation process. Alternatively, alkoxychlorination and alkoxybromination reactions can be performed working solely with stoichiometric $CuCl_2$ or $CuBr_2$ respectively.

1.1.1. Aim of This Work

Processes leading to the generation of C−O bonds from multiple bonds have been reported in the literature, but these approaches are substantially devoted to the functionalization of alkenes and allenes. Related alkoxylation reactions involving alkynes are somewhat limited.[2]

That is why, pursuing our ongoing project on intramolecular transition metal-catalyzed amination and alkoxylation reactions,[3] we have investigated a copper-catalyzed alkoxylation / halogenation sequence of alkynyl derivatives. In particular, we focused on the use of alkynyl ureas and secondary amides to lead to a range of haloalkylidene-substutited heterocycles (Scheme 2).[4] It should be note that among the reported alkoxylation, reactions based on the use of secondary amides or ureas as nucleophiles represent a useful tool to perform directly functionalized oxygenated heterocycles. Indeed, in principle, starting from alkynyl ureas and secondary amides the formation of an intramolecular bond could involve both the nitrogen and / or the oxygen atoms.[5] However, in our procedure, as we see, the cyclization will take place only via the addition of the oxygen atom to the triple bond, leading to oxygenated heterocycles.

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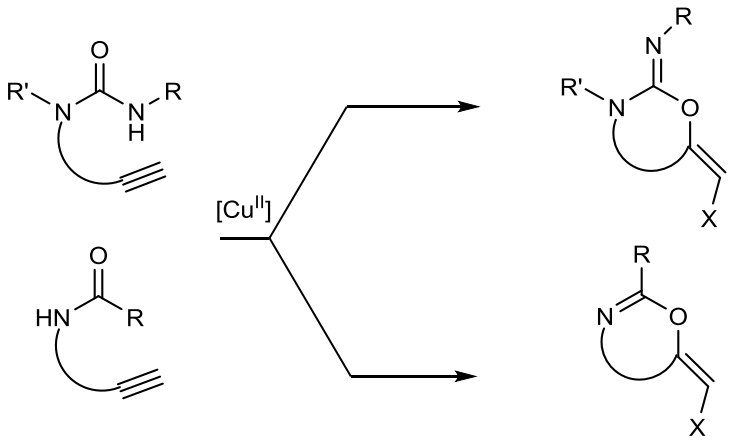
[2] Hintermann, L. *Topics in Organometallic Chemistry* **2010**, *31*, 123. For Pd-catalyzed reactions, see: a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764. b) Cavicchioli, M.; Decortiat, S.; Bouyssi, D.; Goré, J.; Balme, G. *Tetrahedron* **1996**, *52*, 11463. c) Rossi, R.; Bellina, F.; Biagetti, M.; Mannina, L. *Tetrahedron Lett.* **1998**, *39*, 7599. d) Wang, Z.; Lu, X. *J. Org. Chem.* **1996**, *61*, 2254. For Cu-catalyzed reactions, see: e) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 4727. For Au-catalyzed reactions, see: f) Belting, V.; Krause, N. *Org. Biomol. Chem.* **2009**, *7*, 1221. g) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. For Ru-catalyzed reactions, see: h) Li, M.; Hua, R. *J. Org. Chem.* **2008**, *73*, 8658. For Ir-catalyzed reactions, see: i) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem. Int. Ed.* **2005**, *44*, 4949. For Pt-catalyzed reactions, see: j) Hartman, J. W.; Sperry, L. *Tetrahedron Lett.* **2004**, *45*, 3787. For Rh-catalyzed reactions, see: k) Isono, N.; Lautens, M. Org. Lett. 2009, 11, 1329.

[3] a) Broggini, G.; Poli, G.; Beccalli, E. M.; Brusa, F.; Gazzola, S.; Oble, J. *Adv. Synth. Catal*. **2015**, *357*, 677. b) Broggini, G.; Borsini, E.; Fasana, A.; Poli, G.; Liron, F. Eur. *J. Org. Chem*. **2012**, *3617*. c) Broggini, G.; Barbera, V.; Beccalli, E. M.; Borsini, E.; Galli, S.; Lanza, G.; Zecchi, G. *Adv. Synth. Catal*. **2012**, *354*, 159. d) Borsini, E.; Broggini, G.; Fasana, A.; Galli, S.; Khansaa, M.; Piarulli, U.; Rigamonti, M. *Adv. Synth. Catal*. **2011**, *353*, 985. e) Basolo, L.; Bernasconi, A.; Borsini, E.; Broggini, G.; Beccalli, E. M. *ChemSusChem* **2011**, *4*, 1637. f) Basolo, L.; Beccalli, E. M.; Borsini, E.; Broggini, G.; Khansaa, M.; Rigamonti, M. *Eur. J. Org. Chem*. **2010**, 1694. g) Beccalli, E. M.; Broggini, G.; Clerici, F.; Galli, S.; Kammerer, C.; Rigamonti, M.; Sottocornola, S. *Org. Lett*. **2009**, *11*, 1563.

[4] Gazzola, S.; Beccalli, E. M.; Borelli, T.; Castellano, C.; Chiacchio, M. A.; Diamante, D.; Broggini, G. *J. Org. Chem*. **2015**, *80*, 7226.

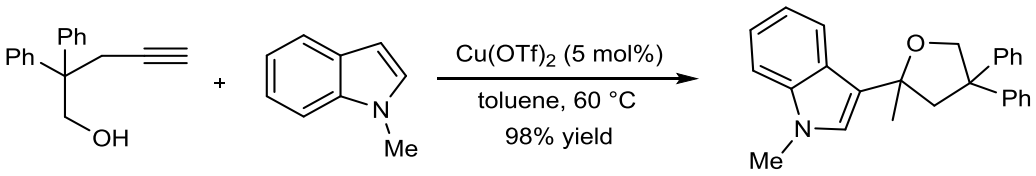
[5] a) Babij, N. R.; Wolfe, J. P.; *Angew. Chem. Int. Ed*. **2013**, *52*, 9247. b) Hopkins, B. A.; Wolfe, J. P.; *Angew. Chem. Int. Ed*. **2012**, *51*, 9886. c) Frits, J. A.; Nakhla, J. S.; Wolfe, J. P. *Org. Lett*. **2006**, *8*, 2531. d) Verniest, G.; Padwa, A. *Org. Lett*. **2008**, *10*, 4379. e) Fritz, J. A.; Wolfe, J. P. *Tetrahedron* **2008**, *64*, 6838. f) Moon, N. G.; Harned, A. M. *Tetrahedron Lett*. **2013**, *54*, 2960. g) Yu, J.; Yang, H.; Fu, H. *Adv. Synth. Catal*. **2014**, *356*, 3669.



Scheme 2: General Cu-Promoted Procedure for Haloalkylidene-Substituted Heterocycles.

The appeal of copper as catalyst arises from its low cost and its tolerance towards many reactive functional groups. Moreover, the copper-catalyzed reactions do not require anaerobic or anhydrous conditions. These properties highly increased the development of processes for carbon-oxygen and carbon-nitrogen bond forming reactions.

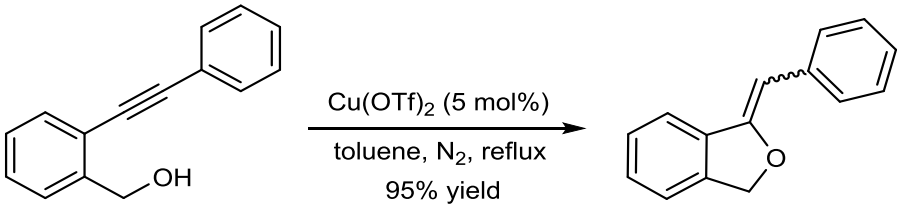
Nevertheless, at the best of our knowledge only a few examples of copper-promoted *exo*-selective intramolecular alkyne alkoxylation have been reported in literature.[6] Among these procedures, in 2009, Patil reported the use of $Cu(OTf)_2$ as a catalyst for tandem hydroalkoxylation–hydroarylation reaction of alkynes bearing hydroxyl group in presence of indoles (Scheme 3).[6c]



Scheme 3: $Cu(OTf)_2$ Catalyzed Hydroalkoxylation-Hydroarylation of Alkynols with Indoles.

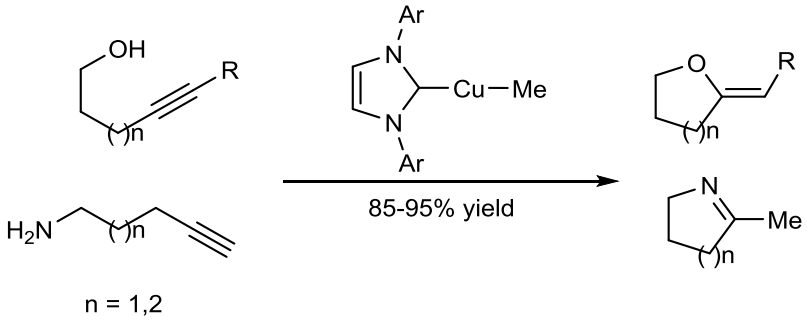
Later, in 2010 by Praveen *et al*., was reported an efficient regioselective $Cu(OTf)_2$-catalyzed 5-*exo-dig* hydroalkoxylation of 2-(ethynyl)benzyl alcohol, which provides a concise access to functionalized phthalans in high yields (Scheme 4).[6b]

[6] a) Pouy, M. J.; Delp, S. A.; Uddin, J.; Ramdeen, V. M.; Cochrane, N. A.; Fortman, G. C.; Cundari Gunnoe, T. B.; Sabat, M.; Myers, W. H. *ACS Catal*. **2012**, *2*, 2182. b) Praven, C.; Iyyappan, C.; Perumal, P. T. *Tetrahedron Lett*. **2010**, *51*, 4767. c) Patil, N. T.; Raut, V. S.; Kavthe, R. D.; Reddy, V. V. N.; Raju, P. V. K. *Tetrahedron Lett*. **2009**, *50*, 6576. d) Wang, Y.; Jiang, M.; Liu, J.-T. *Org. Chem. Front*. **2015**, *2*, 542.



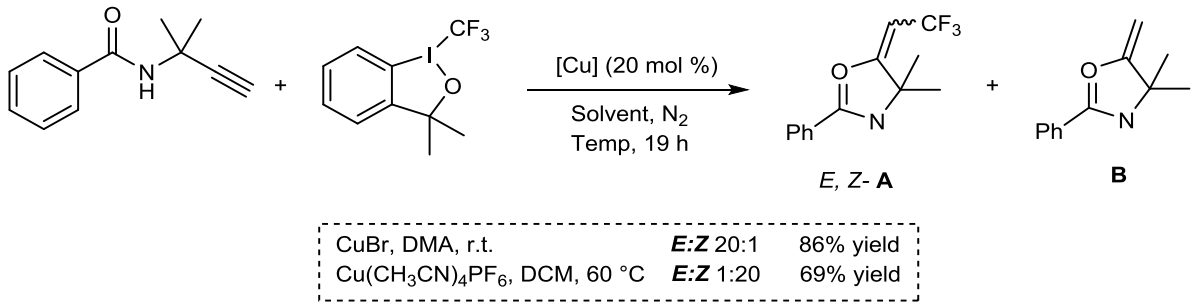
Scheme 4: Copper(II)-Catalyzed Synthesis of Phthalans *via* Hydroalkoxylation of 2-(Ethynyl)benzyl Alcohols.

Successively, intramolecular hydroalkoxylation or hydroamination reactions of alkynes catalyzed by Cu(I) complexes bearing a *N*-heterocyclic carbene ligand are reported by the group of Myers (Scheme 5).[6a]



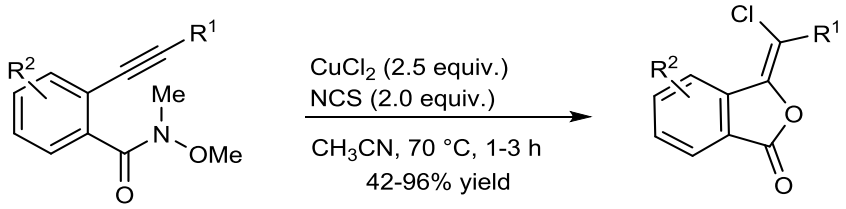
Scheme 5: Intramolecular Hydroalkoxylations and Hydroaminations of Alkynes.

In 2015, a copper-catalyzed stereoselective oxytrifluoromethylation of propargyl amides for the construction of oxazolines was reported by Liu.[6d] This reaction took place in the presence of Togni's reagent under mild conditions, giving the corresponding trifluoromethylated oxazoline derivatives in moderate to good yields (Scheme 6). Using CuBr as catalyst, the *E*-isomer was obtained as major product. However, the formation of *Z*-isomer with excellent stereoselectivity was also achieved when $Cu(CH_3CN)_4PF_6$ as catalyst was used.



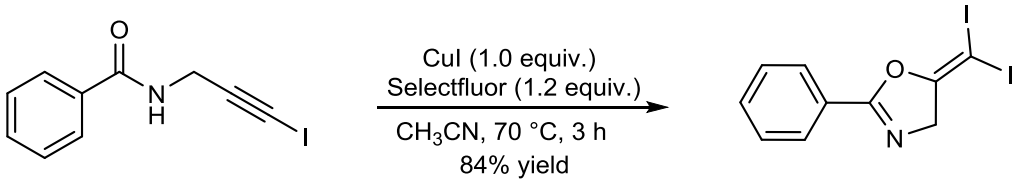
Scheme 6: CuBr Catalyzed Oxytrifluoromethylation of a Propargyl Amide.

A stereoselective alkoxy / chlorocyclization of *N*-alkoxy-2-alkynylbenzamides promoted by $CuCl_2$ and NCS, both in large amounts, has been developed as a synthetic protocol for the preparation of isobenzofuran-1-one derivatives (Scheme 7).[7]



Scheme 7: A Cyclization / Chloration of *N*-Alkoxy-2-alkynylbenzamides.

Recently, the group of Xu has developed a cylization / iodation of terminal propargyl amides in the presence of stoichiometric amount of CuI and Selectfluor as terminal oxidant (Scheme 8).[8]



Scheme 8: Iodocyclization of Terminal Propargyl Amides with CuI and Selectfluor.

In view of these some examples, which involve all an important amount of copper salt, we have desired to extend the scope of alkoxylation-halogenation of alkynes using, on the one hand, special

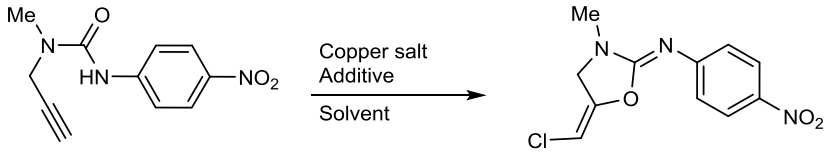
[7] Jithunsa, M.; Ueda, M.; Miyata, O. *Org. Lett*. **2011**, *13*, 518.

[8] Zhang, S.; Chen, Y.; Wang, J.; Pan, Y.; Xu, Z.; Tung, C.-H. *Org. Chem. Front.* **2015**, *2*, 578.

starting materials such as alkynyl ureas or secondary amides, and on the other hand by focusing in the use of a catalytic amount of copper as catalyst.

1.1.2. Alkoxychlorination Sequence

Firstly, to screen the effectiveness of various copper(II)-salts for the alkoxyhalogenation sequence, we explored the reactivity of 4-nitrophenyl propargyl urea **1a**, assumed as a model substrate, treated in presence of a copper salt and an additive in different solvents. The results of this optimization are presented in Table 1.



1a **2a**

Entry*	***Copper salt***	***Additive (equiv)***	***Solvent****	***Time (h)***	***Yield (%)***
1	$CuCl_2$ (1 equiv)	-	MeCN	2	87
2	CuCl (1 equiv)	-	MeCN	6	-
3	$CuCl_2$ (0.5 equiv)	-	MeCN	2	61
4	$CuCl_2$ (1 equiv)	K_2CO_3 (1)	MeCN	2	84
5	$CuCl_2$ (5 mol %)	NCS (1)	MeCN	5	51
6	$CuCl_2$ (10 mol %)	NCS (1)	MeCN	5	54
7	-	NCS (1)	MeCN	8	-
8	$CuCl_2$ (10 mol %)	LiCl (2)	MeCN	8	3
9	$CuCl_2$ (5 mol %)	NCS (1)	Toluene	3	32
10	$CuCl_2$ (5 mol %)	NCS (1)	THF	3	51
11	$CuCl_2$ (5 mol %)	NCS (1)	DMF	3	-
12	$CuCl_2$ (5 mol %)	NCS (1)	DCE	6	18

* Usually, the reactions were carried out at reflux, except the reaction in toluene or DMF, which were conducted at 90 °C or 110 °C, respectively.

** All the cyclization reactions were carried out under air atmosphere.

Table 1: Optimization of Copper-Promoted Alkoxychlorination Conditions on 4-Nitrophenyl Propargyl Urea **1a**.

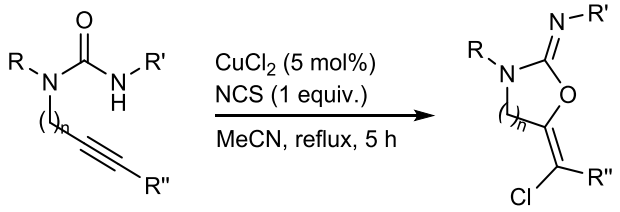
The first trial was conducted in the presence of 1 equivalent of $CuCl_2$ in acetonitrile at room temperature (entry 1) under air atmosphere. The expected oxazole product **2a**, generated by a 5-*exo-dig* cyclization, was isolated in 87% yield with the insertion of a chlorine atom coming from copper-chloride salt. The *E* configuration given to the double carbon-carbon bond was assigned by comparison of the NMR spectrum with those of similar compounds reported in the literature.[9] An experiment realized with one equivalent of copper(I) salt (CuCl) was inefficient, and gave only the recovered starting material (entry 2). Then, reducing by half the amount of copper(II) salt to 0.5 equivalent, the same expected oxazole was isolated, although in lower yield (61%) (entry 3). The treatment with a stoichiometric amount of $CuCl_2$ and a base such as K_2CO_3 did not improve the reaction (entry 4). Afterwards, we tried to find other fruitful additives, which can allow the insertion of the chlorine atom in presence of a catalytic amount of copper-salt. *N*-chlorosuccinimide was proven to be a successful additive permitting to isolate the product **2a** in 51% or 54% yield with a catalyst loading of 5 mol % or 10 mol % respectively (entries 5 and 6). Working only in presence of NCS (entry 7), the reaction failed demonstrating that $CuCl_2$ was essential for the alkoxychlorination sequence. Subsequently, another source of chlorine was investigated as LiCl, unfortunately the result was unsatisfactory (entry 8). Finally, keeping fixed 5 mol % of $CuCl_2$ and a stoichiometric amount of *N*-chlorosuccinimide, a series of conditions in different solvents were screened. However, none of these variations provided the formation of **2a** in better yields (entries 9-12).

Once established the best conditions to perform the sequence (entry 5, 5 mol % of $CuCl_2$ and one equivalent of NCS), various substituted alkynyl ureas were tested to extend the scope of this method.

First, the use of aryl propargyl ureas **1b-i** allowed the formation of (*E*)-5-(chloromethylidene) oxazole compounds **2b-i** (Table 2, entries 1-8). All the cyclization products were obtained in good to excellent yields except for the 4-chlorophenyl-substituted oxazole derivative **2d**. This behavior was completely unexpected and could not be attributed to the chlorine atom since the analogous urea **1i** (bearing a chorine atom in the same position) underwent the reaction in 85% yield. This unsatisfactory outcome provided a complex mixture of degradation products even using a stoichiometric amount of $CuCl_2$. Successively, aryl butynyl ureas were tested in the same reaction conditions permitting in these cases a 6-*exo*-*dig*-process. The cyclization of the ureas **1j-l** furnished the expected 1,3-oxazine products in moderate yields (entries 9-11). Lastly, 1,2-disubstituted alkynes **1n-o** treated in the cyclization /

[9] a) Kimura, M.; Kure, S.; Yoshida, Z.; Tanaka, S.; Fugami, K.; Tamaru, Y. *Tetrahedron Lett*. **1990**, *31*, 4887. b) Ohe, K.; Ishihara, T.; Chatani, N.; Kawasaki, Y.; Murai, S.J. *Org. Chem*. **1991**, *56*, 2267. c) Tam, T.F.; Thomas, E.; Krants, A. *Tetrahedron Lett*. **1987**, *28*, 1127.

chlorination conditions permitted to synthesis of the desired 5-(arylidene)oxazole derivatives (entries 12-13).



1b-i,1n,o **2b-i,2n,o**

*Entry***	*Urea*	*n*	*R*	*R'*	*R''*	*Yield (%)*
1	**1b**	1	Me	C_6H_5	H	**2b** (64)
2	**1c**	1	Me	4-MeO-C_6H_4	H	**2c** (82)
3	**1d**	1	Me	4-Cl-C_6H_4	H	**2d** (12)
4	**1e**	1	Me	1-naphthyl	H	**2e** (98)
5	**1f**	1	Me	3,5-CF_3-C_6H_3	H	**2f** (75)
6	**1g**	1	Bn	C_6H_5	H	**2g** (98)
7	**1h**	1	Bn	4-NO_2-C_6H_4	H	**2h** (71)
8	**1i**	1	Bn	4-Cl-C_6H_4	H	**2i** (85)
9	**1j**	2	Bn	C_6H_5	H	**2j** (28)
10	**1k**	2	Bn	4-NO_2-C_6H_4	H	**2k** (56)
11	**1l**	2	Bn	1-naphthyl	H	**2l** (77)
12	**1n**	1	Me	C_6H_5	C_6H_5	**2n** (41)
13	**1o**	1	Me	4-NO_2-C_6H_4	4-MeO-C_6H_4	**2o** (37)

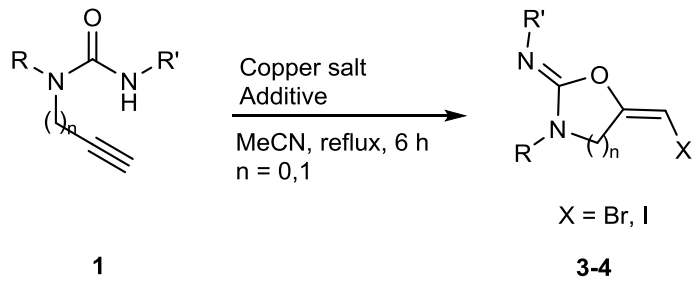
** All the cyclization reactions were carried out under air atmosphere.

Table 2: Scope of Cu(II)-Catalyzed Alkoxychlorination of Alkynyl Ureas.

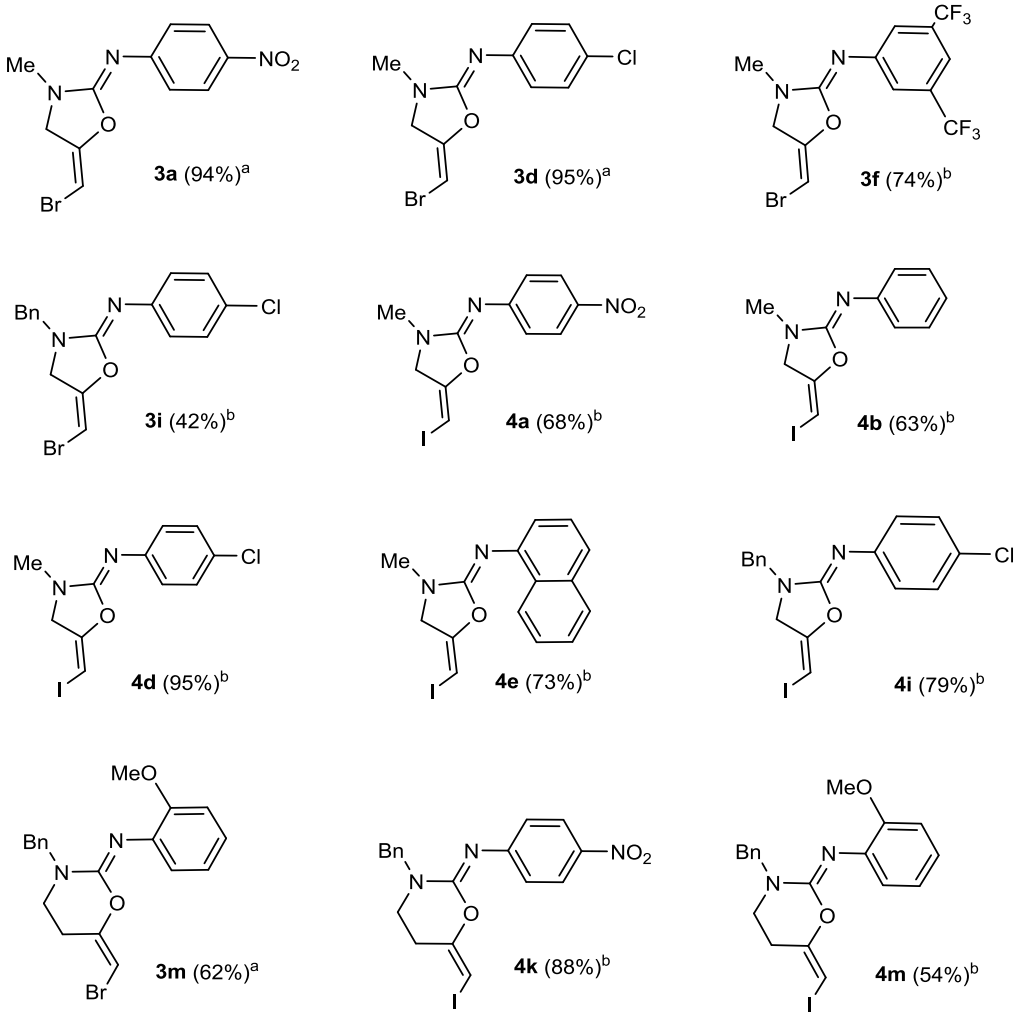
1.1.3. Alkoxybromination and Alkoxyiodination Sequences

Since the applicability of the direct alkoxychlorination of alkynyl ureas is so wide and permits the isolation of the desired product in successful outcomes, we extended the procedure to the synthesis of bromo- and iodoalkylidene heterocycles.

Once adapted the reaction conditions, such as changing the halogen source, various alkoxy / bromo- and iodination sequence could be carried out effectively on various propargyl and butynyl ureas (Table 3).



1 **3-4**



[a] Reaction conditions: alkynyl urea (1 mmol), $CuBr_2$ (1 mmol).

[b] Reaction conditions: alkynyl urea (1 mmol), $CuCl_2$ (5 mol %), NXS (1 mmol).

** All the cyclization reactions were carried out under air atmosphere.

Table 3: Scope of Alkoxybromination and Alkoxyiodination Reactions of Alkynyl Ureas.

The reactions on the alkynyl ureas were performed with two different protocols: using 1 equivalent of $CuBr_2$ (conditions a) or 5 mol % of $CuCl_2$ and a stoichiometric amount of *N*-halosuccinimide (conditions b). More in details, bromo-derivatives **3** were obtained either with stoichiometric $CuBr_2$ or with a catalytic amount of $CuCl_2$ in the presence of 1 equivalent of *N*-bromosuccinimide (NBS). For what concerns compounds **3a**, **d** and **m**, the catalytic conditions b were also tried, and unfortunately the desired products were isolated only in low yields due to a complex tarry mixtures. Whereas for the iodo derivatives **4**, both the oxazole and the 1,3-oxazine products, were synthesized by treatment of alkynyl ureas with catalytic amount of $CuCl_2$ and one equivalent of NIS. In summary, whether for the alkoxybromination and for the alkoxyiodination sequence the isolated yields were good to excellent.

Single X-ray diffraction[10] performed on compound **4i** revealed the presence of two independent molecules in the asymmetric unit, giving unambiguously the structure and the *E* configuration of the alkoxyhalogenation product (Figure 2).

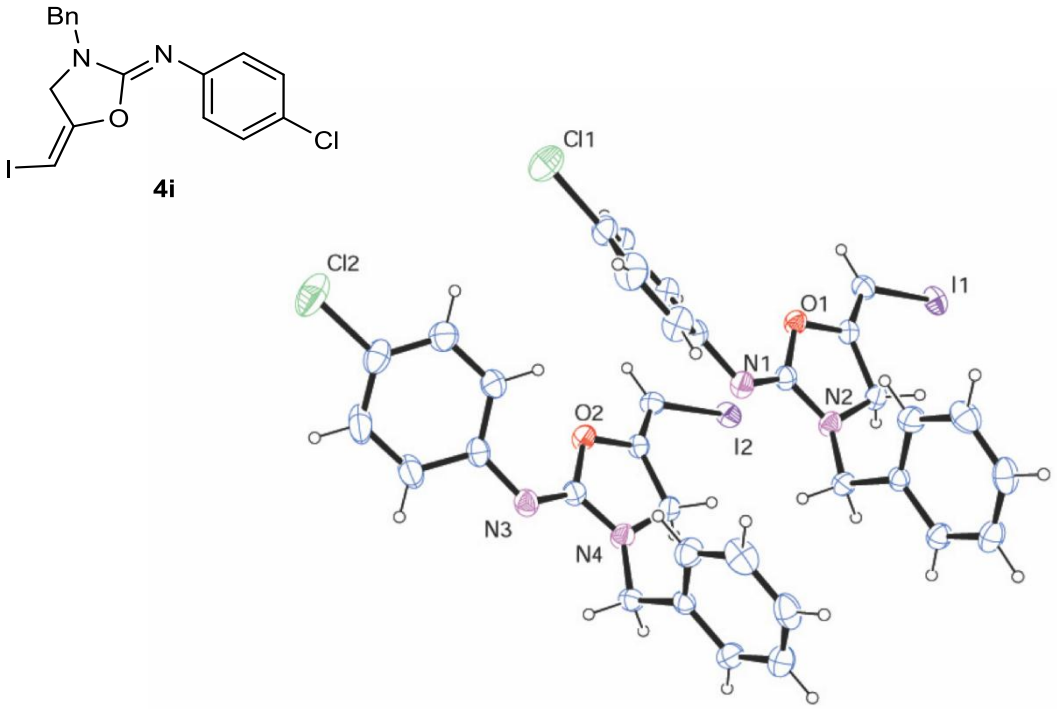
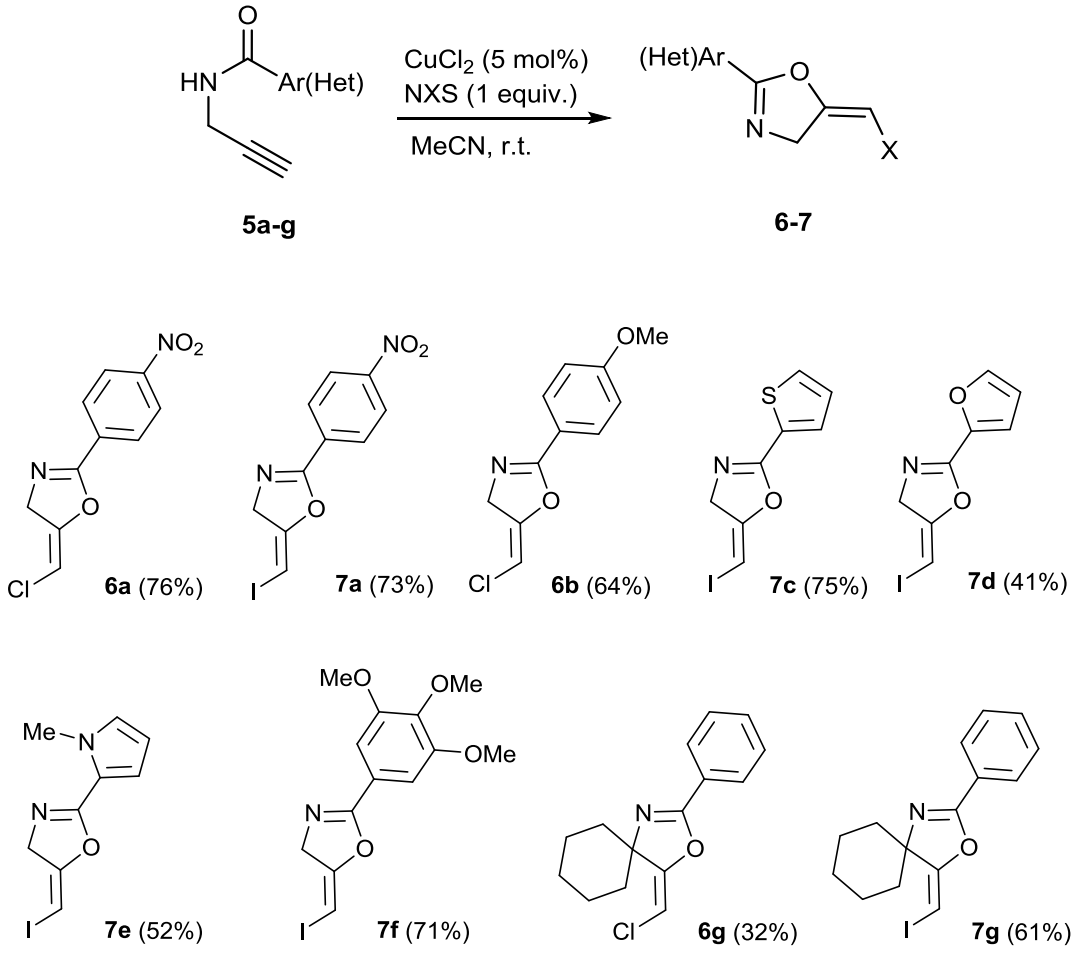


Figure 2: ORTEP view of the X-ray Structure of 5-Iodomethylidene-Substituted Oxazole Derivative **4i**.

[10] We acknowledge for the X-ray analysis Dr. Carlo Castellano, Chemistry Department, Università degli Studi di Milano.

1.1.4. Exploring Other Substrates

Considering the importance of vinyl halides as structural motifs, we extended our investigation to the alkoxyhalogenation of others substrates. Keeping the same optimized conditions in hand, the sequence was performed from propargyl (hetero)aryl amides **5**. However, while alkoxybrominations were unsatisfactory since the desired products were quite difficult to isolate from the complex reaction mixtures, the outcome of the process was satisfactory for both the synthesis of chloro and iodooxazole derivatives from aryl amides bearing either electron-withdrawing or electron-donating groups (**5a, b, f**) (Table 4).



** All the cyclization reactions were carried out under air atmosphere.

Table 4: Alkoxyhalogenation Reaction of Secondary (Hetero)aryl Alkynyl Amides.

The 2-furyl- and 2-(1-methyl)pyrrolyl carboxyamides (**5c-e**) gave the alkoxyiodination products **6c-e** in low yields from a complex mixture enriched with degradation products. In addition, also the α,α-

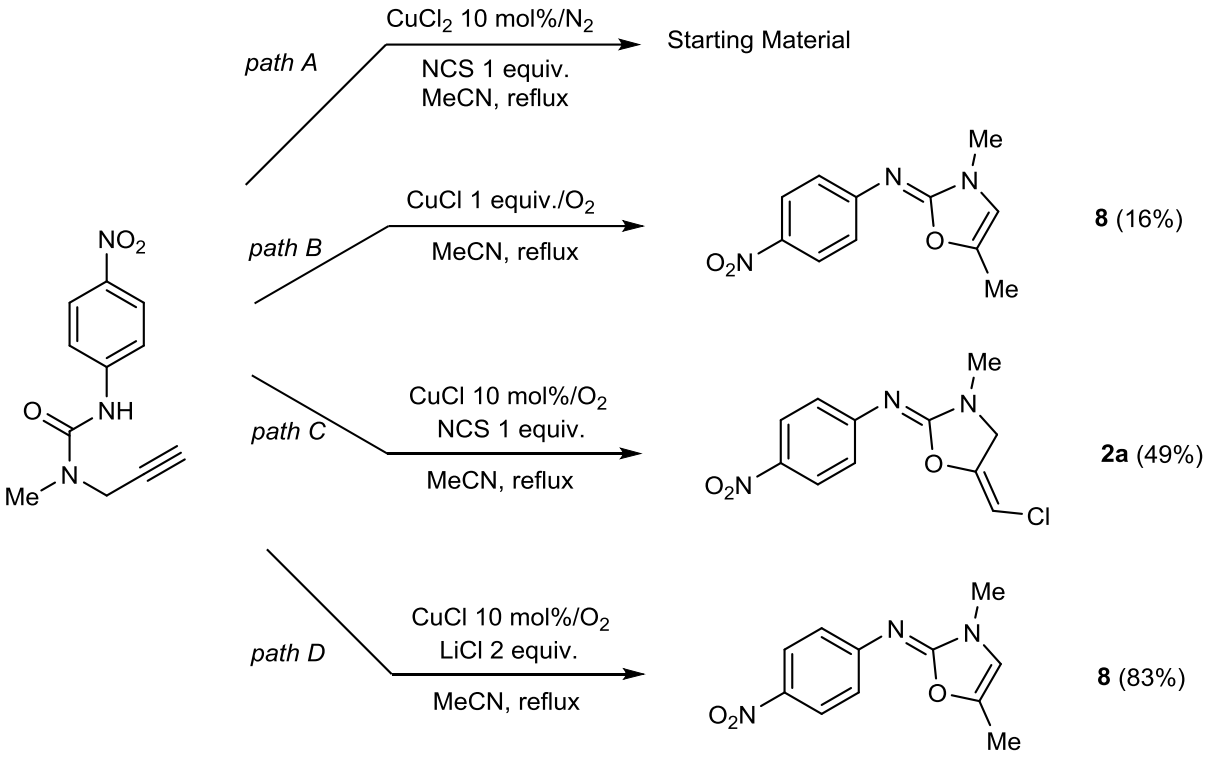
disubstituted propargyl benzamides (**5g**) gave the expected chlorinated or iodinated products **6g** and **7g** in moderate yields.

1.1.5. Searching for Mechanistic Evidences

Some general investigations were carried out in order to gain further insights into the elementary steps of the copper-promoted alkoxyhalogenation reactions.

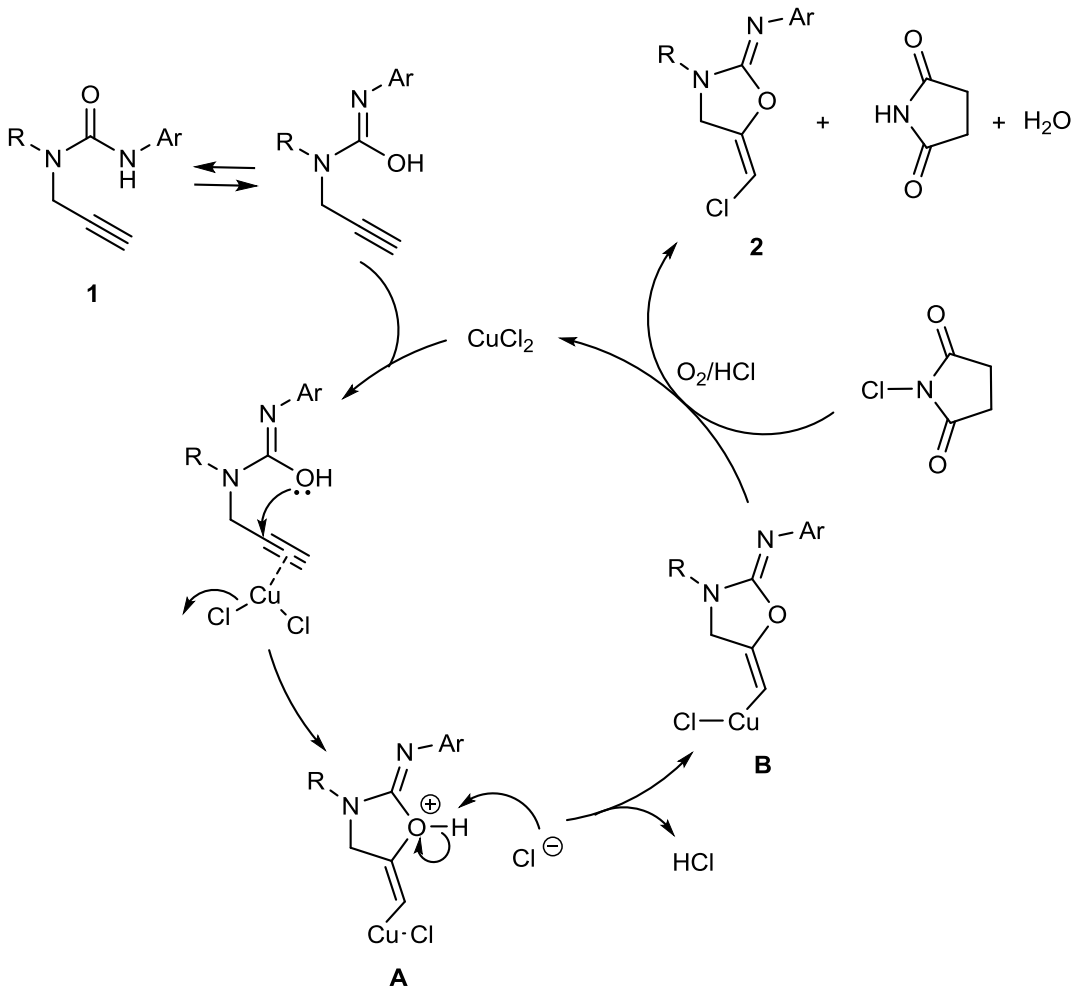
First, we investigated the reaction in standard conditions on our model substrate **1a** in the presence of catalytic amount of $CuCl_2$ and one equivalent of NCS in acetonitrile at reflux under nitrogen atmosphere (Scheme 9, *path A*). The recovered of starting material allowed us to conclude on the essential presence of molecular oxygen which acts as an oxidant able to regenerate the Cu(II) active catalytic species.

To consolidate this hypothesis, bearing in mind the inertness of copper(I) chloride in the reaction, the experiment of entry 2 of Table 1 was repeated in the presence of molecular oxygen atmosphere (*path B*). In this case, this oxygen atmosphere promoted intramolecular C-O bond formation, however followed by proto-demetallation and isomerization process generating only the compound **8** in low yield. Moreover, the addition of NCS to the reaction involving a catalytic amount of CuCl under oxygen atmosphere led to the chloromethylidene product **2a** in 49% yield (*path C*). This result allows determining the fundamental role of NCS as source of chlorine, which is confirmed by the reaction with LiCl as additive furnishing only the hydroalkoxylation / isomerization product **8** (*path D*). The difference in yields shown in *paths B* and *D* could derive from the more effective outcome of the cyclization step using a catalytic amount of CuCl (Scheme 9).



Scheme 9: General Mechanistic Investigations for Copper-Promoted Alkoxyhalogenation Reactions.

Based on these experimental evidences collected, we postulated a plausible mechanism to explain the alkoxyhalogenation reactions with $CuCl_2$ and *N*-halosuccinimide considering only the alkoxychlorination reaction of a general propargyl urea as a model example (Scheme 10).



Scheme 10: Proposed Mechanism of the Cu(II)-Catalyzed Alkoxychlorination Reactions.

The catalytic cycle begins by the formation of a vinyl-copper intermediate **A** generated by an 5-*exo*-*dig* cyclization during the nucleophilic attack of the oxygen atom on the activated carbon-carbon triple bond. Then, a deprotonation of **A** leads to the intermediate **B**. This latter can evolve in either a chloro-demetallation in presence of NCS or a reductive elimination giving the final product **2**. Then, an oxidative treatment in the presence of HCl and molecular oxygen regenerates the copper(II) catalyst.

1.1.6. Conclusions

To sum up, we were able to develop a simple and efficient method of alkoxyhalogenation of alkynyl ureas and secondary amides with copper(II)-salts either in stoichiometric amount or as a catalyst in the presence of *N*-halosuccinimides. Moreover, the exocyclic haloalkylidene moieties could

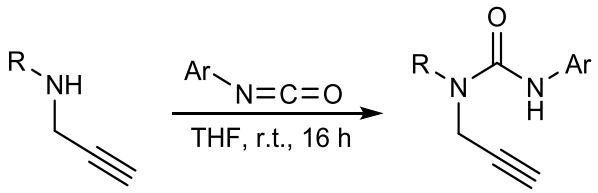
become versatile building blocks in organic synthesis by further functionalizations for example with transition metal-catalyzed reactions as cross coupling processes.

Experimental Part

General methods

Melting points are uncorrected. IR spectra were recorded on a FT-IR spectrophotometer. Column chromatography was performed on a silica gel 60 (mesh size 63-200 μm). Nuclear magnetic resonance spectra were recorded on 200, 300 or 400 MHz spectrometer for ^{1}H NMR and 100 MHz spectrometer for ^{13}C NMR. Chemical shifts (δ) for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million downfield relative to the center-line of the $CDCl_3$ triplet at 7.26 ppm. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the center-line of the $CDCl_3$ triplet at 77.23 ppm. The abbreviations s, d, t and m stand for the resonance multiplicities singlet, doublet, triplet and multiplet, respectively. ^{13}C spectra are ^{1}H decoupled and multiplicities were determined by the APT pulse sequence.

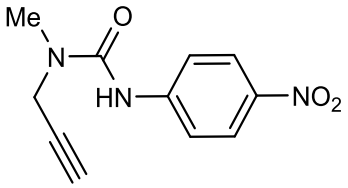
General procedure (GP1) for the preparation of ureas 1a-i.



1a-i

To a solution of alkynyl amine (1 mmol) in THF (5 mL), the suitable isocyanate (1 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 16 h, then the solvent was removed under reduced pressure and the crude product resulted enough pure to be used in the subsequent step without further purification.

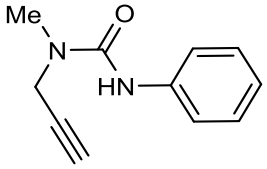
***N'*-Methyl-*N*-(4-nitrophenyl)-*N'*-propargylurea (1a)**



$C_{11}H_{11}N_3O_3$
M.W.: 233,2270

Following **GP1** with *N*-methylpropargylamine (1.0 mmol). The product **1a** was afforded in 99% yield (230 mg, 1.0 mmol). Pale yellow solid, mp: 113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (t, *J* = 2.5 Hz, 1H), 3.13 (s, 3H), 4.20 (d, *J* = 2.5 Hz, 2H), 7.05 (br s, 1H, missing after deuteration), 7.57 (ddd, *J* = 10.0, 5.0, 3.0 Hz, 2H), 8.14 (ddd, *J* = 10.0, 5.0, 3.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.5 (q), 38.2 (t), 73.2 (d), 78.3 (s), 118.7 (d), 125.0 (d), 142.7 (s), 145.1 (s), 154.2 (s). IR (cm^{-1}) ν: 1655 (C=O). MS (%) ESI 234 $[M+H]^+$. Anal. calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.82; H, 4.98; N, 17.79.

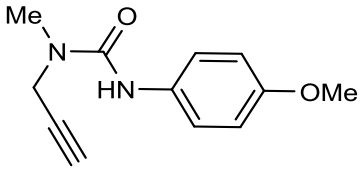
***N'*-Methyl-*N*-phenyl-*N'*-propargylurea (1b)**



$C_{11}H_{12}N_2O$
M.W.: 188,2300

Following **GP1** with *N*-methylpropargylamine (1.0 mmol). The product **1b** was afforded in 93% yield (175 mg, 0.9 mmol). White solid, m.p.: 88 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (t, *J* = 2.5 Hz, 1H), 3.07 (s, 3H), 4.17 (d, *J* = 2.5 Hz, 2H), 6.59 (br s, 1H, missing after deuteration), 7.04 (td, *J* = 8.0, 0.5 Hz, 1H), 7.28 (td, *J* = 8.0, 0.5 Hz, 2H), 7.37-7-39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.2 (q), 37.9 (t), 72.6 (d), 78.9 (s), 120.1 (d), 123.3 (d), 128.8 (d), 138.8 (s), 155.3 (s). IR (cm^{-1}) ν_{max}: 1680 (C=O). MS (%) ESI 189 $[M+H]^+$. Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.38; H, 6.21; N, 14.65.

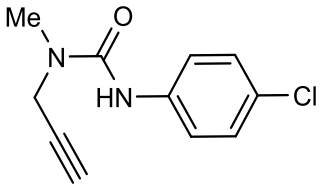
***N*-(4-Methoxyphenyl)-*N'*-methyl-*N'*-propargylurea (1c)**



$C_{12}H_{14}N_2O_2$
M.W.: 218,2560

Following **GP1** with *N*-methylpropargylamine (1.0 mmol). The product **1c** was afforded in 97% yield (211 mg, 1.0 mmol). Light brown solid, m.p.: 77 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (t, *J* = 2.5 Hz, 1H), 3.06 (s, 3H), 3.78 (s, 3H), 4.18 (d, *J* = 2.5 Hz, 2H), 6.41 (br s, 1H, missing after deuteration), 6.83 (d, *J* = 7.0 Hz, 2H), 7.27 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.9 (q), 37.8 (t), 55.4 (q), 72.2 (d), 79.3 (s), 113.9 (d), 122.9 (d), 132.1 (s), 155.8 (s), 156.1 (s). IR (cm^{-1}) ν_{max}: 1664 (C=O). MS (%) ESI 219 $[M+H]^+$. Anal. calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.19; H, 6.23; N, 13.10.

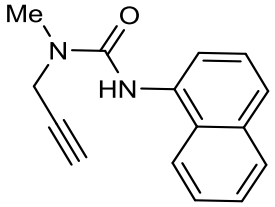
***N*-(4-Chlorophenyl)-*N'*-methyl-*N'*-propargylurea (1d)**



$C_{11}H_{11}ClN_2O$
M.W.: 222, 6720

Following **GP1** with *N*-methylpropargylamine (1.0 mmol). The product **1d** was afforded in 98% yield (217 mg, 1.0 mmol). White solid, m.p.: 105-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (t, *J* = 2.5 Hz, 1H), 3.08 (s, 3H), 4.18 (d, *J* = 2.5 Hz, 2H), 6.55 (br s, 1H, missing after deuteration), 7.23-7.26 (m, 2H), 7.32-7.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3 (q), 38.0 (t), 72.7 (d), 78.7 (s), 121.2 (d), 128.3 (s), 128.8 (d), 137.4 (s), 154.9 (s). IR (cm^{-1}) ν_{max} 1651 (C=O). MS (%) ESI 223 $[M+H]^+$. Anal. calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.05; H, 5.17; N, 12.77.

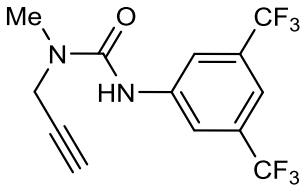
***N'*-Methyl-*N*-(1-naphthyl)-*N'*-propargylurea (1e)**



$C_{15}H_{14}N_2O$
M.W.: 238,2900

Following **GP1** with *N*-methylpropargylamine (1.0 mmol). The product **1e** was afforded in 98% yield (233 mg, 1.0 mmol). White solid, m.p.: 111-112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (t, *J* = 2.5 Hz, 1H), 3.14 (s, 3H), 4.22 (d, *J* = 2.5 Hz, 2H), 6.89 (br s, 1H, missing after deuteration), 7.43-7.53 (m, 3H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.85-7.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.4 (q), 38.2 (t), 72.8 (d), 78.9 (s), 120.9 (d), 121.0 (d), 125.1 (d), 125.7 (d), 125.8 (d), 126.1 (d), 127.9 (s), 128.7 (d), 133.6 (s), 134.1 (s), 156.0 (s). IR (cm^{-1}) ν_{max}: 1648 (C=O). MS (%) ESI 239 $[M+H]^+$. Anal. calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. Found: C, 75.46; H, 6.15; N, 11.56.

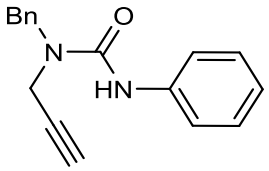
***N*-[3,5-Bis(trifluoromethyl)phenyl]-*N'*-methyl-*N'*-propargylurea (1f)**



$C_{13}H_{10}F_6N_2O$
M.W.: 324,2264

Following **GP1** with *N*-methylpropargylamine (1.0 mmol). The product **1f** was afforded in 94% yield (304 mg, 0.9 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (t, *J* = 2.5 Hz, 1 H), 3.14 (s, 3H), 4.21 (d, *J* = 2.5 Hz, 2H), 6.82 (br s, 1H, missing after deuteration), 7.53 (s, 1H), 7.90 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3 (q), 38.1 (t), 73.2 (d), 78.2 (s), 116.4 (d), 116.6 (d), 119.4 (d), 121.8 (s), 124.5 (s), 131.9 (s), 132.3 (s), 140.3 (s), 154.4 (s). IR (cm^{-1}) ν_{max}: 1662 (C=O). MS (%) ESI 325 $[M+H]^+$. Anal. calcd for $C_{13}H_{10}F_6N_2O$: C, 48.16; H, 3.11; N, 8.64. Found: C, 48.29; H, 2.88; N, 8.85.

***N'*-Benzyl-*N*-phenyl-*N'*-propargylurea (1g)**

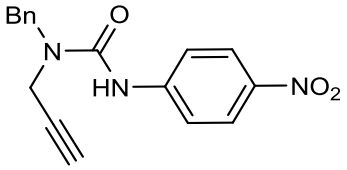


$C_{17}H_{16}N_2O$
M.W.: 264,3280

Following **GP1** with *N*-benzylpropargylamine (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 7:3) to afford **1g** in 35% yield (92 mg, 0.35 mmol). White solid, m.p.: 68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (t, *J* = 2.0 Hz, 1H), 4.20 (d, *J* = 2.0 Hz, 2H), 4.67 (s, 2H), 6.61 (br s, 1H, missing after deuteration), 6.98-7.07 (m, 1H), 7.21-7.46 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 36.7 (t), 50.7 (t), 73.1 (d), 79.0 (s), 119.9 (d), 123.3 (d), 127.4 (d), 127.9 (d), 128.9 (d), 129.1 (d), 136.8 (s), 138.8 (s), 155.4 (s). IR (cm^{-1}) ν_{max}: 1639 (C=O). MS (%) ESI 265 $[M+H]^+$. Anal. calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.22; H, 6.24; N, 10.41.

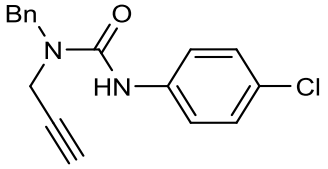
***N'*-Benzyl-*N*-(4-nitrophenyl)-*N'*-propargylurea (1h)**



$C_{17}H_{15}N_3O_3$
M.W.: 309,3250

Following **GP1** with *N*-benzylpropargylamine (1.0 mmol). The product **1h** was afforded in 95% yield (294 mg, 0.95 mmol). White solid, m.p.: 72 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (t, *J* = 2.5 Hz, 1H), 4.21 (d, *J* = 2.5 Hz, 2H), 4.68 (s, 2H), 7.08 (br s, 1H, missing after deuteration), 7.35-7.47 (m, 7H), 8.11 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9 (t), 50.9 (t), 73.7 (d), 78.5 (s), 118.7 (d), 124.9 (d), 127.3 (d), 128.3 (d), 129.2 (d), 136.1 (s), 142.6 (s), 145.1 (s), 154.4 (s). IR (cm^{-1}) ν_{max}: 1647 (C=O). MS (%) ESI 310 $[M+H]^+$. Anal. calcd for $C_{17}H_{15}N_3O_3$: C, 66.01; H, 4.89; N, 13.58. Found: C, 65.84; H, 5.19; N, 13.46.

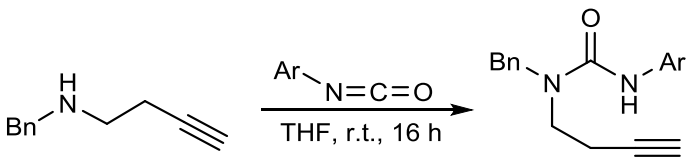
***N'*-Benzyl-*N*-(4-chlorophenyl)-*N'*-propargylurea (1i)**



$C_{17}H_{15}ClN_2O$
M.W.: 298,7700

Following **GP1** with *N*-benzylpropargylamine (1.0 mmol). The product **1i** was afforded in 98% yield (292 mg, 1.0 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (t, *J* = 2.5 Hz, 1H), 4.14 (d, *J* = 2.5 Hz, 2H), 4.63 (s, 2H), 6.88 (br s, 1H, missing after deuteration), 7.20-7.41 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.6 (t), 50.5 (t), 73.2 (d), 78.9 (s), 121.5 (d), 127.4 (d), 128.0 (d), 128.6 (s), 128.7 (d), 129.1 (d), 136.6 (s), 137.5 (s), 155.3 (s). IR (cm^{-1}) ν_{max}: 1663 (C=O). MS (%) ESI 299 $[M+H]^+$. Anal. calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.46; H, 4.81; N, 9.11.

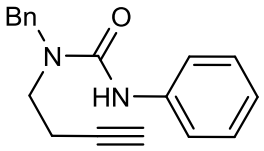
General procedure (GP2) for the preparation of ureas 1j-m.



1j-m

To a solution of *N*-benzylbutynylamine[18] (1.0 mmol) in THF (5 mL), the suitable isocyanate (1.0 mmol) was added dropwise. The resulting mixture was stirred at room temperature for 16 h, then the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (eluent: AcOEt / petroleum ether 4:6).

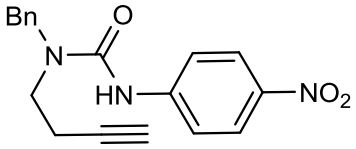
***N'*-Benzyl-*N'*-(butyn-4-yl)-*N*-phenylurea (1j)**



$C_{18}H_{18}N_2O$
M.W.: 278,3550

Following **GP2** with *N*-benzylbutynylamine (1.0 mmol). The product **1j** was afforded in 70% yield (195 mg, 0.7 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10 (t, *J* = 2.5 Hz, 1H), 2.53 (dt, *J* = 6.5, 2.5 Hz, 2H), 3.61 (t, *J* = 6.5 Hz, 2H), 4.67 (s, 2H), 6.69 (br s, 1H, missing after deuteration), 6.99-7.03 (m, 1H), 7.23-7.42 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (t), 47.1 (t), 51.4 (t), 70.6 (d), 82.2 (s), 119.9 (d), 123.0 (d), 127.0 (d), 127.9 (d), 128.9 (d), 129.1 (d), 137.2 (s), 139.1 (s), 155.7 (s). IR (cm^{-1}) ν_{max}: 1666 (C=O). MS (%) ESI 279 $[M+H]^+$. Anal. calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.83; H, 6.71; N, 9.86.

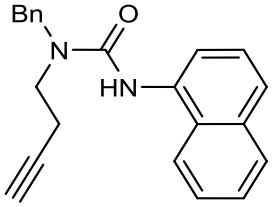
***N'*-Benzyl-*N'*-(butyn-4-yl)-*N*-(4-nitrophenyl)urea (1k)**



$C_{18}H_{17}N_3O_3$
M.W.: 323,3520

Following **GP2** with *N*-benzylbutynylamine (1.0 mmol). The product **1k** was afforded in 78% yield (252 mg, 0.8 mmol). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.14 (t, *J* = 2.5 Hz, 1H), 2.54 (dt, *J* = 6.5, 2.5 Hz, 2H), 3.62 (t, *J* = 6.5 Hz, 2H), 4.67 (s, 2H), 7.23 (br s, 1H, missing after deuteration), 7.31-7.44 (m, 7H), 8.10 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5 (t), 47.0 (t), 51.4 (t), 71.1 (d), 82.0 (s), 118.4 (d), 124.9 (d), 127.0 (d), 128.1 (d), 129.2 (d), 136.6 (s), 142.4 (s), 145.4 (s), 154.8 (s). IR (cm^{-1}) ν_{max}: 1658 (C=O). MS (%) ESI 324 $[M+H]^+$. Anal. calcd for $C_{18}H_{17}N_3O_3$: C, 66.86; H, 5.30; N, 12.90. Found: C, 67.07; H, 5.15; N, 13.14.

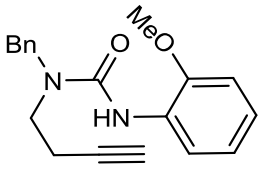
***N'*-Benzyl-*N'*-(butyn-4-yl)-*N*-naphthylurea (1l)**



$C_{22}H_{20}N_2O$
M.W.: 328,4150

Following **GP2** with *N*-benzylbutynylamine (1.0 mmol). The product **1l** was afforded in 63% yield (207 mg, 0.6 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09 (t, *J* = 2.5 Hz, 1H), 2.65 (dt, *J* = 2.5, 6.5 Hz, 2H), 3.76-3.80 (m, 2H), 4.79 (s, 2H), 6.80 (br s, 1H, missing after deuteration), 7.11 (d, *J* = 8.0 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.39-7.49 (m, 7H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.78-7.81 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8 (t), 48.0 (t), 52.2 (t), 70.4 (d), 82.2 (s), 119.9 (d), 120.5 (d), 124.5 (d), 125.6 (d), 125.8 (d), 126.9 (d), 127.3 (s), 128.1 (d), 128.6 (d), 129.3 (d), 133.7 (s), 134.1 (s), 137.2 (s) 156.1 (s). IR (cm^{-1}) ν_{max}: 1667 (C=O). MS (%) ESI 329 $[M+H]^+$. Anal. calcd for $C_{22}H_{20}N_2O$: C, 80.46; H, 6.14; N, 8.53. Found: C, 80.29; H, 6.21; N, 8.75.

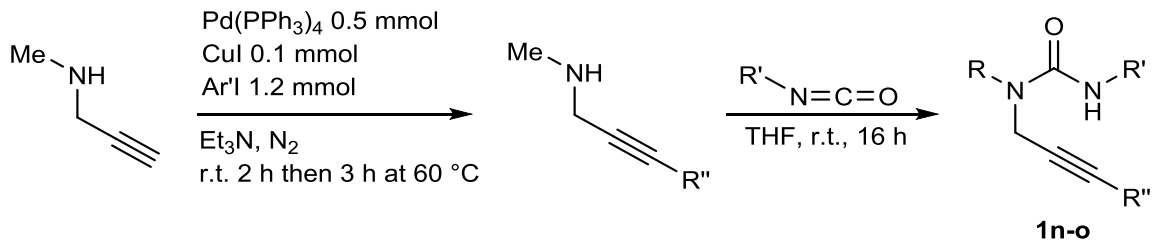
***N'*-Benzyl-*N'*-(butyn-4-yl)-*N*-(2-methoxyphenyl)urea (1m)**



$C_{19}H_{20}N_2O_2$
M.W.: 308,3810

Following **GP2** with *N*-benzylbutynylamine (1.0 mmol). The product **1m** was afforded in 67% yield (206 mg, 0.7 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (t, *J* = 2.5 Hz, 1H), 2.57 (dt, *J* = 2.5, 6.5 Hz, 2H), 3.66 (s, 3H), 3.67 (t, *J* = 6.5 Hz, 2H), 4.67 (s, 2H), 6.77-6.80 (m, 1H), 6.90-6.95 (m, 2H), 7.17 (br s, 1H, missing after deuteration), 7.26-7.41 (m, 5H), 8.15-8.18 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6 (t), 47.5 (t), 51.9 (t), 55.6 (q), 70.2 (d), 81.8 (s), 109.8 (d), 109.9 (s), 119.0 (d), 119.7 (d), 121.1 (d), 122.0 (d), 122.8 (d), 126.9 (d), 127.7 (d), 128.9 (d), 137.1 (s), 147.7 (s), 155.2 (s). IR (cm^{-1}) ν_{max}: 1667 (C=O). MS (%) ESI 309 [M+H]+. Anal. calcd for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.08. Found: C, 74.17; H, 6.68; N, 8.87.

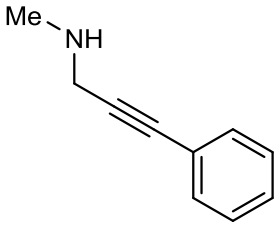
General procedure (GP3) for the preparation of ureas 1n-o.



1n-o

To a solution of *N*-methylpropargylurea (1.0 mmol) in Et_3N (12 mL) and under N_2 atmosphere were added $Pd(PPh_3)_4$ (0.05 mmol), CuI (0.1 mmol) and Ar'I (1.2 mmol). The resulting mixture was stirred at room temperature for 2 h and then heated at 60 °C for 3 h. The solvent was removed under reduced pressure, then the crude was filtered through a short pad of silica with AcOEt and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography.

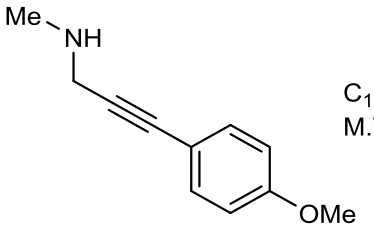
_N_-Methyl-3-phenylprop-2-yn-1-amine



$C_{10}H_{11}N$
M.W.: 145,2050

Colorless oil (156 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 3H), 4.45 (s, 2H), 6.77 (br s, 1H, missing after deuteration), 7.31-7.41 (m, 5H). These data are in good agreement with those reported in the literature.[11]

3-(4-Methoxyphenyl)-*N*-methylprop-2-yn-1-amine



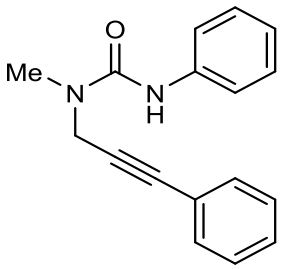
$C_{11}H_{13}N$
M.W.: 175,0997

Yellow oil (150 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 3H), 3.84 (s, 3H), 4.38 (s, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.18 (br s, 1H, missing after deuteration), 7.37 (d, *J* = 9.0 Hz, 2H). These data are in good agreement with those reported in the literature.[12]

[11] Hong, L.; Shao, Y.; Zhang, L.; Zhou, X.; *Chem. Eur. J*. **2014**, *20*, 8551-8555.

[12] Lemhadri, M.; Doucet, H.; Santelli, M. *Synthesis* **2005**, *8*, 1359-1367.

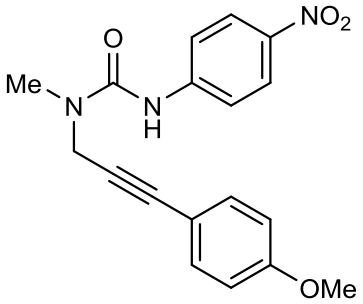
***N'*-Methyl-*N'*-(1-phenylpropyn-3-yl)-*N*-phenylurea (1n)**



$C_{17}H_{16}N_2O$
M.W.: 264,3280

Following **GP3** with *N*-methylpropargylurea (1.0 mmol) The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **1n** in 41% yield (108 mg, 0.4 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (s, 3H), 4.41 (s, 2H), 6.70 (br s, 1H, missing after deuteration), 7.29-7.46 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.3 (q), 38.8 (t), 84.4 (s), 84.4 (s), 119.1 (d), 120.3 (d), 120.5 (d), 122.2 (s), 122.6 (d), 122.9 (d), 128.4 (d), 128.5 (d), 128.7 (d), 131.8 (d), 132.0 (d), 139.2 (s), 155.6 (s). IR (cm^{-1}) ν_{max}: 1637 (C=O). MS (%) ESI 265 $[M+H]^+$. Anal. calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C,77.37; H, 5.89; N, 10.69.

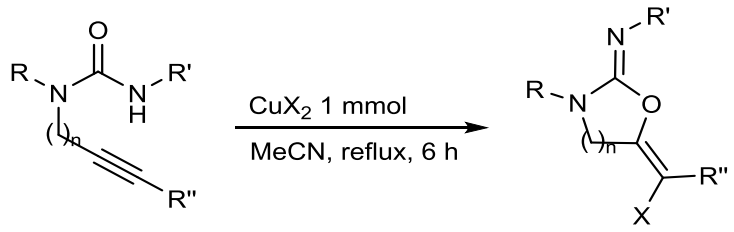
***N'*-Methyl-*N'*-[1-(4-methoxyphenyl)propyn-3-yl]-*N*-(4-nitrophenyl)urea (1o)**



$C_{18}H_{17}N_3O_4$
M.W.: 339,3510

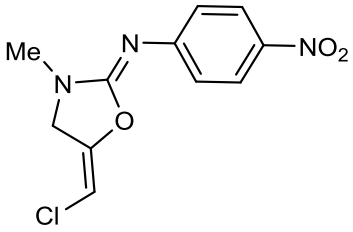
Following **GP3** with *N*-methylpropargylurea (1.0 mmol) The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **1o** in 30% yield (102 mg, 0.3 mmol). Pale orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.17 (s, 3H), 3.82 (s, 3H), 4.40 (s, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.18 (br s, 1H, missing after deuteration), 7.37 (d, *J* = 9.0 Hz, 2H), 7.58 (d, *J* = 9.0 Hz, 2H), 8.15 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5 (q), 39.1 (t), 55.3 (q), 81.9 (s), 85.0 (s), 113.3 (d), 114.3 (s), 117.9 (d), 124.9 (d), 133.2 (d), 142.4 (s), 145.6 (s), 154.5 (s), 159.92 (s). IR (cm^{-1}) ν_{max}: 1629 (C=O). MS (%) ESI 340 $[M+H]^+$. Anal. calcd for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.87; H, 4.81; N, 12.21.

General procedure (GP4) for stoichiometric intramolecular alkoxyhalogenation of alkynyl ureas.



A solution of alkynyl urea (1.0 mmol) and CuX_2 (1 mmol) in MeCN (14 mL) was heated at reflux for 6 h under air atmosphere. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography.

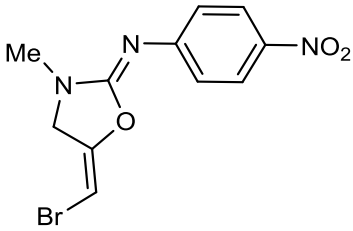
(*E*)-5-(Chloromethylidene)-3-methyl-2-[(4-nitrophenyl)imino]-oxazolidine (2a)



$C_{11}H_{10}ClN_3O_3$
M.W.: 267,6690

Following **GP4** with urea **1a** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **2a** in 87% yield (232 mg, 0.9 mmol). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.14 (s, 3H), 4.32 (d, *J* = 3.0 Hz, 2H), 6.00 (t, *J* = 3.0 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7 (q), 49.8 (t), 96.7 (d), 123.7 (d), 124.6 (d), 142.8 (s), 147.3(s), 150.6 (s), 152.8 (s). IR (cm^{-1}) ν_{max}: 1662 (C=N). MS (%) ESI 268 $[M+H]^+$. Anal. calcd for $C_{11}H_{10}ClN_3O_3$: C, 49.36; H, 3.77; N, 15.70. Found: C, 49.59; H, 3.54; N, 15.85.

(*E*)-5-(Bromomethylidene)-3-methyl-2-[(4-nitrophenyl)imino]-oxazolidine (3a)

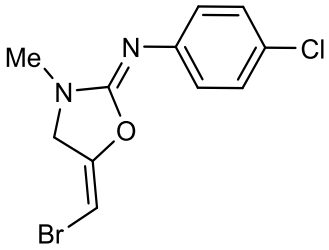


$C_{11}H_{10}BrN_3O_3$
M.W.: 312,1230

Following **GP4** with urea **1a** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **3a** in 94% yield (292 mg, 0.9 mmol). White solid, m.p.: 210-211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 3H), 4.18 (d, *J* = 3.0 Hz, 2H), 5.90 (t, *J* = 3.0 Hz, 1H), 7.07 (d, *J* = 9.0 Hz, 2H), 8.07 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7 (q), 51.1 (t), 83.3 (d), 123.7 (d), 124.6 (d), 142.7 (s), 148.1 (s),

150.4 (s), 153.2 (s). IR (cm^{-1}) ν_{max}: 1658 (C=N). MS (%) ESI 312 $[M+H]^+$. Anal. calcd for $C_{11}H_{10}BrN_3O_3$: C, 42.33; H, 3.23; N, 13.46. Found: C, 42.52; H, 3.47; N, 13.21.

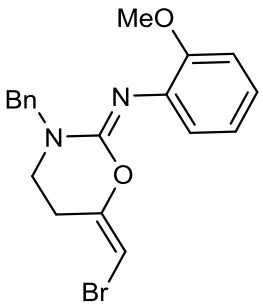
(*E*)-5-(Bromomethylidene)-2-[(4-chlorophenyl)imino]-3-methyl-oxazolidine (3d)



$C_{11}H_{10}BrClN_2O$
M.W.: 301,5680

Following **GP4** with urea **1d** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **3d** in 95% yield (285 mg, 0.9 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.03 (s, 3H), 4.16 (d, *J* = 3.0 Hz, 2H), 5.86 (t, *J* = 3.0 Hz, 1H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7 (q), 51.1 (t), 82.5 (d), 124.7 (d), 127.6 (s), 128.6 (d), 144.8 (s), 148.5 (s), 149.9 (s). IR (cm^{-1}) ν_{max}: 1653 (C=N). MS: *m/z* 301 (M^+). Anal. calcd for $C_{11}H_{10}BrClN_2O$: C, 43.81; H, 3.34; N, 9.29. Found: C, 43.90; H, 3.58; N, 9.55.

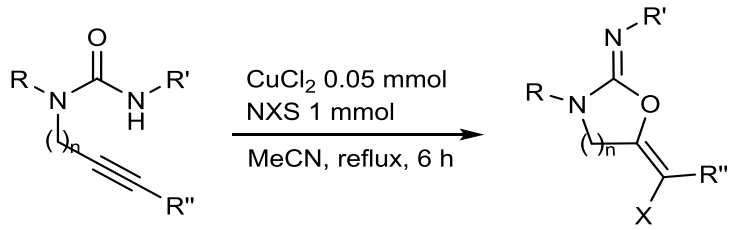
(*E*)-3-Benzyl-6-(bromomethylidene)-2-[(2-methoxyphenyl)imino]-2,3,4,5-tetrahydro-2*H*-1,3-oxazine (3m)



$C_{19}H_{19}BrN_2O_2$
M.W.: 387,2770

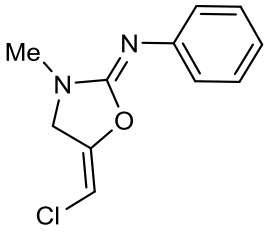
Following **GP4** with urea **1m** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **3m** in 62% yield (239 mg, 0.6 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.74 (t, *J* = 6.0 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 3.81 (s, 3H), 4.82 (br s, 2H), 5.77 (s, 1H), 6.82-7.08 (m, 3H), 7.30-7.45 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 25.1 (t), 41.9 (t), 53.3 (t), 56.0 (q), 89.1 (d), 114.6 (d), 123.5 (d), 127.8 (d), 128.3 (d), 128.9 (d), 131.9 (s), 136.5 (s), 149.4 (s), 152.7 (s), 162.2 (s). IR (cm^{-1}) ν_{max}: 1641 (C=N). MS (%) ESI 387 $[M+H]^+$. Anal. calcd for $C_{19}H_{19}BrN_2O_2$: C, 58.93; H, 4.95; N, 7.23. Found: C, 59.19; H, 4.74; N, 7.49.

General procedure (GP5) for catalytic intramolecular alkoxyhalogenation of alkynyl ureas.



A solution of alkynyl urea (1.0 mmol), $CuCl_2$ (0.05 mmol) and the suitable NXS (1 mmol) in MeCN (14 mL) was heated at reflux for 6 h under air atmosphere. The solvent was removed under reduced pressure and, when required, the crude product was purified by silica gel column chromatography.

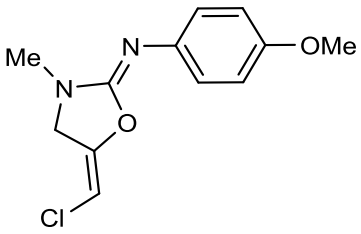
(*E*)-5-(Chloromethylidene)-3-methyl-2-(phenylimino)oxazolidine (2b)



$C_{11}H_{11}ClN_2O$
M.W.: 222,6720

Following **GP5** with urea **1b** (1 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **2b** in 64% yield (142 mg, 0.6 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 3H), 4.17 (d, *J* = 3.0 Hz, 2H), 5.90 (t, *J* = 3.0 Hz, 1H), 7.03-7.09 (m, 3H), 7.29 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6 (q), 49.7 (t), 95.7 (d), 122.7 (d), 123.3 (d), 128.6 (d), 146.3 (s), 148.2 (s), 149.5 (s). IR (cm^{-1}) ν_{max}: 1643 (C=N). MS (%) ESI 223 $[M+H]^+$. Anal. calcd for $C_{11}H_{11}ClN_2O$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.45; H, 5.29; N, 12.28.

(*E*)-5-(Chloromethylidene)-2-[(4-methoxyphenyl)imino]-3-methyloxazolidine (2c)

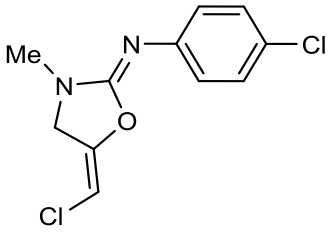


$C_{12}H_{13}ClN_2O_2$
M.W.: 252,6980

Following **GP5** with urea **1c** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **2c** in 82% yield (207 mg, 0.8 mmol). White solid, m.p.: 137 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (s, 3H), 3.76 (s, 3H), 4.19 (d, *J* = 3.0 Hz, 2H), 5.89 (t, *J* = 3.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8 (q), 49.8 (t), 55.4 (q), 95.5 (d), 113.9 (d), 124.1 (d), 139.2 (s), 148.1 (s), 149.3 (s), 155.3 (s). IR (cm^{-1}) ν_{max}:

1657 (C=N). MS (%) ESI 253 $[M+H]^+$. Anal. calcd for $C_{12}H_{13}ClN_2O_2$: C, 57.04; H, 5.19; N, 11.09. Found: C, 57.21; H, 4.99; N, 11.37.

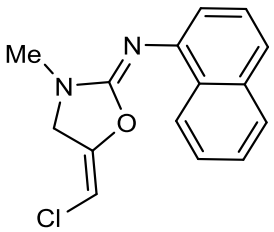
(*E*)-5-(Chloromethylidene)-2-[(4-chlorophenyl)imino]-3-methyloxazolidine (2d)



$C_{11}H_{10}Cl_2N_2O$
M.W.: 257,1140

Following **GP5** with urea **1d** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **2d** in 12% yield (30 mg, 0.1 mmol). White solid, m.p.: 188 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.15 (s, 3H), 4.30 (d, *J* = 3.0 Hz, 2H), 5.97 (t, *J* = 3.0 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.1 (q), 50.3 (t), 97.2 (d), 124.8 (d), 128.8 (d), 142.4 (s), 147.4 (s), 151.2 (s), 167.3 (s). IR (cm^{-1}) ν_{max}: 1661 (C=N). MS (%) ESI 257 $[M+H]^+$. Anal. calcd for $C_{11}H_{10}Cl_2N_2O$: C, 51.38; H, 3.92; N, 10.90. Found: C, 51.60; H, 3.73; N, 11.15.

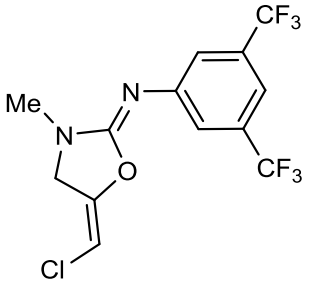
(*E*)-5-(Chloromethylidene)-3-methyl-2-[(1-naphthyl)imino]-oxazolidine (2e)



$C_{15}H_{13}ClN_2O$
M.W.: 272,7320

Following **GP5** with urea **1e** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **2e** in 98% yield (266 mg, 0.9 mmol). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.12 (s, 3H), 4.20 (d, *J* = 3.0 Hz, 2H), 5.85 (t, *J* = 3.0 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.43-7.51 (m, 3H), 7.59 (d, *J* = 8.0 Hz, 1H) 7.84 (dd, *J* = 6.5, 3.0 Hz, 1H), 7.25 (dd, *J* = 6.5, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8 (q), 49.9 (t), 95.7 (d), 117.9 (d), 122.7 (d), 124.1 (d), 125.1 (d), 125.9 (d), 127.8 (d), 129.3 (s), 134.3 (s), 142.7 (s), 148.0 (s), 149.6 (s). IR (cm^{-1}) ν_{max}: 1668 (C=N). MS (%) ESI 273 $[M+H]^+$. Anal. calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; N, 10.27. Found: C, 65.87; H, 5.11; N, 10.51.

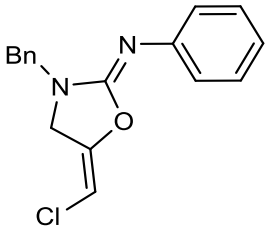
(*E*)-2-[3,5-Bis(trifluoromethyl)phenylimino]-5-(chloromethylidene)-3-methyloxazolidine (2f)



$C_{13}H_9ClF_6N_2O$
M.W.: 358,6684

Following **GP5** with urea **1f** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **2f** in 75% yield (268 mg, 0.7 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 3H), 4.30 (d, *J* = 3.0 Hz, 2H), 5.99 (t, *J* = 3.0 Hz, 1H), 7.50 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9 (q), 50.2 (t), 97.9 (d), 116.6 (d), 123.3 (q, *J* = 271.0, Hz), 123.9 (d), 131.9 (q, *J* = 33.0 Hz), 145.9 (s), 147.0 (s), 151.7 (s). IR (cm^{-1}) ν_{max}: 1668 (C=N). MS (%) ESI 359 $[M+H]^+$. Anal. calcd for $C_{13}H_9ClF_6N_2O$: C, 43.53; H, 2.53; N, 7.81. Found C, 43.76; H, 2.29; N, 7.99.

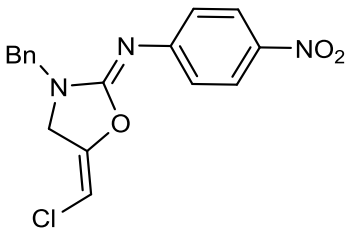
(*E*)-3-Benzyl-5-(chloromethylidene)-2-(phenylimino)oxazolidine (2g)



$C_{17}H_{15}ClN_2O$
M.W.: 298,7700

Following **GP5** with urea **1g** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **2g** in 98% yield (292 mg, 0.9 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (d, *J* = 3.0 Hz, 2H), 4.74 (br s, 2H), 5.91 (t, *J* = 3.0 Hz, 1H), 7.06-7.11 (m, 3H), 7.27-7.44 (m, 7H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 47.2 (t), 48.8 (t), 96.3 (d), 119.9 (d), 123.3 (d), 123.7 (d), 128.1 (d), 128.4 (d), 128.9 (d), 145.3 (s), 148.1 (s), 149.9 (s), 171.1 (s). IR (cm^{-1}) ν_{max}: 1632 (C=N). MS (%) ESI 299 $[M+H]^+$. Anal. calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found: C, 68.58; H, 5.17; N, 9.21.

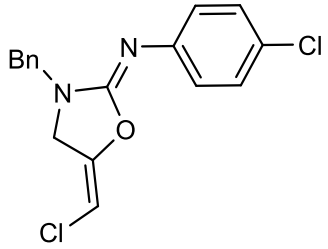
(*E*)-3-Benzyl-5-(chloromethylidene)-2-[(4-nitrophenyl)imino]-oxazolidine (2h)



$C_{17}H_{14}ClN_3O_3$
M.W.: 343,7670

Following **GP5** with urea **1h** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **2h** in 71% yield (243 mg, 0.7 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (d, *J* = 3.0 Hz, 2H), 4.68 (s, 2H), 5.99 (t, *J* = 3.0 Hz, 1H), 7.17(d, *J* = 9.0 Hz, 2H), 7.35-7.44 (m, 5H), 8.15 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 47.1 (t), 48.7 (t), 97.0 (d), 123.8 (d), 124.7 (d), 124.9 (d), 125.1 (d), 128.3 (d), 128.6 (d), 135.0 (s), 142.8 (s), 147.5 (s), 150.3 (s), 153.0 (s). IR (cm^{-1}) ν_{max}: 1590 (C=N). MS (%) ESI 344 $[M+H]^+$. Anal. calcd for $C_{17}H_{14}ClN_3O_3$: C, 59.40; H, 4.10; N, 12.22. Found: C, 59.58; H, 3.78; N, 12.31.

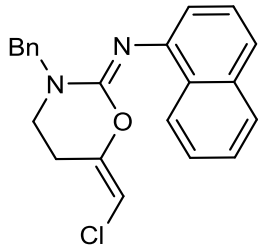
(*E*)-3-Benzyl-5-(chloromethylidene)-2-[(4-chlorophenyl)imino]-oxazolidine (2i)



$C_{17}H_{14}Cl_2N_2O$
M.W.: 333,2120

Following **GP5** with urea **1i** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **2i** in 85% yield (282 mg, 0.8 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (d, *J* = 3.0 Hz, 2H), 4.63 (s, 2H), 5.92 (t, *J* = 3.0 Hz, 1H), 7.03 (d, *J* = 9.0 Hz, 2H), 7.24 (d, *J* = 9.0 Hz, 2H), 7.37-7.41 (m, 5H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 47.1 (t), 48.7 (t), 96.1 (d), 124.7 (d), 127.7 (s), 128.8 (d), 128.9 (d), 129.1 (d), 129.2 (d), 135.5 (s), 144.8 (s), 148.0 (s), 149.3 (s). IR (cm^{-1}) ν_{max}: 1669 (C=N). MS (%) ESI 333 $[M+H]^+$. Anal. calcd for $C_{17}H_{14}Cl_2N_2O$: C, 61.28; H, 4.23; N, 8.41. Found: C, 61.11; H, 4.40; N, 8.69.

(*E*)-3-Benzyl-6-(chloromethylidene)-2-(phenylimino)-2,3,4,5-tetrahydro-*2H*-1,3-oxazine (2j)

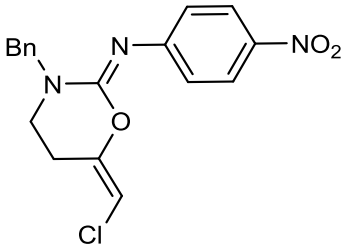


$C_{22}H_{19}ClN_2O$
M.W.: 362,8570

Following **GP5** with urea **1j** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **2j** in 28% yield (87 mg, 0.2 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.79 (td, *J* = 6.0, 1.5 Hz, 2H), 3.28 (t, *J* = 6.0 Hz, 2H), 4.82 (s, 2H), 5.88 (t, *J* = 1.5 Hz, 1H), 7.01-7.05 (m, 3H), 7.26-7.42 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.4 (t), 41.8 (t), 53.3 (t), 101.6 (d), 122.4 (d), 123.6 (d), 127.7 (d), 128.2 (d), 128.4 (d), 128.5 (d), 128.7 (d), 136.7 (s), 140.9

(s), 146.2 (s), 148.9 (s). IR (cm^{-1}) ν_{max}: 1641 (C=N). MS (%) ESI 313 $[M+H]^+$. Anal. calcd for $C_{22}H_{19}ClN_2O$: C, 69.12; H, 5.48; N, 8.96. Found: C, 69.31; H, 5.62; N, 8.65.

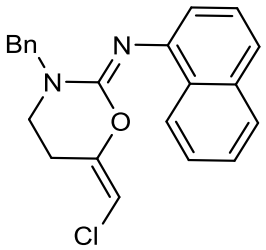
(*E*)-3-Benzyl-6-(chloromethylidene)-2-[(4-nitrophenyl)imino]-2,3,4,5-tetrahydro-*2H*-1,3-oxazine (2k)



$C_{18}H_{16}ClN_3O_3$
M.W.: 357,7940

Following **GP5** with urea **1k** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **2k** in 56% yield (199 mg, 0.5 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.84 (t, *J* = 6.0 Hz, 2H), 3.36 (t, *J* = 6.0 Hz, 2H), 4.84 (s, 2H), 5.94 (br s, 1H), 7.11 (d, *J* = 8.5 Hz, 2H), 7.34-7.40 (m, 5H), 8.15 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9 (t), 42.0 (t), 53.7 (t), 102.6 (d), 123.9 (d), 124.6 (d), 128.0 (d), 128.1 (d), 128.9 (d), 135.9 (s), 142.5 (s), 145.1 (s), 147.1 (s), 148.3 (s). IR (cm^{-1}) ν_{max}: 1641 (C=N). MS (%) ESI 358 $[M+H]^+$. Anal. calcd for $C_{18}H_{16}ClN_3O_3$: C, 60.42; H, 4.51; N, 11.74. Found: C, 60.71; H, 4.29; N, 11.95.

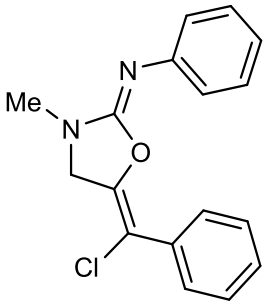
(*E*)-3-Benzyl-6-(chloromethylidene)-2-(naphthylimino)-2,3,4,5-tetrahydro-*2H*-1,3-oxazine (2l)



$C_{22}H_{19}ClN_2O$
M.W.: 362,8570

Following **GP5** with urea **1l** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **2l** in 77% yield (278 mg, 0.8 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.81-2.85 (m, 2H), 3.37 (t, *J* = 6.0 Hz, 2H), 4.91 (s, 2H), 5.73 (s, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 7.33-7.58 (m, 9H), 7.95-8.08 (m, 1H), 8.12-8.24 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.3 (t), 42.2 (t), 53.6 (t), 101.6 (d), 113.8 (s), 117.9 (d), 124.2 (d), 124.7 (d), 125.0 (s), 125.4 (d), 126.0 (d), 126.3 (d), 126.7 (d), 127.7 (d), 128.8 (d), 129.4 (s), 131.2 (s), 136.9 (s), 142.7 (s). IR (cm^{-1}) ν_{max}: 1641 (C=N). MS (%) ESI 363 $[M+H]^+$. Anal. calcd for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72. Found: C, 72.98; H, 5.12; N, 8.05.

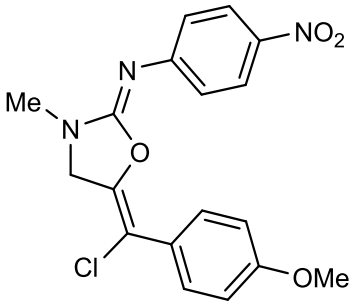
(*Z*)-5-[Chloro(phenyl)methylidene]-3-methyl-2-(phenylimino)-oxazolidine (2n)



$C_{17}H_{15}ClN_2O$
M.W.: 298,7700

Following **GP5** with urea **1n** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **2n** in 41% yield (122 mg, 0.4 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (s, 3H), 4.41 (s, 2H), 7.24-7.46 (m, 10H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 34.4 (q), 38.9 (t), 83.9 (s), 84.6 (s), 120.3 (d), 122.4 (s), 123.4 (d), 128.4 (d), 128.6 (d), 128.8 (d), 131.8 (d), 137.6 (s), 138.8 (s), 155.5 (s). IR (cm^{-1}) ν_{max}: 1668 (C=N). MS (%) ESI 299 $[M+H]^+$. Anal. calcd for $C_{17}H_{15}ClN_2O$: C, 68.34; H, 5.06; N, 9.38. Found C, 68.19; H, 5.35; N, 9.62.

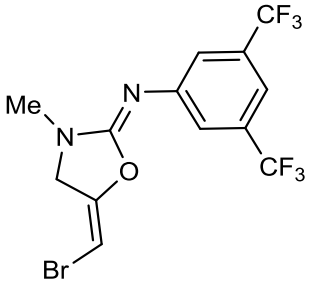
(*Z*)-5-[Chloro(4-methoxyphenyl)methylidene]-3-methyl-2-[(4-nitrophenyl)imino]oxazolidine (2o)



$C_{18}H_{16}ClN_3O_4$
M.W.: 373,7930

Following **GP5** with urea **1o** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **2o** in 37% yield (138 mg, 0.4 mmol). White solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H), 3.84 (s, 3H), 4.51 (s, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 9.0 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 2H), 8.13 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.8 (q), 52.1 (t), 55.4 (q), 111.2 (s), 113.7 (d), 123.7 (d), 124.6 (d), 128.6 (d), 139.9 (s), 142.8 (s),145.6 (s),151.5 (s),152.5 (s),159.7 (s). IR (cm^{-1}) ν_{max}: 1671 (C=N). MS (%) ESI 374 $[M+H]^+$. Anal. calcd for $C_{18}H_{16}ClN_3O_4$: C, 57.84; H, 4.31; N, 11.24. Found C, 57.99; H, 4.04; N, 11.47.

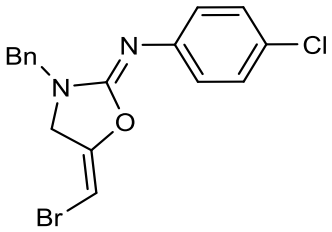
(*E*)-5-(Bromomethylidene)-2-[3,5-bis(trifluoromethyl)phenylimino]-3-methyloxazolidine (3f)



$C_{13}H_9BrF_6N_2O$
M.W.: 403,1224

Following **GP5** with urea **1f** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **3f** in 74% yield (297 mg, 0.7 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 3H), 4.24 (d, *J* = 3.0 Hz, 2H), 5.96 (t, *J* = 3.0 Hz, 1H), 7.47 (br s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7 (q), 51.2 (t), 83.7 (d), 116.1 (d), 123.7 (d), 123.4 (q, *J* = 271.0 Hz), 131.8 (q, *J* = 32.5 Hz), 147.2 (s), 147.8 (s), 151.2 (s). IR (cm^{-1}) ν_{max}: 1653 (C=N). MS (%) ESI 403 $[M+H]^+$. Anal. calcd for $C_{13}H_9BrF_6N_2O$: C, 38.73; H, 2.25; N, 6.95. Found: C, 38.43; H, 2.06; N, 7.13.

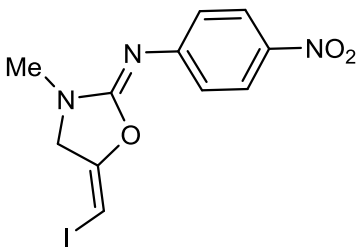
(*E*)-3-Benzyl-5-(bromomethylidene)-2-[(4-chlorophenyl)imino]-oxazolidine (3i)



$C_{17}H_{14}BrClN_2O$
M.W.: 377,6660

Following **GP5** with urea **1i** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:4) to afford **3i** in 42% yield (157 mg, 0.4 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (d, *J* = 3.0 Hz, 2H), 4.68 (s, 2H), 5.89 (t, *J* = 3.0 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 2H), 7.20-7.29 (m, 2H), 7.32-7.46 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7 (t), 48.8 (t), 83.7 (d), 124.9 (d), 128.1 (d), 128.3 (d), 128.7 (d), 129.0 (d), 132.1 (s), 134.8 (s), 143.2 (s), 148.1 (s), 150.8 (s). IR (cm^{-1}) ν_{max}: 1641 (C=N). MS: *m/z* 377 (M^+). Anal. calcd for $C_{17}H_{14}BrClN_2O$: C, 54.06; H, 3.74; N, 7.42. Found: C, 54.10; H, 3.97; N, 7.65.

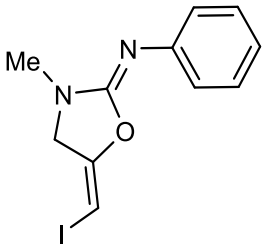
(*E*)-5-(Iodomethylidene)-3-methyl-2-[(4-nitrophenyl)imino]-oxazolidine (4a)



$C_{11}H_{10}IN_3O_3$
M.W.: 359,1235

Following **GP5** with urea **1a** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **4a** in 68% yield (244 mg, 0.7 mmol). White solid, m.p.: 133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 3H), 4.22 (d, *J* = 3.0 Hz, 2H), 5.80 (t, *J* = 3.0 Hz, 1H), 7.13 (d, *J* = 9.0 Hz, 2H), 8.14 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6 (q), 50.5 (d), 53.4 (t), 123.8 (d), 124.6 (d), 142.5 (s), 149.9 (s), 151.3 (s), 153.1 (s). IR (cm^{-1}) ν_{max}: 1642 (C=N). MS: *m/z* 359 (M^+). Anal. calcd for $C_{11}H_{10}IN_3O_3$: C, 36.79; H, 2.81; N, 11.70. Found: C, 37.02; H, 2.52; N, 11.91.

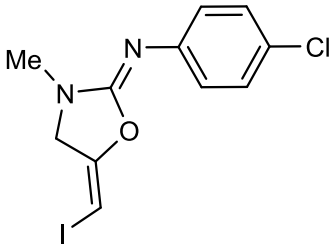
(*E*)-5-(Iodomethylidene)-3-methyl-2-(phenylimino)oxazolidine (4b)



$C_{11}H_{11}IN_2O$
M.W.: 314,1265

Following **GP5** with urea **1b** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **4b** in 63% yield (197 mg, 0.6 mmol). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 3H), 4.17 (d, *J* = 2.5 Hz, 2H), 5.80 (t, *J* = 3.0 Hz, 1H), 7.02-7.08 (m, 2H), 7.25-7.30 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.9 (q), 49.6 (d), 53.6 (t), 122.9 (d), 123.3 (d), 128.7 (d), 145.3 (s), 150.5 (s), 150.6 (s). IR (cm^{-1}) ν_{max}: 1644 (C=N). MS: *m/z* 314 (M^+). Anal. calcd for $C_{11}H_{11}IN_2O$: C, 42.06; H, 3.53; N, 8.92. Found: C, 42.01; H, 3.77, N, 8.59.

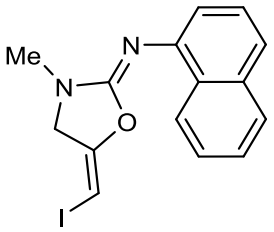
(*E*)-2-[(4-Chlorophenyl)imino]-5-(iodomethylidene)-3-methyloxazolidine (4d)



$C_{11}H_{10}ClIN_2O$
M.W.: 348,5685

Following **GP5** with urea **1d** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **4d** in 95% yield (330 mg, 0.9 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.97 (s, 3H), 4.08 (d, *J* = 2.5 Hz, 2H), 5.64 (t, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 7.0, 2.0 Hz, 1H), 7.18 (dd, *J* = 7.0, 2.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6 (q), 49.5 (d), 53.4 (t), 124.8 (d), 128.5 (d), 137.6 (s), 144.9 (s), 150.5 (s), 178.2 (s) IR (cm^{-1}) ν_{max}: 1649 (C=N). MS (%) ESI 349 $[M+H]^+$. Anal. calcd for $C_{11}H_{10}ClIN_2O$: C, 37.90; H, 2.89; N, 8.04. Found: C, 38.12; H, 2.61; N, 8.29.

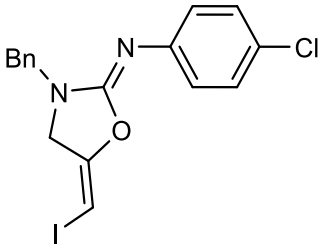
(*E*)-5-(Iodomethylidene)-2-[(1-naphthyl)imino]-3-methyloxazolidine (4e)



$C_{15}H_{13}IN_2O$
M.W.: 364,1865

Following **GP5** with urea **1e** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **4e** in 73% yield (266 mg, 0.7 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (s, 3H), 4.05 (d, *J* = 2.5 Hz, 2H), 5.62 (t, *J* = 2.5 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.46-7.55 (m, 3H), 7.61 (d, *J* = 8.0 Hz, 2H) 7.87-7.89 (m, 1H), 8.30-8.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.7 (q), 49.4 (d), 53.5 (t), 118.0 (d), 122.7 (d), 124.2 (d), 125.1 (d), 125.9 (d), 126.0 (d), 127.8 (d), 129.4 (s), 134.3 (s), 142.7 (s), 150.2 (s), 150.7 (s). IR (cm^{-1}) ν_{max}: 1653 (C=N). MS (%) ESI 365 $[M+H]^+$. Anal. calcd for $C_{15}H_{13}IN_2O$: C, 49.47; H, 3.60; N, 7.69. Found: C, 49.22; H, 3.89; N, 7.83.

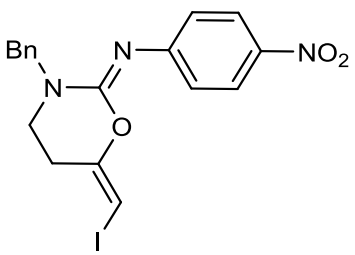
(*E*)-3-Benzyl-2-[(chlorophenyl)imino]-5-(iodomethylidene)-oxazolidine (4i)



$C_{17}H_{14}ClIN_2O$
M.W.: 424,6665

Following **GP5** with urea **1i** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:4) to afford **4i** in 79% yield (334 mg, 0.8 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.99 (d, *J* = 3.0 Hz, 2H), 4.63 (s, 2H), 5.68 (t, *J* = 3.0 Hz, 1H), 7.06 (d, *J* = 9.0 Hz, 2H), 7.24-7.27 (m, 2H), 7.34-7.43 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 48.7 (t), 49.6 (d), 50.7 (t), 124.8 (d), 128.1 (d), 128.2 (d), 128.6 (d), 128.9 (d), 127.7 (s), 135.6 (s) 144.8 (s), 149.9 (s), 150.6 (s). IR (cm^{-1}) ν_{max}: 1641 (C=N). MS (%) ESI 425 $[M+H]^+$. Anal. calcd for $C_{17}H_{14}ClIN_2O$: C, 48.08; H, 3.32; N, 6.60. Found: C, 47.76; H, 3.57; N, 6.43.

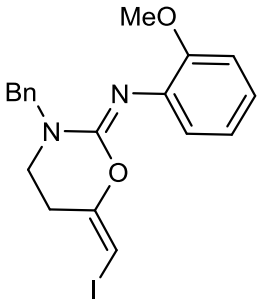
(*E*)-3-Benzyl-6-(iodomethylidene)-2-[(4-nitrophenyl)imino]-2,3,4,5-tetrahydro-2*H*-1,3-oxazine (4k)



$C_{18}H_{16}IN_3O_3$
M.W.: 449,2485

Following **GP5** with urea **1k** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **4k** in 88% yield (395 mg, 0.9 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.83 (t, *J* = 6.0 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 2H), 4.78 (s, 2H), 5.77 (s, 1H), 7.07 (dd, *J* = 7.0, 2.0 Hz, 2H), 7.33-7.39 (m, 5H), 8.13 (dd, *J* = 7.0, 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3 (t), 42.3 (t), 53.4 (t), 58.2 (d), 123.9 (d), 124.5 (d), 127.9 (d), 128.1 (d), 128.8 (d), 136.2 (s), 142.1 (s), 146.6 (s), 150.9 (s), 154.0 (s). IR (cm^{-1}) ν_{max}: 1641 (C=N). MS (%) ESI 450 $[M+H]^+$. Anal. calcd for $C_{18}H_{16}IN_3O_3$: C, 48.12; H, 3.59; N, 9.35. Found: C, 48.15; H, 3.90; N, 9.19.

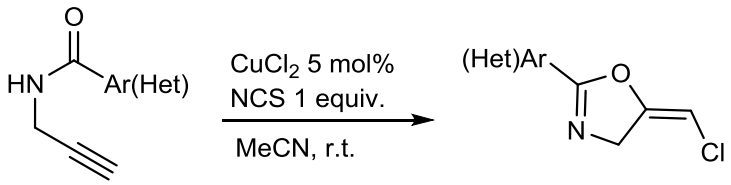
(*E*)-3-Benzyl-5-(iodomethylidene)-2-[(2-methoxyphenyl)imino]-2,3,4,5-tetrahydro-2*H*-1,3-oxazine (4m)



$C_{19}H_{19}IN_2O_2$
M.W.: 434,2775

Following **GP5** with urea **1m** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **4m** in 54% yield (234 mg, 0.5 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.76 (td, *J* = 6.0, 1.0 Hz, 2H), 3.27 (t, *J* = 6.0 Hz, 2H), 3.82 (s, 3H), 4.89 (br s, 2H), 5.64 (s, 1H), 6.87-6.92 (m, 2H), 7.02 (t, *J* = 7.0 Hz, 2H), 7.30-7.39 (m, 3H), 7.45 (d, *J* = 7.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8 (t), 42.3 (t), 53.7 (t), 55.8 (q), 58.1 (d), 111.3 (d), 120.8 (d), 124.6 (d), 127.8 (d), 128.3 (d), 128.7 (d), 136.4 (s), 145.8 (s), 151.1 (s), 152.0 (s), 154.1 (s). IR (cm^{-1}) ν_{max}: 1653 (C=N). MS (%) ESI 435 $[M+H]^+$. Anal. calcd for $C_{19}H_{19}IN_2O_2$: C, 52.55; H, 4.41; N, 6.45. Found: C, 52.81; H, 4.59; N, 6.17.

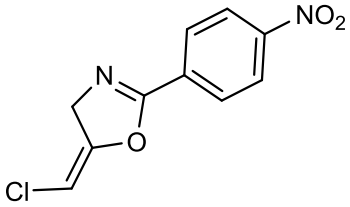
General procedure (GP6) for catalytic intramolecular alkoxychlorination of alkynyl amides.



5a,b,g **6**

A solution of alkynyl amide[13] (1.0 mmol), $CuCl_2$ (5 mol %) and NCS (1 mmol) in MeCN (14 mL) was stirred at room temperature under air atmosphere until all reagent consumption monitored by TLC (12-24 h). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography.

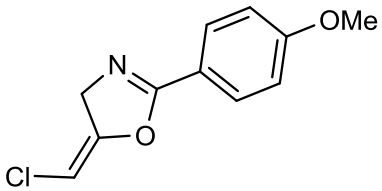
(*E*)-5-(Chloromethylidene)-2-(4-nitrophenyl)-4,5-dihydrooxazole (6a)



$C_{10}H_7ClN_2O_3$
M.W.: 238,6270

Following **GP6** with amide **5a** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **6a** in 76% yield (180 mg, 0.7 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (d, *J* = 3.0 Hz, 2H), 6.13 (t, *J* = 3.0 Hz, 1H), 8.14-8.19 (m, 2H), 8.30-8.34 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.2 (t), 95.8 (d), 123.8 (d), 129.2 (d), 131.4 (s), 131.9 (s), 149.9 (s), 162.0 (s). IR (cm^{-1}) ν_{max}: 1661 (C=N). MS (%) ESI 239 $[M+H]^+$. Anal. calcd for $C_{10}H_7ClN_2O_3$: C, 50.33; H, 2.96; N, 11.74. Found: C, 50.51; H, 2.65; N, 11.88.

(*E*)-5-(Chloromethylidene)-2-(4-methoxyphenyl)-4,5-dihydrooxazole (6b)

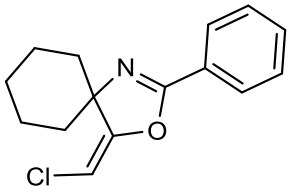


$C_{11}H_{10}ClNO_2$
M.W.: 233,6560

Following **GP6** with amide **5b** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:3) to afford **6b** in 64% yield (142 mg, 0.6 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.74 (br s, 2H), 6.07 (br s, 1H), 6.94 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7 (t), 55.4 (q), 94.5 (d), 114.0 (d), 114.2 (d), 117.7 (s), 118.4 (s), 129.9 (d), 162.7 (s), 163.0 (s). IR (cm^{-1}) ν_{max}: 1664 (C=N). MS (%) ESI 224 $[M+H]^+$. Anal. calcd for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; N, 6.26. Found: C, 58.79; H, 4.78; N, 6.01.

[13] a) Beccalli, E. M.; Borsini, E.; Broggini, G.; Palmisano, G.; Sottocornola, S. *J. Org. Chem*. **2008**, *73*, 4746. b) Hashmi, A. S. K.; Jaimes, M. C. B.; Schuster, A. M.; Rominger, F. *J. Org. Chem*. **2012**, *77*, 6394.

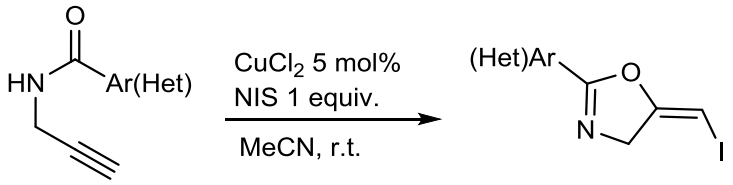
(*E*)-4-(Chloromethylidene)-3-oxa-2-phenyl-1-azaspiro[4,5]dec-1-ene (6g)



$C_{15}H_{16}ClNO$
M.W.: 261,7490

Colorless oil (83 mg, 32%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23-2.05 (m, 8H), 2.35-2.50 (m, 2H), 6.07 (s, 1H), 7.38-7.54 (m, 3H), 7.99 (d, *J* = 6.0 Hz, 2H). These data are in good agreement with those reported in the literature.[10a]

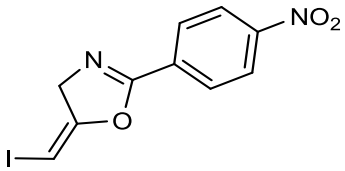
General procedure (GP7) for catalytic intramolecular alkoxyiodination of alkynyl amides.



5a,c,d,e,f,g **7**

A solution of alkynyl amide (1.0 mmol), $CuCl_2$ (5 mol %) and NIS (1 mmol) in MeCN (14 mL) was stirred at room temperature under air atmosphere until all reagent disappeared monitored by TLC (12-24 h). The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography.

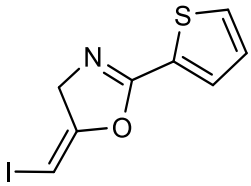
(*E*)-5-(Iodomethylidene)-2-(4-nitrophenyl)-4,5-dihydrooxazole (7a)



$C_{10}H_7IN_2O_3$
M.W.: 330,0815

Following **GP7** with amide **5a** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **7a** in 73% yield (240 mg, 0.7 mmol). White solid, m.p.: 125°C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.68 (d, *J* = 3.0 Hz, 2H), 5.88 (t, *J* = 3.0 Hz, 1H), 8.16 (d, *J* = 8.5 Hz, 2H), 8.32 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 48.3 (d), 61.4 (t), 123.8 (d), 129.0 (d), 132.2 (s), 149.9 (s), 157.3 (s), 162.2 (s). IR (cm^{-1}) ν_{max}: 1661 (C=N). MS (%) ESI 331 $[M+H]^+$. Anal. calcd for $C_{10}H_7IN_2O_3$: C, 36.39; H, 2.14; N, 8.49. Found: C, 36.61; H, 1.88; N, 8.26.

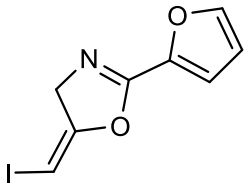
(*E*)-5-(Iodomethylidene)-2-(thiophen-2-yl)-4,5-dihydrooxazole (7c)



C_8H_6INOS
M.W.: 291,1065

Pale yellow solid (218 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64 (d, *J* = 3.0 Hz, 2H), 5.84 (t, *J* = 3.0 Hz, 1H), 7.16 (dd, *J* = 5.0, 3.5 Hz, 1H), 7.58 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.77 (d, *J* = 3.5 Hz, 1H). These data are in good agreement with those reported in the literature.[14]

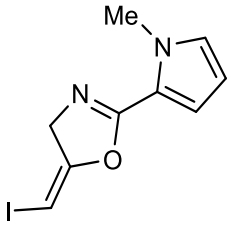
(*E*)-2-(Furan-2-yl)-5-(iodomethylidene)-4,5-dihydrooxazole (7d)



$C_8H_6INO_2$
M.W.: 275,0455

Grey solid (112 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.64(d, *J* = 3.0 Hz, 2H), 5.83 (t, *J* = 3.0 Hz, 1H), 6.56 (dd, *J* = 3.5, 2.0 Hz, 1H), 7.12 (d, *J* = 3.5 Hz, 1H), 7.63 (d, *J* = 2.0 Hz, 1H). These data are in good agreement with those reported in the literature.[12]

(*E*)-5-(Iodomethylidene)-2-(methylpirrol-2-yl)-4,5-dihydrooxazole (7e)

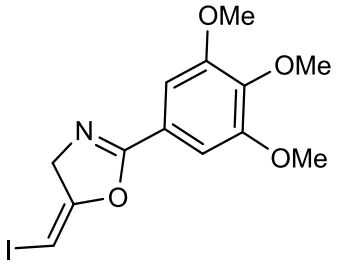


$C_9H_9IN_2O$
M.W.: 288,0885

Following **GP7** with amide **5e** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: Et_2O / petroleum ether 1:9) to afford **7e** in 52% yield (149 mg, 0.5 mmol). Pale yellow solid, m.p.: 108-109 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.94 (s, 3H), 4.58 (d, *J* = 3.0 Hz, 2H), 5.69 (t, *J* = 3.0 Hz, 1H), 6.15 (dd, *J* = 4.0, 2.5 Hz, 1H), 6.75-6.90 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.1 (q), 46.9 (d), 60.7 (t), 108.7 (d), 116.9 (d), 119.4 (s), 129.7 (d), 156.9 (s), 158.5 (s). IR (cm^{-1}) ν_{max}: 1645 (C=N). MS (%) ESI 289 $[M+H]^+$. Anal. calcd for $C_9H_9IN_2O$: C, 37.52; H, 3.15; N, 9.72. Found: C, 37.21; H, 3.41; N, 9.47.

[14] Zhang, S.; Chen, Y.; Wang, J.; Pan, Y.; Xu, Z.; Tung, C.-H. *Org. Chem. Front.* **2015**, *2*, 578.

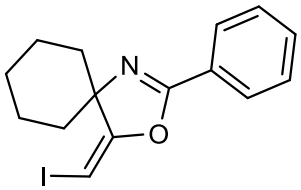
(*E*)-5-(Iodomethylidene)-2-(3,4,5-trimethoxyphenyl)-4,5-dihydrooxazole (7f)



$C_{13}H_{14}INO_4$
M.W.: 375,1625

Following **GP7** with amide **5f** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:4) to afford **7f** in 71% yield (266 mg, 0.7 mmol). White solid, m.p.: 107-108 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.89-3.96 (m, 9H), 4.69 (d, *J* = 3.0 Hz, 2H), 7.16 (d, *J* = 3.0 Hz, 1H), 7.27-7.32 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.0 (t), 56.6 (q), 61.2 (d), 104.1 (d), 122.3 (s), 135.8 (s), 140.9 (s), 147.6 (s), 153.8 (s). IR (cm^{-1}) ν_{max}: 1671 (C=N). MS (%) ESI 376 $[M+H]^+$. Anal. calcd for $C_{13}H_{14}INO_4$: C, 41.62; H, 3.76; N, 3.73. Found: C, 41.35; H, 4.03; N, 3.51.

(*E*)-4-(Iodomethylidene)-2-phenyl-3-oxa-1-azaspiro[4.5]dec-1-ene (7g)



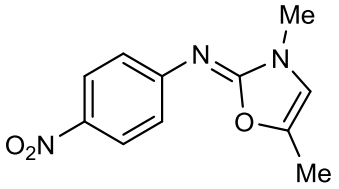
$C_{15}H_{16}INO$
M.W.: 353,2035

Colorless oil (215 mg, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.23-2.07 (m, 8H), 2.49-2.59 (m, 2H), 5.74 (s, 1H), 7.41-7.55 (m, 3H), 8.00 (d, *J* = 6.0 Hz, 2H). These data are in good agreement with those reported in the literature.[12]

General procedure (GP8) for stoichiometric intramolecular alkoxylation of urea (1a) (*path B*, Scheme 3). A solution of urea **1a** (1.0 mmol), CuCl (1.0 mmol) in MeCN (14 mL) was stirred at reflux under oxygen atmosphere for 5 hours. The solvent was removed under reduced pressure and the crude product **8** was purified by silica gel column chromatography.

General procedure (GP9) for catalytic intramolecular alkoxylation of urea (1a) (*path D*, Scheme 3). A solution of urea **1a** (1.0 mmol), CuCl (10 mol %), LiCl (3.0 mmol) in MeCN (14 mL) was stirred at reflux under oxygen atmosphere for 5 hours. The solvent was removed under reduced pressure and the crude product **8** was purified by silica gel column chromatography.

3,5-Dimethyl-2-[(4-nitrophenyl)imino]-4,5-dihydrooxazole (8)



$C_{11}H_{11}N_3O_3$
M.W.: 233,2270

Following **GP8** with amide **1a** (1.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:2) to afford **8** in 16% yield (37 mg, 0.2 mmol). Yellow oil. Following **GP9** with amide **1a** (1.0 mmol). The product **8** was afforded in 83% yield (193 mg, 0.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (d, *J* = 1.5 Hz, 3H), 3.29 (s, 3H), 6.11 (d, *J* = 1.5 Hz, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), 8.32 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4 (q), 30.2 (q), 110.4 (d), 117.6 (s), 124.5 (d), 127.0 (d), 141.1 (s), 146.1 (s), 152.6 (s). IR (cm^{-1}) ν_{max}: 1641 (C=N). MS (%) ESI 234 $[M+H]^+$. Anal. calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.74; H, 5.06; N, 18.29.

1.2 Palladium(II)-Catalyzed Oxidative Alkoxyarylation Reactions of Alkenols

Abstract

An original and unexpected method to perform an alkoxylation / arylation sequence of 3-aza-5-alkenols, under oxidative Pd-catalyzed conditions, has been described. The reaction, which involves $PdCl_2(CH_3CN)_2$ as catalyst and a stoichiometric amount of aryl stannanes in presence of copper salt as oxidant, occurs selectively through a 7-*endo*-cyclization process with a resulting 1,1-difunctionnalization (intramolecular alkoxylation, intermolecular arylation) of the starting terminal olefin. Conversely, when the reaction is run in absence of an aryl source, the same 7-*endo*-cyclization process was not observed confirming its peculiarity.

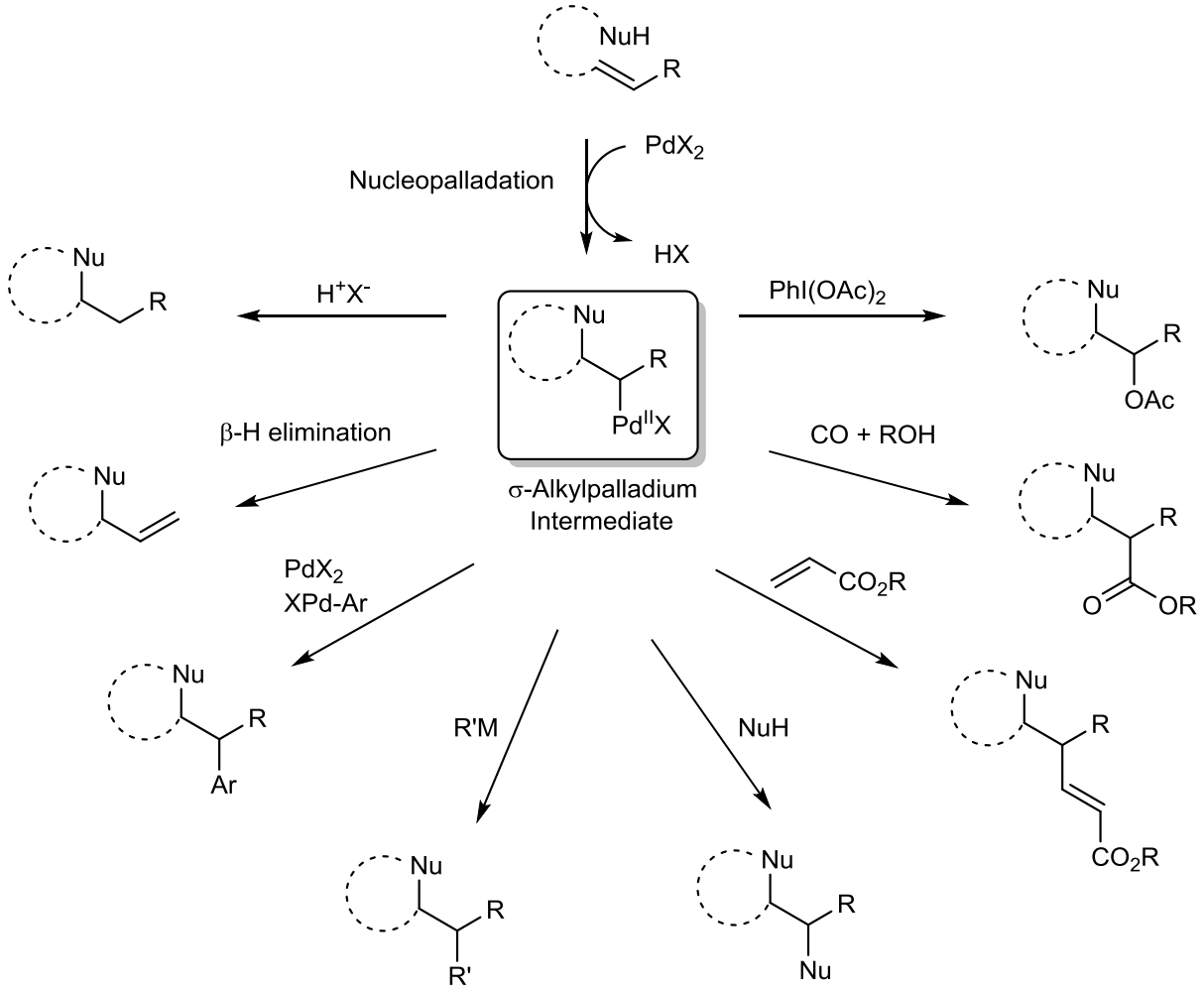
1.2.1. Introduction / Aim of This Work

In the panorama of transition metal-catalyzed reactions, palladium-catalyzed heterocyclizations onto alkenes have a particular importance for synthetic chemists because of the complexity formed, the atom and economical approach and the prevalence of the heterocyclic products in bioactive targets.[15]

The coordination of an alkene to a palladium(II) complex renders a typically electron-rich alkene more electrophilic. This π-complex formed can be attacked by a heteroatom nucleophile such as oxygen (water, alcohols, and acetate ions) or as nitrogen (amines, amides, carbamates).[16] This sequence is named nucleopalladation (oxypalladation or aminopalladation). Then, the resulting σ-alkyl Pd(II) intermediate can participate in a range of subsequent transformations including β-hydride elimination (Wacker-type reaction), alkoxycarbonylation, Heck reaction, arylation or protodemetallation, leading to various functionalized heterocyclic scaffolds (Scheme 11).

[15] For books on this subject, see: a) Bäckvall, J.-E. In Modern Oxidation Methods; Wiley-VCH: Weinheim, 2004. b) Tsuji, J. In Palladium Reagents and Catalysts, 2nd ed.; Wiley: New York, 2004. c) Negishi, E -I. In Handbook of Organopalladium Chemistry for Organic Synthesis; John Wiley & Sons, Inc.: New York, 2002.

[16] For a selection of reviews on nucleopalladation, see: a) Kočovský, P.; Bäckvall, J.-E. *Chem. Eur. J.* **2015**, *21*, 36. b) McDonald, R. I.; Liu, G.; Stahl, S. S. *Chem. Rev.* **2011**, *111*, 2981. c) Keith, J. A.; Henry, P. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 9038. d) Minatti, A.; Muñiz, K. *Chem. Soc. Rev.* **2007**, *36*, 1142. e) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318.



Scheme 11: Different Possible Functionalizations of the σ-Alkylpalladium Intermediate.

This research field has grown considerably and a range of palladium-catalyzed oxidation reactions are routinely used in synthetic chemistry laboratories. Thus, the last years, the research interest of the Broggini's group has focused, inter alia, to the development of this type of various intramolecular palladium-catalyzed reactions affording heterocyclic products.[17] For example, a 6-*exo*-*trig* cyclization catalyzed by Pd(II) species has been described and allowing the synthesis of 1,4-oxazine derivatives from 3-aza-5-alkenols in mild aerobic conditions (Figure 3, path a).[18] From a mechanistic point of view, after nucleopalladation involving a 6-*exo*-*trig* cyclization process, the σ-alkylpalladium complex undergoes a subsequent β-hydride elimination / isomerization sequence leading to the final

[17] a) Broggini, G.; Beccalli, E. M.; Borelli, T.; Brusa, F.; Gazzola, S.; Mazza, A. *Eur. J. Org. Chem.* **2015**, 4261-4268. b) Broggini, G.; Barbera, V.; Beccalli, E. M.; Chiacchio, U.; Fasana, A.; Galli, S.; Gazzola, S. *Adv. Synth. Catal.* **2013**, *355*, 1640-1648. c) Borsini, E.; Broggini, G.; Fasana, A.; Galli, S.; Khansaa, M.; Piarulli, U.; Rigamonti, M. *Adv. Synth. Catal.* **2011**, *353*, 985-994.

[18] Broggini, G.; Beccalli, E. M.; Borsini, E.; Fasana, A.; Zecchi, G. *Synlett* **2011**, 227-230.

product and a Pd(0) species after HCl elimination. At this point, this later complex is reoxidized in presence of molecular oxygen.

In the continuity of this study, in order to extend the applicability of this kind of starting materials (3-aza-5-alkenols), and to synthesize more functionalized heterocycles, we envisaged to trap the σ-alkylpalladium complex intermediate by a subsequent arylation step. Furthermore, we focused on the use of the couple palladium(II) / copper(II) as catalyst and oxidizing agent, respectively, since this couple has proved his efficiency during double functionalizations of C-C multiple bonds in one-pot processes.[19] In the beginning of this study, we centered our attention, for the development of this oxidative cyclization of 3-aza-5-alkenols in alkoxyarylative conditions, with the use of arylstannanes. Furthermore, in that case with these arene sources (R_3SnAr), we observed that the 7-*endo*-cyclization prevails to the most common 6-*exo*-one, and the arylation occurred in the same carbon than the alkoxylation (Figure 3, path b). Thus, in the presence of this aryl source, the mechanism should not follow the same elementary steps, namely an oxypalladation and a transmetalation.

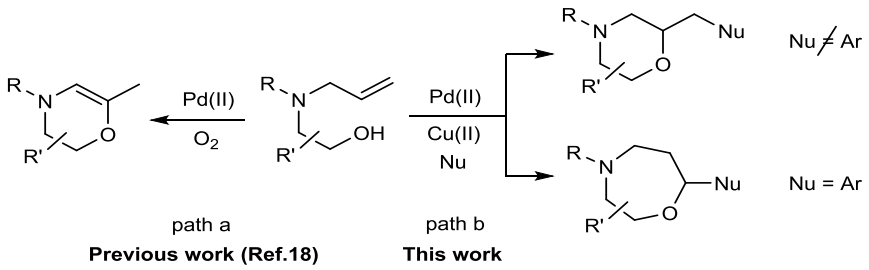


Figure 3: Possible Pd-Catalyzed *exo*- and *endo*-Cyclization of 3-Aza-5-alkenols.

Before to present our efforts on optimization of this original Pd-catalyzed oxidative alkoxyarylations of alkenols, we will describe some examples of oxypalladation reactions developed on alkenes.[20] It should be noted that this type of reaction is also reported from alkynes and allenes, but we will not present them in this part.

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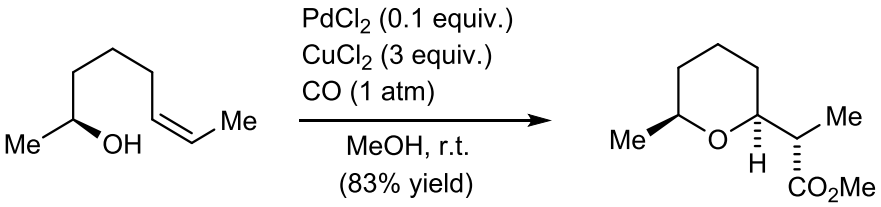
[19] Beccalli, E. M.; Broggini, G.; Gazzola, S.; Mazza, A. *Org. Biomol. Chem*. **2014**, *12*, 6767-6789.

[20] For selected examples of intramolecular oxidative Pd-catalyzed reactions on alkenes, see: a) Chen, P.-Y.; Huang, K.-S.; Tsai, C.-C.; Wang, T.-P.; Wang, E.-C. *Org. Lett*. **2012**, *14*, 4930-4933. b) Alonso, F.; Sanchez, D.; Soler, T.; Yus, M. *Adv. Synth. Catal*. **2008**, *350*, 2118-2126. c) Szolcsanyi, P.; Gracza, T. *Chem. Commun*. **2005**, 3948-3950. For selected examples of analogous reactions on alkynes, see: d) Watanabe, K.; Iwata, Y.; Adachi, S.; Nishikawa, T.; Yoshida, Y.; Kameda, S.; Ide, M.; Saikaw, Y.; Nakata, M. *J. Org. Chem*. **2010**, *75*, 5573-5579. For selected examples of analogous reactions on allenes, see: e) Le Bras, J.; Muzart, J. *Chem. Soc. Rev*. **2014**, *43*, 3003-3040. f) Alcaide, B.; Almendros, P.; Rodriguez-Acebes, R. *J. Org. Chem*. **2006**, *71*, 2346-2351. For recent reviews on the development of the σ-

Furthermore, given the unexpected structures of our final products, we will concentrate also in the presentation of original functionalizations of terminal alkenes achieved in presence of arylstannanes.[21]

a) Oxypalladations

The first intramolecular oxypalladation of alkenes was reported in 1984 and occurred jointly with a carbonylation. The process, catalyzed by a Pd(II) complex, starts with π-coordination to the double bond, followed by an intramolecular anti-oxypalladation. Then, the desired methyl ester is produced by trapping the resulting σ-alkylpalladium with a carbonylation / esterification sequence. The cycle is completed by reoxidation of the generated palladium(0) species in presence of Cu(II) salt as oxidizing agent (Scheme 12).[22]



Scheme 12: Intramolecular Oxypalladation / Carbonylation of Alkenes.

Usually, the intramolecular oxypalladation can take place via either an anti- or a syn-addition process of the nucleophile, which allows a stereocontrol of the reaction, and depends to structure of the starting material (neighboring group effects) or experimental conditions used.

In the next example involving an oxypalladation followed by arylation, the stereochemical course is controlled by a phosphine ligand. Indeed, the reaction that involves the use of a monodentate phosphine led to syn-palladation via the alkoxide coordination to palladium, in contrast the use of a bidentate phosphine ligand, a strongly chelating agent which prevents the alkoxide coordination, afforded the product attributed to trans-oxypalladation (Scheme 13).[23]

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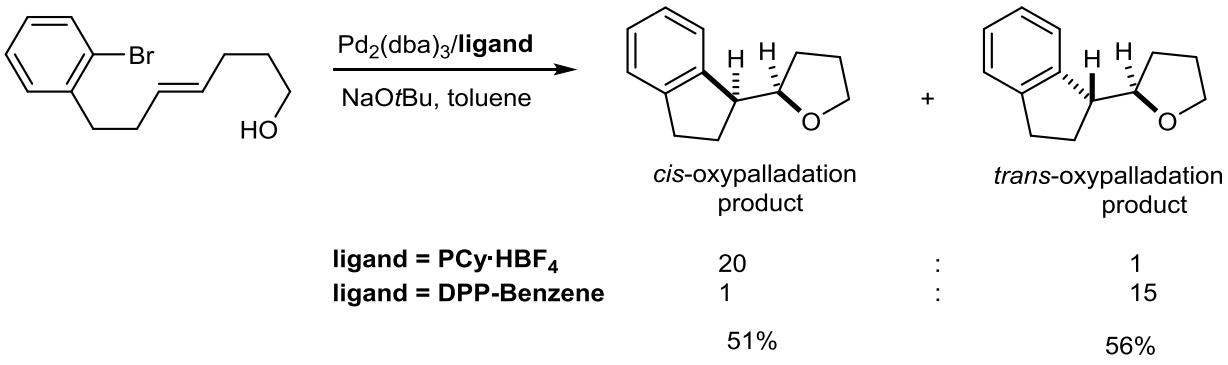
alkylpalladium intermediat see: a) Kočovsky, P.; Bäckvall, J.-E. *Chem. Eur. J*. **2015**, *21*, 36. b) McDonald, R. I.; Liu, G.; Stahl, S. *Chem. Rev*. **2011**, *111*, 2981.

[21] a) Gligorich, K. M.; Cummings, S. A.; Sigman, M. S. *J. Am. Chem. Soc*. **2007**, *129*, 14193. b) Urkalan, K. B.; Sigman, M. S. *Angew. Chem. Int. Ed*. **2009**, *48*, 3146. c) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. *Org. Lett*. **2010**, *12*, 2848-2851. d) Satterfield, A. D.; Kubota, A.; Sanford, M. S. *Org. Lett*. **2011**, *13*, 1076.

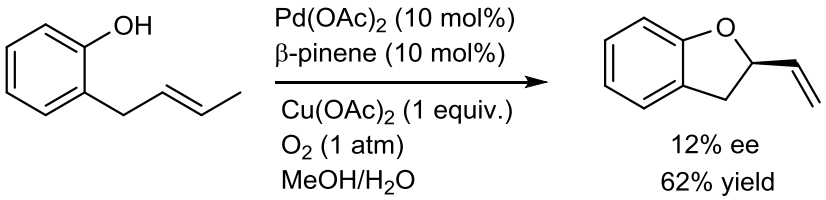
[22] Semmelhack, M. F.; Bodurov, C. *J. Am. Chem. Soc*. **1984**, *106*, 1496-1498.

[23] Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc*. **2006**, *128*, 2893.



Scheme 13: Different Stereochemical Outcomes by Variation of the Achiral Ligand.

In 1978, was also reported an example of enantioselective Pd(II)-catalyzed oxypalladation followed by β-hydride elimination from ortho-allyl phenols. The use of β-pinene as chiral ligand led to a low enantiomeric excess (Scheme 14).[24]



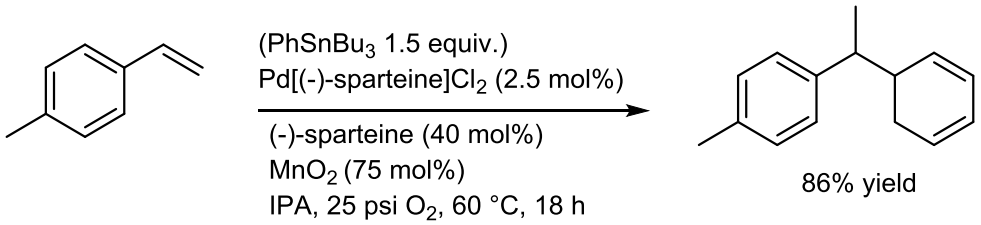
Scheme 14: Enantioselective Oxypalladation / β-hydride Elimination.

b) Functionalizations of alkenes

For this part, we will focus only on examples involving the functionalization of alkenes in presence of arylstannanes.

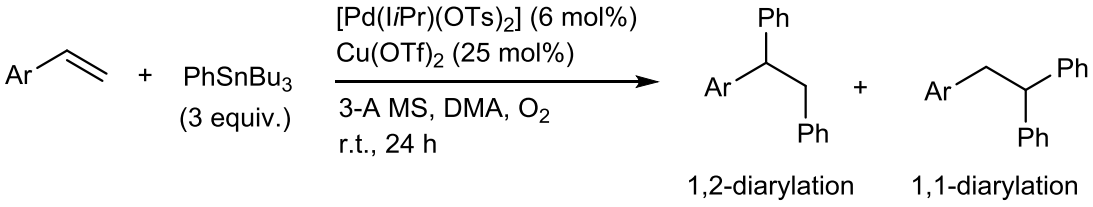
First of all, in 2007, Sigman presented a palladium(II)-catalyzed reductive coupling of styrene with organostannanes using a tandem alcohol (2-propanol) oxidation under aerobic conditions (Scheme 15). To a mechanistic point of view, oxidation of 2-propanol with a Pd catalyst leads to the formation of a Pd(II)-hydride. Coordination and insertion of the alkene into this hydride complex yields a σ-alkyl intermediate. This latter undergoes a transmetalation and a subsequent reductive elimination which generates the reductive coupling product as well as the reduced catalyst Pd(0). This Pd(0) complex is reoxydized in presence of aerobic conditions (Scheme 15).[19a]

[24] Hosokawa, T.; Miyagi, S.; Murahashi, S.-I-; Sonoda, A. *J. Org. Chem*. 43, *14*, **1978**, 2752-2757.



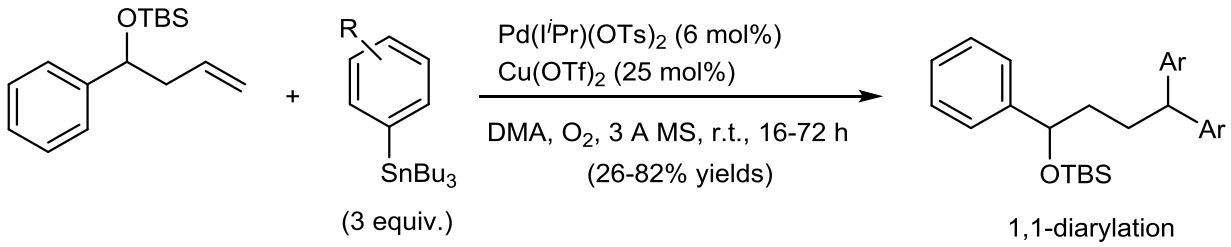
Scheme 15: Palladium-Catalyzed Reductive Coupling of Styrenes and Organostannanes.

Two years later, Sigman[19b] reported a palladium-catalyzed oxidative difunctionalization of terminal alkenes with organostannanes and molecular oxygen. A cationic palladium complex catalyzes the transformations which can lead to 1,2- or 1,1-difunctionalization depending on the type of terminal double bond (conjugated or nonconjugated) (Scheme 16). The authors proposed an oxidative-Heck type reaction for the first arylation, while the second functionalization proceeds via a π-benzyl intermediate.



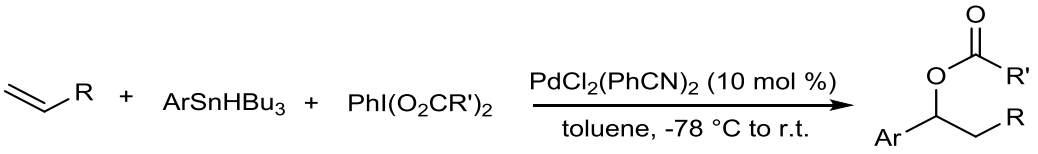
Scheme 16: 1,2-Diarylation of Styrene.

Following this study, the same author, in 2010, disclosed the scope of this palladium(II)-catalyzed oxidative 1,1-diarylation reaction of terminal olefins using aryl stannanes.[19c]



Scheme 17: 1,1-Diarylation of Terminal Olefins.

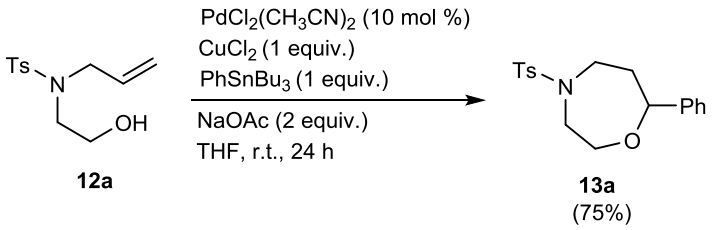
Lastly, following the same concept, in 2011 Sanford[19d] described the 1,1-arylacetoxylation of different α-olefins using organostannanes and hypervalent iodine oxidants (Scheme 18). In this case, the π-benzyl intermediate is oxidized by the hypervalent iodine.



Scheme 18: 1,1-Aryloxygenation of Terminal Olefins.

1.2.2. Optimization of the Conditions

About our subject, we began our optimizations for the alkoxyarylation sequence by using the conditions described by the group of Jung for a Pd(II)-catalyzed aryl-alkenyl coupling (oxidative Heck-type coupling) in presence of copper salt as oxidant and aryl stanannes.[25] In conditions almost similar, our model substrate (3-aza-5-alkenol) **12a** treated with 10 mol % of $PdCl_2(CH_3CN)_2$, a stoichiometric amount of phenyl(tributyl)stannane, an excess of $CuCl_2$ and NaOAc in tetrahydrofuran at room temperature for 24 hours, gave the 4-tosyl-7-phenyl-oxazepane **13a** as the sole product (Scheme 19).



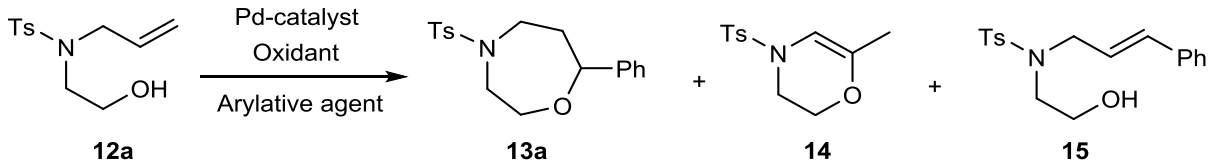
Scheme 19: Alkoxyarylation Reaction of the 3-Aza-5-alkenol **12a**.

To improve this yield, we tested further conditions varying the palladium-catalyst, the oxidant, the solvent and also the temperature of the reaction. The results are presented on Table 5. Firstly, the reaction performed without base gave the desired oxazepane **13a** in 78% yield (entry 2). The use of half the amount of palladium(II)-catalyst led to the expected product, however with a low yield (entry 3). The reaction realized without Pd(II) catalyst furnished the unchanged starting material proving its

[25] Parrish, J. P.; Jung, Y. C.; Shin, S. I.; Jung, K. W. *J. Org. Chem.* **2003**, *67*, 7127-7130.

essential role for the outcome of the sequence (entry 4). Then, other Pd(II)-catalysts such as $Pd(OAc)_2$ or $Pd(TFA)_2$ were tested and shown a similar catalytic activity but lower yields were obtained (entries 5-6). Different solvents were screened and, while DMF and dioxane were suitable solvents for the reaction, CH_2Cl_2 did not allow a complete convertion after 24 hours. Furthermore, a heating at 100 °C in DMF allowed increasing the yield from 61% to 86% (entries 7-10). Thereafter, we interested in the change of oxidant. Thus, an exclusive or prevalent formation of 6-methyl-4-tosyl-3,4-dihydro-*2H*-1,4-oxazine (**14**) was due to the change of the oxidant agent from $CuCl_2$ to $Cu(OAc)_2$ or catalytic $CuCl_2$ in molecular oxygen. This product arose from an alkoxylation / β-hydride elimination / isomerization sequence (entries 11-12).

Finally, taking into account the data present in the literature we envisaged to modify also the aryl source employing organoboron reagents instead of arylstannanes.[26] Performing the reaction in the best conditions showed in entry 2, both with $PhB(OH)_2$ or 4-methylphenylboronic acid only starting material was recovered (entries 13-14). Furthermore, a heating at reflux gave only the formation of a complex mixture of products (entry 15). Then, following conditions successfully employed for the functionalization of alkenes reported by Mori,[27] we treated the substrate **12a** with 4-methylphenylboronic acid in the presence of $Pd(OAc)_2$ as catalyst, $Cu(OAc)_2$ and LiOAc in DMF at 100 °C (entry 16). After 18 hours as reaction time, the crude mixture revealed only the arylation product **15**, isolated in 36% yield. The same outcome of reaction was observed using $PdCl_2(CH_3CN)_2$ as catalyst instead of $Pd(OAc)_2$ (entry 17). Finally, we probed the conditions usefully exploited for the arylative cyclization of alkenyl amines, which are $PdCl_2(CH_3CN)_2$ as catalyst with $Cu(OAc)_2$, 4-methylphenylboronic acid and Et_3N as additive in MeCN at reflux (entry 18).[28] However, despite the complete conversion of the substrate, product **13a** was not detected in the crude mixture, from which only compound **15** was isolated in 44% yield.



12a **13a** **14** **15**

[26] a) Andappan, M. M. S.; Nilsson, P.; Von Schenck, H. *J. Org. Chem.* **2004**, *69*, 5212-5218. b) Jung, J. C.; Mishra, R. K.; Yoon, C. H.; Jung, K. W. *Org. Lett.* **2003**, *5*, 2231-2234.

[27] Du, X.; Suguro, M.; Hirabayashi, K.; Mori, A. *Org. Lett.* **2001**, *3*, 3313-3316.

[28] Zheng, J.; Huang, L.; Huang, C.; Wu, W.; Jiang, H. *J. Org. Chem.* **2015**, *80*, 1235-1242.

Entry	*Catalyst*	*Oxidant*	*Arylative agent*	*Solvent*	*Temp. (°C)*	*Product (%)[a]*
1[b]	$PdCl_2(CH_3CN)_2$	$CuCl_2$	Bu_3SnPh	THF	25	**13a** (75)
2	$PdCl_2(CH_3CN)_2$	$CuCl_2$	Bu_3SnPh	THF	25	**13a** (78)
3[c]	$PdCl_2(CH_3CN)_2$	$CuCl_2$	Bu_3SnPh	THF	25	**13a** (62)
4	-	$CuCl_2$	Bu_3SnPh	THF	25	S.M.
5	$Pd(OAc)_2$	$CuCl_2$	Bu_3SnPh	THF	25	**13a** (64)
6	$Pd(TFA)_2$	$CuCl_2$	Bu_3SnPh	THF	25	**13a** (67)
7	$PdCl_2(CH_3CN)_2$	$CuCl_2$	Bu_3SnPh	DMF	25	**13a** (61)
8	$PdCl_2(CH_3CN)_2$	$CuCl_2$	Bu_3SnPh	dioxane	25	**13a** (49)
9	$PdCl_2(CH_3CN)_2$	$CuCl_2$	Bu_3SnPh	CH_2Cl_2	25	**13a** (13)
10[d]	$PdCl_2(CH_3CN)_2$	$CuCl_2$	Bu_3SnPh	DMF	100	**13a** (86)
11	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	Bu_3SnPh	THF	25	**14** (47)
12[e]	$PdCl_2(CH_3CN)_2$	$CuCl_2/O_2$	Bu_3SnPh	THF	25	**13a** (8) + **14** (42)
13	$PdCl_2(CH_3CN)_2$	$CuCl_2$	$PhB(OH)_2$	THF	25	S.M.
14	$PdCl_2(CH_3CN)_2$	$CuCl_2$	4-tolylB$(OH)_2$	THF	25	S.M.
15	$PdCl_2(CH_3CN)_2$	$CuCl_2$	$PhB(OH)_2$	THF	Reflux	-[f]
16[g]	$Pd(OAc)_2$	$Cu(OAc)_2$	4-tolylB$(OH)_2$	DMF	100	**15** (36)
17[h]	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	4-tolylB$(OH)_2$	DMF	100	**15** (40)
18[i]	$PdCl_2(CH_3CN)_2$	$Cu(OAc)_2$	4-tolylB$(OH)_2$	MeCN	Reflux	**15** (44)

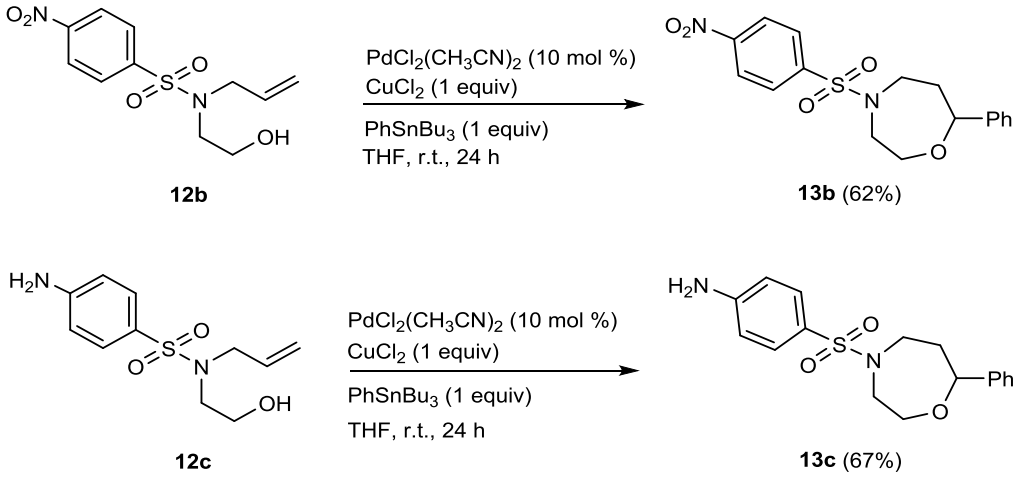
[a] Yields of isolated products. [b] Reaction performed in the presence of NaOAc (2 equiv). [c] 5 mol % of $PdCl_2(CH_3CN)_2$ instead of 10 mol %. [d] The reaction was completed after 8 h. [e] $CuCl_2$ (10 mol %). [f] A complex mixture of tarry products was obtained. [g] **12a** (0.4 mmol), $Pd(OAc)_2$ (10 mol %), $Cu(OAc)_2$ (2 equiv), 4-tolylB$(OH)_2$ (1 equiv), LiOAc (3 equiv), DMF (10 mL) at 100 °C for 18 h. [h] Conditions (*h*) with $PdCl_2(CH_3CN)_2$ (10 mol %) as catalyst. [i] **12a** (0.4 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), $Cu(OAc)_2$ (3 equiv), 4-tolylB$(OH)_2$ (0.6 mmol), Et_3N (2 equiv), MeCN (5 mL) at reflux for 24 h.

Table 5: Optimization Conditions for 7-*endo*-*trig*-Alkoxyarylation Reaction.

With these optimized conditions in hand, $PdCl_2(CH_3CN)_2$ 10 mol %, $CuCl_2$ 1 equivalent, $PhSnBu_3$ 1 equivalent in THF at room temperature, the scope of this procedure was investigated. Due to the mildness of the procedure, we decided to keep these conditions even if in DMF at 100 °C the yield of the isolated product was partially increased.

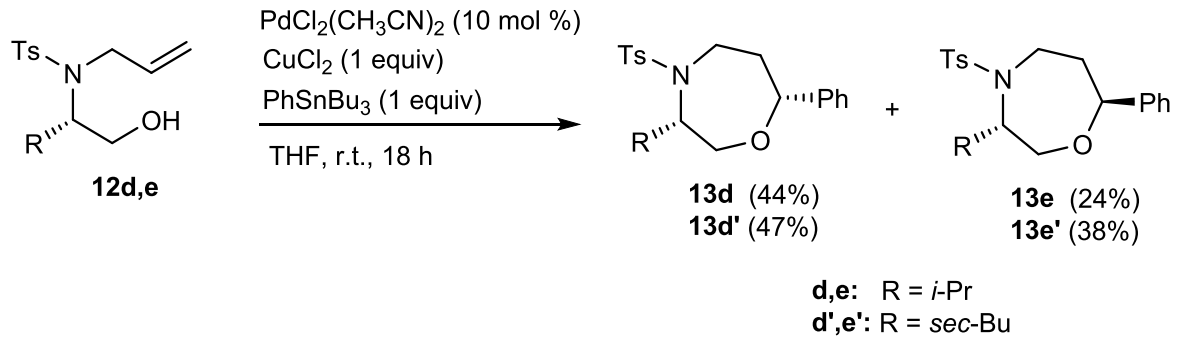
1.2.3. Scope

The efficient access to oxazepane ring via a selective 7-*endo-trig* cyclization, prompted us to extent this method to other 3-aza-5-alkenol derivatives. For that, the optimal alkoxyarylative conditions previously optimized were used in order to have evidences for a general behaviour of this catalytic system. The effect of the substitution on the sulfonyl moiety present on the nitrogen atom was investigated first (Scheme 20). Electron-withdrawing *para*-substitution, such as nitro (**12b**) or electron-donating *para*-substitution, such as amine (**12c**) also led to the corresponding oxazepanes **13b** and **13c** in modest yields.



Scheme 20: Alkoxylation Process on 3-Aza-5-alkenols **12b** and **12c**.

Then, this method was extended to a more challenging diastereoselective variant from 3-aza-5-alkenol compounds **12d-e**, which arose from (+)-valinol and (+)-isoleucinol respectively. In the previously developed conditions, these two enantiopure alkenols led to the two diastereoisomeric 7-membered ring products (**13d-d'** and **13e-e'**) in a separable mixture (1,8 / 1 and 1,2 / 1 respectively) (Scheme 21). Thus, this reaction was ineffective from the stereochemical point of view, but very selective under the 7-*endo* approach and the 1,1-difunctionalization of the terminal olefin.



Scheme 21: Enantiopure Chiral Substrates Cyclization.

The X-ray crystal structure analysis of the compounds **13e'** allowed to confirm the oxazepane structure as well as to assign the *S*-configuration to the new stereocenter.[29] The similarity of the ^{1}H and ^{13}C NMR spectra permitted the assignment of the absolute configuration to all diastereomers (Figure 4).

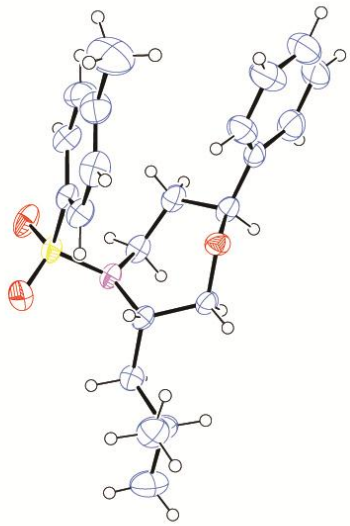
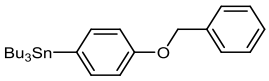
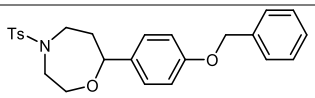
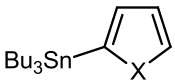
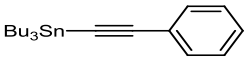
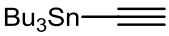
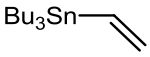


Figure 4: ORTEP Drawing of Compound **13e'**.

[29] We acknowledge for the X-ray analysis Dr. Carlo Castellano, Chemistry Department, Università degli Studi di Milano.

1.2.4. Different Organotin Derivatives

To better understand the central role of the $PhSnBu_3$ as phenyl source, reactions with substrate **12a** and others organotin derivatives were carried out in the standard conditions of Table 5, Entry 2. On the one hand, 4-benzyloxyphenyl(tributyl)stannane performed well, affording the oxazepane **20** in 80% via a 7-*endo-trig* process (Table 6, entry 1). On the other hand, furan-yl or thiophene-yl substituted stannanes, as well alkynyl or alkenyl(tributyl)stannanes gave only complex mixtures of degradation (entries 2-5). Thus, the overall results obtained suggest that only arylstannanes are efficient for this intramolecular alkoxylation reaction on 3-aza-5-alkenols.

Entry	***R***	***Time (h)***	***Product***
1		18	 **20** (80%)
2	 X = O, S	24	Degradation compounds
3		24	Degradation compounds
4		24	Degradation compounds
5		24	Degradation compounds

[a] The reaction was performed under the conditions of Table 5, Entry 2: **12a** (0.4 mmol), $PdCl_2(CH_3CN)_2$ (10 mol %), $CuCl_2$ (1.0 equiv.), organotin derivative (1 equiv.), THF (5 mL) at room temperature.

Table 6: Different Stannanes Employed for the Alkoxyarylation Reaction.

Given this limitation of reactivity to arylstannanes, and in order to generalize this unexpected cyclization involving only a 7-*endo*-*trig* process with a 1,1-difunctionalization of the double bond, we considered some extensions to other transformations can complete the catalytic process.

1.2.5. Applicability of the 7-endo-Cyclization

First, carbonylative conditions (1 atm) were used on the alkenols **12a,b** with a catalytic amount of $PdCl_2(CH_3CN)_2$ (5 mol %) and a stoichiometric amount of $CuCl_2$ in methanol at room temperature for 24 h. In these cases, an alkoxylation / carboalkoxylation sequence occuried. However, only the 6-*exo*-*trig* cyclization took place, affording the corresponding 2-[(methoxycarbonyl)methyl]-morpholines (**16a** and **16b**) with 65% and 74% yields, respectively (Scheme 22, equation 1).

An alkoxychlorination process was also investigated under two different conditions based on the presence of $PdCl_2(CH_3CN)_2$ as catalyst (Scheme 22, equations 2 and 3). Either experiment realized with an excess of $CuCl_2$ in THF at room temperature or with NCS as the chlorine source in CH_2Cl_2 at room temperature, the cyclization occurred with formation of the 5-chloromethyl-morpholine **17**, via here again a 6-*exo*-*trig* cyclization.

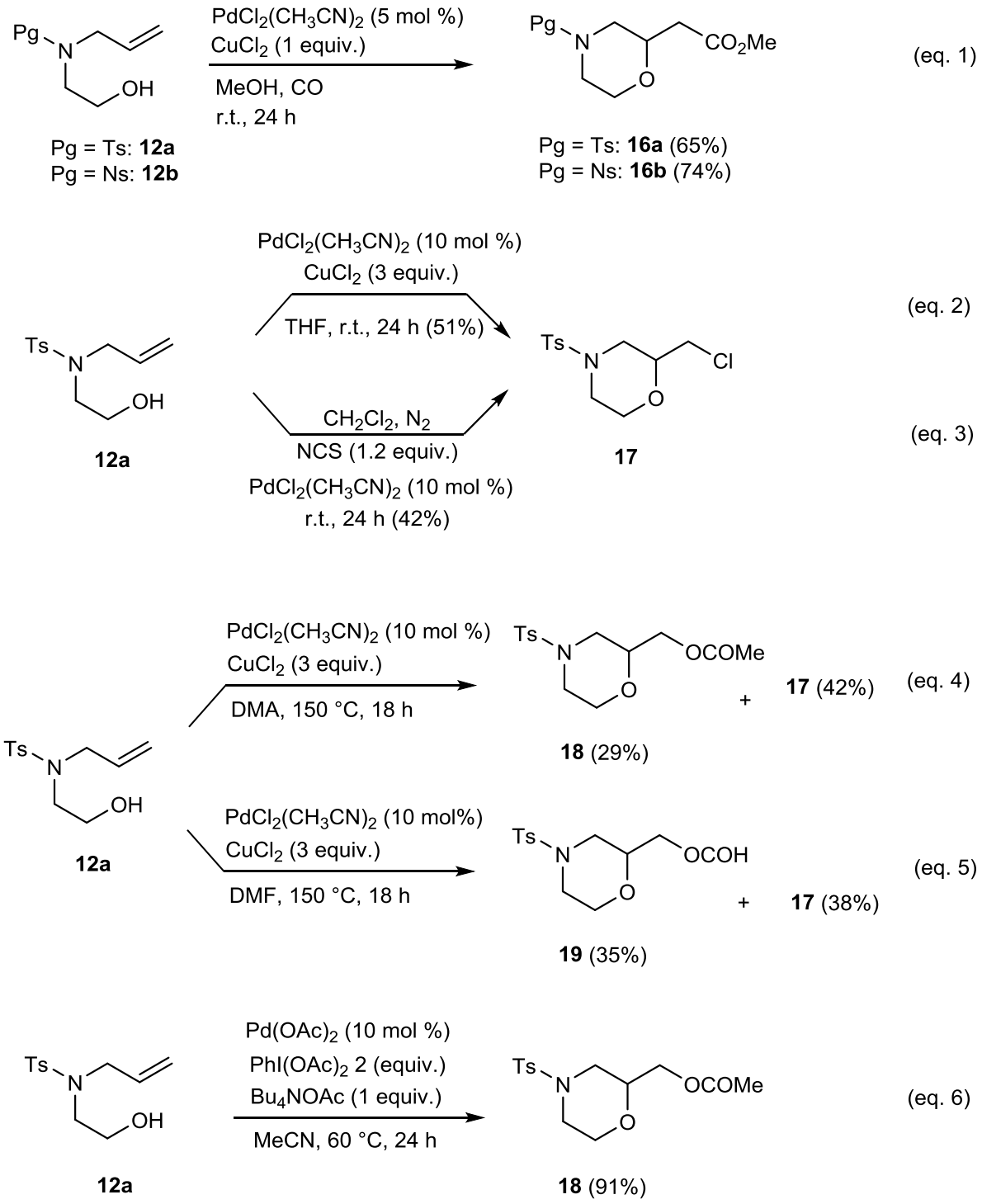
Following our previously work on the arylation / esterification procedure performed on indolyl allylamides,[30] we tested this sequence on the substrate **12a** using our previous reported conditions. The best results were obtained by use of $PdCl_2(CH_3CN)_2$ as catalyst and 3 equivalents of $CuCl_2$ in DMA or in DMF at 150 °C. These trials led to the acetoxy-morpholine **18** and the formic ester **19** respectively, in mixture with the chloro-derivative **17** (Scheme 22, equations 4 and 5). Worthy of note, despite the low selectivity, the outcome of the reaction also supplied only 6-membered ring products.

Finally, established conditions for Pd-catalyzed amino- or oxy-acetoxylation of alkenes in the presence of $PhI(OAc)_2$ as oxidant were tested.[31] It should be noted that for a mechanistic point of view, these sequences involve Pd(IV)-intermediates. In the event, the treatment of **12a** with $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2 equiv.), Bu_4NOAc (1 equiv.) in acetonitrile at 60 °C for 24 h, selectively gave the 5-acetoxymethyl-morpholine **18** with good yields (Scheme 22, equation 6).

---

[30] Broggini, G.; Barbera, V.; Beccalli, E. M.; Borsini, E.; Galli, S.; Lanza, G.; Zecchi, H. *Adv. Synth. Catal*. **2012**, *354*, 159.

[31] a) Rajabi, J.; Lorion, M. M.; Ly, V.; Liron, F.; Oble, J.; Prestat, G.; Poli, G. *Chem. Eur. J*. **2014**, *20*, 1539. b) Manick, A.D.; Duret, G.; Tran, D. N.; berhal, F.; Prestat, G. *Org. Chem. Front*. **2014**, *1*, 1058. c) Martinez, C.; Wu, Y.; Weinstein, A. B.; Stahl, S. S.; Liu, G.; Mũniz, K. *J. Org. Chem*. **2013**, *78*, 6309. d) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc*. **2005**, *127*, 7690.



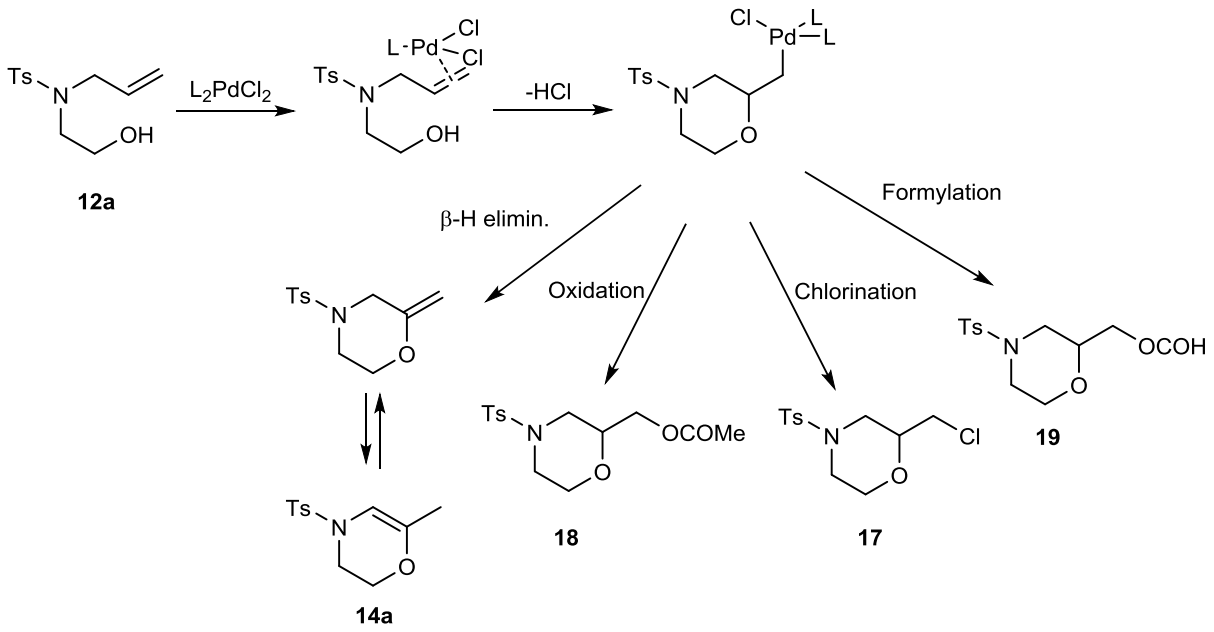
Scheme 22: Different Synthetic Transformations.

According these results collected in Scheme 22, which involved in all the cases a 6-*exo*-*trig* cyclization, we can confirm the exclusive behaviour of the Pd-catalyzed 7-*endo*-*trig* alkoxylation / arylation sequence using arylstannanes.

1.2.6. Mechanistic Investigations

Given these results, which involved a 7-*endo-trig* process during the alkoxyarylation reaction or a 6-*exo-trig* cyclization during the other oxypalladation / functionalization (carbonylation, acyloxylation, chloration) sequence; we suggested two different mechanistic pathways.

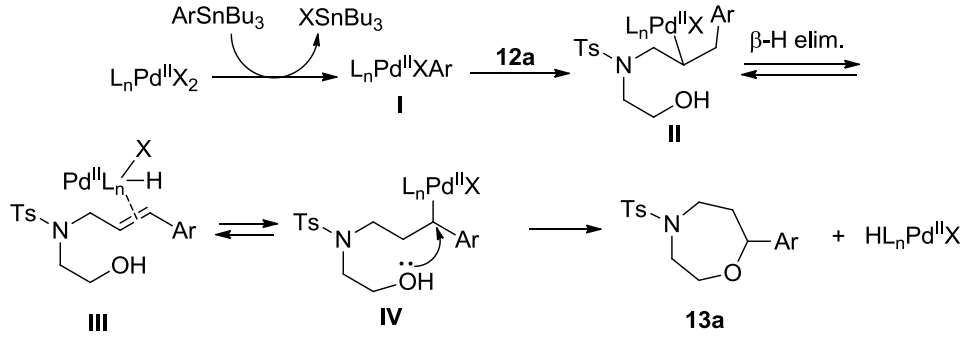
First, for the well-documented sequences reported in the Scheme 22, we proposed that the reactions likely proceed via an intramolecular 6-*exo-trig* oxypalladation step, which affords the corresponding cyclic oxypalladated intermediate. This latter can either evolve along diverse pathways such as β-H elimination, oxidation by a strong oxidant like $PhI(OAc)_2$, chloration in presence of chorine source and formylation in presence of DMF (Scheme 23).



Scheme 23: Complexation of Pd(II) and Evolution of the σ-Alkylpalladium Intermediate.

However, we cannot consider that this cyclic oxypalladated intermediate is trapped via a transmetalation step, since the reactions realized in presence of arylstannanes do not occur via a 6-*exo-trig* cyclization but via a 7-*endo-trig* process. That why, a second mechanistic pathway could be postulated for the alkoxyarylation reaction. For that, we relied on some papers concerning the Pd-catalyzed oxidative 1,1-diarylation of terminal olefins using aryl stannanes previously presented.

Thus, we suggested the formation of an intermediate Pd(Ar)Cl complex via a transmetalation between Bu_3SnAr and the palladium(II) catalyst **I**.[32] Then, a carbopalladation step followed by a reversible dehydropalladation led to the arylated intermediate **III** and a H[Pd]Cl complex probably still complexed to the double bond. Finally, we envisaged an olefin reinsertion to give a new Pd-π-benzyl complex **IV**, which can be trap intramolecularly by the hydroxy-moiety leading to the final product.

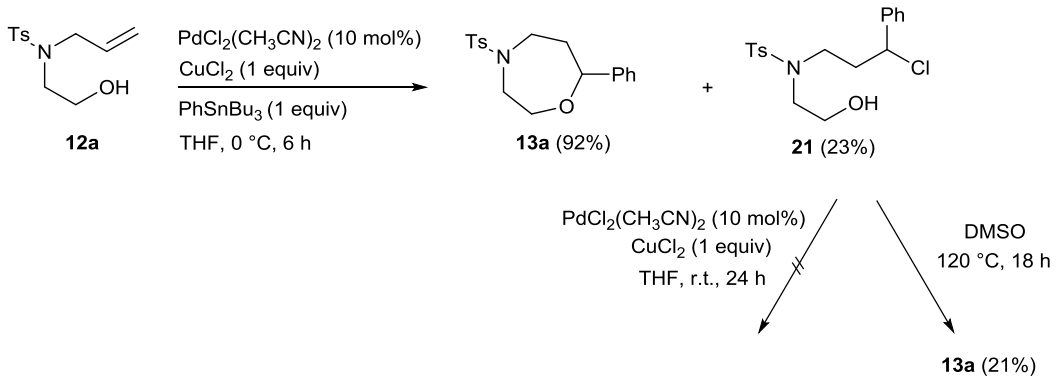


Scheme 24: Proposed Mechanism for the 7-*endo*-*trig* Cyclization Depicted on Substrate **12a**.

Given that analogous reaction conditions are known to allow the arylchlorination of alkenes,[33] and in order to exclude the participation of a chlorophenyl derivative as possible first-formed intermediate before the cyclization, we investigated the behavior of the compound **21**. This latter has been obtained during a reaction realized in standard conditions at 0 °C (Scheme 25). Then, two experiments have shown that the intramolecular displacement of the chlorine atom of **21** by the hydroxyl group was efficient only working at 120 °C in DMSO, whereas the couple palladium(II) / copper(II) as catalyst and oxidizing agent did not afford the cyclization.

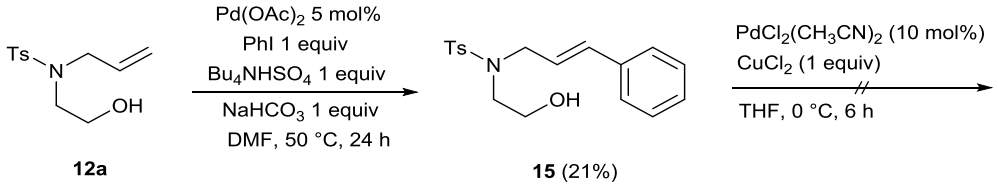
[32] For the transmetalation process between Bu3SnAr and palladium(II) species, see: Stille, J. K. Angew. Chem. Int. Ed. 1986, 25, 508.

[33] a) Kalyani, D.; Sanford, M. S. J. Am. Chem. Soc. 2008, 130, 2150-2151. b) Kalyani, D.; Satterfield, A. D.; Sanford, M. S. J. Am. Chem. Soc. 2010, 132, 8419-8427.



Scheme 25: Investigating the Behavior of the Chlorophenyl Derivative.

On the other hand, an hydroalkoxylation process on a first-formed arylated double bond intermediate was ruled out due to the unsuccessful Pd(II)-catalyzed oxidative cyclization performed on the derivative **15**, which was prepared by a Mizoroki-Heck reaction in the Jeffery conditions from the substrate **12a** (Scheme 26)**.**



Scheme 26: Unsuccessful Pd(II)-Catalyzed Oxidative Cyclization Performed on the Derivative **15**.

Following these experiments and based on reported mechanisms involving a Pd-π-benzyl complex obtained after an oxidative Heck coupling / olefin reinsertion sequence, we believe that the postulated mechanism in the Scheme 24 is the most likely.

1.2.7. Conclusions

In conclusion, we have developed a direct alkoxyarylation of unactivated 3-aza-5-alkenols in presence of arylstannanes as aryl source. Oxidative palladium-catalyzed conditions in presence of a copper(II) salt as oxidant provided expedient access to 7-*endo-trig* cyclizations. The originality of this process is linked to the seven-membered ring formation, which the alkoxylation and the arylation occurred in the same carbon.

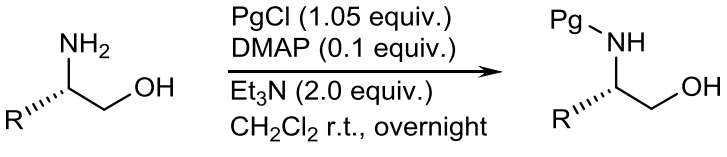
In perspective, the scope of this process by varying the arylstannane partner, as well the starting material 3-aza-5-alkenol should be investigated in more details. Furthermore the ability of the catalytic system to promote this reaction in mild conditions at room temperature open up the possibility to develop a stereoselective process using chiral ligands.

Experimental Part

General methods

Organic solvents were routinely dried and / or distilled prior to use and stored over molecular sieves under argon. Melting points were determined by the capillary method with a Büchi B-540 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400 MHz or a Varian Oxford 300 MHz spectrometer. Chemical shifts are given as δ values in ppm relative to residual solvent peaks ($CHCl_3$ or DMSO-d_6) as the internal reference. ^{13}C NMR spectra are ^{1}H-decoupled and the determination of the multiplicities was achieved by the APT pulse sequence. Coupling constants (*J*) are given in Hertz (Hz). The ^{1}H and ^{13}C NMR spectra were completely assigned by using a combination of ^{13}C APT and ^{2}D NMR experiments (COSY and HSQC). Elemental analyses were executed on Perkin-Elmer CHN Analyzer Series II 2400. Thin-layer chromatographic separations were performed on Merck silica-gel 60-F_{254} pre-coated. Preparative separations were performed by flash chromatography by using Merck silica gel 0.035-0.070 mm.

General procedure (GP10) for the preparation of compounds 9a,b-d,e.

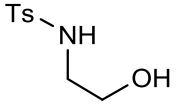


9

Pg = Ts, Ns
R = H, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

To a solution of aminoalcohol (1.0 equiv.), DMAP (0.1 mmol) and triethylamine (2.0 mmol) in CH_2Cl_2 (2.0 M) at 0 °C, was added a solution of the suitable chloride dropwise (1.05 equiv.) in CH_2Cl_2 (10 mL). The resulting mixture was stirred at room temperature overnight. The precipitated was washed with water (3 x 25 mL) and brine (1 x 25 mL), then dried over Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding protected aminoalcohol **9**.

***N*-(4-Methylbenzenesulfonyl)-ethanolamine (9a)**

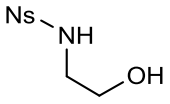


$C_9H_{13}NO_3S$
M.W.: 215,0616

White solid (43% yield, 925 mg, 4.3 mmol), mp: 54-56 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 3.02 (t, *J* = 5.0 Hz, 2H), 3.12-3.35 (m, 1H), 3.65 (t, *J* = 5.0 Hz, 2H), 5.63-6.01 (br s, 1H, missing after

deuteration), 7.26 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[34]

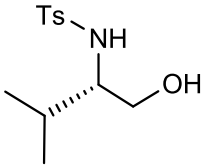
_N_-(4-Nitrobenzenesulfonyl)-ethanolamine (9b)



$C_8H_{10}N_2O_5S$
M.W.: 246,2370

Pale yellow solid (32% yield, 838 mg, 3.4 mmol), mp: 129-130 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.86 (t, *J* = 6.0 Hz, 2H), 3.37 (q, *J* = 5.5 Hz, 2H), 4.75 (t, *J* = 5.5 Hz, 1H), 7.91 (br, 1H, missing after deuteration), 8.06 (d, *J* = 7.0 Hz, 2H), 8.42 (d, *J* = 7.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[35]

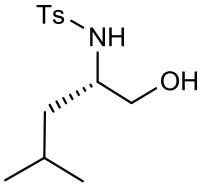
(*S*)-*N*-(4-Methylbenzenesulfonyl)-valinol (9d)



$C_{12}H_{19}NO_3S$
M.W.: 257,3480

White solid (95% yield, 2.44 g, 9.5 mmol), mp: 87-89 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (d, *J* = 6.5.Hz, 6H), 1.67-1.81 (m, 1H), 2.40 (s, 3H), 2.56 (br s, 1H, missing after deuteration), 2.96-3.05 (m, 1H), 3.47-3.61 (m, 2H), 5.35 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[36]

(*S*)-*N*-(4-Methylbenzenesulfonyl)-leucinol (9e)



$C_{13}H_{21}NO_3S$
M.W.: 271,3750

White solid (45% yield, 1.22 g, 4.5 mmol), mp: 99 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.63 (d, *J* = 6.5 Hz, 3H), 0.76 (d, *J* = 6.5 Hz, 3H), 1.22-1.27 (m, 2H), 1.40-1.50 (m, 1H), 2.43 (s, 3H), 2.43-2.51 (br s, 1H, missing after deuteration), 3.25-3.33 (m, 1H), 3.45 (dd, *J* = 11.5 Hz, 1H), 3.58 (dd, *J* = 11.5 Hz, 1H), 5.17

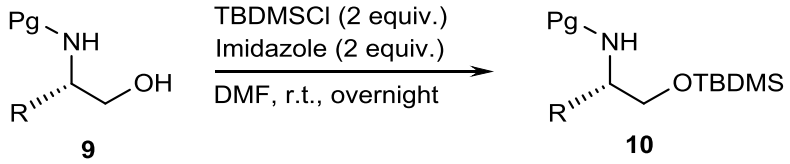
[34] Elliott, Luke D.; Wrigglesworth, Joe W.; Cox, B.; Lloyd-Jones, Guy C.; Booker-Milburn, Kevin I *Org. Lett.* **2011**, *13*, 728-731.

[35] Sabot, C.; Guérard, K. C.; Canesi, S. *Chem. Commun*., **2009**, 2941-2943.

[36] Gandon, L.; Russel, A.; Güveli, T.; Brodwolf, A.; Kariuki, B. M.; Spencer, N.; Snaith, J.S. *J. Org. Chem*. **2006**, *71*, 5198-5207.

(d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.78-7.81 (dd, *J* = 11.5 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[37]

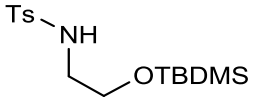
General procedure (GP11) for the preparation of compounds 10a,b-d,e.



9 **10**

A solution of the corresponding compound **9** (1.0 equiv.), *tert*-butyldimethylsilyl chloride (2.0 equiv.) and imidazole (2.0 equiv.) in DMF (0.2 M) was stirred at room temperature overnight. The precipitate was hydrolized with brine (20 mL), extracted three times with Et_2O (3 x 20 mL) and dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding *O*-(*tert*-butyldimethylsilyl)-*N*-protected aminoalcohol **10**.

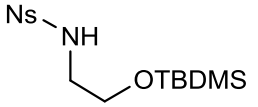
***O*-(*tert*-Butyldimethylsilyl)-*N*-(4-methylbenzenesulfonyl)-ethanolamine (10a)**



$C_{15}H_{27}NO_3SSi$
M.W.: 329,5300

Colorless oil (72% yield, 2.37 g, 7.2 mmol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 6H), 0.84 (s, 9H), 2.42 (s, 3H), 3.04 (dd, *J* = 5.5, 11.0 Hz, 2H), 3.61 (t, *J* = 5.5 Hz, 2H), 4.88 (br s, 1H, missing after deuteration), 7.31 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[38]

***O*-(*tert*-Butyldimenthylsilyl)-*N*-(4-nitrobenzenesulfonyl)-ethanolamine (10b)**



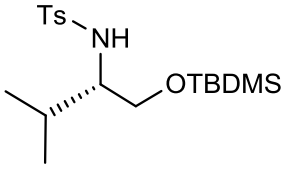
$C_{14}H_{24}N_2O_5SSi$
M.W.: 360,5000

White solid (94% yield, 3.53 g, 9.8 mmol), mp: 72 °C. ^{1}H (600 MHz, $CDCl_3$) δ 0.02 (s, 6H), 0.84 (s, 9H), 3.12 (q, *J* = 5.3 Hz, 2H), 3.65 (t, *J* = 5.3 Hz, 1H), 4.95 (t, *J* = 5.3 Hz, 1H), 8.06 (d, *J* = 9.4 Hz, 2H), 8.37 (d, *J* = 9.4 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[29]

[37] Wunnermann, S.; Frolich, R.; Hoppe, D. *Eur. J. Org. Chem*. **2008**, *4*, 684.

[38] Sato, Y.; Saito, N.; Mori, M. *Tetrahedron* **1998**, *54*, 1153-1168.

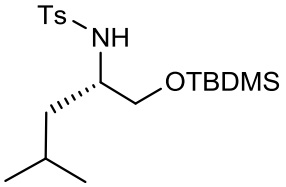
(*S*)-*O*-(*tert*-Butyldimethylsilyl)-*N*-(4-methylbenzenesulfonyl)-valinol (10d)



$C_{18}H_{33}NO_3SSi$
M.W.: 371,6110

White solid (70% yield, 2.60 g, 7.0 mmol), mp: 87-89 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.06 (s, 3H), -0.05 (s, 3H), 0.75 (d, *J* = 6.5 Hz, 6H), 0.89 (s, 9H), 1.67-1.81 (m, 1H), 2.40 (s, 3H), 2.56 (br s, 1H, missing after deuteration), 2.96-3.05 (m, 1H), 3.47-3.61 (m, 2H), 5.35 (d, *J* = 8.5 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[30]

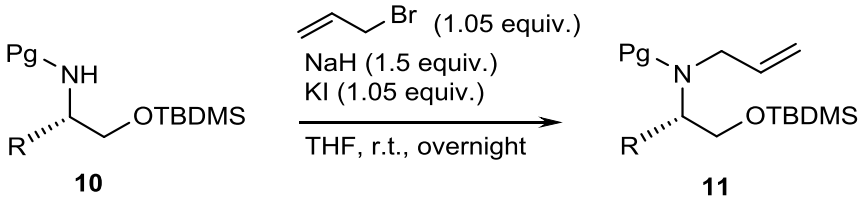
(*S*)-*O*-(*tert*-Butyldimethylsilyl)-*N*-(4-methylbenzenesulfonyl)-leucinol (10e)



$C_{19}H_{35}NO_3SSi$
M.W.: 385,6380

Colorless oil (67% yield, 2.57 g, 6.6 mmol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ -0.06 (s, 3H), -0.05 (s, 3H), 0.75-0.81 (m, 6H) 0.83 (s, 9H), 1.18-1.42 (m, 2H), 1.50-1.65 (m, 1H), 2.43 (s, 3H), 3.08-3.16 (m, 1H), 3.54-3.57 (m, 2H), 4.76 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[30]

General procedure (GP12) for the preparation of compounds 11a,b-d,e.

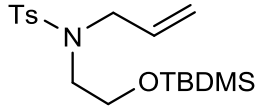


In a mixture of sodium hydride (1.5 equiv.) in THF (10 mL) at 0 °C under Argon atmosphere, KI was added (1.05 equiv.) and a solution of the corresponding compound **10** (1.0 equiv.) in THF (10 mL) was dropped.

The reaction mixture was stirred for 30 minutes at room temperature, then cooled at 0 °C. A solution of allyl bromide (1.05 equiv.) in THF (5 mL) was dropped and the mixture was stirred at room temperature overnight.

The mixture was concentrated at reduced pressure, washed with water (30 mL), extracted three times with diethyleter (3 x 30 mL). Dried on Na_2SO_4, and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding compound **11**.

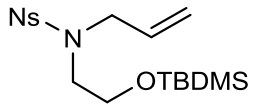
***N*-Allyl-*O*-(*tert*-butyldimethylsilyl)-*N*-(4-benzenesulfonyl)-ethanolamine (11a)**



$C_{18}H_{31}NO_3SSi$
M.W.: 369,5950

Following **GP12** with aminoalcohol **10a** (1.0 equiv, 0.3 mmol) and allyl bromide (1.05 equiv., 0.24mL, 0.3 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:8) to afford **11a** in 91% yield (3.36 g, 9.1 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.84 (s, 9H), 2.39 (s, 3H), 3.18 (t, *J* = 8.0 Hz, 2H), 3.68 (t, *J* = 8.0 Hz, 2H), 3.84 (d, *J* = 8.0 Hz, 2H), 5.08-5.14 (m, 2H), 5.58-5.62 (m, 1H), 7.26 (d, *J* = 4.0 Hz, 2H), 7.67 (d, *J* = 4.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.4 (q), 21.5 (q), 26.0 (q), 45.1 (s), 49.8 (t), 52.2 (t), 61.1 (t), 119.4 (t), 127.1 (d), 127.3 (d), 129.8 (d), 133.0 (s), 143.7 (s). MS: (*m/z*) 369 (M^+). Anal. Calcd for $C_{18}H_{31}NO_3SSi$: C, 58.50; H, 8.45; N, 3.79. Found: C, 58.69; H, 8.16; N, 4.05.

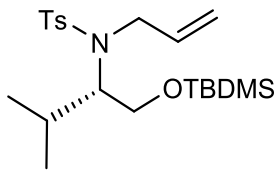
***N*-Allyl-*O*-(*tert*-butyldimethylsilyl)-*N*-(4-nitrobenzenesulfonyl)-ethanolamine (11b)**



$C_{17}H_{28}N_2O_5SSi$
M.W.: 400,5650

Following **GP12** with aminoalcohol **10b** (1.0 equiv, 0.2 mmol) and allyl bromide (1.05 equiv., 0.24 mL, 0.2 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 8:2) to afford **11b** in 80% yield (3.32 g, 8.3 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 6H), 0.83 (s, 9H), 3.29 (t, *J* = 6.0 Hz, 2H), 3.72 (t, *J* = 6.0 Hz, 2H), 3.94 (d, *J* = 6.0 Hz, 2H), 5.12-5.17 (m, 2H), 5.56-5.66 (m, 1H), 8.00 (d, *J* = 9.0 Hz, 2H), 8.31 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.5 (q), 18.1 (s), 25.8 (q), 48.9 (t), 51.7 (t), 61.9 (t), 119.4 (t), 124.3 (d), 128.3 (d), 132.4 (d), 146.3 (s), 149.9 (s). MS: (*m/z*) 402 (M^+). Anal. Calcd for $C_{17}H_{30}N_2O_5SSi$: C, 50.72; H, 7.51; N, 6.96. Found: C, 50.93; H, 7.28; N, 6.72.

(*S*)-*N*-Allyl-*O*-(*ter*t-butyldimethylsilyl)-*N*-(4-methylbenzenesulfonyl)-valinol (11d)

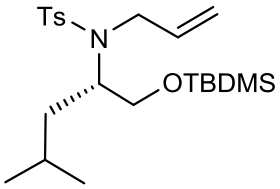


$C_{21}H_{37}NO_3SSi$
M.W.: 411,6760

Following **GP12** with aminoalcohol **10d** (1.0 equiv, 2.7 mmol) and allyl bromide (1.05 equiv., 0.24 mL, 2.8 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:9) to afford **11d** in 60% yield (2.46 g, 6.0 mmol). Orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.88 (s, 9H), 0.94-0.99 (m, 6H), 1.96-2.07 (m, 1H), 2.45 (s, 3H), 3.58-3.60 (m, 1H), 3.61 (d, *J* = 8.5 Hz, 1H), 3.71-3.75 (m, 1H), 3.85-3.90 (m, 1H), 3.98-4.04 (m, 1H), 5.07 (d, *J* = 8.0 Hz, 1H),

5.18 (d, *J* = 8.0 Hz, 1H), 5.89-5.93 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.8 (q), 18.1 (s), 19.9 (q), 20.7 (q), 25.7 (q), 27.5 (d), 47.9 (t), 63.3 (t), 65.7 (d), 116.4 (t), 127.4 (d), 129.3 (d), 136.5 (s), 142.6 (s). MS: (*m/z*) 411 (M^+). Anal. Calcd for $C_{21}H_{37}NO_3SSi$: C, 61.27; H, 9.06; N, 3.40. Found: C, 61.35; H, 8.78; N, 3.16.

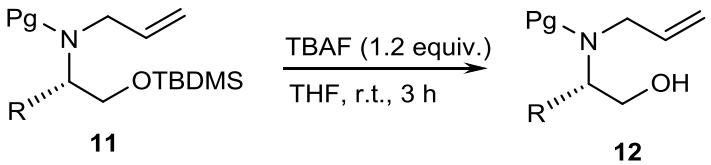
(*S*)-*N*-Allyl-*O*-(*tert*-butyldimethylsylil)-*N*-(4-methylbenzenesulfonyl)-leucinol (11e)



$C_{22}H_{39}NO_3SSi$
M.W.: 425,2420

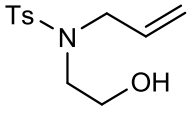
Following **GP12** with aminoalcohol **10e** (1.0 equiv, 0.2 mmol) and allyl bromide (1.05 equiv. 0.24 mL, 0.2 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 2:8) to afford **11e** in 65% yield (2.76 g, 6.5 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 6H), 0.80-0.84 (m, 6H), 0.84 (s, 9H), 1.39 (t, *J* = 6.0 Hz, 2H), 1.48 (m, 1H), 2.40 (s, 3H), 3.52-3.55 (m, 2H), 3.84-3.89 (m, 3H), 5.04-5.17 (m, 2H), 5.76-5.84 (m, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.6 (q), 17.9 (s), 22.1 (q), 22.8 (q), 24.3 (q), 25.8 (d), 38.8 (t), 47.2 (t), 57.7 (d), 64.8 (t), 116.7 (t), 127.3 (d), 129.4 (d), 136.6 (d), 138.6 (s), 142.8 (s). MS: (*m/z*) 425 (M^+). Anal. Calcd for $C_{22}H_{39}NO_3SSi$: C, 62.07; H, 9.23; N, 3.29. Found: C, 62.31; H, 8.94; N, 3.47.

General procedure (GP13) for the preparation of compounds 12a-e.



A mixture of the corresponding compound **11** (1.0 equiv.) and tetrabutylammonium fluoride (1.2 equiv.) in THF (0.2 M) was stirred at room temperature for 3 h. The solvent was evaporated at reduced pressure, water was added (20 mL) and the reaction mixture was extracted three times with CH_2Cl_2 (3 x 25 mL), then dried over Na_2SO_4, and the mixture concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product **12**.

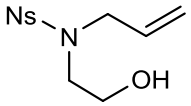
***N*-Allyl-*N*-(4-methylbenzenesulfonyl)-ethanolamine (12a)**



$C_{12}H_{17}NO_3S$
M.W.: 255,3320

Pale yellow oil (79% yield, 2.01 g, 7.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03 (br s, 1H, missing after deuteration), 2.31 (t, *J* = 5.5 Hz, 2H), 2.45 (s, 3H), 3.70 (t, *J* = 5.5 Hz, 2H), 3.87 (d, *J* = 6.5 Hz, 2H), 5.14-5.21 (m, 2H), 5.58-5.71 (m, 1H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[39]

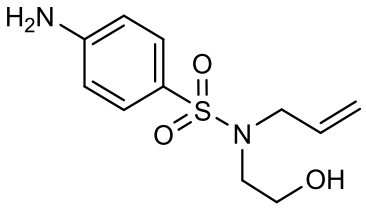
_N_-Allyl-_N_-(4-nitrobenzenesulfonyl)-ethanolamine (12b)



$C_{11}H_{14}N_2O_5S$
M.W.: 286,0623

Following **GP13** with **11b** (1.0 equiv, 1.25 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:1) to afford **12b** in 40% yield (1.14 g, 4.0 mmol). Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.28 (t, *J* = 5.5 Hz, 2H), 3.71 (t, *J* = 5.5 Hz, 2H), 3.87 (d, *J* = 6.5 Hz, 2H), 5.15 (dd, *J* = 2.5, 13.5 Hz, 2H), 5.54-5.64 (m, 1H), 7.97 (d, *J* = 8.0 Hz, 2H), 8.30 (d, *J* = 8.0, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 49.7 (t), 51.7 (t), 60.8 (t), 119.7 (t), 124.1 (d); 128.2 (d), 132.1 (d), 137.1 (s), 163.9 (s). MS: (*m/z*) 286 (M^+). Anal. Calcd for $C_{11}H_{14}N_2O_5S$: C, 46.15; H, 4.93; N, 9.78. Found: C, 45.89; H, 5.07; N, 9.55.

_N_-Allyl-_N_-(4-aminobenzenesulfonyl)-ethanolamine (12c)



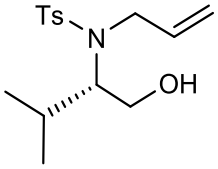
$C_{11}H_{16}N_2O_3S$
M.W.: 256,3200

Following **GP13** with **11b**[40] (1.0 equiv., 1.25 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:1) to afford **12c** in 22% yield (563 mg, 2.2 mmol). Dark yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.54 (t, *J* = 6.0 Hz, 2H), 3.81 (t, *J* = 6.0 Hz, 2H), 4.03-4.04 (m, 2H), 5.08 (dd, *J* = 2.5, 13.0 Hz, 2H), 5.72-5.79 (m, 1H), 6.58 (d, *J* = 9.5 Hz, 2H), 7.94 (d, *J* = 9.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.9 (t), 53.7 (t), 60.0 (t), 110.6 (d), 116.9 (t), 126.2 (d), 131.7 (d), 136.9 (s), 153.3 (s). MS: (*m/z*) 256 (M^+). Anal. Calcd for $C_{11}H_{16}N_2O_3S$: C, 51.55; H, 6.29; N, 10.93. Found: C, 51.43; H, 6.53; N, 11.19.

[39] Poornachandran, M.; Raghunathan, R. *Tetrahedron* **2008**, *64*, 6461-6474.

[40] Both **12b** and **12c** derive from **11b** using **GP13**. The *N*-Allyl-*N*-(4-aminobenzenesulfonyl)-ethanolamine is obtained carrying the deprotection for 24 hours instead that for 3 hours.

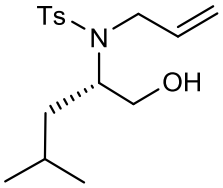
(*S*)-*N*-Allyl-*N*-(4-methylbenzenesulfonyl)-valinol (12d)



$C_{15}H_{23}NO_3S$
M.W.: 297,4130

Yellow oil (96% yield, 2.85 g, 9.6 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.62 (d, *J* = 8.5 Hz, 3H), 0.84 (d, *J* = 8.0 Hz, 3H), 1.99 (m, 1H), 2.34 (s, 3H), 3.42 (dd, *J* = 10.0, 4.5 Hz, 1H), 3.68 (dd, *J* = 9.0, 5.0 Hz, 2H), 3.89 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.15 (dd, *J* = 9.0, 5.0 Hz, 1H), 5.13 (m, 2H), 5.82 (m, 1H), 7.21 (d, *J* = 8.0, 2H), 7.67 (d, *J* = 8.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[41]

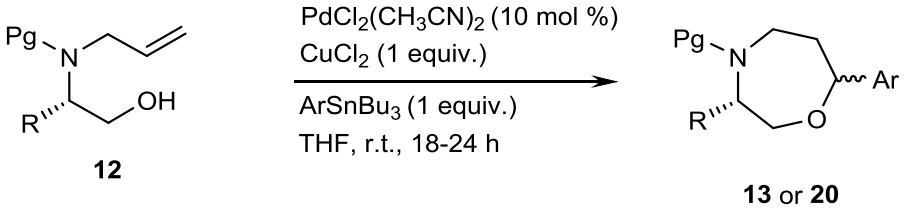
(*S*)-*N*-Allyl-*N*-(4-methylbenzenesulfonyl)-leucinol (12e)



$C_{16}H_{25}NO_3S$
M.W.: 311,4400

Colorless oil (73% yield, 2.27 g, 7.3 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.69 (t, *J* = 6.5 Hz, 6H), 1.15 (t, *J* = 7.0 Hz, 2H), 1.26-1.37 (m, 1H), 2.33 (s, 3H), 3.47 (br s, 2H), 3.66-3.74 (m, 1H), 3.78-3.87 (m, 2H), 5.03-5.17 (m, 2H), 5.72-5.85 (m, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[42]

General procedure (GP14) for the preparation of oxazepanes 13a-e' and 20.



12 **13** or **20**

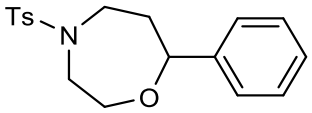
Pg = Ts, Ns, NH_2PhSO_2
R = H, $CH(CH_3)_2$, $CH_2CH(CH_3)_2$

A mixture of the corresponding allylaminoalcohol **12** (1.0 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol %), $CuCl_2$ (1.0 equiv.), and the suitable aryl tributyl stannane (1.0 equiv.) in THF (0.2 M) was stirred at room temperature for 18-24 h. The solvent was evaporated under reduced pressure, water was added (10 mL) then it was extracted three times with CH_2Cl_2 (3 x 10 mL), then dried over Na_2SO_4, and the solvent

[41] Aurich, H. G.; Gentes, C.; Harms, K. *Tetrahedron* **1995**, *51*, 10497.
[42] Bera, S.; Panda, G. *ACS Comb. Sci*. **2012**, *14*, 1-4.

was removed under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding oxazepane **13** or **20**.

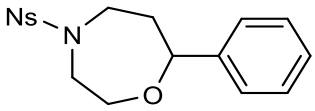
7-Phenyl-4-(4-methylbenzenesulfonyl)-1,4-oxazepane (13a)



$C_{18}H_{21}NO_3S$
M.W.: 331,4300

Following **GP14** with **12a** (1.0 equiv, 0.75 mmol) and phenyl(tributyl) stannane (1.0 equiv., 0.24 mL, 0.74 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **13a** in 78% yield (258 mg, 0.08 mmol). White solid, mp: 104-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.10-2.20 (m, 1H), 2.25-2.40 (m, 1H), 2.45 (s, 3H); 3.25 (ddd, *J* = 13.0, 10.0, 3.0 Hz, 1H), 3.34 (ddd, *J* = 12.5, 7.5, 4.5 Hz, 1H), 3.63 (dt, *J* = 13.0, 6.0 Hz, 1H), 3.71 (dt, *J* = 13.5, 3.0 Hz, 1H), 3.78 (ddd, *J* = 12.5, 7.5, 4.5 Hz, 1H), 4.11 (dt, *J* = 13.0, 3.0 Hz, 1H), 4.68 (dd, *J* = 9.5, 4.5 Hz, 1H), 7.40-7.20 (m, 7H), 7.72 (d, *J* = 8.5, 2H). These spectroscopic data are in good agreement with those reported in the literature.[43]

7-Phenyl-4-(4-nitrobenzenesulfonyl)-1,4-oxazepane (13b)

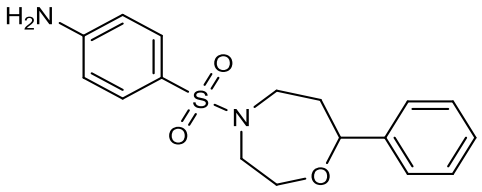


$C_{17}H_{18}N_2O_5S$
M.W.: 362,4000

Following **GP14** with **12b** (1.0 equiv, 0.28 mmol) and phenyl(tributyl) stannane (1.0 equiv., 0.09 mL, 0.28 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **13b** in 62% yield (224 mg, 0.06 mmol). White solid, mp: 112-113 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92-2.03 (m, 1H), 2.24-2.31 (m, 1H), 3.27 (ddd, *J* = 13.0, 10.0, 3.0 Hz, 1H), 3.35-3.42 (m, 1H), 3.54-3.59 (m, 1H), 3.67 (dt, *J* = 13.5, 3.0 Hz, 1H), 3.73 (ddd, *J* = 12.5, 7.5, 4.5 Hz, 1H), 4.08 (dt, *J* = 13.0, 3.0 Hz, 1H), 4.62 (dd, *J* = 9.5, 4.5 Hz, 1H), 7.14-7.28 (m, 5H), 7.94 (d, *J* = 8.5, 2H), 8.33 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9 (t), 46.3 (t), 51.7 (t), 69.9 (t), 81.6 (d), 124.5 (d), 125.5 (d), 127.6 (d), 128.1 (d), 128.5 (d), 142.4 (s), 149.9 (s), 150.0 (s). MS: (*m/z*) 362 (M^+). Anal. Calcd for $C_{17}H_{18}N_2O_5S$: C, 56.34; H, 5.01; N, 7.73. Found: C, 56.11; H, 5.27; N, 7.48.

[43] Gharpure, S., Prasad, J. V. K. *Eur. J. Org. Chem*. **2013**, 2076-2079.

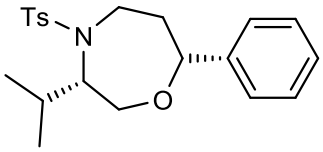
4-(4-Aminobenzenesulfonyl)-7-phenyl-1,4-oxazepane (13c)



$C_{17}H_{20}N_2O_3S$
M.W.: 332, 4180

Following **GP14** with **12c** (1.0 equiv, 0.3 mmol) and phenyl(tributyl) stannane (1.0 equiv., 0.09 mL, 0.3 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:1) to afford **13c** in 67% yield (222 mg, 0.07 mmol). Pale orange solid, mp: 93 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88-1.92 (m, 1H), 1.99-2.07 (m, 1H), 2.65-2.77 (m, 2H), 3.40-3.55 (m, 2H), 4.07-4.22 (m, 2H), 5.15 (dd, *J* = 9.0 Hz, 1H), 6.29 (d, *J* = 9.0 Hz, 2H), 7.11-7.27 (m, 5H), 8.01 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.6 (t), 33.9 (t), 46.8 (t), 65.0 (t), 89.2 (d), 111.0 (d), 126.2 (d), 126.3 (d), 128.4 (d), 128.6 (d), 137.4 (s), 140.8 (s), 149.4 (s). MS: (*m/z*) 332 (M^+). Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43. Found: C, 61.47; H, 5.81; N, 8.65.

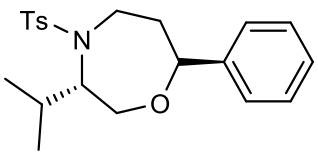
(3S,7R)-3-Isopropyl-7-phenyl-4-(4-methylbenzenesulfonyl)-1,4-oxazepane (13d)



$C_{21}H_{27}NO_3S$
M.W.: 373,1712

Following **GP14** with **12d** (1.0 equiv, 0.02 mmol) and phenyl(tributyl) stannane (1.0 equiv., 0.24 mL, 0.02 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **13d** in 44% yield (164 mg, 0.04 mmol). White solid, mp: 84-86 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 6H), 1.42-1.44 (m, 1H), 1.63-1.65 (m, 2H), 2.45 (s, 3H), 3.41-3.46 (m, 2H), 3.55-3.60 (m, 2H), 4.23 (dd, *J* = 11.5, 13.0 Hz, 1H), 4.53 (dd, *J* = 2.5, 8.0 Hz, 1H), 7.22-7.25 (m, 2H), 7.30-7.33 (m, 5H), 7.75 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4 (q), 20.1 (q), 26.9 (d), 37.5 (t), 40.5 (d), 65.2 (d), 71.4 (t), 81.6 (d), 125.4 (d), 127.1 (d), 127.2 (d), 128.3 (d), 129.6 (d), 138.1 (s), 143.1 (s), 143.3 (s). MS: (*m/z*) 373 (M^+). Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.38; H, 7.57; N, 3.82.

(3S,7R)-3-isopropyl-7-phenyl-4-(4-methylbenzenesulfonyl)-1,4-oxazepane (13d')

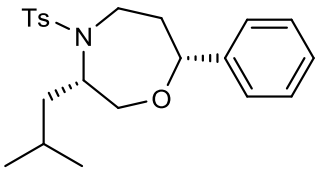


$C_{21}H_{27}NO_3S$
M.W.: 373,1712

Following **GP14** with **12d** (1.0 equiv, 0.02 mmol) and phenyl(tributyl) stannane (1.0 equiv., 0.24 mL, 0.02 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt /

petroleum ether 4:6) to afford **13d'** in 24% yield (89 mg, 0.02 mmol). White solid, mp: 103-105 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.00 (s, 3H), 1.71-1.73 (m, 1H), 1.81-1.85 (m, 1H), 2.11 (dd, *J* = 7.5, 14.5 Hz, 1H), 2.45 (s, 3H), 3.35 (ddd, *J* = 1.5, 12.0, 16.0 Hz, 1H), 3.61 (dd, *J* = 5.0, 13.5 Hz, 1H), 3.98 (td, *J* = 5.5, 8.5 Hz, 1H), 4.08-4.13 (m, 1H), 4.19 (dd, *J* = 8.5, 13.5 Hz, 1H), 4.38 (dd, *J* = 7.5, 11.5 Hz, 1H), 6.87 (dd, *J* = 6.0, 8.0 Hz, 2H), 7.20-7.32 (m, 5H), 7.80 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.4 (q), 20.2 (q), 30.1 (d), 36.2 (t), 42.6 (t), 63.8 (d), 69.7 (t), 84.1 (d), 125.7 (d), 127.4 (d), 127.6 (d), 128.1 (d), 129.6 (d), 139.7 (s), 142.3 (s), 142.9 (s). MS: (*m/z*) 373 (M^+). Anal. Calcd for $C_{21}H_{27}NO_3S$: C, 67.53; H, 7.29; N, 3.75. Found: C, 67.44; H, 7.51; N, 3.57.

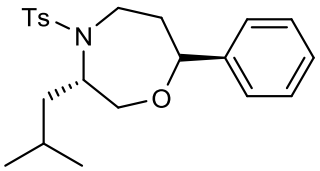
(3S,7R)-3-Isobutyl-7-phenyl-4-(4-methylbenzenesulfonyl)-1,4-oxazepane (13e)



$C_{22}H_{29}NO_3S$
M.W.: 387,1868

Following **GP14** with **12e** (1.0 equiv, 0.54 mmol) and phenyl(tributyl) stannane (1.0 equiv., 0.18 mL, 0.54 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:9) to afford **13e** in 47% yield (181 mg, 0.05 mmol). White solid, mp: 118-120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (s, 6H), 1.42-1.49 (m, 1H), 1.60-1.66 (m, 1H), 1.95-2.01 (m, 1H), 2.32-2.43 (m, 1H), 2.44 (s, 3H), 3.31-3.38 (m, 1H), 3.41-3.45 (m, 1H), 3.65-3.74 (m, 2H), 3.94 (dd, *J* = 2.0, 13.0 Hz, 1H), 4.03-4.07 (m, 1H), 4.56 (dd, *J* = 5.0, 8.5 Hz, 1H), 7.26-7.32 (m, 7H), 7.73-7.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.4 (q), 22.8 (q), 24.6 (d), 38.0 (t), 39.3 (t), 40.2 (t), 56.6 (d), 73.5 (t), 81.9 (d), 125.4 (d), 127.0 (d), 127.3 (d), 128.4 (d), 129.5 (s), 129.6 (d), 137.9 (s), 143.2 (s). MS: (*m/z*) 387 (M^+). Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.18; H, 7.54; N, 3.61. Found: C, 68.15; H, 7.76; N, 3.85.

(3S,7R)-3-Isobutyl-7-phenyl-4-(4-methylbenzenesulfonyl)-1,4-oxazepane (13e')

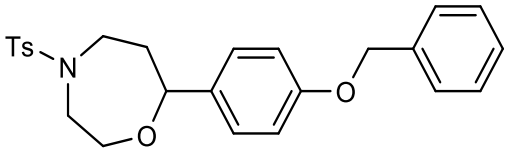


$C_{22}H_{29}NO_3S$
M.W.: 387,1868

Following **GP14** with **12e** (1.0 equiv, 0.54 mmol) and phenyl(tributyl) stannane (1.0 equiv., 0.18 mL, 0.54 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:9) to afford **13e'** in 38% yield (147 mg, 0.04 mmol). White solid, mp: 123-124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (s, 6H), 1.31-1.37 (m, 1H), 1.45-1.52 (m, 1H), 1.65 (td, *J* = 6.5, 13.5 Hz, 1H), 1.75 (dt, *J* = 4.0, 14.0 Hz, 1H), 1.82-1.92 (m, 1H), 2.45 (s, 3H), 3.30-3.43 (m, 2H), 4.02-4.06 (m, 1H), 4.16 (dd, *J* = 5.5, 13.5 Hz, 1H), 4.23-4.30 (m, 1H), 4.35-4.39 (dd, *J* = 4.0, 11.5 Hz, 1H), 6.90 (dd, *J* = 3.0,

7.5 Hz, 2H), 7.21-7.32 (m, 5H), 7.79 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.3 (q), 23.1 (q), 24.6 (d), 36.7 (t), 40.5 (t), 41.3 (t), 56.5 (d), 72.0 (t), 84.3 (d), 125.7 (d), 127.5 (d), 128.2 (d), 129.6 (d), 139.5 (s), 142.3 (s), 142.9 (s). MS: (*m/z*) 387 (M^+). Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.18; H, 7.54; N, 3.61. Found: C, 68.01; H, 7.79; N, 3.87.

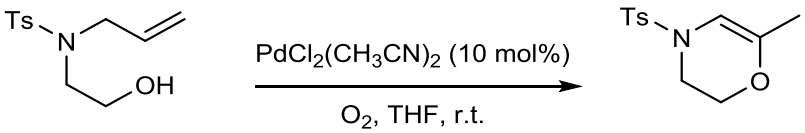
7-[4-(Benzyloxy)phenyl]-4-(4-methylbenzenesulfonyl)-1,4-oxazepane (20)



$C_{25}H_{27}NO_4S$
M.W.: 437,5540

Following **GP14** with **12a** (1.0 equiv, 0.39 mmol) and (4-benzyloxyphenyl)tributyl stannane (1.0 equiv., 0.16 mL, 0.39 mmol). The crude produt was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **20** in 80% yield (349 mg, 0.08 mmol). White solid, mp: 140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.93-1.99 (m, 1H), 2.16-2.21 (m, 1H), 2.37 (s, 3H), 3.15-3.19 (m, 1H), 3.23-3.29 (m, 1H), 3.48-3.54 (m, 1H), 3.58-3.70 (m, 2H), 3.99 (dt, *J* = 13.0, 3.0 Hz, 1H), 4.54 (dd, *J* = 5.5, 9.5 Hz, 1H), 4.97 (s, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.24-7.35 (m, 7H), 7.63 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5 (q), 37.6 (t), 46.2 (t), 51.7 (t), 69.8 (t), 70.0 (t), 81.1 (d), 114.8 (d), 126.9 (d), 127.0 (d), 127.4 (d), 127.9 (d), 128.6 (d), 129.8 (d), 135.3 (s), 135.9 (s), 136.9 (s), 143.4 (s), 158.1 (s). MS: (*m/z*) 437 (M^+). Anal. Calcd for $C_{25}H_{27}NO_4S$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.74; H, 5.98; N, 3.47.

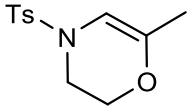
Procedure for the synthesis of compound 14.



12a **14**

A mixture of *N*-allyl-*N*-(4-methylbenzenesulfonyl)-aminoethanol **12a** (1.0 equiv, 0.47 mmol) and $PdCl_2(CH_3CN)_2$ (10 mol %) was stirred at room temperature for 24 hours under oxygen atmosphere. The solvent was evaporated under reduced pressure, water was added (10 mL) then it was extracted three times with CH_2Cl_2 (3 x 10 mL), then dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding compound **14**.

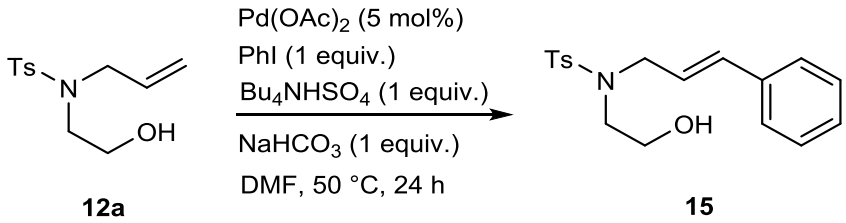
6-Methyl-4-(4-methylbenzenesulfonyl)-3,4-dihydro-*2H*-1,4-oxazine (14)



$C_{12}H_{15}NO_3S$
M.W.: 253,3160

Colorless oil (81% yield, 8 mg, 0.003 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.73 (s, 3H), 2.43 (s, 3H), 3.45 (t, *J* = 4.5 Hz, 2H), 3.59 (t, *J* = 4.5 Hz, 2H), 5.83 (s, 1H), 7.32 (t, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.8 (q), 21.5 (q), 42.8 (t), 63.0 (t), 100.0 (d), 127.4 (d), 129.8 (d), 133.9 (s), 140.3 (s), 143.8 (s). These spectroscopic data are in good agreement with those reported in the literature.

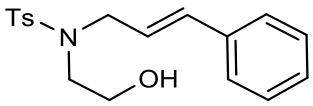
Procedure for the synthesis of compound 15.



12a **15**

A mixture of *N*-allyl-*N*-(4-methylbenzenesulfonyl)-aminoethanol **12a** (1.0 equiv, 0.47 mmol) and phenyl iodobenzene (1.0 equiv., 0.052 mL, 0.47 mmol) was stirred in DMF at 50 °C for 24 hours. An acqueous solution of NH_4Cl was added (10 mL) then it was extracted three times with Et_2O (3 x 10 mL), then dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding compound **15**.

***N*-Cinnamyl-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (15)**

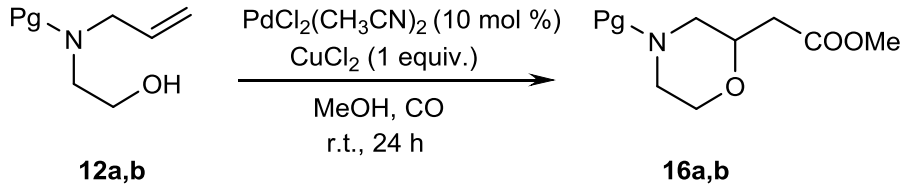


$C_{18}H_{21}NO_3S$
M.W.: 331,4300

White solid (80% yield, 124 mg, 0.4 mmol), mp: 54-58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.29 (t, *J* = 5.5 Hz, 2H), 3.75 (t, *J* = 5.0 Hz, 2H), 4.02 (dd, *J* = 1.0, 7.0 Hz, 2H), 5.98 (dt, *J* = 6.5, 16.0 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 7.28 (m, 7H), 7.74 (d, *J* = 8.5 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[44]

[44] Bezason, M.; Pottel, J.; Bilbeisi, R.; Tomieux, S.; Cueto, M.; Moitessier, N. *J. Org. Chem*. **2013**, *78*, 872-885.

General procedure (GP15) for the preparation of compounds 16a-b.

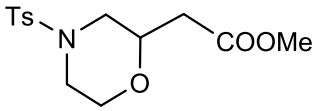


12a,b **16a,b**

Pg = Ts, Ns

A mixture of the corresponding compound **12** (1.0 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol %) and $CuCl_2$ (1.0 equiv.) in MeOH (0.2 M) was stirred in CO atmosphere at room temperature for 24 h. The solvent was evaporated at reduced pressure, then water was added (10 mL) and the reaction mixture was extracted three times with CH_2Cl_2 (3 x 25mL), dried over Na_2SO_4, and the product concentrate at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding morpholine **16**.

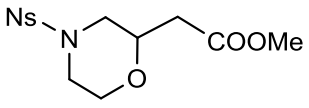
2-[(Methoxycarbonyl)methyl]-4-(4-methylbenzenesulfonyl)morpholine (16a)



$C_{14}H_{19}NO_5S$
M.W.: 313,3680

Following **GP15** with *N*-allyl-*N*-(4-methylbenzenesulfonyl)-aminoethanol **12a** (1.0 equiv, 0.3 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:3) to afford **16a** in 65% yield (203 mg, 0.06 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (t, *J* = 11.0 Hz, 1H), 2.14-2.46 (m, 3H), 2.42 (s, 3H), 3.48 (d, *J* = 11.5 Hz, 1H), 3.60-3.70 (m, 2H), 3.68 (s, 3H), 3.85-3.89 (m, 1H), 3.95-4.00 (m, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.62 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (q), 38.1 (t), 45.2 (t), 49.6 (t), 51.9 (d), 65.9 (t), 71.7 (d), 127.8 (d), 129.8 (d), 132.2 (s), 144.0 (s), 170.4 (s). MS: (*m/z*) 313 (M^+). Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47. Found: C, 53.89; H, 6.16; N, 4.68.

2-[(Methoxycarbonyl)methyl]-4-(4-nitrobenzenesulfonyl)morpholine (16b)

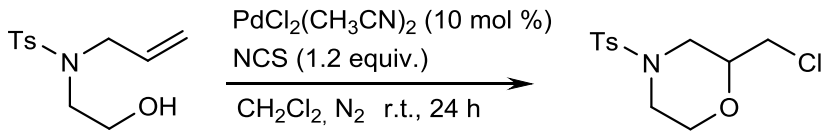


$C_{13}H_{16}N_2O_7S$
M.W.: 344,3380

Following **GP15** with *N*-Allyl-*N*-(4-nitrobenzenesulfonyl)-aminoethanol **12b** (1.0 equiv, 0.3 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **16b** in 74% yield (266 mg, 0.08 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (t, *J* = 11.0 Hz, 1H), 2.19-2.48 (m, 3H), 3.52 (d, *J* = 12.0 Hz, 1H), 3.59-3.66 (m, 2H), 3.60 (s, 3H), 3.83-3.92 (m, 2H), 7.88 (d, *J* = 9.0 Hz, 2H), 8.34 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 37.9 (t), 45.2 (t), 49.5

(t), 52.1 (q), 65.8 (t), 71.8 (d), 124.6 (d), 128.9 (d), 130.3 (s), 141.7 (s), 170.2 (s). MS: (*m/z*) 344 (M^+). Anal. Calcd for $C_{13}H_{16}N_2O_7S$: C, 45.35; H, 4.68; N, 8.14. Found: C, 45.07; H, 4.91; N, 7.98.

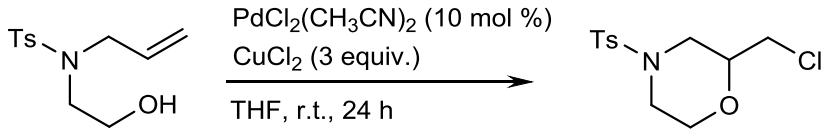
Procedure for the synthesis of compound 17 using NCS as chlorine source.



12a **17**

A mixture of *N*-allyl-*N*-(4-methylbenzenesulfonyl)-aminoethanol **12a** (1.0 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol %) and NCS (1.2 equiv.) in CH_2Cl_2 (0.2 M) was stirred under nitrogen atmosphere at room temperature for 24 h. After the total consumption of starting material the reaction was quenched with a saturated aqueous solution of ammonium chloride, washed with an aqueous NaOH 3M solution, then with brine. The combined aqueous layers were extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding morpholine **17** (42% yield, 121 mg).

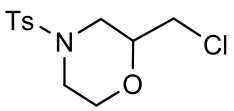
Procedure for the synthesis of compound 17 using $CuCl_2$ as chlorine source.



12a **17**

A mixture of *N*-allyl-*N*-(*p*-toluenesulfonyl)-aminoethanol **12a** (1.0 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol %) and $CuCl_2$ (3 equiv.) in THF (0.2 M) was stirred under air atmosphere at room temperature for 24 h. After the total consumption of starting material the reaction was quenched with a saturated aqueous solution of ammonium chloride, washed with an aqueous NaOH 3M solution, then with brine. The combined aqueous layers were extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, filtered and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding morpholine **17** (51% yield, 147 mg).

2-(Chloromethyl)-4-(4-methylbenzenesulfonyl)-morpholine (17)

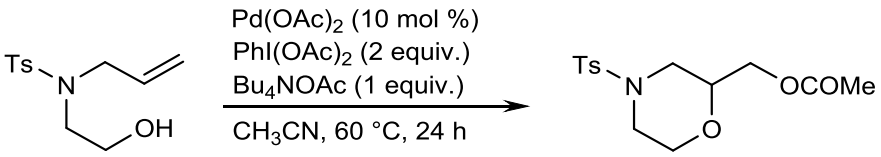


$C_{12}H_{16}ClNO_3S$
M.W.: 289,7740

The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 4:6) to afford **17**. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 1.95-2.11 (m, 1H), 2.12 (s, 3H), 2.12-2.15

(m, 1H), 2.95-3.05 (m, 2H), 3.21-3.43 (m, 4H), 3.72 (d, *J* = 11.5 Hz, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H). ^{13}C-NMR ($CDCl_3$): δ 21.1 (q), 43.9 (t), 45.5 (t), 48.3 (t), 65.7 (t), 74.3 (d), 128.0 (d), 129.7 (d), 133.4 (s), 143.4 (s). MS: (*m/z*) 289 (M^+). Anal. Calcd for $C_{12}H_{16}ClN_3OS$: C, 49.74; H, 5.57; N, 4.83. Found: C, 49.79; H, 5.38; N, 5.08.

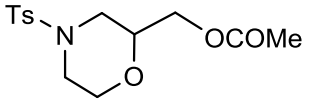
Procedure for the synthesis of compound 18.



12a **18**

A mixture of *N*-allyl-*N*-(4-methylbenzenesulfonyl)-aminoethanol **12a** (1.0 equiv.), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (2.0 equiv.) and Bu_4NOAc (1.0 equiv.) in CH_3CN (0.2 M) was stirred at 60 °C for 24 h. After completion, the reaction was dissolved in CH_2Cl_2 (5 mL) and washed with water (5 mL). The resulting organic extract was washed with brine, separated and the brine layer was extracted with CH_2Cl_2 (10 mL). The combined organics were dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding product **18**.

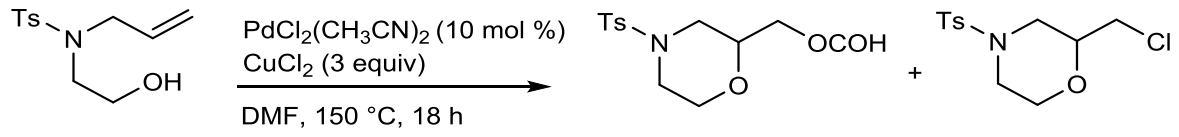
5-Acetoxymethyl-morpholine (18)



$C_{14}H_{19}NO_5S$
M.W.: 313,3680

The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 3:7) to afford **18** in 42% yield (10 mg, 0.03 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.11 (dd, *J* = 4.0, 11.0 Hz, 1H), 2.35 (dd, *J* = 3.5, 10.0 Hz, 1H), 2.38 (s, 3H), 3.46 (d, *J* = 11.5 Hz, 1H), 3.54 (d, *J* = 11.0 Hz, 1H), 3.59-3.65 (m, 1H), 3.69-3.75 (m, 1H), 3.87 (dd, *J* = 10.0, 11.5 Hz, 1H), 3.92-4.03 (m, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.57 (d, *J* = 8.0 Hz, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 20.8 (q), 21.6 (q), 45.4 (t), 47.4 (t), 64.2 (t), 65.9 (t), 73.0 (d), 127.9 (d), 129.8 (d), 132.1 (s), 144.1 (s), 170.6 (s). MS: (*m/z*) 313 (M^+). Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47. Found: C, 53.39; H, 6.30; N, 4.73.

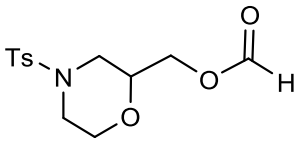
Procedure for the synthesis of compound 19.



12a **19** **17**

A mixture of *N*-allyl-*N*-(4-methylbenzenesulfonyl)-aminoethanol **12a** (1.0 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol %) and $CuCl_2$ (3 equiv.) in DMF (0.2 M) was stirred under air atmosphere at 150 °C for 18 h. After completion, the mixture was dissolved in Et_2O and washed for three times with an aqueous solution of NH_4Cl (20 mL x 3). The combined organic phases were dried over Na_2SO_4 and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding morpholine **19**.

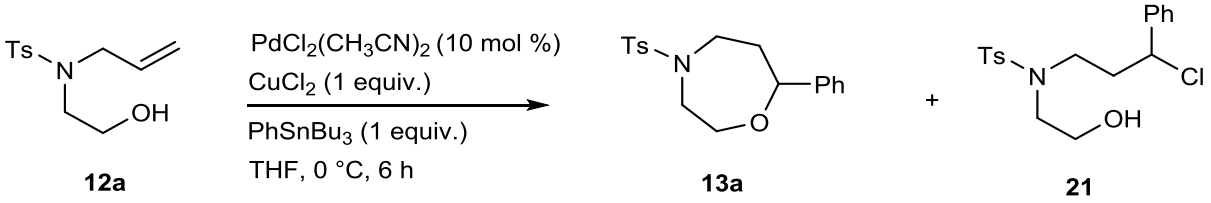
[4-(4-Methylbenzenesulfonyl)-morpholin-2-yl]methyl formate (19)



$C_{13}H_{17}NO_5S$
M.W.: 299,3410

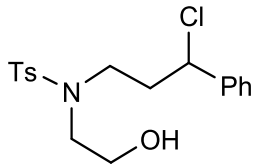
The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:1) to afford **19** in 35% yield (104 mg, 0.04 mmol). Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.12-2.17 (m, 1H), 2.39 (s, 3H), 3.36-3.67 (m, 5H), 3.86-3.90 (m, 1H), 4.09 (d, *J* = 5.0 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.5 Hz, 2H), 7.97 (s, 1H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.6 (q), 45.3 (t), 47.1 (t), 63.5 (t), 66.0 (t), 72.7 (d), 127.9 (d), 129.9 (d), 131.9 (s), 144.2 (s), 160.4 (s). MS: (*m/z*) 299 (M^+). Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68. Found: C, 51.98; H, 5.97; N, 4.42.

Procedure for the synthesis of compound 21.



A mixture of the *N*-allyl-*N*-(4-methylbenzenesulfonyl)-aminoethanol **12a** (1.0 equiv.), $PdCl_2(CH_3CN)_2$ (10 mol %), $CuCl_2$ (1 equiv.), and phenyl(tributyl) stannane (1 equiv.) in THF (0.2 M) was stirred at 0 °C for 6 h. The solvent was evaporated under reduced pressure, water was added (10 mL) then it was extracted three times with CH_2Cl_2 (3 x 10 mL), then dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding oxazepane **13a** and the compound **21**.

***N*-(3-Chloro-3-phenylpropyl)-*N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (21)**



$C_{18}H_{22}ClNO_3S$
M.W.: 367,8880

The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / petroleum ether 1:1) to afford **21** in 30% yield (110 mg, 0.03 mmol). Pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34-2.40 (m, 2H), 2.43 (s, 3H), 3.24-3.27 (m, 2H), 3.30-3.34 (m, 2H), 3.72-3.78 (m, 2H), 4.92 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.28-7.36 (m, 7H), 7.67-7.70 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 21.5 (q), 39.3 (t), 47.9 (t), 51.7 (t), 60.7 (d), 61.3 (t), 126.8 (d), 127.3 (d), 128.5 (d), 128.7 (d), 129.8 (d), 135.6 (s), 140.8 (s), 143.7 (s). MS: (*m/z*) 367 (M^+). Anal. Calcd for $C_{18}H_{22}ClNO_3S$: C, 58.77; H, 6.03; N, 3.81. Found: C, 59.01; H, 5.78; N, 3.87.

Chapter 2

Intermolecular Pd-Catalyzed Allylic Amination of β,γ-Unsaturated Compounds

Abstract

Two complementary Pd-catalyzed protocols enabling the γ-selective intermolecular allylic amination of but-3-enoic acid derivatives are reported. These transformations can be successfully achieved via either a direct Pd(II)-catalyzed protocol or by way of a one-pot Pd(II) / Pd(0)-catalyzed sequence, depending on the nature of the nitrogen nucleophile used.

Introduction

In the last ten years, efforts to develop increasingly effective step-economical syntheses have been highly pursued in organic chemistry. One way to reach this goal is to reduce the number of steps for a required transformation via activation of normally non reactive C-H bonds, instead of passing through the classical pre-oxidized functional groups.[45] However, C-H bonds are ubiquitous in organic molecules, and their activation, even if possible, may raise selectivity issues. C-H bonds have high kinetic barriers and their reactivity strongly depends on the hybridization of the carbon atom. In particular, due to their low polarity and acidity, $C(sp)^3$-H bonds are among the most difficult to activate, with the exception of those situated in allylic positions (Table 7).

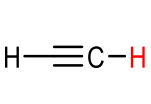
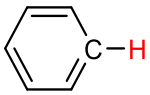
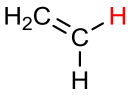
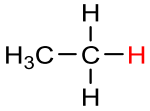
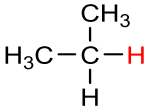
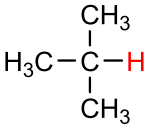
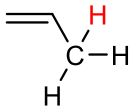
Type of C-H	C(sp)	$C(sp^2)_{arom}$	$C(sp^2)_{vinyl}$	$C(sp^3)_{1°}$	$C(sp^3)_{2°}$	$C(sp^3)_{3°}$	$C(sp^3)_{allylic}$
Structure							
BDE (kj/mol)	552.2	473.0	460.2	410.8	397.9	389.9	361.1
pK_a	~25	43	44	~50	~50	~50	43

Table 7: Bond-Dissociation Energy of Selected Hydrocarbon C-H Bonds (kJ/mol) and pK_a.[46]

Consequentially, a special interest has been directed toward the development of direct functionalization of allylic C-H bonds.

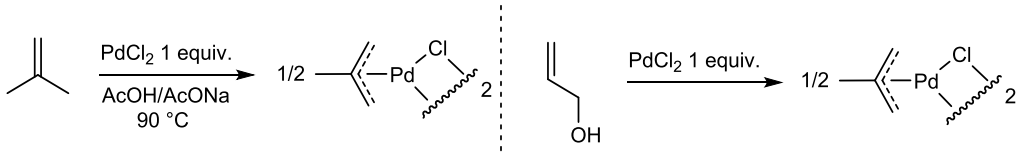
Among the transition metals able to promote such activation, palladium is the most attractive one, due to its low toxicity, its great tolerance towards a large number of functional groups, permitting to avoid protection chemistry, and its relative insensitivity toward water and oxygen. In this frame,

[45] a) Roudesly, F.; Oble, J.; Poli, G. *J. Mol. Cat. A. Chem.* **2016**, in press, DOI: 10.1016/j.molcata.2016.06.020. b) Yu, J.-Q. *Catalytic Transformations via C-H Activation*, vols 1 and 2, *Science of Synthesis*, Thieme, 2016.
[46] McMillen, D. F.; Golden, D. M. Ann. Rev. Phys*. Chem*. **1982**, *33*, 493.

some examples of direct Pd-catalyzed allylic functionalizations have been recently reported, mainly concerning acetoxylation[47] and amination.[48]

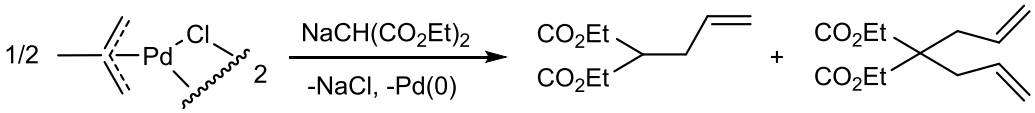
2.1. Pioneering Works

The first example of preparation of the π-allylpalladium chloride dimer starting from a stoichiometric amount of $PdCl_2$ and methylpropane or allylic alcohol was reported independently by Hüttel[49] and Hafner[50] in 1959 (Scheme 27).



Scheme 27: First Generation of π-Allylpalladium Complex from Pd(II).

Only a few years later, Tsuji[51] reported the first synthetic use of these π-allylpalladium complexes as allylating agents, permitting the formation of a carbon-carbon bond. For example, he showed that diethyl malonate could react smoothly with the dimer, affording the allylated product (Scheme 28).



Scheme 28: First Use of π-Allylpalladium Complexes.

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[47] For review dealing with early works, see: a) Muzart, J.; *Bull. Soc. Chim. Fr*. **1986**, 65-77; b) Rawlinson, D. J.; Sosnovsky, G. *Synthesis* **1973**, 567-603; c) Akermark, B.; Zetterberg, K.; *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E.-i. Negishi), John Wiley & Sons, New York, **2002**, p.1875-1885; d) Hosokawa, T.; Murahashi, S.-I. *Other Intramolecular Oxypalladation-Dehydropalladations Reactions*, in: *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), John Wiley & Sons, New York, **2002**, vol.2, p. 2141-2159; e) Henry, P.M. *Palladium Catalyzed Oxidation of Hydrocarbons*, D. Reidel Publishing Co., Dordrecht, The Netherlands, **1980**.

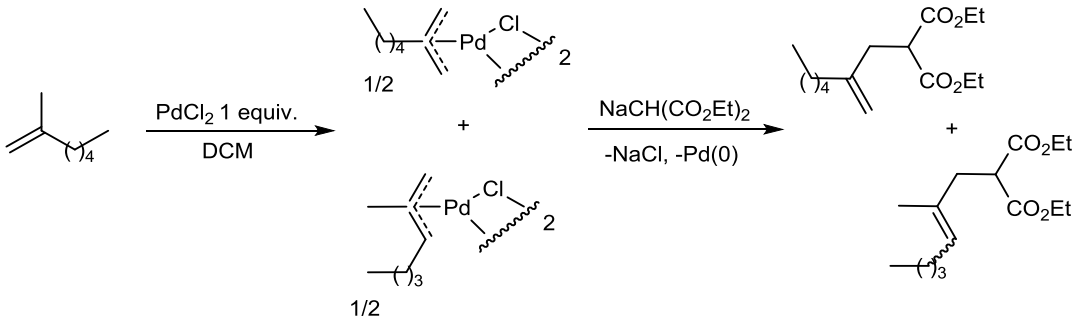
[48] For a recent review, see: Ramirez, T.A.; Zhao, B.; Shi, B. *Chem. Soc. Rev*. **2012**, *41*, 931-942.

[49] a) Hüttel, R.; Kratzer, J. *Angew. Chem*. **1959**, *71*, 456. b) Hüttel, R.; Bechter, M. *Angew. Chem*. **1959**, *71*, 456. c) Hüttel, R.; Kratzer, J.; Bechter, M. *Chem. Ber*. **1961**, *94*, 766.

[50] Smidt, J.; Hafner, W. *Angew. Chem*. **1959**, *71*, 284.

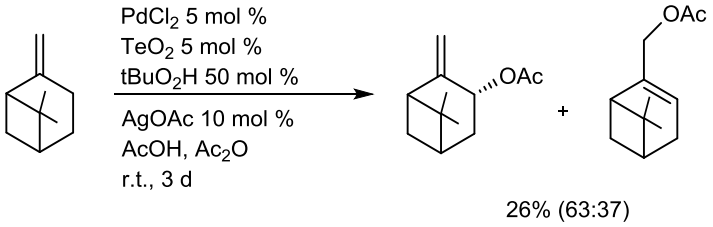
[51] Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett*. **1965**, *6*, 4387.

In 1973, Trost[52] described another use of this complex in synthesis, combining Hüttel's $PdCl_2$-mediated activation with the reactivity proposed by Tsuji. However, the stoichiometric use of the metal and the lack of regioselectivity (the allylic malonates were obtained in a mixture with 63% yield) limited the interest towards this synthetic procedure (Scheme 29).



Scheme 29: Non Selective Synthesis of Allylated Malonates.

In 1982 Uemura[53] reported the first palladium(II)-catalyzed allylation, in which TeO_2 and *t*-BuO_2H were used as in situ co-oxidizing agents in the context of an oxidative Pd(II)-catalyzed allylation (Scheme 30).

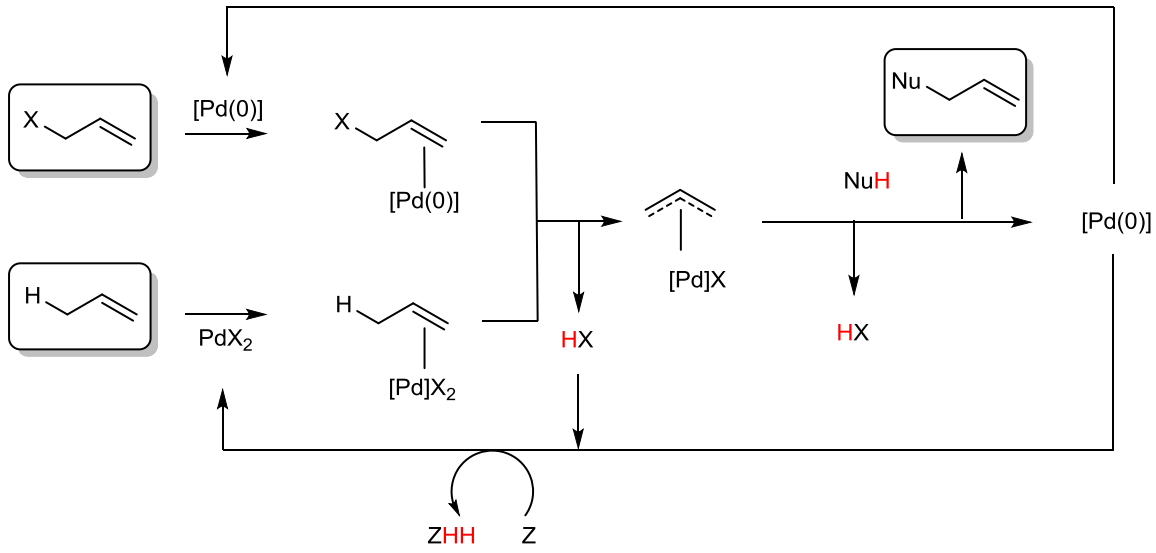


Scheme 30: First Oxidative Allylation Pd(II)-Catalyzed.

The above allylation probably represented the first oxidative Pd(II)-catalyzed allylation, as opposed to the previously described one, based on oxidative addition of a Pd(0) complex to an alkene bearing an allylic leaving group (Scheme 31).

[52] a) Trost, B. M.; Fullerton, T. J. *J. Am. Soc. Rev*. **1973**, *95*, 292. b) Trost, B. M.; Weber, L. *J. Am. Soc. Rev*. **1975**, *97*, 1611.

[53] Uemura, S.; Fukuzawa, S. I.; Toshimitsu, A.; Okano, M. *Tetrahedron Lett*. **1982**, *23*, 87.



Scheme 31: Possible Pd-Catalyzed Allylation Path.

Both the paths involve a common π-allyl Pd intermediate. However, while the former path (top of the scheme) generates the allylic intermediate via oxidative addition of an alkene bearing an allylic leaving group to a Pd(0) complex, the latter path (bottom of the scheme) requires interaction between an alkene bearing an allylic H atom and a Pd(II) complex. In both cases the π-allyl Pd complex can be trapped by various nucleophiles, which produces the allylated produt and a Pd(0) complex. While the former path is a redox neutral process, the latter one is an oxidative process, the initial Pd^{II} species ending-up up as a Pd^{0} complex. Therefore, if catalysis is desired for this path, a terminal oxidizing agent (TOx) is needed, so as to bring the zero-valent Pd back to the original oxidation state. Such oxidant could be, for example, $CuCl_2$, as firstly reported in 1959 by Smidt[54] in the Wacker process, or benzoquinone, as reported at the same time by Moiseev *et al*.[55]

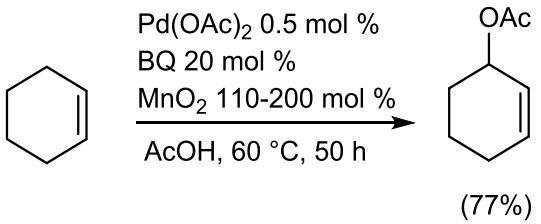
A number of direct inter- or intra-molecular functionalizations of the C-H allylic bond are achievable through oxidative Pd(II)-catalysis, using oxygen-, nitrogen- or carbon-based nucleophiles.[56] A list of selected examples is reported in the following paragraphs.

[54] Smidt, J.; Hafner, W. *Angew. Chem*. **1959**, *71*, 284.
[55] Moiseev, I. I.; Vargaftik, M. N.; Syrkin, Y. K. *Dokl. Akad. Nauk SSSR* **1960**, *133*, 377.
[56] Liron, F.; Oble, J.; Lorion, M. M.; Poli, G. *Eur. J. Org. Chem*. **2014**, 5863.

2.2. Direct Intermolecular Allylic Oxylation Reactions

Among the huge number of Pd(II)-catalyzed allylation processes reported in the literature, a good number are oxidative protocols, possibly relying on allylic C-H activation.

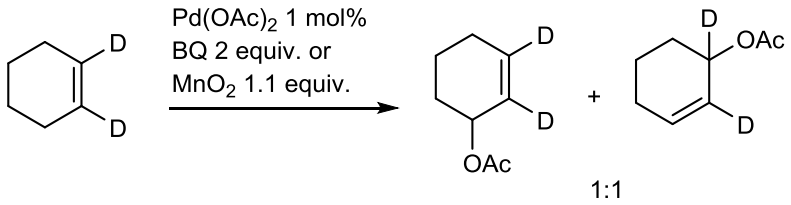
Åkermark[57] described the first Pd(II)-catalyzed allylic acetoxylation of cyclic and acyclic olefins using BQ / MnO_2 as the oxidizing system (Scheme 32).



Scheme 32: Allylic Acetoxylation Reported by Åkermark.

At that time, the mechanism of this acetoxypalladiation could not be unambiguously determined, as it was not clear if it involved a C-H allylic activation or an acetoxypalladation / dehydropalladiation sequence.

To clarify this issue, Bäckvall[58] subsequently addressed a related study on a deuterated substrate. In particular, 1,2-dideuteriocyclohex-1-ene afforded a 1:1 ratio of α- and γ-acetoxylation products, that was only in accord with intermediate C-H activation path (Scheme 33). Which demonstrated that the acetoxylation of cyclohexene involves a C-H activation mechanism.



Scheme 33: Allylic Oxidation of 1,2-Dideuterocyclohexene.

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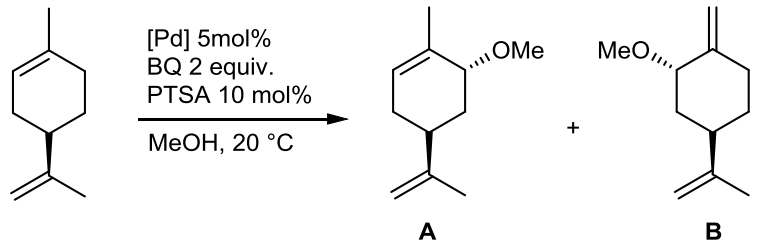
[57] Hansonn, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem*. **1990**, *55*, 975-984.

[58] a) H. Grennberg, V. Simon, J.-E. Bäckvall, J. *Chem. Soc. Chem. Commun*. **1994**, 265–266. b) Grennberg, H.; Bäckvall, J.-E. *Chem. Eur. J.* **1998**, *4*, 1083–1089.

Later, Mortreux[59] studied the oxidation of limonene and showed that in both cases of acetoxylation and methoxylation the reaction occurred with highly regio- and stereoselectivity (Scheme 34).



Scheme 34: Allylic Etherification of Limonene.

The variation of the palladium source resulted in a change of diasteroselectivity (Table 8).

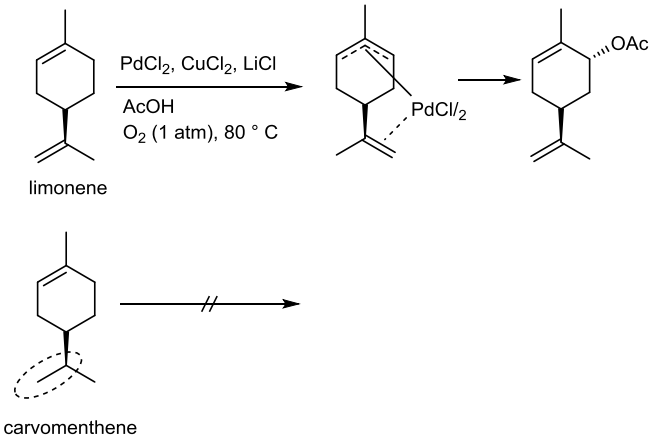
[Pd]	***Compound A***	***Compound B***
$Pd(OAc)_2$	7%	93%
Li_2PdCl_4	87%	Traces

Table 8: Diasteroselectivity as a Function of the Pd Source in the Allylic Mehtoxylation of Limonene.

Thereafter, Gusevskaya[60] demonstrated that the presence of the extracyclic unsaturation in limonene could direct the formation of the π-allyl complex. Indeed, carvomenthene, which is devoid of the extracyclic unsaturation did not undergo allylic acetoxylation, even at high temperatures (Scheme 35).

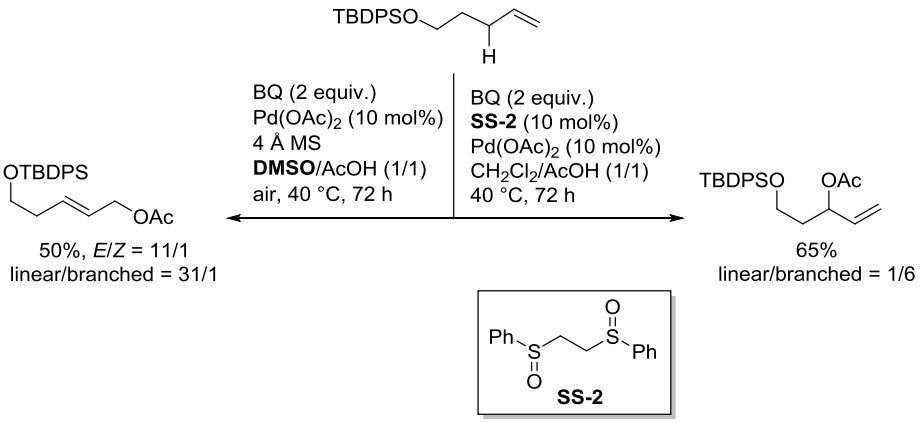
[59] El Firdoussi, L.; Baqqa, A.; Allaoud, S.; Ait Allal, B.; Karim, A.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A* **1998**, 135, 11–22.

[60] Speziali, M. G.; Robles-Dutenhefner, P.A.; Gusevskaya, E. V. *Organometallics* **2007**, *26*, 4003–4009.



Scheme 35: Influence of an Additional Olefin.

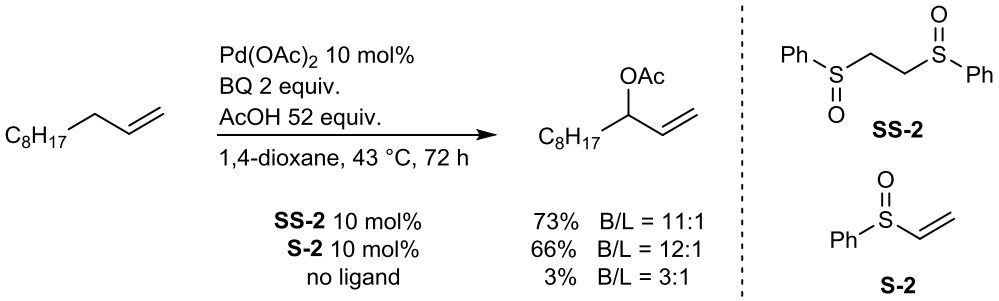
More recently, White *et al*. found that direct allylic oxidation of terminal alkenes could be performed in a regioselective manner to give the linear or the branched allylic acetate, depending on the reaction conditions. The use of DMSO as co-solvent led to the linear allylic acetate, whereas the presence of a 1,2-disulfoxide ligand such as **SS-2** led to the preferential formation of the branched product (Scheme 36).[61]



Scheme 36: Influence of the Type of Sulfoxide on the Regioselectivity of Pd(II)-Catalyzed Allylic Acetoxylation.

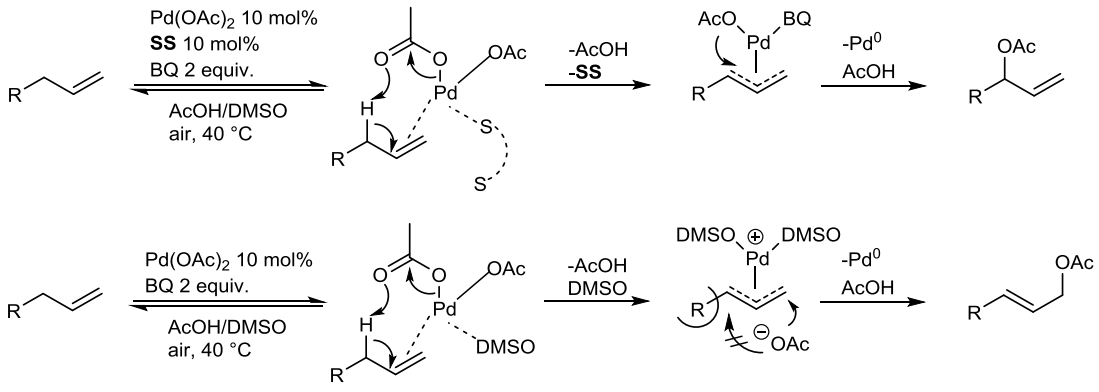
[61] a) Chen, M. S.; White, M. C. *J. Am. Chem. Soc*. **2004**, *126*, 1346-1347; b) Delcamp, J. H.; White, M. C. *J. Am. Chem. Soc.* **2006**, *128*, 15076-15077; c) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc*. **2005**, *127*, 6970-6971.

To better understand the mechanism involved and the role of the sulfoxide ligand, White's team realized several studies.[62] For example, treatment of 1-undecene with $Pd(OAc)_2$, BQ and acetic acid in dioxane as solvent does not give allylic acetoxylation acetoxylation in the absence of the sulfoxide ligand. In contrast, in the presence of the disulfoxide ligand **SS-2** or the monosulfoxide ligand **S-2** the allylation product is obtained in almost the same yield and with the same regioselectivity (Scheme 37).



Scheme 37: Influence of the Sulfoxide Ligands.

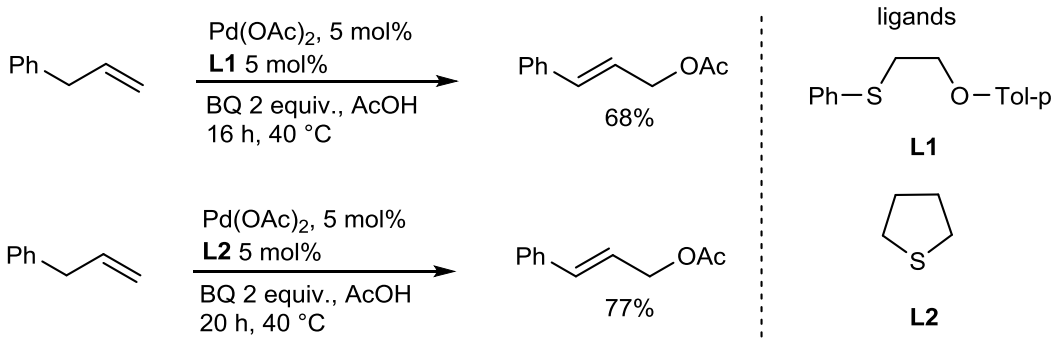
Different working models have been advanced to account for the different regioselectivities observed as a function of the sulfoxide ligand used. The branched product, obtained when a disulfoxide ligand is employed, is postulated to derive from an inner sphere attack of acetate anion at the allyl internal position of the neutral BQ-coordinated η^3-allyl complex (Scheme 38, top). Instead, the linear *E*-configurated allylic product, obtained as major isomer when using DMSO, is proposed to derive from an outer sphere attack of acetate anion to a cationic η^3-allyl complex (Scheme 38, bottom).



Scheme 38: Proposed Scenario for the Pd(II)-Catalyzed Acetoxylation of Terminal Alkenes in the Presence of Sulfoxide Ligands.

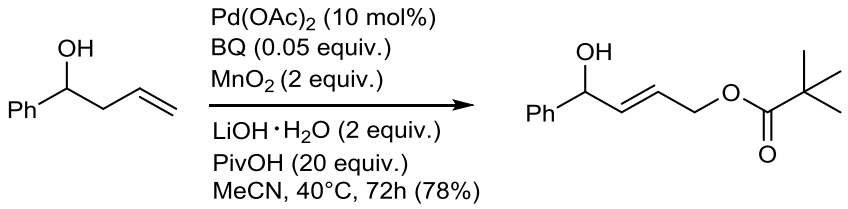
[62] Chen, M.S.; Prabagaran, N.; labenz, N.A.; White, M.C. *J. Am. Chem. Soc*. **2005**, *127*, 6970.

Stambuli reported an alkoxythioether ligand **L1** was able to promote the Pd-catalyzed linear allylic acetoxylation of terminal alkenes (Scheme 39). A set of experiments excluded the involvement of a branched-to-linear equilibration of the allylic acetate product as well as of a η^3-allyl complex. The same team showed later that tetrahydrotiophene **L2** behaved even better than the previously found alkoxythioether ligand (Scheme 39).[63]



Scheme 39: Pd(II)-Catalyzed Allylic Acetoxylation in the Presence of Thioether-Based Ligands.

Le Bras and Muzart developed a process for allylic acyloxylation of terminal alkenes under basic conditions achieving very good regio- and stereoselectivities in favor of the linear and *E*-configured products (Scheme 40).[64]



Scheme 40: Acyloxylation of Homoallylic Benzyl Alcohol.

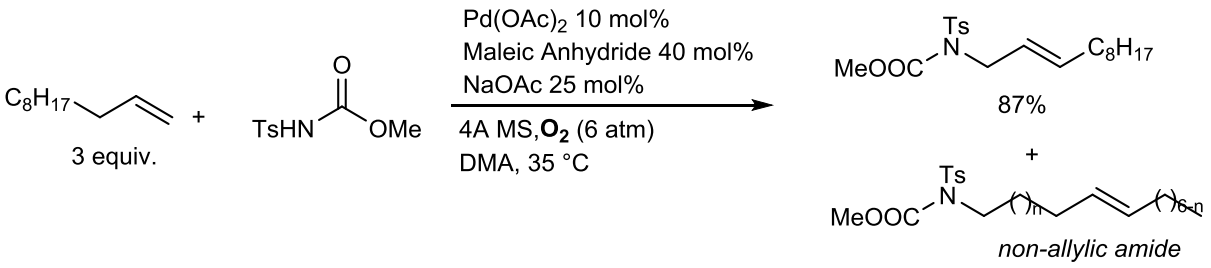
The mechanism is supposed to involve a complex, in which the palladium coordination sphere is saturated by the acyloxy ligand.

[63] Le, C.C.; Kunchithapatham, K.; Henderson, W.H.; Check, C.T.; Stambuli, J.P. *Chem. Eur. J.* **2013**, *19*, 11153-11157.
[64] Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem*. **2010**, *75*, 1771-1774.

2.3. Direct Intermolacular Allylic Amination Reactions

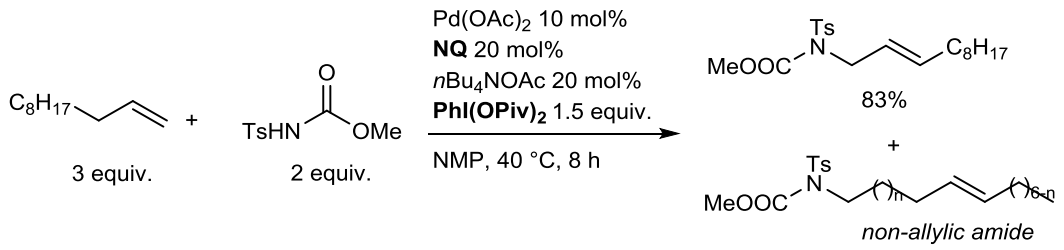
The groups of White and Liu developed at the same time protocols of direct Pd-catalyzed allylic aminations, using both terminal alkenes and *N*-tosylcarbamates as nitrogen nucleophiles.

On one hand, Liu *et al*. reported an aerobic oxidative amination protocol using molecular oxygen in dimethylacetamide affording linear derivatives via an allylic C-H activation (Scheme 41).[65]



Scheme 41: Intermolecular Direct Allylic Amination Reaction in Aerobic Conditions.

Besides the allylic product, a considerable amount of non-allylic amide was obtained (70 / 30 allylic non allylic). A possible reason for the formation of this isomer was judged by the authors to stem from the slow reoxidation step of Pd(0) by molecular oxygen. The same group later developed a new, more efficient oxidizing system, based on naphthoquinone (NQ) and $PhI(OPiv)_2$ that allowed to lower the allylic / non-allylic ratio to 93 / 7 (Scheme 42).[66]

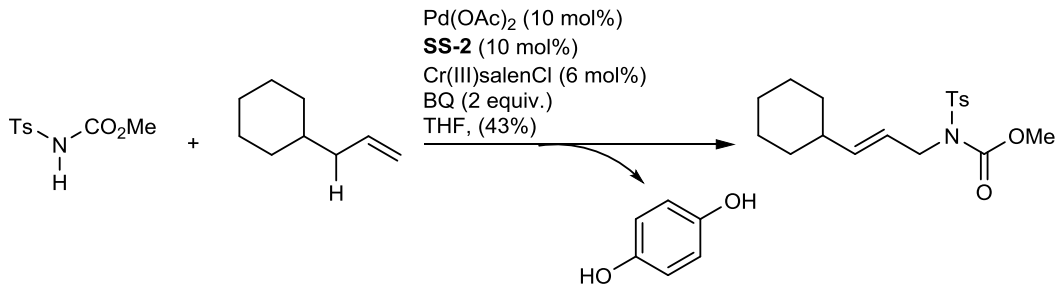


Scheme 42: Intermolecular Direct Allylic Amination using NQ / $PhI(OPiv)_2$ as Oxidizing System.

[65] Liu, G.; Yin, G.; Wu, L. *Angew. Chem. Int. Ed*. **2008**, *47*, 4733-4736. *Angew. Chem*. **2008**, 120, 4811.
[66] Yin, G.; Wu, Y.; Liu, G.; *J. Am. Chem. Soc*. **2010**, *132*, 11978-11987.

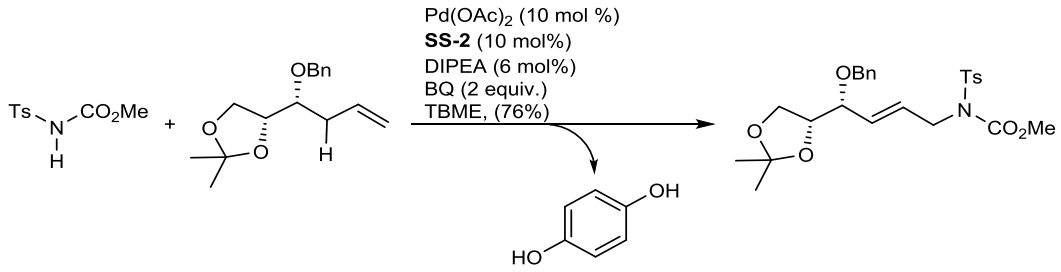
Control experiments confirmed that a π-allylpalladium intermediate is involved in the mechanism and that the C-H activation and the nucleophilic trapping steps are irreversible.

On the other hand, Christina White disclosed a related Pd^{II}-catalyzed direct allylic amination of terminal alkenes based on the use of Cr^{III}(salen)-Cl as a second catalyst.[67] In this case, the reaction affords exclusively the linear product (Scheme 43).



Scheme 43: Direct Allylic Intermolecular Amination Reaction.

The same group later developed an alternative protocol for direct allylic amination using a Brønsted base instead of the previously described Cr^{III}-salen-Cl Lewis acid.[68] Optimal yields of linear derivatives are obtained with the Hunig's base (DIPEA) as additive in *tert*-butyl methyl ether (TBME) as solvent (Scheme 44).

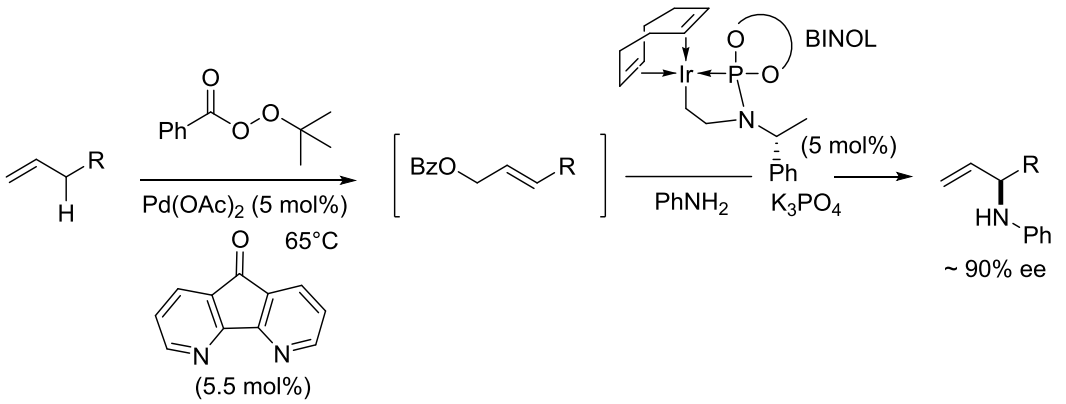


Scheme 44: Brøensted-Base-Promoted Allylic C-H Amination.

More recently, the Hartwig's group reported an enantioselective strategy based on the one-pot two-step (Pd / Ir catalysis) conversion of terminal alkenes into branched allylic amines through the

[67] Reed, S. A.; White, M. C. *J. Am. Chem. Soc*. **2008**, *130*, 3316-3318.
[68] Rice, G. T.; White, M. C. *J. Am. Chem. Soc*. **2009**, *131*, 11707-11711.

intermediacy of linear allyic benzoates.[69] The first Pd-catalyzed step may be considered as a variant of the Cu(II)-catalyzed Kharasch-Sosnovsky reaction.[70]



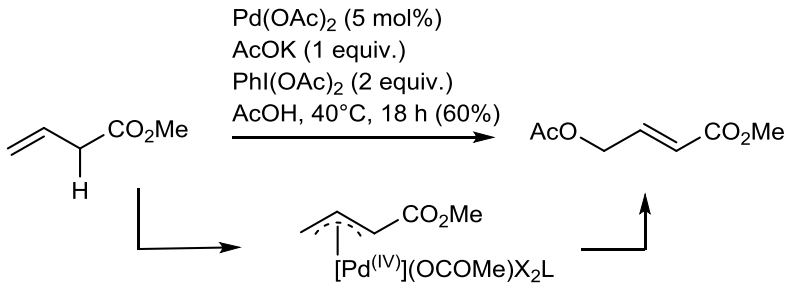
Scheme 45: Enantioselective Strategy Based on the One-Pot Two-Step Conversion of Terminal Alkenes.

2.4. Aim of This Work

As we saw, the development of reactions that directly and selectively convert C-H bonds into C-N bonds, avoiding the preparation and handling of oxidized intermediates, is highly desirable. In this frame, α-olefins can be considered an ideal low-cost starting material for such catalytic functionalizations to produce more complex structures for fine chemistry purposes. Even if some palladium-catalyzed allylic aminations on olefins are already known, a number of challenging variations are still waiting for improvement. In particular, at the best of our knowledge, Szabò reported the only example of an allylic oxylation of but-3-enoates. In this case, a hypervalent iodine species was used as the terminal oxidizing. The authors propose for this transformation a Pd(II) / Pd(IV) mechanism involving a highly electrophilic η^3-allyl-palladium Pd(IV) complex (Scheme 46).

[69] Sharma, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2013**, *135*, 17983-17989.

[70] Beckwith, A. L. J. Zavitsas, A. A. *J. Am. Chem. Soc.* **1986**, *108*, 8230-8234.

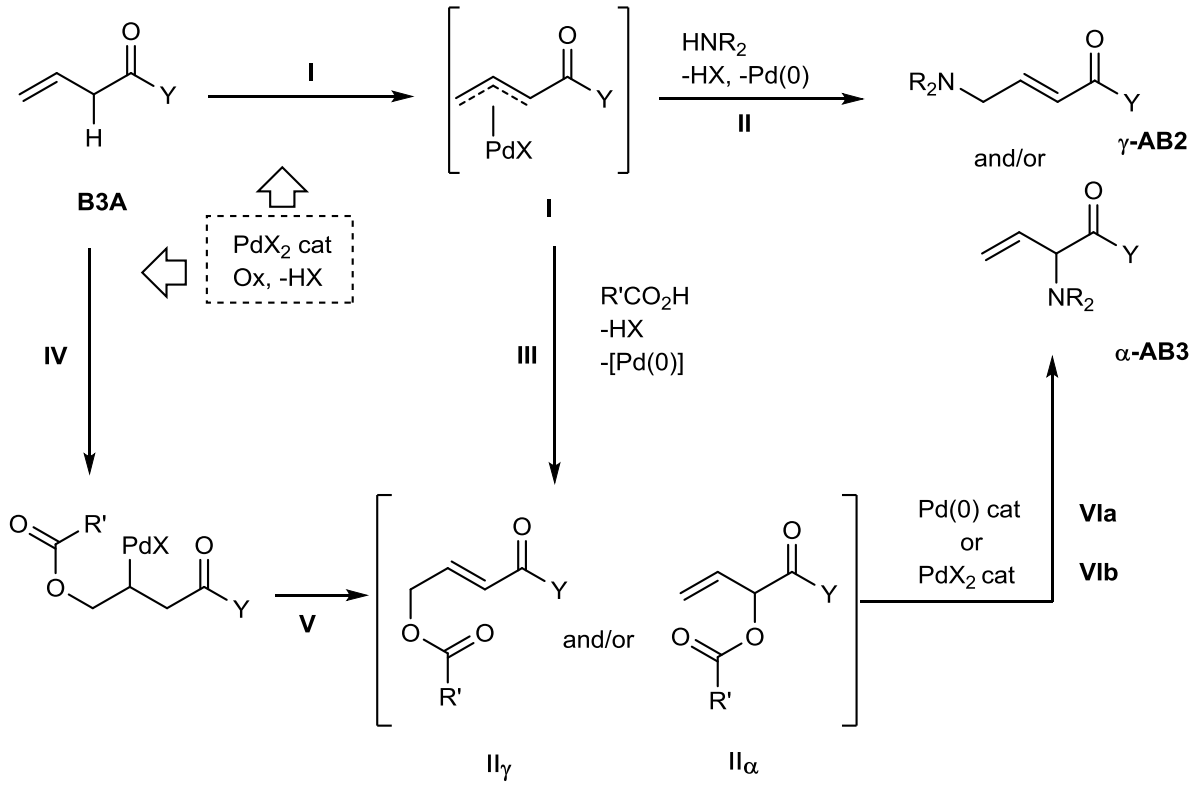


Scheme 46: Allylic Acetoxylation Using a Hypervalent Iodine Species as Terminal Oxidant (TOx).

Accordingly, we decided to develop a hitherto unknown method for the dehydrogenative Pd-catalyzed allylic amination of butenoic acid derivative. In particular, we reasoned that the allylic C-H activation of a but-3-enoic acid (B3A) derivative is expected to afford the corresponding π-allylpalladium complex more readily than the but-2-enoic acid B2A derivative for two reasons: a) the B3A isomer, being non conjugated, is less stable and more reactive than the B2A, b) Pd-catalyzed allylic activations are known only on terminal alkenes. Subsequent *in situ* direct trapping of the π-allyl complex **I** with a suitable nitrogen nucleophile[71] should afford the desired allylic amination product **γ-AB2** or **α-AB3.** Alternatively, trapping of **I** by an acyloxy ligand (step **III**) or via an acyloxypalladation / dehydropalladation sequence (step **IV** and **V**) may lead to products **IIα** or **IIγ,**[72] which may in turn be converted into α- or γ-amino but-2-enoic derivatives (step **VI**) via a redox-neutral Pd(0)- or Pd(II)-catalyzed allylic amination (Scheme 47).

[71] For a review on the basics of the Pd-catalyzed allylation reactions, see: Poli, G.; Prestat, G.; Liron, F.; Kammere-Pentier, C.; Kazmaier, U. *Top. Organomet. Chem*. **2011**, *38*, 1.

[72] For an example assumed to take place via this mechanism, see: Bottarelli, P.; Costa, M.; Della Ca', N.; Fava, E. *Tetrahedron Lett*. **2013**, *54*, 2362.



Scheme 47: Possible Synthetic Routes to Allylic Amination of B3A Derivatives.

Pursuing our interest in the synthesis of nitrogen containing scaffolds via palladium-catalyzed allylic amination,[73] we decided to focus our attention on the synthesis of γ-AB2 derivatives from B3A compounds via either a direct oxidative path {Pd(II) / [Ox]} or a one-pot consecutive path {Pd(II) / [Ox]+Pd(0)}.

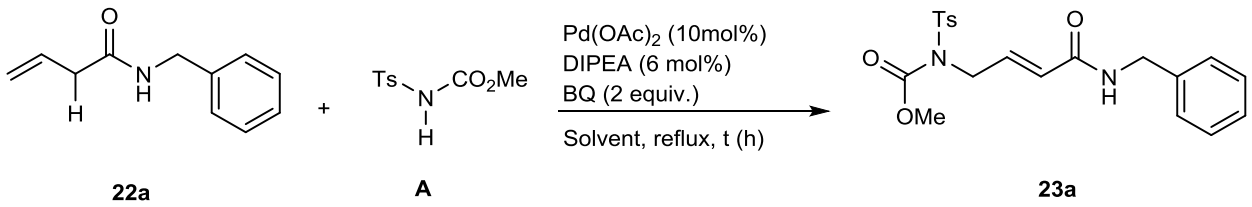
2.5. Direct Oxidative Path {Pd(II) / [Ox]}

2.5.1. First Experiments and Optimization

Our investigation began with the study of the direct Pd(II)-catalyzed strategy, choosing the reaction between benzyl amide **22a** and *N*-tosyl-carbamate **A** as the model transformation. The

[73] (a) Lorion, M. M.; Duarte, F. J. S.; Calhorda, M. J.; Oble, J.; Poli, G. *Org. Lett.* **2016**, *18*, 1020. (b) Duarte, F. J. S.; Poli, G.; Calhorda M. J. *ACS Catal.* **2016**, *6*, 1772. (c) Lorion, M. M.; Oble, J. Poli, G. *Pure Appl. Chem.* **2016**, *88*, 381-389 (d) Rajabi, J.; Lorion, M. M.; Ly, V. L.; Liron, F.; Oble, J.; Prestat, G.; Poli, G. *Chem. Eur. J.* **2014**, *20*, 1539. (e) Lorion, M. M.; Nahra, F.; Ly, V. L.; Mealli, C.; Mesaoudi, A.; Liron, F.; Oble, J.; Poli, G. *Chem. Today.* **2014**, *32*, 30. (f) Nahra, F.; Liron, F.; Prestat, G.; Mealli, C.; Messaoudi, A.; Poli, G. *Chem. Eur. J.* **2009**, *15*, 11078.

reaction conditions developed by White[74] and coworkers [$Pd(OAc)_2$ (10 mol %), **SS-2** (15 mol %), *N*,*N*-diisopropylethylamine (DIPEA)(6 mol %) and benzoquinone (BQ) (2 equiv.)] for a similar allylic amination using the same nucleophile was taken as a starting point (Scheme 48).



22a **A** **23a**

Scheme 48: Model Transformation.

Use of TBME as the solvent at reflux for 72 hours afforded the desired γ-AB2 aminated product **23a** in 72% yield, with no traces of the α-AB3 isomer (Table 9, entry 1). Interestingly, similar results could also be obtained running the reaction without the disulfoxide ligand **SS-2** (entry 2). Change of solvent to THF or DMSO, with or without disulfoxide ligand, did not improve the yields (entries 3, 4, 5). To our satisfaction, switch to acetonitrile as solvent at reflux for 24 hours increased the yield to 95% (entry 6).

Entry	***Ligand***	***Solvent***	***Time (t)***	***Yield (%)***
1	**SS-2** 15 mol %	TBME	72	72
2	-	TBME	72	75
3	**SS-2** 15 mol %	THF	72	53
4	-	THF	18	66
5	-	DMSO	24	50
6	**-**	**CH_3CN**	**24**	**95**

Table 9: Optimization of Pd(II)-Catalyzed Direct Amination.

With the optimized conditions in hand [$Pd(OAc)_2$ 10 mol %, DIPEA 6 mol %, BQ (2 equiv.) in CH_3CN (0.2 M) at reflux for 24 h] we turned to study the scope of the amination of other B3A derivatives with *N*-tosyl-carbamate **A**.

[74] Qi, X.; Rice, G. T.; lall, M. S.; Plummer, M. S.; White, M. C. *Tetrahedron*, **2010**, *66*, 4816.

2.5.2. Scope:

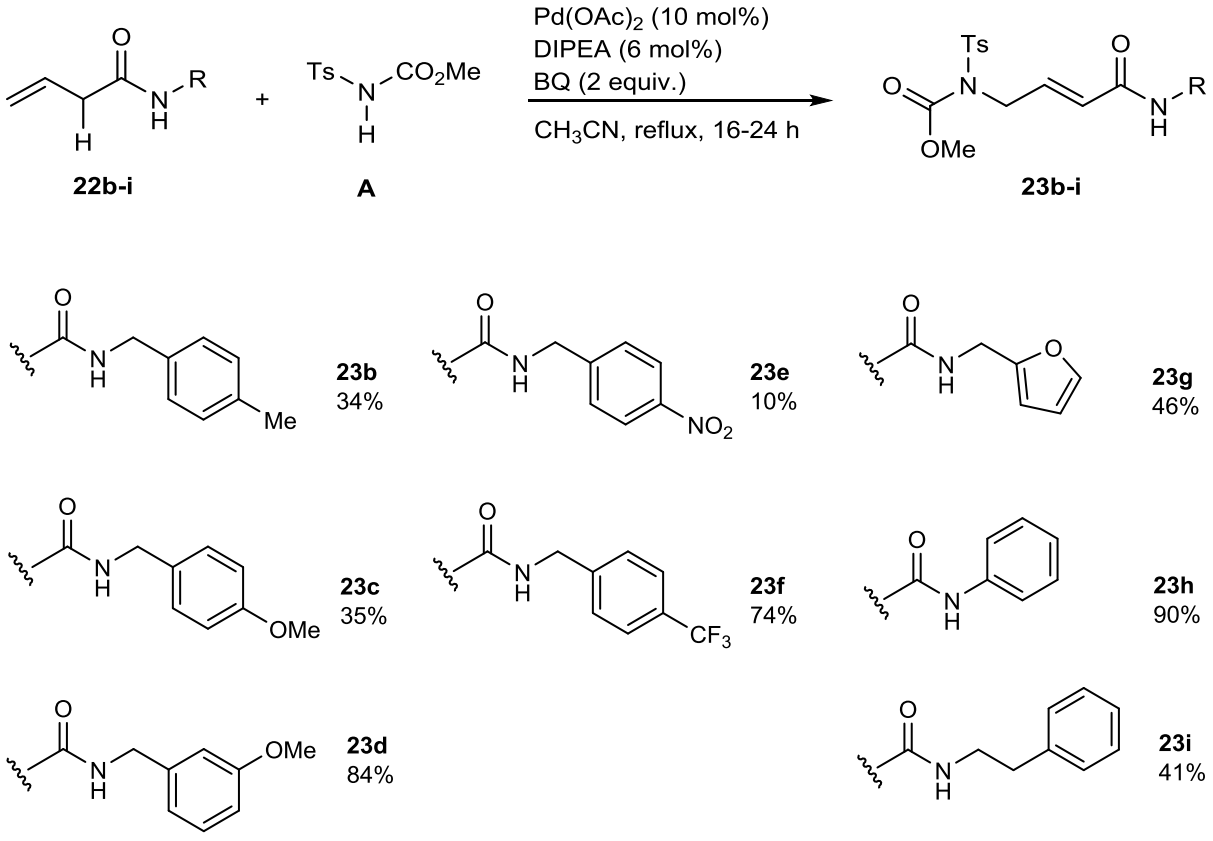
Substitution on the B3A derivative

The effect of the substitution on the aromatic ring of various *N*-benzyl 3-butenamides was initially investigated.

Electron-donors in *para*-position such as in (**22b-c**) gave the corresponding γ-AB2 amides in moderate yields (~35%), probably due to instability of the products in the oxidizing medium, while a donor in *meta*-position reestablished a satisfactory 84% yield (**22d**).

Two contrasting behaviors were observed with *para* electron-withdrawing groups. While the nitro group afforded only low yields of the desired product (**22e**) (due to troublesome product isolation), the trifluoromethyl group gave the desired γ-AB2 amide in good yield (**22f**).

N-Furfuryl (**22g**), *N*-phenyl (**22h**), and *N*-phenylethyl B3A secondary amides (**22i**) led to the expected derivatives in good to moderate yields (Scheme 49).



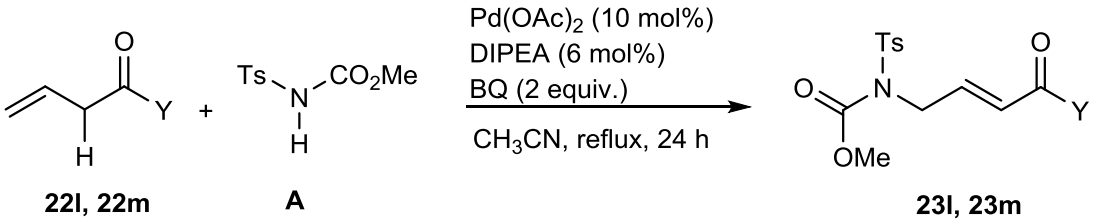
Scheme 49: Scope of the Pd(II)-Catalyzed Allylic Amination with *N*-Tosyl-carbamate **A**.

In sharp contrast to the above mentioned secondary amides, tertiary amides did not display any reactivity (**22j–k**) (Figure 5).

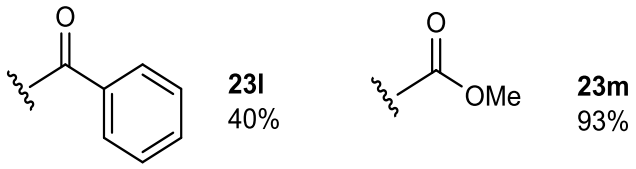
22j **22k**

Figure 5: Unreactive Tertiary Amides Tested.

Next, the same reaction could be successfully extended to a ketone (**22l**) and an ester (**22m**) (Scheme 49).



22l, 22m **A** **23l, 23m**

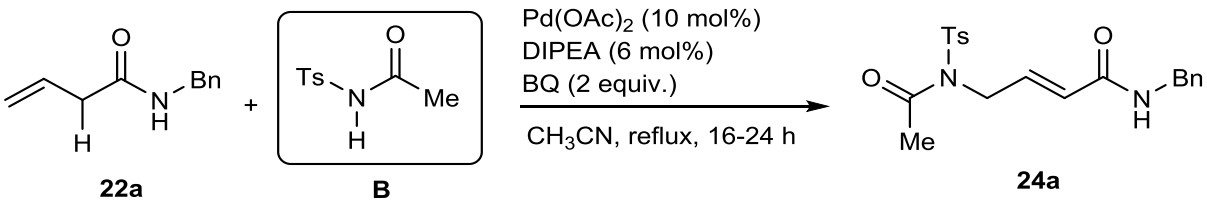


23l 40% **23m** 93%

Scheme 49: Extension of the Reaction to a Ketone and an Ester.

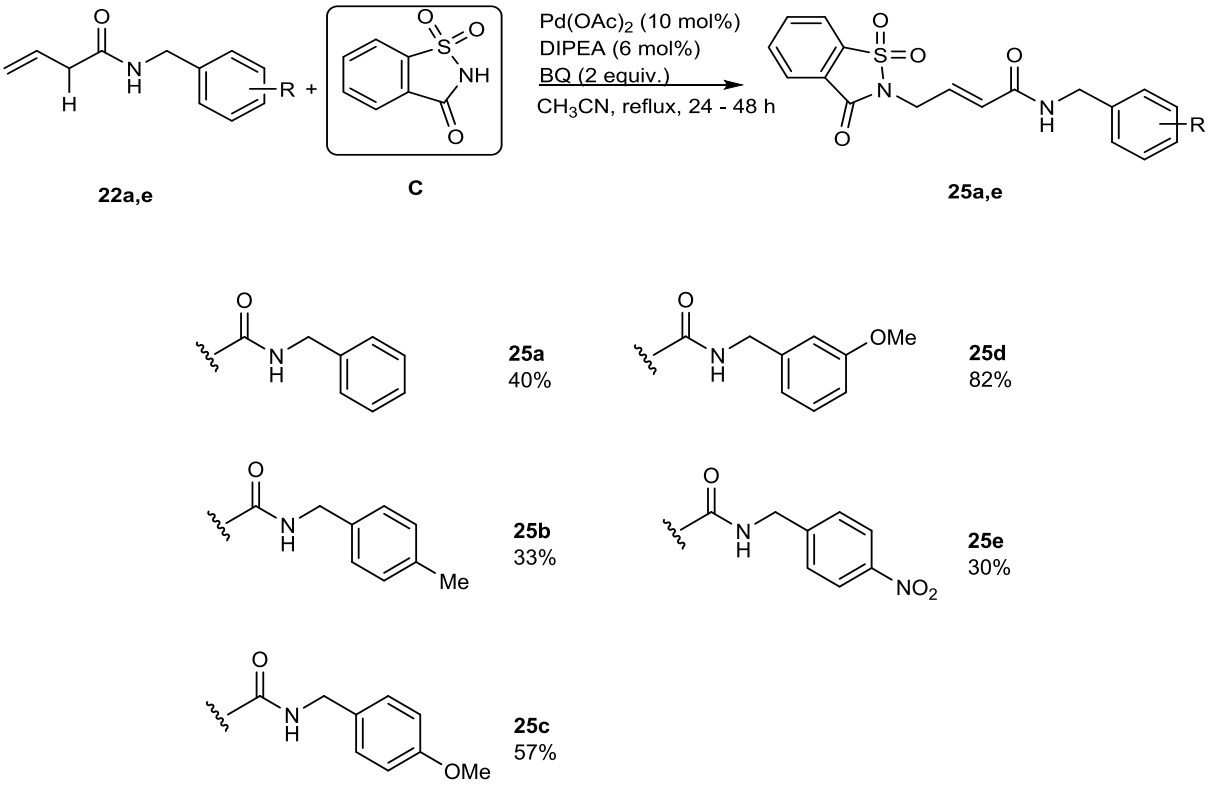
The Nitrogen Nucleophiles

Variation of the nitrogen nucleophile was studied next. Without surprise, reaction of *N*-tosyl-acetamide **B** with the model allyl amide **22a** gave the desired γ-AB2 amide **24a** in 61% yield (Scheme 50).



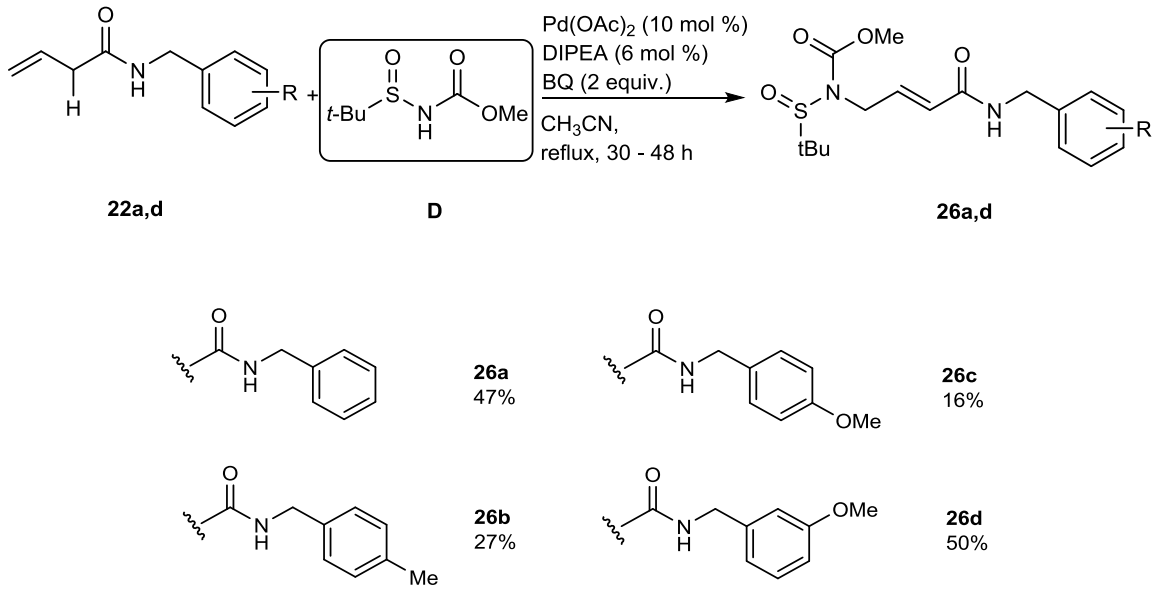
Scheme 50: Scope of Pd(II)-Catalyzed Allylic Amination with *N*-Tosyl-acetamide **B**.

Saccharin **C** was also tested, which reacted with five different B3A derivatives to afford the corresponding γ-AB2 amides in moderate to good yields (**25a-e**) (Scheme 51)



Scheme 51: Scope of Pd(II)-Catalyzed Allylic Amination with Saccharin **C**.

Moderate yields of the expected γ-AB2 products could be also isolated when using *N*-sulfinyl-carbamate **D** as nitrogen nucleophile (Scheme 52).



Scheme 52: Scope of Pd(II)-Catalyzed Allylic Amination with *N*-Sulfinyl-Carbamate **D**.

In contrast, *N*-tosylamine, phthalimide and camphorsultam gave no reaction when submitted to reaction conditions analogous to those above mentioned (Figure 6).

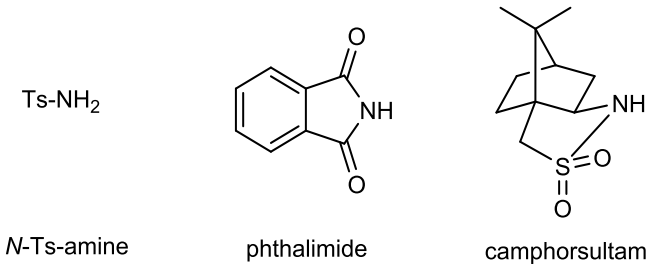


Figure 6: Nucleophiles Tested.

These results suggest that the ideal pK_a for the nitrogen nucleophiles is in the window 5-6, while nucleophiles with higher pK_a values do not work (Figure 7).

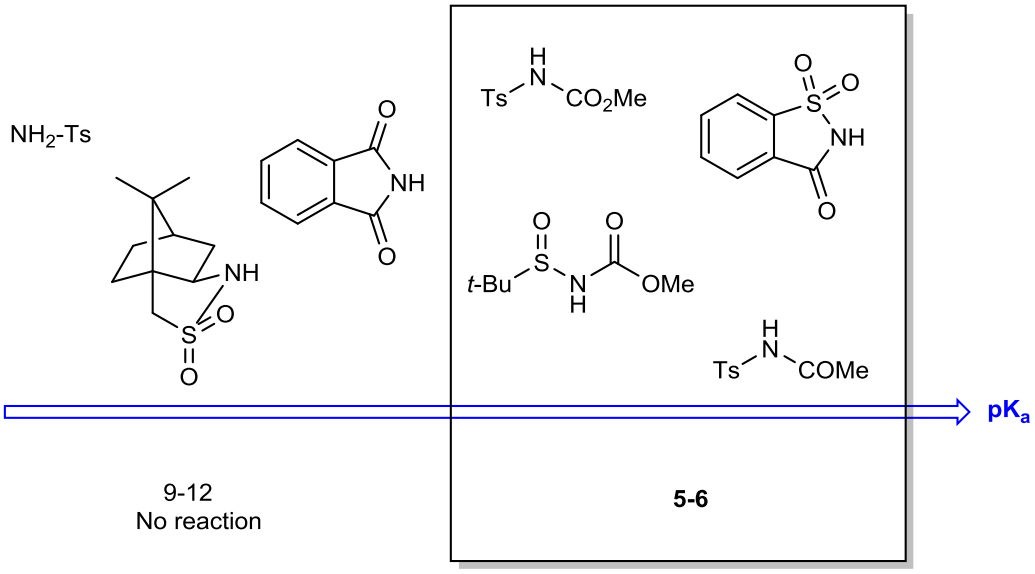


Figure 7: Window of Necessary pK_a.

2.6. Sequential One-Pot Pd(II) / Pd(0) Protocol

As anticipated in Scheme 47, a second strategy we pursued involved a two-step procedure entailing an initial oxidative Pd(II)-catalyzed allylic acyloxylation of the B3A derivates, followed by a Pd(0)-catalyzed amination.

2.6.1. 1st step: Oxidative Allylic Acyloxylation

Although both the above mentioned reactions are known as separate transformations, prior to our study no attempt to run them in serial was reported. Indeed, the oxidative Pd(II) allylic acetoxylation of alkene is a very well established reaction (see above), as well as the Pd(0)-catalyzed allylation of nitrogen nucleophiles such as *N*-phthalimide (pK_a of 8.3).[75]

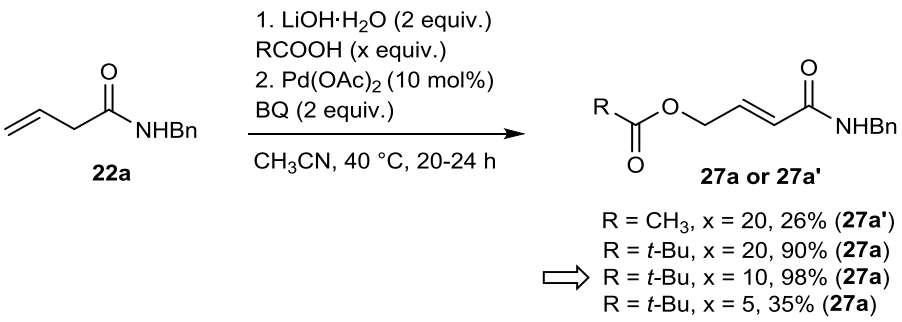
Our starting point was a protocol by Le Bras and Muzart, which reported a dehydrogenative Pd(II)-catalyzed acyloxylation using the couple LiOH / RCOOH.[76]

[75] Science of Synthesis, Houben-Weyl Methods of Molecular Transformations, Thieme ED. 2005, Vol 22, Chapt21.2 F. A. Luzzio, in *Product Class 2: Triacylamines, Imines (Diacylamines), and Related Compounds*, p 259.

[76] Thiery, E.; Aouf, C.; Belloy, J.; Harakat, D.; Le Bras, J.; Muzart, J. *J. Org. Chem*. **2010**, *75*, 1771.

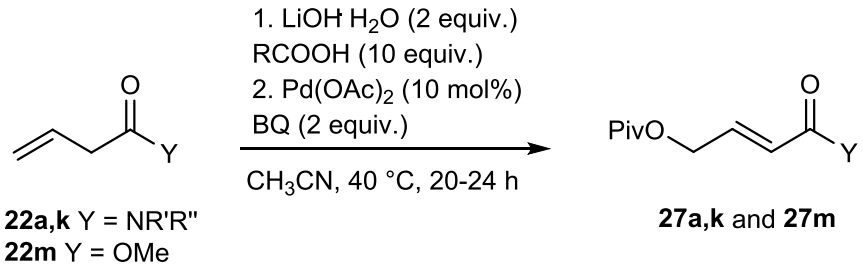
As previously done for the direct Pd(II)-catalyzed amination protocol, the B3A amide **22a** was chosen as model molecule to perform some preliminary screening to assess the influence of the nature and the amount of the added carboxylic acid.

After a few trials, we decided to use 10 equivalent of carboxylic acid as optimal amount to perform the reaction (Scheme 53).



Scheme 53: Screening of the Carboxylic Acid Amount.

The best conditions to perform the pivaloxylation step turned out to be: pivalic acid (10.0 equiv.), LiOH monohydrate (2.0 equiv.), $Pd(OAc)_2$ (10 mol %) and BQ (2.0 equiv.) in acetonitrile at 40 °C for 20-24 h (Scheme 54).

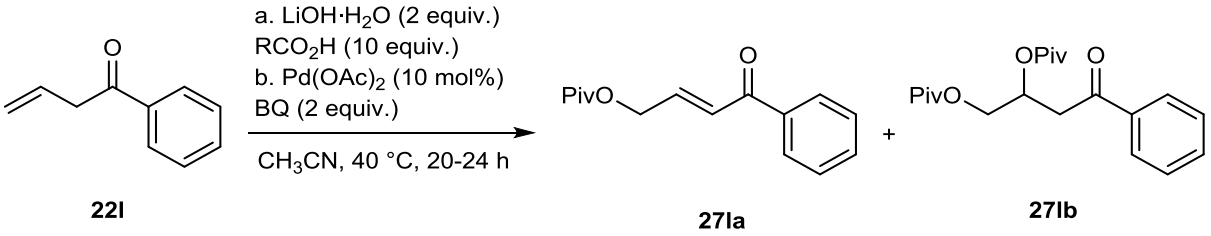


Scheme 54: Pd(II)-Catalyzed Allylic Pivaloxylation Step.

Gratifyingly, this protocol was effective with all the secondary and tertiary amides tested (**22a,k**), as well as with an ester (**22m**), giving the corresponding γ-oxylated but-2-enyl acid derivatives (γ-OB2A) in good yields (35–98% yield).

Keton (**22l**), in contrast to what previously observed in the direct amination, gave an unseparable mixture of two of the expected 4-pivaloxy-1-phenylbut-2-en-1-one (**27la**) and 3,4-

dipivaloxy-1-phenylbutan-1-one (**27lb**), deriving from the conjugate addition of pivalate anion to the α,β-unsaturated ketone (**27la**).



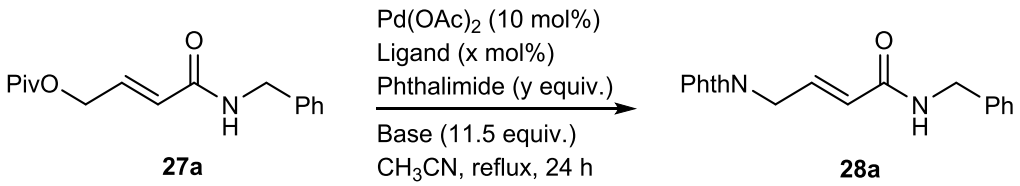
22l **27la** **27lb**

Scheme 55: Inseparable Mixture of Compounds.

2.6.2. 2nd step: Isohypsic Pd(0)-Catalyzed Amination

Once optimized the first pivaloxylation step, we focused on the second part of the transformation: the isohypsic Pd(0)-catalyzed amination. Pursuing the idea of eventually merge the double processes in a single operation, this second step was first tried in acetonitrile as solvent and with $Pd(OAc)_2$ as catalyst.

It is important to highlight that a Pd(0)-catalyzed allylation reaction normally requires a phosphine ligand to prevent the dimerization of the transient π-allyl complex and, when $Pd(OAc)_2$ pre-catalys is used, to reduce the metal to the real Pd(0) catalyst. Moreover, in some cases also a base is needed to carry out a preliminary deprotonation of the nucleophile.[77] The pivaloxylation step needed a considerable amount of pivalic acid. Therefore, in order to obtain basic / buffered conditions in the second step of the final one-pot reaction, addition of an excess amount of base was necessary. Accordingly, we decided to use 11.5 equivalents of a base in the reaction between of phthalimide with γ-OB2A **27a** (Table 10), selected as our model isohypsic allylation reaction.



27a **28a**

[77] Giambastiani, G.; Poli, G. *J. Org. Chem*. **1998**, *63*, 9608.

Entry	*Ligand(x %)*	*PhthNH (y equiv.)*	*Base*	*Yield (%)[a]*
1	PPh_3 (40)	1.5	NEt_3	SM
2	DPPE (20)	1.5	NEt_3	SM
3	DPPF (20)	1.5	NEt_3	28
4	XANTPHOS (20)	1.5	NEt_3	25
5	BINAP (20)	1.5	NEt_3	30
6[b]	BINAP (20)	1.5	NEt_3	34
7	BINAP (20)	1.5	DIPEA	40
8[c]	**BINAP (20)**	**3.0**	**DIPEA**	**83**

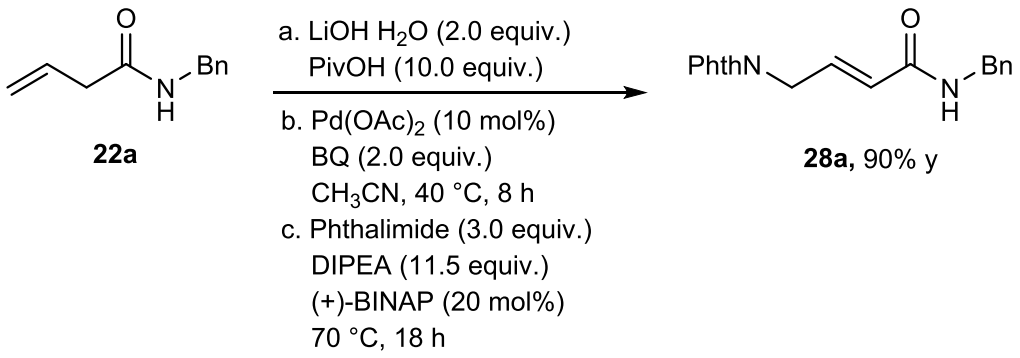
[a] Isolated yields, [b] Reaction time = 48 h, [c] Reaction conditions: Substrate **27a** (1.0 equiv.), phtalimide (3.0 equiv.), $Pd(OAc)_2$ (10 mol %), (+)-BINAP (20 mol %), DIPEA (11.5 equiv.) in acetonitrile (0.2 M).

Table 10: Optimization of the Pd(0)-Catalyzed Amination of **27a** with Phtalimide.

Triethylamine was first tested as the base. The use of the monodentate Ph_3P (entry 1) or of the bidentate dppe (entry 2) gave no reaction, only starting material being recovered. Instead, the use of the bidentate ligands DPPF, XANTPHOS and BINAP afforded the expected γ-AB2A product **28a** in moderate yields (entries 3-5). Judging BINAP as the most promising ligand, we stuck to this ligand as to screen further conditions. However, increase of the reaction time to 48 hours did not produce any significant change in the yield (entry 6).

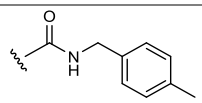
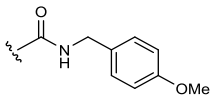
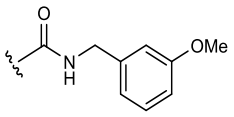
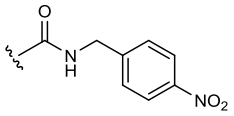
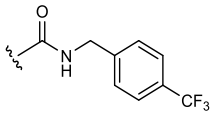
Switch of the base from NEt_3 to DIPEA (Hunig's base) brought about a moderate yield improvement (entry 7). Finally, raising the amount of phthalimide to 3.0 equivalents allowed isolating **28a** in satisfactory yield (83%) (entry 8).

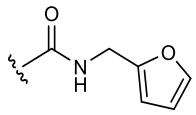
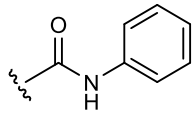
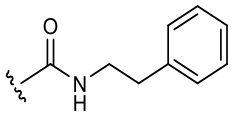
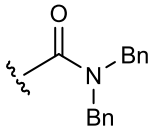
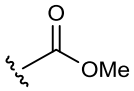
Once obtained the best conditions for both the separated steps, we moved to merge the two protocols into a single operation. The initial allylic pivaloxylation was carried out on **22a** following the conditions of Scheme 54, at 40 °C during 8 hours. Then, without any work-up, DIPEA, phthalimide and BINAP were added and the resulting mixture was brought to reflux for further 18 hours. This one-pot protocol gave the desired γ-AB2 derivative **28a** with an excellent 90% yield (Scheme 56).



Scheme 56: Sequential One-Pot Pd(II) / Pd(0) Catalyzed Allylic Amination on Model Substrate **22a**.

This sequential protocol was next tested on other B3A amides. Electron-donor groups in *para*-position of a B3A *N*-benzyl amide gave the expected γ-AB2 products in moderate yields (entry 1-2), while the product was afforded in more satisfactory yield in the case of a *meta*-substitution (entry 3). However, the use of electron withdrawing groups in *para*-position was not tolerated (entry 4-5), and in the final crude mixture was detected only the acyloxylated compound derived from the first step of the procedure. Also *N*-furfuryl-, *N*-phenyl- and *N*-phenylethyl B3A amides gave the corresponding γ-AB2 product in good to moderate yields (entry 6-8). As seen with the direct amination, no reaction occurred with a tertiary amide or an ester (entry 9-10).

Entry	***B3A Substrate***	***γ-AB2 Product***	***Yield (%)***
1		**28b**	22
2		**28c**	53
3		**28d**	76
4		**28e**	Traces[a]
5		**28f**	0[b]

6		**28g**	20
7		**28h**	32[c]
8		**28i**	82
9		**28j**	0[d]
10		**28m**	0[d]

[a] Reaction conditions: (a) pivalic acid (10.0 equiv), $LiOH{\cdot}H_2O$ (2.0 equiv); (b) $Pd(OAc)_2$ (10 mol %), BQ (2.0 equiv), starting material (1 equiv), MeCN (0.2 M); (c) phthalimide (3.0 equiv), (+)-BINAP (20 mol %), DIPEA (11.5 equiv). [b] Yield of isolated product. [c] Only pivaloxylated compound **26** was detected at the end of the reaction. [d] Phthalimide (1.5 equiv) was used.

Table 11: Scope of the Sequential One-Pot Pd(II) / Pd(0)-Catalyzed Allylic Amination.

Albeit still speculative, these results can be explained on the basis of an H-bond directed addition of phthalimide anion on the distal allyl terminus of the transient π-allylpalladium complex.[78]

However, the H-bond may be disrupted if the amide's substituent is too electron-withdrawing, as in the case of amides **22e** and **22f** (entries 5 and 6, Table 11). This working model is also in accord with the fact that tertiary amides and esters, lacking the directing H atom, are completely inert (Figure 8).

[78] For a precedent of H-bond-directed addition of phthalimide to π-allylpalladium moieties, see: a) Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, P. S. *J. Am. Chem. Soc*. **2003**, *125*, 5115. b) Cook, G. R.; Shanker, P. S.; Pararajasingham, K. *Angew. Chem. Int. Ed*. **1999**, *38*, 110.

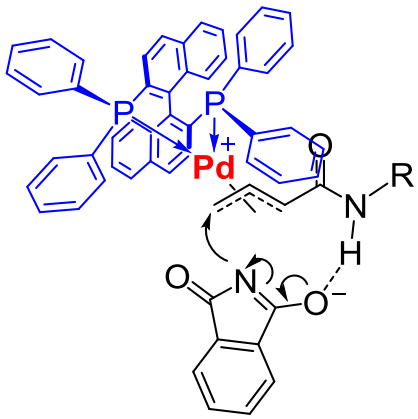


Figure 8: Working Model for the Addition of Phthalimide Enolate in the Transient Intermediate.

2.7. Conclusions

To conclude, in this chapter we developed two complementary strategies for the palladium-catalyzed dehydrogenative amination of B3A derivatives, allowing to build-up various γ-AB2 products. The acidity of the NH function in the nitrogen nucleophiles determines the appropriate protocol to select. Namely: a direct oxidative Pd(II)-catalyzed allylic amination in the case of the more acidic *N*-nucleophiles, and a one-pot Pd(II)-catalyzed pivaloxylation / Pd(0)-catalyzed amination sequence for the less acidic phthalimides.

Experimental Part

General methods

Unless otherwise mentioned, all reactions were carried out under an argon atmosphere. Glassware was flame-dried under an argon gas flow prior to use. Reactions were run in flasks or sealed tubes with magnetic stirring. Reagents and solvents were purchased from commercial sources and used as received. CH_2Cl_2, THF, MeCN and DMF were dried on a Mbraun purification system MB SPS-800. Nucleophiles were synthesized according to literature procedures: TsNHCOOMe,[79] TsNHCOMe,[80] *t*-BuSONHCOOMe.[81] TLC was performed on Merck 60 F254 silica gel and revealed with either a ultra-violet lamp (λ = 254 nm) or a specific color reagent (potassium permanganate, *p*-anisaldehyde, etc.).

Silica gel (Merck Geduran® SI 60, 40-63 mm) was used for flash column chromatography. Preparative thin layer chromatography was realized with PLC silica gel 60 F_{254} (1 mm, 20x20 cm.). Melting points were measured in capillary tubes on Stuart Scientific SMP3 apparatus and are uncorrected. IR spectra were recorded on a Brucker Tensor 27 (ATR diamond) and reported as characteristic bands (cm^{-1}).

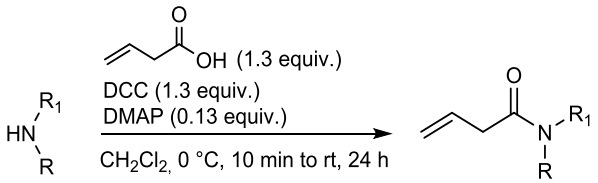
NMR spectra (^1H, ^{13}C) were recorded on a Bruker AM 300 MHz or a Bruker AVANCE 400 MHz spectrometers. NMR experiments were carried out in deuterochloroform ($CDCl_3$) and deuterodimethylsulfoxyde (DMSO-d_6). Chemical shifts are given in parts per million (ppm) using the $CDCl_3$ residual signal as reference (δ^1H = 7.26 ppm, $\delta^{13}C$ = 77.2 ppm), and the DMSO-d_6 residual signal as reference (δ^1H = 2.50 ppm, $\delta^{13}C$ = 39.5 ppm). The terms m, s, d, t, and q represent multiplet, singlet, doublet, triplet and quadruplet, respectively. Coupling costants (*J*) are given in Hertz (Hz). The ^1H and ^{13}C NMR spectra were completely assigned by using a combination of ^{13}C DEPT and 2D NMR experiments (COSY, HSQC and HMBC). High-resolution mass spectra (HRMS) were recorded at the institute Parisien de Chimie Moléculaire (FR 2769) (electrospray source).

[79] Reed, S. A.; Mazzotti, A. R.; White, M. C. *J. Am. Chem. Soc*. **2009**, *131*, 11701.

[80] Xie, W.; Yang, J.; Wang, B.; Li, B. *J. Org. Chem*. **2014**, *79*, 8278.

[81] Mistico, L.; Ay, E.; Huynh, V.; Bourderioux, A.; Chaumeil, H.; Chemla, F.; Ferrerira, F.; Oble, J.; Péerez-Luna, A.; Poli, G.; Prestat, G. *J. Organomet. Chem*. **2014**, *76*, 124.

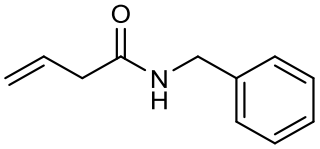
General procedure (GP16) for the synthesis of allyl-amides 22a-j.



22a-j

To a stirred solution of corresponding amine (1.0 or 2.0 equiv.) in CH_2Cl_2 (0.2 M) were added at 0 °C DCC (1.3 equiv.), DMAP (0.13 equiv.) and 3-butenoic acid (1.3 equiv.) The reaction mixture was stirred for 10 minutes at 0 °C, then for 24 hours at room temperature. The precipitate was filtered off and washed with CH_2Cl_2 (25 mL). Then the organic layer was hydrolyzed with saturated aqueous $NaHCO_3$, extracted and dried over $MgSO_4$ and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding allyl-amide **22**.

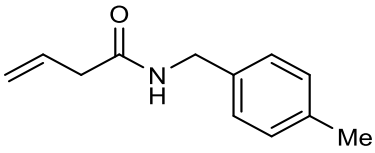
***N*-Benzyl-3-butenamide (22a)**



$C_{11}H_{13}NO$
M.W.: 175,0997

Following **GP16** with benzylamine (1 equiv., 10.02 mL, 9.3 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **22a** in quantitative yield (1.9 g, 10.8 mmol). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.09 (td, *J* = 1.5, 7.0 Hz, 2H), 4.48 (d, *J* = 6.0 Hz, 2H), 5.23-5.29 (m, 2H), 5.91-6.07 (m, 2H), 7.29-7.40 (m, 5H). These spectroscopic data are in good agreement with those reported in the literature.[82]

***N*-(4-Methylbenzyl)-3-butenamide (22b)**



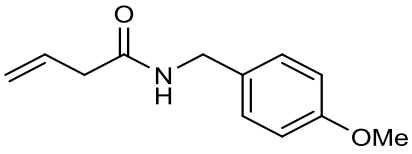
$C_{12}H_{15}NO$
M.W.: 189,1154

Following **GP16** with 4-methylbenzylamine (1 equiv., 500 mg, 4.1 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **22b** in 76% yield (588 mg, 3.11 mmol). White solid, mp: 100-102 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.26 (s, 3H), 2.97 (dt, *J* = 7.0, 1.5 Hz, 2H), 4.32 (d, *J* = 5.5 Hz, 2H), 5.11-5.17 (m, 2H), 5.77 (br s, 1H), 5.86 (ddt, *J* = 16.5, 10.5, 7.0 Hz, 1H), 7.05-7.10 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (q), 41.6 (t), 43.4 (t), 119.9 (t),

[82] Orliac, A.; Gomez Pardo, D.; Bombrun, A.; Cossy, J. *Org. Lett.* **2013***, 15,* 902.

127.8 (d), 129.4 (d), 131.3 (d), 135.1 (s), 137.3 (s), 170.2 (s). IR (cm^{-1}) ν: 3291, 1626, 1532, 1412. HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NNaO$ $[M+Na]^+$: 212.1046, found: 212.1046.

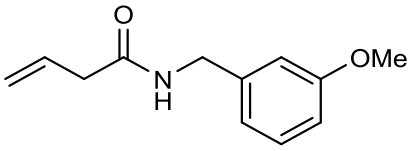
_N_-(4-Methoxybenzyl)-3-butenamide (22c)



$C_{12}H_{15}NO_2$
M.W.: 205,1103

Following **GP16** with 4-methoxybenzylamine (1 equiv., 0.47 mL, 3.64 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **22c** in 96% yield (715 mg, 3.5 mmol). White solid, mp: 88-90 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.06 (dt, *J* = 7.0, 1.5 Hz, 2H), 3.82 (s, 3H), 4.40 (d, *J* = 5.5 Hz, 2H), 5.21-5.26 (m, 2H), 5.81 (br s, 1H), 5.90-6.01 (m, 1H), 6.87-6.91 (m, 2H), 7.20-7.25 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.6 (t), 43.2 (t), 55.3 (q), 114.1 (d), 119.9 (t), 129.1 (d), 130.2 (s), 131.3 (d), 159.1 (s), 170.2 (s). IR (cm^{-1}) ν: 3285, 1636, 1548, 1511, 1300, 1173. HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NNaO_2$ $[M+Na]^+$: 228.0995, found: 228.0992.

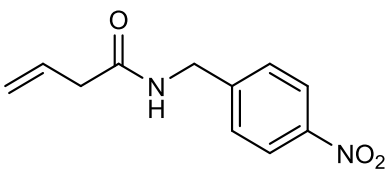
_N_-(3-Methoxybenzyl)-3-butenamide (22d)



$C_{12}H_{15}NO_2$
M.W.: 205,1103

Following **GP16** with 3-methoxybenzylamine (1 equiv., 0.47 mL, 3.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **22d** in 82% yield (611 mg, 2.97 mmol). Orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.06 (dt, *J* = 7.0, 1.5 Hz, 2H), 3.81 (s, 3H), 4.42 (d, *J* = 6.0 Hz, 2H), 5.21-5.26 (m, 2H), 5.91-5.99 (m, 1H), 6.01 (m, 1H), 6.82-6.87 (m, 3H), 7.23-7.28 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.6 (t), 43.6 (t), 55.2 (q), 112.9 (d), 113.3 (d), 119.8 (t), 119.9 (d), 129.7 (d), 131.3 (d), 139.7 (s), 159.8 (s), 170.4 (s). IR (cm^{-1}) ν: 3180, 1575, 1541, 1320. HRMS (ESI) *m/z* calcd for $C_{12}H_{15}LiNO_2$ $[M+Li]^{2+}$: 212.1258, found: 212.1264.

_N_-(4-Nitrobenzyl)-3-butenamide (22e)

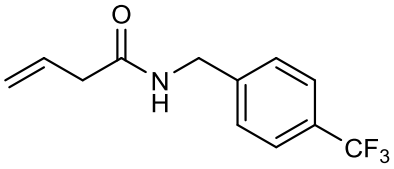


$C_{11}H_{12}N_2O_3$
M.W.: 220,0848

Following **GP16** with 4-nitrobenzylamine hydrochloride (1 equiv., 300 mg, 1.6 mmol) and DMAP (1.2 equiv., 233 mg, 1.9 mmol). The crude product was purified by flash chromatography on silica gel

(eluent: AcOEt / CycloHexane 1:1) to afford **22e** in 60% yield (200 mg, 0.91 mmol). White solid, mp: 83-85 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.13 (dt, *J* = 7.0, 1.0 Hz, 2H), 4.57 (d, *J* = 6.0 Hz, 2H), 5.27-5.32 (m, 2H), 5.98 (tdd, *J* = 7.0, 10.0, 17.5 Hz, 1H), 6.05 (br s, 1H), 7.44-7.47 (m, 2H), 8.19-8.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.5 (t), 42.8 (t), 120.5 (t), 123.9 (d), 128.2 (d), 130.9 (d), 145.1 (s), 145.7 (s), 170.6 (s). IR (cm^{-1}) ν: 3229, 3055, 2926, 1638, 1601, 1545, 1509, 1345. HRMS (ESI) *m/z* calcd for $C_{11}H_{12}N_2NaO_3$ $[M+Na]^+$: 243.0740, found: 243.0743.

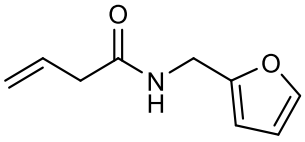
***N*-(4-(Trifluoromethyl)benzyl)but-3-enamide (22f)**



$C_{12}H_{12}F_3NO$
M.W.: 243,0871

Following **GP16** with 4-(trifluoromethyl)benzylamine (1 equiv., 500 mg, 5.8 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **22f** in 70% yield (990 mg, 4.07 mmol). White solid, mp: 118-120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.09 (dt, *J* = 7.0, 1.5 Hz, 1H), 4.50 (d, *J* = 6.0 Hz, 2H), 5.23-5.29 (m, 2H), 5.96 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 1H), 6.09 (br s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.5 (t), 43.0 (t), 120.2 (t), 125.6 (s), 125.7 (d), 127.8 (d), 131.1 (s), 142.3 (d), 170.6 (s). ^{31}F NMR ($CDCl_3$): δ - 62.54. IR (cm^{-1}) ν: 3476, 1647, 1545, 1328, 1029. HRMS (ESI) *m/z* calcd for $C_{12}H_{12}F_3NNaO$ $[M+Na]^+$: 266.0763, found: 266.0761.

***N*-(2-Furanylmethyl)-3-butenamide (22g)**

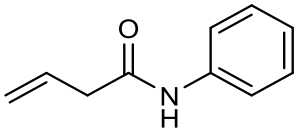


$C_9H_{11}NO_2$
M.W.: 165.0790

Following **GP16** with furfurylamine (2 equiv., 1.03 mL, 11.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **22g** in 52% yield (490 mg, 2.97 mmol). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.96 (t, *J* = 5.5 Hz, 2H), 4.31-4.38 (m, 2H), 5.09-5.15 (m, 2H), 5.79-5.95 (m, 1H), 6.14 (q, *J* = 3.0 Hz, 1H), 6.25-6.27 (m, 1H), 6.95 (br s, 1H), 7.27 (q, *J* = 2.5 Hz, 1H). These spectroscopic data are in good agreement with those reported in the literature.[83]

[83] Jacobi, P. A.; Li, Y. *J. Am. Chem. Soc.* **2001**, *123*, 9307.

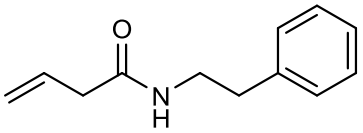
***N*-Phenyl-3-butenamide (22h)**



$C_{10}H_{11}NO$
M.W.: 161.0841

Following **GP16** with aniline (2 equiv., 1.05 mL, 5.8 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 4:6) to afford **22h** in 68% yield (630 mg, 3.9 mmol). White solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.21 (td, *J* = 1.0, 7.0 Hz, 2H), 5.31-5.37 (m, 2H), 6.06 (ddd, *J* = 7.0, 11.1, 16.0 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.29-7.37 (m, 2H), 7.53-7.56 (m, 3H). These spectroscopic data are in good agreement with those reported in the literature.[84]

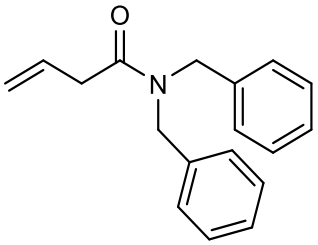
***N*-Phenethyl-3-butenamide (22i)**



$C_{12}H_{15}NO$
M.W.: 189,1154

Following **GP16** with phenylethylamine (2 equiv., 1.46 mL, 11.0 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **22i** in 40% yield (424 mg, 2.24 mmol). Pale yellow solid, mp: 63-65 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.83 (t, *J* = 7.0 Hz, 2H), 2.97 (td, *J* = 1.5, 7.0 Hz, 2H), 3.50 (q, *J* = 7.0 Hz, 2H), 5.16-5.23 (m, 2H), 5.89 (ddd, *J* = 7.0, 10.5, 17.5 Hz, 1H), 6.08 (br s, 1H), 7.17-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.6 (t), 40.6 (t), 41.7 (t), 119.8 (t), 126.5 (d), 128.6 (d), 128.7 (d), 131.3 (d), 138.8 (s), 170.4 (s). IR (cm^{-1}) ν: 3264, 3078, 2930, 1633, 1552. HRMS (ESI) *m/z* calcd for $C_{12}H_{15}NNaO$ $[M+Na]^+$: 212.1046, found: 212.1039.

***N,N*-Dibenzyl-3-butenamide (22j)**



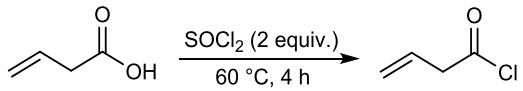
$C_{18}H_{19}NO$
M.W.: 265.1467

Following **GP16** with dibenzylamine (1 equiv., 0.31 mL, 1.6 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **22j** in 69% yield (290 mg, 1.1 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.28 (dt, *J* = 6.5, 1.5 Hz, 2H), 4.49 (s, 2H), 4.65 (s, 2H), 5.14-5.24 (m, 2H), 6.09 (ddd, *J* = 6.5, 10.0, 17.0, 1H), 7.20-7.43 (m, 10H). ^{13}C NMR ($CDCl_3$, 100

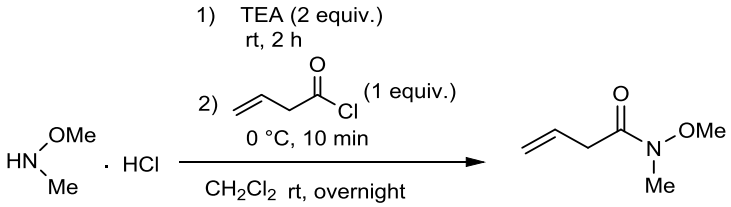
[84] Abdou, A. M.; Botros, S.; Hassan, R. A.; Kamel, M. M.; Taber, D. F.; Taher, A. T. *Tetrahedron* **2015**, *71*, 139.

MHz) δ 38.7 (t), 53.1 (t), 117.9 (t), 126.4 (t), 127.5 (d), 127.7 (d), 128.2 (d), 128.4 (d), 128.6 (d), 129.0 (d), 131.7 (d), 136.4 (s), 137.3 (s), 171.5 (s). IR (cm^{-1}) ν: 3027, 2919, 1646, 1418, 696. HRMS (ESI) *m/z* calcd for $C_{18}H_{19}NNaO$ $[M+Na]^+$: 288.1359, found: 288.1361.

Procedure for the synthesis of *N*-methoxy-*N*-methylbut-3-enamide (22k)

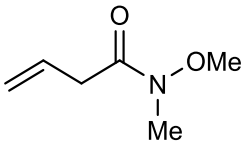


Thionyl chloride (2 equiv.) was added dropwise to the 3-butenoic acid (1 equiv.). The mixture was stirred for 4 hours at 60 °C, carefully evaporated and immediately used without purification.



22k

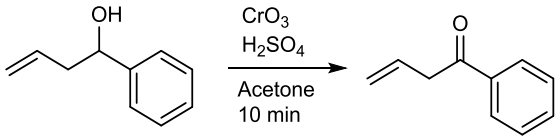
A mixture of *N,O*-dimethylhydroxylamine hydrochloride (1 equiv., 604 mg, 6.2 mmol) and triethylamine (2 equiv., 12.4 mmol, 1.72 mL) in dichloromethane (30 mL) was stirred for 2 hours at room temperature; then, at 0 °C, the but-3-enoyl chloride freshly prepared (1 equiv., 648 mg, 6.2 mmol) was added dropwise and the mixture was stirred for 10 minutes at 0 °C, then at rt overnight. The mixture was hydrolyzed with a HCl 1N solution, then with a saturated aqueous $NaHCO_3$ solution and water. The organic layer was extracted and dried over $MgSO_4$, filtered and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent: AcOEt / CycloHexane 6:4) to afford the amide **22k** in 54% yield (430 mg, 3.33 mmol).



$C_6H_{11}NO_2$
M.W.: 129,0790

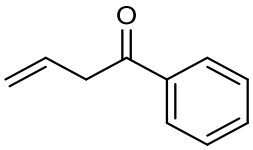
Pale yellow oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.18 (s, 3H), 3.23 (d, *J* = 7.0 Hz, 2H), 3.69 (s, 3H), 5.15-5.16 (m, 1H), 5.18-5.19 (m, 1H), 5.92-6.02 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 25.2 (q), 37.2 (t), 61.3 (q), 118.1 (t), 131.2 (d), 172.4 (s). IR (cm^{-1}) ν: 2969, 1664, 1381, 1176, 1002. HRMS (ESI) *m/z* calcd for $C_6H_{11}NNaO_2$ $[M+Na]^+$: 152.0687, found: 152.0682.

Procedure for the synthesis of Phenyl Allyl Ketone (22l)



22l

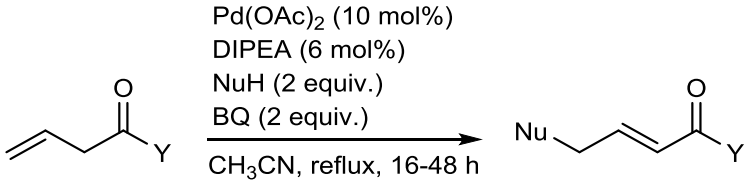
Under air atmosphere, at 20 °C, to a solution of 1-phenylbut-3-en-1-ol (1 equiv., 300 mg, 2.02 mmol) in acetone (10 mL) was added using a dropping funnel a solution of Jones reagent (1.5 mL). After 10 minutes, the time required for change the color of the solution from orange to blue, the mixture was hydrolyzed with water and extracted with diethyl ether. Then the organic layer was washed with saturated aqueous $NaHCO_3$, extracted and dried over $MgSO_4$ and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent: AcOEt / CycloHexane 1:1) to afford the ketone **22l** in 80% yield (235 mg, 1.61 mmol).



$C_{10}H_{10}O$
M.W.: 146,0732

Colorless oil. ^1H NMR ($CDCl_3$, 400 MHz) δ 3.76 (td, *J* = 1.5, 8.0 Hz, 2H), 5.18-5.27 (m, 2H), 6.09 (tdd, *J* = 7.0, 10.5, 17.5 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.97 (d, *J* = 7.5 Hz, 2H). These spectroscopic data are in good agreement with those reported in the literature.[85]

General procedure (GP17) for the Pd(II)-catalyzed direct amination.



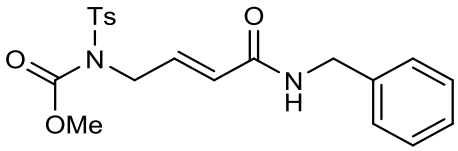
22 **23, 24, 25, 26**

In a sealed tube, but-3-enoic acid derivative **22** (1 equiv.) was dissolved in CH_3CN (0.2 M) and subsequently $Pd(OAc)_2$ (10 mol %), nucleophile (2 equiv.) DIPEA (6 mol %) and BQ (2 equiv.) were added to the mixture. Then the reaction was stirred at reflux for 16-24 hours and, after cooling to r.t., was hydrolyzed with a saturated aqueous K_2CO_3 solution and diluted with Et_2O. The organic layer was extracted, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product

[85] Moriyama, K.; Takemura, M.; Togo, H. *J. Org. Chem.* **2014**, *79*, 6094.

was purified by silica gel column chromatography (eluent: AcOEt / CycloHexane) to afford the aminated compound **23**, **24**, **25** or **26** depending on the nucleophile used.[86]

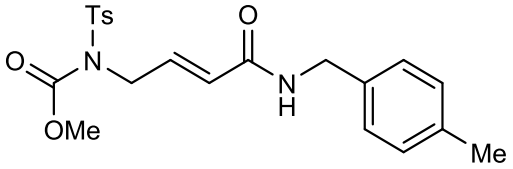
Methyl (*E*)-(4-(benzylamino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (23a)



$C_{20}H_{22}N_2O_5S$
M.W.: 402,1249

Following **GP17** with amide **22a** (1 equiv., 100 mg, 0.57 mmol) and methyl tosylcarbamate **A** (2 equiv., 260 mg, 1.13 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23a** in 95% yield (219 mg, 0.54 mmol). White solid, mp: 145-146 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 3.73 (s, 3H), 4.55 (dd, *J* = 6.0, 2.0 Hz, 2H), 4.63 (dd, *J* = 5.0, 2.0 Hz, 2H), 5.84 (br s, 1H), 6.03 (dt, *J* = 15.0, 2.0 Hz, 1H), 6.91 (dt, *J* = 15.0, 5.5 Hz, 1H), 7.35 (m, 7H), 7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (q), 43.8 (t), 47.4 (t), 54.0 (q), 125.4 (d), 127.6 (d), 128.0 (d), 128.6 (d), 128.8 (d), 129.4 (d), 136.0 (s), 137.9 (s), 138.3 (s), 145.0 (d), 152.4 (s), 164.5 (s). IR (cm^{-1}) ν: 3317, 1737, 1673, 1634, 1440, 1165, 981, 700. HRMS (ESI) m/z calcd for $C_{20}H_{22}N_2NaO_5S$ $[M+Na]^+$: 425.1142, found: 425.1149.

Methyl (*E*)-(4-((4-methylbenzyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (23b)

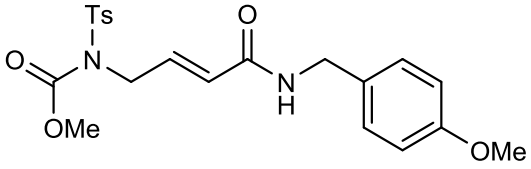


$C_{21}H_{24}N_2O_5S$
M.W.: 416,1406

Following **GP17** with amide **22b** (1 equiv., 100 mg, 0.53 mmol) and methyl tosylcarbamate **A** (2 equiv., 242 mg, 1.06 mmol) for 16 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23b** in 34% yield (34 mg, 0.082 mmol). Beige solid, mp: 171-172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 2.44 (s, 3H), 3.71 (s, 3H), 4.48 (d, *J* = 5.5 Hz, 2H), 4.60 (dd, *J* = 2.0, 5.5 Hz, 2H), 5.82 (br s, 1H), 6.00 (td, *J* = 2.0, 15.0 Hz, 1H), 6.78 (td, *J* = 5.5, 15.5 Hz, 1H), 7.16-7.22 (m, 4H), 7.28-7.33 (m, 2H), 7.83-7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (q), 21.6 (t), 43.6 (t), 47.4 (q), 54.1 (d), 125.5 (d), 128.0 (d), 128.6 (d), 129.4 (d), 134.9 (s), 136.0 (s), 137.4 (s), 138.2 (s), 144.9 (d), 152.4 (s), 164.5 (s). IR (cm^{-1}) ν: 3292, 2926, 1623, 1359, 1232, 1168. HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_5S$ $[M+Na]^+$: 439.1298, found: 439.1305.

[86] Sometimes, traces of HBQ (less than 5%) are present in the product.

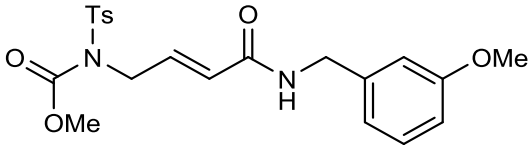
Methyl (*E*)-(4-((4-methoxybenzyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (23c)



$C_{21}H_{24}N_2O_6S$
M.W.: 432,1355

Following **GP17** with amide **22c** (1 equiv., 100 mg, 0.49 mmol) and methyl tosylcarbamate **A** (2 equiv., 223 mg, 0.97 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23c** in 35% yield (73 mg, 0.17 mmol). White solid, mp: 158-159 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3H), 3.71 (s, 3H), 3.83 (s, 3H), 4.47 (d, *J* = 6.0 Hz, 2H), 4.61 (dd, *J* = 2.0, 5.5 Hz, 2H), 5.73 (br s, 1H), 6.00 (td, *J* = 2.0, 15.0 Hz, 1H), 6.85-6.92 (m, 3H), 7.24-7.33 (m, 4H), 7.82-7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 43.3 (t), 47.4 (t), 54.1 (q), 55.3 (q), 114.1 (d), 125.5 (d), 128.6 (d), 129.4 (d), 129.5 (s), 130.0 (d), 136.0 (s), 138.2 (s), 145.0 (d), 152.4 (s), 159.2 (s), 164.4 (s). IR (cm^{-1}) ν: 3297, 2960, 1744, 1624, 1515, 1358, 1168, 770. HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_6S$ $[M+Na]^+$: 455.1247, found: 455.1260.

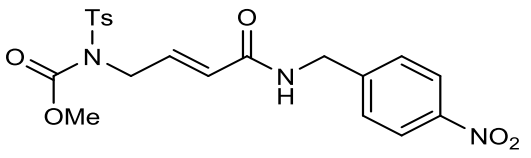
Methyl (*E*)-(4-((3-methoxybenzyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (23d)



$C_{21}H_{24}N_2O_6S$
M.W.: 432,1355

Following **GP17** with amide **22d** (1 equiv., 100 mg, 0.49 mmol) and methyl tosylcarbamate **A** (2 equiv., 223 mg, 0.97 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23d** in 84% yield (176 mg, 0.4 mmol). White solid, mp: 127-128 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.42 (s, 3H), 3.68 (s, 3H), 3.79 (s, 3H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.58 (dd, *J* = 2.0, 5.5 Hz, 2H), 6.04 (td, *J* = 2.0, 15.5 Hz, 1H), 6.22 (t, *J* = 6.0 Hz, 1H), 6.83-6.88 (m, 4H), 7.28-7.31 (m, 3H), 7.80-7.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (q), 43.6 (t), 47.4 (t), 54.0 (q), 55.2 (q), 113.0 (d), 113.5 (d), 120.1 (d), 125.6 (d), 128.5 (d), 129.5 (d), 129.7 (d), 135.9 (s), 138.1 (s), 139.6 (s), 145.0 (d), 152.3 (s), 159.9 (s), 164.7 (s). IR (cm^{-1}) ν: 3292, 2955, 1744, 1627, 1357, 1165, 765. HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_6S$ $[M+Na]^+$: 455.1247, found: 455.1232.

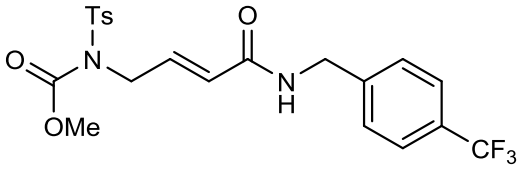
Methyl (*E*)-(4-((4-nitrobenzyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (23e)



$C_{20}H_{21}N_3O_7S$
M.W.: 447,1100

Following **GP17** with amide **22e** (1 equiv., 100 mg, 0.45 mmol) and methyl tosylcarbamate **A** (2 equiv., 208 mg, 0.98 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23e** in 10% yield (16 mg, 0.036 mmol). Pale yellow solid, mp: 182-184 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3H), 3.62 (s, 3H), 4.52-4.55 (m, 4H), 6.00-6.05 (m, 2H), 6.86 (td, *J* = 5.0, 15.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.38-7.40 (m, 2H), 7.74-7.76 (m, 2H), 8.10-8.14 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 43.0 (t), 47.5 (t), 54.1 (q), 123.9 (d), 124.7 (d), 128.4 (d), 128.5 (d), 129.5 (d), 135.9 (s), 139.4 (s), 145.1 (d), 145.5 (s), 147.4 (s), 153.3 (s), 164.9 (s). IR (cm^{-1}) ν: 3304, 2921, 1743, 1626, 1517, 1346, 1164, 776. HRMS (ESI) *m/z* calcd for $C_{20}H_{21}N_3NaO_7S$ $[M+Na]^+$: 470.0992, found: 470.1004.

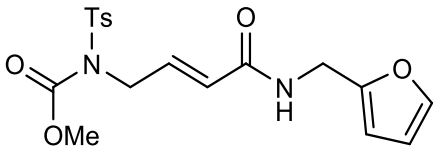
Methyl (*E*)-(4-oxo-4-((4-(trifluoromethyl)benzyl)amino)but-2-en-1-yl)(tosyl)carbamate (23f)



$C_{21}H_{21}F_3N_2O_5S$
M.W.: 470,1123

Following **GP17** with amide **22f** (1 equiv., 100 mg, 0.41 mmol) and methyl tosylcarbamate **A** (2 equiv., 188 mg, 0.82 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23f** in 74% yield (142 mg, 0.30 mmol). White solid, mp: 173-174 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 3.62 (s, 3H), 4.49 (d, *J* = 6.0 Hz, 2H), 4.52 (dd, *J* = 5.0, 2.0 Hz, 2H), 5.91 (br s, 1H), 5.98 (dt, *J* = 15.0, 1.5 Hz, 1H), 6.83 (dt, *J* = 15.5, 5.0 Hz, 1H), 7.22-7.24 (m, 2H), 7.33-7.36 (m 2H), 7.52-7.54 (m, 2H), 7.74-7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (q), 43.2 (t), 47.4 (t), 54.1 (q), 116.1 (d), 125.0 (s), 125.6 (d), 125.7 (d), 128.0 (d), 128.5 (s), 129.5 (d), 135.9 (s), 138.9 (s), 142.0 (s), 145.0 (d), 152.3 (s), 164.8 (s). ^{19}F NMR ($CDCl_3$, 282 MHz) δ - 62.53. IR (cm^{-1}) ν: 3316, 2925, 1737, 1676, 1636, 1361, 1169, 911, 733. HRMS (ESI) *m/z* calcd for $C_{21}H_{21}F_3N_2NaO_5S$ $[M+Na]^+$: 493.1015, found: 493.1012.

Methyl (*E*)-(4-((furan-2-ylmethyl)amino)-4-oxobut-2-en-1-yl)(tosyl)carbamate (23g)

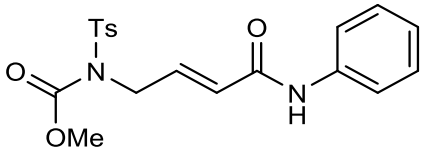


$C_{18}H_{20}N_2O_6S$
M.W.: 392,1042

Following **GP17** with amide **22g** (1 equiv., 100 mg, 0.60 mmol) and methyl tosylcarbamate **A** (2 equiv., 277 mg, 1.2 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 7:3) to afford **23g** in 46% yield (109 mg, 0.28 mmol). Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 3.61 (s, 3H), 4.42 (d, *J* = 5.5 Hz, 2H), 4.51 (dd, *J* = 2.0, 5.5 Hz, 2H), 5.93

(td, *J* = 2.0, 15.5 Hz, 1H), 5.96 (br s, 1H), 6.17-6.19 (m, 1H), 6.25 (dd, *J* = 2.0, 3.5 Hz, 1H), 6.78 (td, *J* = 5.0, 15.5 Hz, 1H), 7.22-7.24 (m, 2H), 7.28 (dd, *J* = 1.0, 2.0 Hz, 1H), 7.73-7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 36.6 (t), 47.4 (t), 54.0 (q), 107.7 (d), 110.5 (d), 125.2 (d), 128.5 (d), 129.5 (s), 135.9 (s), 138.5 (d), 142.3 (d), 145.0 (d), 150.9 (s), 152.4 (s), 164.6 (s). IR (cm^{-1}) ν: 3304, 2956, 1747, 1628, 1357, 1165, 759. HRMS (ESI) *m/z* calcd for $C_{18}H_{20}N_2NaO_6S$ $[M+Na]^+$: 415.0934, found: 415.0938.

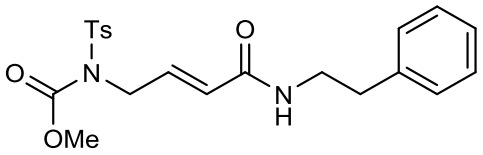
Methyl (*E*)-(4-oxo-4-(phenylamino)but-2-en-1-yl)(tosyl)carbamate (23h)



$C_{19}H_{20}N_2O_5S$
M.W.: 388,1093

Following **GP17** with amide **22h** (1 equiv., 50 mg, 0.31 mmol) and methyl tosylcarbamate **A** (2 equiv., 142 mg, 0.62 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23h** in 90% yield (52 mg, 0.14 mmol). Brown solid, mp: 153-155 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34 (s, 3H), 3.63 (s, 3H), 4.56 (dd, *J* = 2.0, 5.0 Hz, 2H), 6.14 (td, *J* = 2.0, 15.0 Hz, 1H), 6.89 (td, *J* = 5.0, 15.0 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 7.18-7.26 (m, 4H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.62 (br s, 1H), 7.75-7.78 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (q), 47.5 (t), 54.1 (q), 119.9 (d), 124.4 (d), 126.0 (d), 128.5 (d), 129.0 (d), 129.5 (d), 135.9 (s), 136.3 (s), 139.2 (s), 145.0 (d), 152.4 (s), 162.9 (s). IR (cm^{-1}) ν: 3353, 2916, 1689, 1536, 1440, 1254, 1185, 1080. HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_2NaO_5S$ $[M+Na]^+$: 411.0985, found: 411.0975.

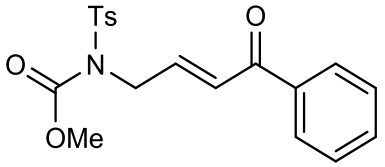
Methyl (*E*)-(4-oxo-4-(phenethylamino)but-2-en-1-yl)(tosyl)carbamate (23i)



$C_{21}H_{24}N_2O_5S$
M.W.: 416,1406

Following **GP17** with amide **22i** (1 equiv., 100 mg, 0.53 mmol) and methyl tosylcarbamate **A** (2 equiv., 243 mg, 1.01 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23i** in 41% yield (90 mg, 0.22 mmol). White solid, mp: 145-147 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 2.78 (t, *J* = 7.0 Hz, 2H), 3.50-3.56 (m, 2H), 3.61 (s, 3H), 4.50 (dd, *J* = 2.0, 5.5 Hz, 2H), 5.48 (br s, 1H), 5.85 (td, *J* = 2.0, 15.5 Hz, 1H), 6.74 (td, *J* = 5.5, 15.5 Hz, 1H), 7.12-7.27 (m, 7H), 7.73-7.76 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 35.6 (t), 40.7 (t), 47.3 (t), 54.0 (q), 125.6 (d), 126.6 (d), 128.5 (d), 128.7 (d), 128.8 (d), 129.4 (d), 135.9 (s), 137.9 (s), 138.7 (s), 144.9 (d), 152.4 (s), 164.7 (s). IR (cm^{-1}) ν: 3309, 3026, 2960, 1745, 1627, 1546, 1398, 1128, 907. HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N_2NaO_5S$ $[M+Na]^+$: 439.1298, found: 439.1311.

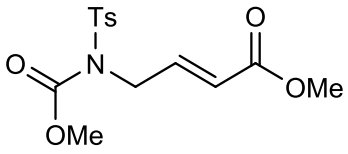
Methyl (*E*)-(4-oxo-4-phenylbut-2-en-1-yl)(tosyl)carbamate (23l)



$C_{19}H_{19}NO_5S$
M.W.: 373,0984

Following **GP17** with phenyl allyl ketone **22l** (1 equiv., 100 mg, 0.68 mmol) and methyl tosylcarbamate **A** (2 equiv., 309 mg, 1.35 mmol) for 24 hours. The residue was taken up in DCM and treated with an equal volume of 1N KOH for 15 minutes. After decantation and phase separation, the organic layer was drid over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23l** in 40% yield (102 mg, 0.27 mmol). Brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.45 (s, 3H), 3.74 (s, 3H), 4.76 (dd, *J* = 2.0, 6.0 Hz, 2H), 7.02 (td, *J* = 6.0, 15.5 Hz, 1H), 7.13 (td, *J* = 2.0, 15.5 Hz, 1H), 7.31-7.37 (m, 2H), 7.49-7.52 (m, 2H), 7.57-7.62 (m, 1H), 7.87-7.93 (m, 2H), 7.95 (td, *J* = 2.0, 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.7 (q), 47.9 (t), 54.2 (q), 126.8 (d), 128.6 (d), 128.7 (d), 129.5 (d), 133.1 (s), 136.0 (d), 137.3 (s), 141.8 (s), 145.1 (d), 152.4 (s), 189.7 (s). IR (cm^{-1}) ν: 2958, 1737, 1676, 1359, 1169, 907, 729. HRMS (ESI) *m/z* calcd for $C_{19}H_{19}NNaO_5S$ $[M+Na]^+$: 396.0876, found: 396.0884.

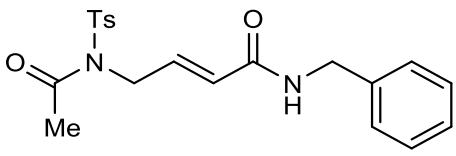
Methyl (*E*)-4-[(*N*-(methoxycarbonyl)-4-methylphenyl)sulfonamido]but-2-enoate (23m)



$C_{14}H_{17}NO_6S$
M.W.: 327,0777

Following **GP17** with methyl but-3-enoate (1 equiv., 50 mg, 0.5 mmol) and methyl tosylcarbamate **A** (2 equiv., 228 mg, 0.99 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **23m** in 93% yield (137 mg, 0.42 mmol). Beige solid, mp: 132-133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.47 (s, 3H), 3.73 (s, 3H), 3.77 (s, 3H), 4.62 (dd, *J* = 2.0, 3.5 Hz, 2H), 6.04 (td, *J* = 2.0, 15.5 Hz, 1H), 6.94 (td, *J* = 5.5, 15.5 Hz, 1H), 7.34-7.36 (m, 2H), 7.84-7.86 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (q), 47.2 (t), 51.7 (q), 54.1 (q), 123.0 (d), 128.6 (d), 129.5 (d), 135.9 (s), 142.2 (s), 145.1 (d), 152.3 (s), 166.2 (s). IR (cm^{-1}) ν: 2955, 1749, 1716, 1435, 1356, 1167. HRMS (ESI) *m/z* calcd for $C_{14}H_{17}NNaO_6S$ $[M+Na]^+$: 350.0669, found: 350.0668.

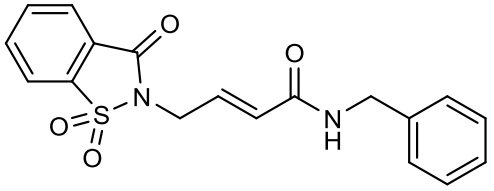
(*E*)-*N*-Benzyl-4-(*N*-tosylacetamido)but-2-enamide (24a)



$C_{20}H_{22}N_2O_4S$
M.W.: 386,1300

Following **GP17** with amide **22a** (1 equiv., 100 mg, 0.57 mmol) and *N*-tosylacetamide **B** (2 equiv., 261 mg, 1.14 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **24a** in 61% yield (133 mg, 0.34 mmol). Beige solid, mp: 161-162 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (s, 3H), 2.36 (s, 3H), 4.43 (d, *J* = 6.0 Hz, 2H), 4.51 (dd, *J* = 2.0, 5.0 Hz, 2H), 5.69 (br s, 1H), 5.88 (dt, *J* = 15.0, 2.0 Hz, 1H), 6.77 (dt, *J* = 15.0, 5.0 Hz, 1H), 7.21-7.30 (m, 7H), 7.69-7.72 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6 (q), 24.6 (q), 43.8 (t), 47.0 (t), 125.7 (d), 127.7 (d), 127.8 (d), 128.0 (d), 128.8 (d), 129.9 (s), 136.4 (s), 137.9 (s), 138.1 (d), 138.6 (d), 145.3 (s), 164.5 (s). IR (cm^{-1}) ν: 3315, 2923, 1705, 1635, 1557, 1355, 1242, 1154. HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N_2NaO_4S$ $[M+Na]^+$: 409.1192, found: 409.1178.

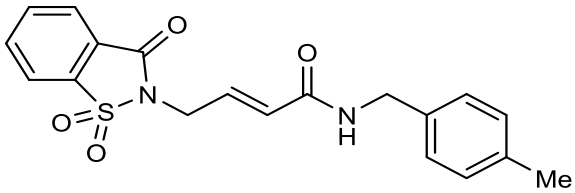
(*E*)-*N*-Benzyl-4-(1,1-dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)but-2-enamide (25a)



$C_{18}H_{16}N_2O_4S$
M.W.: 356,0831

Following **GP17** with amide **22a** (1 equiv., 100 mg, 0.57 mmol) and saccharin **C** (2 equiv., 208 mg, 1.14 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **25a** in 40% yield (80 mg, 0.02 mmol). White solid, mp: 149-150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.40-4.44 (m, 4H), 5.75 (br s, 1H), 6.01 (td, *J* = 2.0, 15.0 Hz, 1H), 6.84 (td, *J* = 5.5, 15.5 Hz, 1H), 7.17-7.27 (m, 5H), 7.75-7.87 (m, 3H), 7.98-8.00 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (t), 43.8 (t), 121.1 (d), 125.3 (d), 126.7 (d), 127.1 (d), 127.6 (d), 127.9 (s), 128.7 (d), 134.5 (d), 135.0 (d), 135.6 (s), 137.7 (s), 137.8 (d), 158.5 (s), 164.2 (s). IR (cm^{-1}) ν: 3312, 1744, 1625, 1325, 1185, 973, 752. HRMS (ESI) *m/z* calcd for $C_{18}H_{16}N_2NaO_4S$ $[M+Na]^+$: 379.0723, found: 379.0709.

(*E*)-4-(1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)-*N*-(4-methylbenzyl)but-2-enamide (25b)

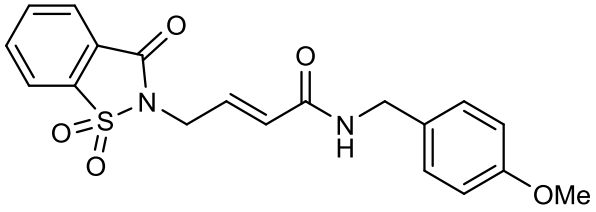


$C_{19}H_{18}N_2O_4S$
M.W.: 370,0987

Following **GP17** with amide **22b** (1 equiv., 100 mg, 0.53 mmol) and saccharin **C** (2 equiv., 193 mg, 1.05 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **25b** in 33% yield (64 mg, 0.17 mmol). White solid, mp: 171-172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H), 4.37 (d, *J* = 5.5 Hz, 2H), 4.41 (dd, *J* = 2.0, 5.5 Hz, 2H), 5.66 (br s, 1H), 5.99 (td, *J* = 2.0, 15.0 Hz, 1H), 6.83 (td, *J* = 5.5, 15.0 Hz, 1H), 7.04-7.10 (m, 4H), 7.77-7.87 (m, 3H),

7.98-8.01 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (q), 39.2 (t), 43.6 (t), 121.1 (d), 125.3 (d), 126.8 (d), 127.1 (d), 127.9 (s), 129.4 (d), 134.5 (d), 134.7 (s), 135.0 (d), 135.5 (s), 137.3 (s), 137.7 (d), 158.5 (s), 164.2 (s). IR (cm^{-1}) ν: 3291, 2922, 1731, 1621, 1334, 1186. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2NaO_4S$ $[M+Na]^+$: 393.0879, found: 393.0876.

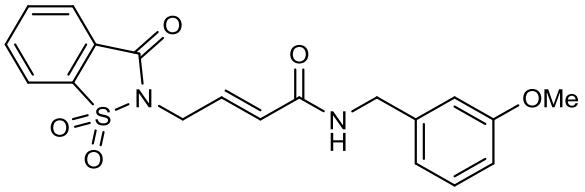
(*E*)-4-(1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)-*N*-(4-methoxybenzyl)but-2-enamide (25c)



$C_{19}H_{18}N_2O_5S$
M.W.: 386,0936

Following **GP17** with amide **22c** (1 equiv., 100 mg, 0.49 mmol) and saccharin **C** (2 equiv., 178 mg, 0.97 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **25c** in 57% yield (106 mg, 0.27 mmol). White solid, mp: 164-165 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 3H), 4.44 (d, *J* = 5.5 Hz, 2H), 4.51 (dd, *J* = 2.0, 5.5 Hz, 2H), 5.74 (br s, 1H), 6.08 (td, *J* = 2.0, 15.0 Hz, 1H), 6.85-6.88 (m, 2H), 6.93 (td, *J* = 5.5, 15.5 Hz, 1H), 7.20-7.23 (m, 2H), 7.85-7.97 (m, 3H), 8.09 (ddd, *J* = 1.0, 1.5, 7.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (t), 43.3 (t), 55.3 (q), 114.1 (d), 121.2 (d), 125.3 (d), 126.7 (d), 127.1 (s), 129.3 (s), 129.9 (d), 134.5 (d), 135.0 (d), 135.5 (s), 137.7 (d), 158.5 (s), 159.1 (s), 164.1 (s). IR (cm^{-1}) ν: 3293, 2933, 1734, 1513, 1182, 909, 730. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2NaO_5S$ $[M+Na]^+$: 409.0829, found: 409.0836.

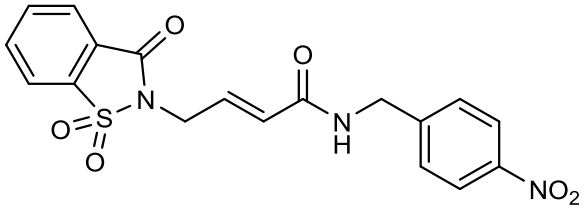
(*E*)-4-(1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)-*N*-(3-methoxybenzyl)but-2-enamide (25d)



$C_{19}H_{18}N_2O_5S$
M.W.: 386,0936

Following **GP17** with amide **22d** (1 equiv., 100 mg, 0.48 mmol) and saccharin **C** (2 equiv., 178 mg, 0.97 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **25d** in 82% yield (154 mg, 0.4 mmol). White solid, mp: 138-140 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (s, 3H), 4.48 (d, *J* = 6.0 Hz, 2H), 4.52 (dd, *J* = 2.0, 5.5 Hz, 2H), 5.80 (br s, 1H), 6.10 (td, *J* = 2.0, 15.2 Hz, 1H); 6.82-6.84 (m, 3H), 6.93 (td, *J* = 5.5, 15.5 Hz, 1H), 7.25 (dd, *J* = 7.5, 9.0 Hz, 1H), 7.87-7.95 (m, 3H), 8.02-8.11 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (t), 43.8 (t), 55.2 (q), 113.2 (d), 113.4 (d), 120.2 (d), 121.0 (d), 125.4 (d), 126.7 (d), 127.1 (s), 129.8 (d), 134.5 (d), 135.0 (d), 135.7 (s), 137.8 (s), 139.3 (d), 158.5 (s), 159.9 (s), 164.2 (s). IR (cm^{-1}) ν: 3287, 2921, 1731, 1625, 1331, 1213, 1013. HRMS (ESI) *m/z* calcd for $C_{19}H_{18}N_2NaO_5S$ $[M+Na]^+$: 409.0829, found: 409.0840.

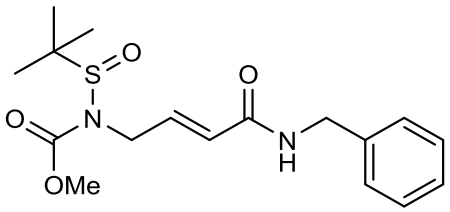
(*E*)-4-(1,1-Dioxido-3-oxobenzo[d]isothiazol-2(3H)-yl)-*N*-(4-nitrobenzyl)but-2-enamide (25e)



$C_{18}H_{15}N_3O_6S$
M.W.: 401,0682

Following **GP17** with amide **22e** (1 equiv., 65 mg, 0.29 mmol) and saccharin **C** (2 equiv., 108 mg, 0.59 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **25e** in 30% yield (35 mg, 0.09 mmol). Beige solid, mp: 168-169 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.44 (dd, *J* = 2.0, 5.5 Hz, 2H), 4.52 (d, *J* = 6.5 Hz, 2H), 5.93 (br s, 1H), 6.07 (td, *J* = 2.0, 15.5 Hz, 1H), 6.88 (td, *J* = 5.5, 15.5 Hz, 1H), 7.35-7.39 (m, 2H), 7.77-7.89 (m, 3H), 8.00 (ddd, *J* = 7.5, 1.5, 1.0 Hz, 1H), 8.08-8.11 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (t), 42.9 (t), 121.1 (d), 123.9 (d), 125.4 (d), 126.1 (d), 127.0 (s), 128.3 (d), 134.6 (d), 135.1 (d), 136.6 (s), 137.7 (d), 145.4 (s), 147.4 (s), 158.6 (s), 164.5 (s). IR (cm^{-1}) ν: 3291, 2924, 1735, 1519, 1344, 1259, 968, 730. HRMS (ESI) *m/z* calcd for $C_{18}H_{15}N_3NaO_6S$ $[M+Na]^+$: 424.0574, found: 424.0584.

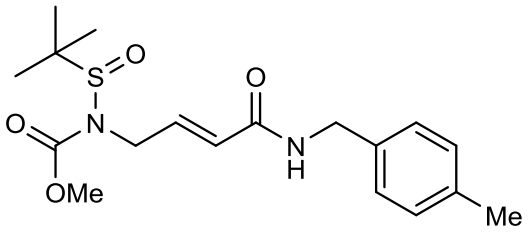
Methyl (*E*)-(4-(benzylamino)-4-oxobut-2-en-1-yl)(*tert*-butylsulfinyl)carbamate (26a)



$C_{17}H_{24}N_2O_4S$
M.W.: 352,1457

Following **GP17** with amide **22d** (1 equiv., 100 mg, 0.57 mmol) and *N*-*tert*-butylsulfinyl carbamate **D** (2 equiv., 204 mg, 1.14 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **26a** in 47% yield (93 mg, 0.26 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (s, 9H), 3.77 (s, 3H), 3.94 (ddd, *J* = 2.0, 5.5, 17.0 Hz, 1H), 4.12 (ddd, *J* = 2.0, 5.5, 17.0 Hz, 1H), 4.46 (d, *J* = 6.0 Hz, 2H), 5.95 (td, *J* = 1.5, 15.5, 1H), 6.08 (br s, 1H), 6.80 (td, *J* = 5.5, 15.5 Hz, 1H), 7.27-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (q), 39.1 (t), 43.7 (t), 53.6 (q), 60.2 (s), 125.7 (d), 127.5 (d), 127.9 (d), 128.7 (d), 138.0 (s), 139.3 (d), 155.4 (s), 164.9 (s). IR (cm^{-1}) ν: 3327, 2951, 1702, 1670, 1494, 1371, 1250, 1033. HRMS (ESI) *m/z* calcd for $C_{17}H_{24}N_2NaO_4S$ $[M+Na]^+$: 375.1349, found: 375.1334.

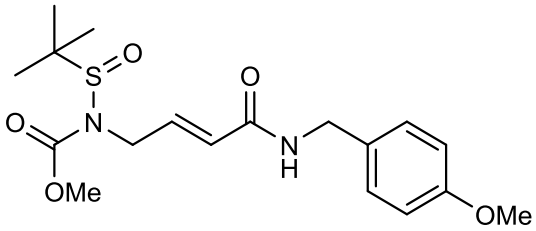
Methyl (*E*)-(tert-butylsulfinyl)4-[(4-methylbenzyl)amino-4-oxobut-2-en-1-yl]carbamate (26b)



$C_{18}H_{26}N_2O_4S$
M.W.: 366,1613

Following **GP17** with amide **22b** (1 equiv., 100 mg, 0.53 mmol) and *N-tert*-butylsulfinyl carbamate **D** (2 equiv., 190 mg, 1.06 mmol) for 30 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 6:4) to afford **26b** in 27% yield (51 mg, 0.14 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 2.26 (s, 3H), 3.70 (s, 3H), 3.87 (ddd, *J* = 2.0, 5.5, 17.0 Hz, 1H), 4.04 (ddd, *J* = 1.5, 6.0, 17.0 Hz, 1H), 4.37 (d, *J* = 6.0 Hz, 2H), 5.73 (br s, 1H), 5.83 (td, *J* = 1.5, 15.5 Hz, 1H), 6.73 (ddd, *J* = 5.5, 6.0, 15.5 Hz, 1H), 7.05-7.12 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (q), 29.7 (q), 39.1 (t), 43.6 (t), 53.6 (q), 60.2 (s), 125.8 (d), 128.0 (d), 129.4 (d), 134.9 (s), 137.3 (s), 139.3 (d), 155.4 (s), 164.7 (s). IR (cm^{-1}) ν: 3295, 2925, 1717, 1674, 1634, 1443, 1307, 1089, 907, 729. HRMS (ESI) *m/z* calcd for $C_{18}H_{26}KN_2O_4S$ $[M+K]^+$: 405.1245, found: 405.1232.

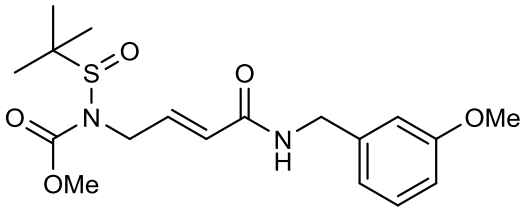
Methyl (*E*)-(tert-butylsulfinyl)(4-((4-methoxybenzyl)amino)-4-oxobut-2-en-1-yl)carbamate (26c)



$C_{18}H_{26}N_2O_5S$
M.W.: 382,1562

Following **GP17** with amide **22c** (1 equiv., 100 mg, 0.49 mmol) and *N-tert*-butylsulfinyl carbamate **D** (2 equiv., 174 mg, 0.97 mmol) for 30 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **26c** in 16% yield (29 mg, 0.08 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 3.70 (s, 3H), 3.72 (s, 3H), 3.87 (ddd, *J* = 2.0, 5.5, 17.0 Hz, 1H), 4.01-4.08 (m, 1H), 4.35 (d, *J* = 6.0 Hz, 2H), 5.68 (br s, 1H), 5.83 (td, *J*= 2.0, 15.0 Hz, 1H), 6.72 (td, *J* = 6.0, 15.5 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (q), 39.1 (t), 43.3 (t), 53.6 (q), 55.3 (q), 60.2 (s), 114.1 (d), 125.8 (d), 129.3 (d), 130.0 (s), 139.3 (d), 155.4 (s), 159.1 (s), 164.7 (s). IR (cm^{-1}) ν: 2927, 1717, 1513, 1250, 1089, 909, 731. HRMS (ESI) *m/z* calcd for $C_{18}H_{26}KN_2O_5S$ $[M+K]^+$: 421.1194, found: 421.1199.

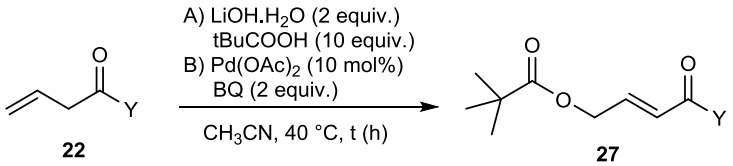
Methyl (*E*)-(tert-butylsulfinyl)(4-((3-methoxybenzyl)amino)-4-oxobut-2-en-1-yl)carbamate (26d)



$C_{18}H_{26}N_2O_5S$
M.W.: 382,1562

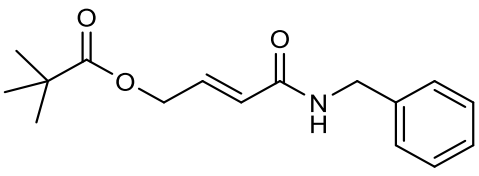
Following **GP17** with amide **22d** (1 equiv., 100 mg, 0.49 mmol) and *N-tert*-butylsulfinyl carbamate **D** (2 equiv., 175 mg, 0.97 mmol) for 48 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **26d** in 50% yield (93 mg, 0.24 mmol). Pale brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 3.70 (s, 3H), 3.72 (s, 3H), 3.87 (ddd, *J* = 2.0, 5.5, 17.0 Hz, 1H), 4.05 (ddd, *J* = 1.5, 6.0, 17.0 Hz, 1H), 4.38 (d, *J* = 6.0 Hz, 2H), 5.86 (td, *J* = 1.5, 15.5 Hz, 1H), 5.90 (br s, 1H), 6.69-6.80 (m, 4H), 7.15-7.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.5 (q), 39.1 (t), 43.7 (t), 53.6 (q), 55.2 (q), 60.2 (s), 113.0 (d), 113.5 (d), 120.2 (d), 125.7 (d), 129.7 (d), 139.4 (s), 139.5 (d), 155.4 (s), 159.8 (s), 164.8 (s). IR (cm^{-1}) ν: 3294, 2958, 1716, 1675, 1634, 1442, 1264, 907, 728. HRMS (ESI) *m/z* calcd for $C_{18}H_{26}KN_2O_5S$ $[M+K]^+$: 421.1194, found: 421.1

General procedure (GP18) for the Pd(II)-catalyzed direct acyloxylation.



A flask was charged with $LiOH{\cdot}H_2O$ (2 equiv.) and *t*$BuCO_2H$ (10 equiv.) and the mixture was heated at 40 °C for 10 minutes. Then BQ (2 equiv.), $Pd(OAc)_2$ (10 mol %) and CH_3CN (0.2 M) were added. The mixture was stirred for 15 minutes at rt, then the corresponding amide **22** (1 equiv.) was added. The mixture was stirred at 40 °C until the completion of the reaction. After cooling to rt, the mixture was filtered through a SiO_2 pad and washed with Et_2O (40 mL). NaOH (2M) was added and the mixture was stirred for 15 minutes. The organic phase was hydrolyzed with H_2O, extracted with Et_2O, dried over $MgSO_4$, filtered and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding pivaloxylated product **27**.

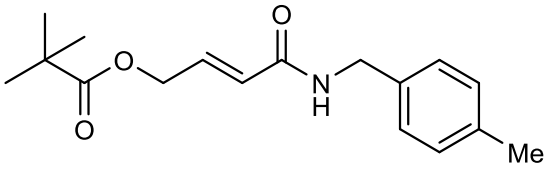
(*E*)-4-(Benzylamino)-4-oxobut-2-en-1-yl pivalate (27a)



$C_{16}H_{21}NO_3$
M.W.: 275,1521

Following **GP18** with **22a** (1 equiv., 300 mg, 1.70 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27a** in 98% yield (458 mg, 1.67 mmol). White solid, mp: 66-68 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (s, 9H), 4.50 (d, *J* = 6.0 Hz, 2H), 4.69 (dd, *J* = 5.0, 2.0 Hz, 2H), 6.02 (d, *J* = 15.5 Hz, 1H), 6.15 (br s, 1H), 6.84-6.90 (m, 1H), 7.26-7.35 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3 (q), 38.9 (s), 43.8 (t), 62.9 (t), 124.3 (d), 127.7 (d), 128.0 (d), 128.8 (d), 137.9 (s), 138.1 (d), 165.0 (d), 178.0 (d). IR (cm^{-1}) ν: 3247, 2968, 1727, 1678, 1629, 1278, 1159. HRMS (ESI) *m/z* calcd for $C_{16}H_{21}NNaO_3$ $[M+Na]^+$: 298.1419, found: 298.1414.

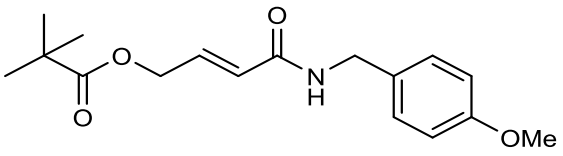
(*E*)-4-[(4-Methylbenzyl)amino]-4-oxobut-2-en-1-yl pivalate (27b)



$C_{17}H_{23}NO_3$
M.W.: 289,1678

Following **GP18** with amide **22b** (1 equiv., 100 mg, 0.53 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27b** in 50% yield (75 mg, 0.26 mmol). White solid, mp: 144-145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (s, 9H), 2.24 (s, 3H), 4.34-4.36 (m, 2H), 4.57-4.60 (m, 2H), 5.92 (td, *J* = 2.0, 15.5 Hz, 2H), 6.10 (br s, 1H), 6.72-6.79 (m, 1H), 7.03-7.09 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1 (q), 27.2 (q), 38.8 (s), 43.5 (t), 62.8 (t), 124.3 (d), 127.9 (d), 129.3 (d), 134.9 (s), 137.3 (s), 137.6 (d), 164.8 (s), 177.9 (s). IR (cm^{-1}) ν: 3242, 2971, 1733, 1673, 1622, 1281, 1142. HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NNaO_3$ $[M+Na]^+$:312.1570, found: 312.1570.

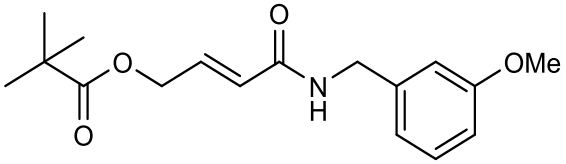
(*E*)-4-[(4-Methoxybenzyl)amino]-4-oxobut-2-en-1-yl pivalate (27c)



$C_{17}H_{23}NO_4$
M.W.: 305,3740

Following **GP18** with amide **22c** (1 equiv., 300 mg, 1.5 mmol) for 23 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27c** in 70% yield (306 mg, 1.00 mmol). Brown solid, mp: 125-127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (s, 9H), 3.82 (s, 3H), 4.47 (dd, *J* = 1.5, 5.5 Hz, 2H), 4.73 (dd, *J* = 2.0, 4.5 Hz, 2H), 5.82 (br s, 1H), 5.99 (dt, *J* = 1.5, 15.0 Hz, 1H), 6.87-6.93 (m, 3H), 7.23-7.26 (m, 2H).^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (q), 38.8 (s), 43.3 (t), 55.3 (q), 62.7 (t), 114.1 (d), 116.1 (d), 124.1 (s), 129.3 (d), 137.9 (d), 159.1 (s), 164.7 (s), 177.9 (s). IR (cm^{-1}) ν: 3371, 2961, 1712, 1674, 1513, 1245, 1161. HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NNaO_4$ $[M+Na]^+$: 328.1519, found: 328.1518.

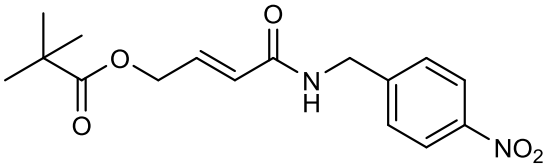
(*E*)-4-[(3-Methoxybenzyl)amino]-4-oxobut-2-en-1-yl pivalate (27d)



$C_{17}H_{23}NO_4$
M.W.: 305,1627

Following **GP18** with amide **22d** (1 equiv., 100 mg, 0.48 mmol) for 23 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27d** in 62% yield (91 mg, 0.20 mmol). Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9H), 3.72 (s, 3H), 4.41 (d, *J* = 6.0 Hz, 2H), 4.63 (dd, *J* = 2.0, 5.0 Hz, 2H), 5.84 (br s, 1H), 5.92 (td, *J* = 2.0, 15.5 Hz, 1H), 6.73-6.85 (m, 4H), 7.16-7.20 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (q), 38.8 (s), 43.7 (t), 55.2 (q), 62.8 (t), 113.0 (d), 113.6 (d), 120.1 (d), 124.1 (d), 129.8 (d), 137.9 (s), 139.5 (d), 159.9 (s), 164.7 (s), 177.9 (s). IR (cm^{-1}) ν: 3271, 2969, 1729, 1675, 1632, 1541, 1263, 1145. HRMS (ESI) *m/z* calcd for $C_{17}H_{23}NNaO_4$ $[M+Na]^+$: 328.1519, found: 328.1521.

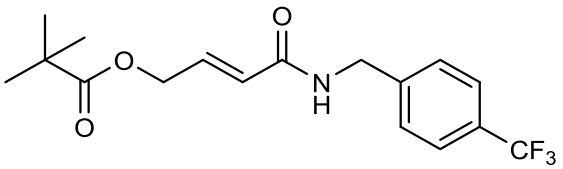
(*E*)-4-[(4-Nitrobenzyl)amino]-4-oxobut-2-en-1-yl pivalate (27e)



$C_{16}H_{20}N_2O_5$
M.W.: 320,1372

Following **GP18** with amide **22e** (1 equiv., 100 mg, 0.45 mmol) for 24 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27e** in 75% yield (109 mg, 0.34 mmol). White solid, mp: 112-113 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9H), 4.54 (dd, *J* = 3.0, 6.5 Hz, 2H), 4.65 (dd, *J* = 2.0, 4.0 Hz, 2H), 5.98 (m, 1H), 6.15 (br s, 1H), 6.84 (ddd, *J* = 15.0, 6.0, 3.5 Hz, 1H), 7.37 (dd, *J* = 2.5, 9.0 Hz, 2H), 8.06-8.10 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (q), 38.8 (s), 42.9 (t), 62.7 (t), 123.5 (d), 123.8 (d), 128.3 (d), 138.8 (d), 145.7 (s), 147.3 (s), 165.1 (s), 177.8 (s). IR (cm^{-1}) ν: 3267, 2974, 1730, 1673, 1633, 1518, 1345, 1145. HRMS (ESI) *m/z* calcd for $C_{16}H_{20}N_2NaO_5$ $[M+Na]^+$: 343.1264, found: 343.1257.

(*E*)-4-Oxo-4-[(4-(trifluoromethyl)benzyl)amino]but-2-en-1-yl pivalate (27f)

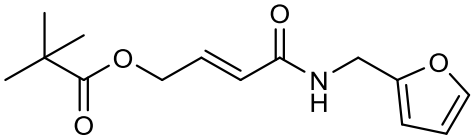


$C_{17}H_{20}F_3NO_3$
M.W.: 343.1395

Following **GP18** with amide **22f** (1 equiv., 300 mg, 1.23 mmol) for 23 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27f** in 91%

yield (382 mg, 1.1 mmol). Orange viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 9H), 4.46 (d, *J* = 6.0 Hz, 2H), 4.63 (dd, *J* = 2.0, 5.0 Hz, 2H), 5.95 (dt, *J* = 15.5, 2.0 Hz, 1H), 6.19 (br s, 1H), 6.82 (dt, *J* = 15.5, 5.0 Hz, 1H), 7.30-7.32 (m, 2H), 7.48-7.50 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1 (q), 38.8 (s), 43.4 (t), 62.7 (t), 123.7 (d), 124.0 (*J* = 273.5 Hz, s), 125.6 (*J* = 3.5 Hz, d), 127.9 (d), 129.8 (*J* = 31.5 Hz, s), 138.5 (d), 142.0 (s), 165.1 (s), 177.9 (s). ^{19}F NMR ($CDCl_3$, 282 MHz) δ - 62.53. IR (cm^{-1}) ν: 3276, 3076, 1728, 1676, 1634, 1324, 1158, 906, 728. HRMS (ESI) *m/z* calcd for $C_{17}H_{20}F_3NNaO_3$ $[M+Na]^+$: 366.1287, found: 366.1285.

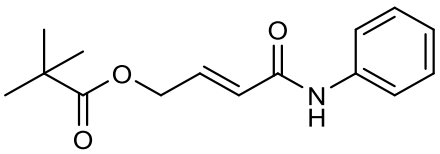
(*E*)-4-[(Furan-2-ylmethyl)amino]-4-oxobut-2-en-1-yl pivalate (27g)



$C_{14}H_{19}NO_4$
M.W.: 265,1314

Following **GP18** with amide **22g** (1 equiv., 150 mg, 0.9 mmol) for 22 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27g** in 35% yield (80 mg, 0.30 mmol). Yellow solid, mp: 125 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 9H), 4.44 (d, *J* = 5.5 Hz, 2H), 4.63 (dd, *J* = 1.5, 5.0 Hz, 2H), 5.90 (br s, 1H), 5.92 (td, *J* = 1.5, 15.0 Hz, 1H), 6.17-6.18 (m, 1H), 6.25 (dd, *J* = 2.0, 3.0 Hz, 1H), 6.81 (ddd, *J* = 4.5, 5.0, 15.0 Hz, 1H), 7.29 (dd, *J* = 1.0, 2.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (q), 36.5 (t), 38.8 (s), 62.7 (t), 107.7 (d), 110.5 (d), 123.9 (d), 138.0 (d), 142.3 (d), 150.9 (s), 164.6 (s), 177.8 (s). IR (cm^{-1}) ν: 3230, 2966, 1730, 1672, 1626, 1151, 752. HRMS (ESI) *m/z* calcd for $C_{14}H_{19}NNaO_4$ $[M+Na]^+$: 288.1206, found: 288.1201.

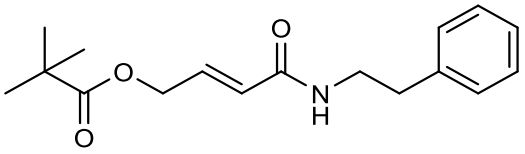
(*E*)-4-Oxo-4-(phenylamino)but-2-en-1-yl pivalate (27h)



$C_{15}H_{19}NO_3$
M.W.: 261,1365

Following **GP18** with amide **22h** (1 equiv., 200 mg, 1.24 mmol) for 20 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27h** in 44% yield (142 mg, 0.54 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9H), 4.64 (dd, *J* = 2.0, 5.0 Hz, 2H), 6.10 (td, *J* = 2.0, 15.5 Hz, 1H), 6.88 (td, *J* = 5.0, 15.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.78 (br s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (q), 38.9 (s), 62.8 (t), 120.1 (d), 124.6 (d), 124.9 (d), 129.0 (d), 137.8 (s), 138.7 (d), 163.2 (s), 177.9 (s). IR (cm^{-1}) ν: 3269, 2927, 1730, 1678, 1642, 1543, 1442, 1149, 754. HRMS (ESI) *m/z* calcd for $C_{15}H_{19}NNaO_3$ $[M+Na]^+$ 284.1257, found: 284.1267.

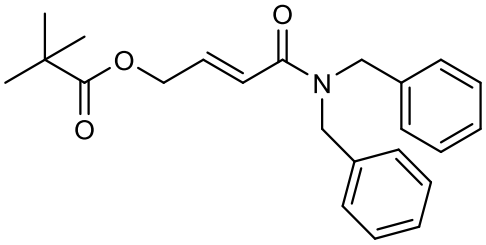
(*E*)-4-Oxo-4-(phenethylamino)but-2-en-1-yl pivalate (27i)



$C_{17}H_{23}NO_3$
M.W.: 289,1678

Following **GP18** with amide **22i** (1 equiv., 150 mg, 0.8 mmol) for 22 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27i** in 83% yield (191 mg, 0.66 mmol). Pale yellow viscous oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9H), 2.79 (t, *J* = 7.0 Hz, 2H), 3.51-3.56 (m, 2H), 4.62 (dd, *J* = 2.0, 5.0 Hz, 2H), 5.46 (s, 1H), 5.83 (dt, *J* = 15.5, 2.0 Hz, 1H), 6.76 (dt, *J* = 15.5, 5.0 Hz, 1H), 7.12-7.26 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.2 (q), 33.9 (t), 35.6 (s), 40.7 (t), 62.8 (t), 124.4 (d), 126.6 (d), 128.7 (d), 128.8 (d), 137.5 (s), 138.7 (d), 164.9 (s), 177.8 (s). IR (cm^{-1}) ν: 3283, 2931, 2359, 1731, 1676, 1632, 1282, 1151, 738. HRMS (ESI) *m/z* calcd for $C_{17}H_{23}KNO_3$ $[M+K]^+$: 328.1310, found: 328.1312.

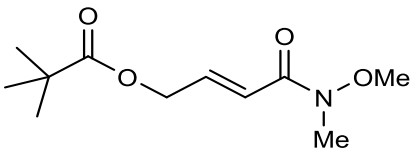
(*E*)-4-(Dibenzylamino)-4-oxobut-2-en-1-yl pivalate (27j)



$C_{23}H_{27}NO_3$
M.W.: 365,1991

Following **GP18** with amide **22j** (1 equiv., 100 mg, 0.4 mmol) for 22 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 4:6) to afford **27j** in 60% yield (81 mg, 0.22 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 9H), 4.54 (s, 2H), 4.71 (s, 2H), 4.76 (dd, *J* = 4.5, 2.0 Hz, 2H), 6.49 (dt, *J* = 15.0, 2.0 Hz, 1H), 7.07 (dt, *J* = 15.0, 4.5 Hz, 1H), 7.19 (d, *J* = 7.0 Hz, 2H), 7.44-7.25 (m, 8H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.1 (q), 38.8 (s), 48.9 (t), 50.0 (t), 62.9 (t), 121.0 (d), 126.4 (d), 127.5 (d), 127.7 (d), 128.4 (d), 128.6 (d), 129.0 (d), 136.4 (s), 137.1 (s), 140.1 (d), 166.5 (s), 177.7 (s). IR (cm^{-1}) ν: 3030, 2971, 2359, 1730, 1667, 1625, 1426, 1362, 1278, 1150, 960. HRMS (ESI) *m/z* calcd for $C_{23}H_{27}NNaO_3$ $[M+Na]^+$ 388.1883, found: 388.1896.

(*E*)-4-(Methoxy(methyl)amino)-4-oxobut-2-en-1-yl pivalate (27k)

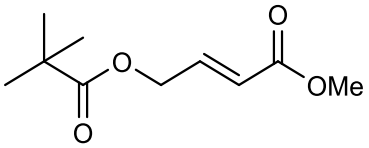


$C_{11}H_{19}NO_4$
M.W.: 229,1314

Following **GP18** with amide **22k** (1 equiv., 60 mg, 0.46 mmol) for 26 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **27k** in 48%

yield (51 mg, 0.22 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (s, 9H), 3.23 (s, 3H), 3.68 (s, 3H), 4.74-4.75 (m, 2H), 6.58 (d, *J* = 15.5 Hz, 1H), 6.91-6.96 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.3 (q), 32.5 (q), 39.0 (s), 61.8 (q), 63.1 (t), 119.6 (d), 140.2 (d), 166.1 (s), 177.8 (s). IR (cm^{-1}) ν: 2971, 1730, 1669, 1633, 1364. HRMS (ESI) *m/z* calcd for $C_{11}H_{19}NNaO_4$ $[M+Na]^+$: 252.1212, found: 252.1206.

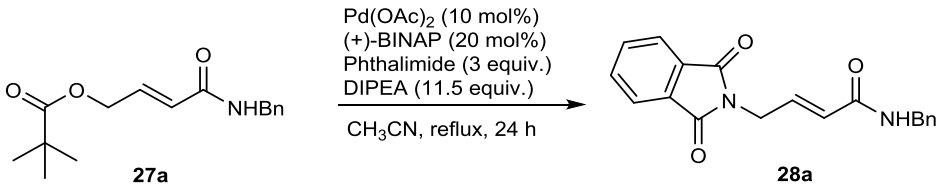
Methyl (*E*)-4-(pivaloyloxy)but-2-enoate (27m)



$C_{10}H_{16}O_4$
M.W.: 200,1049

Following **GP18** with methyl 3-butenoate **22m** (commercially available) (1 equiv., 100 mg, 0.99 mmol) for 22 hours. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 4:6) to afford **27m** in 81% yield (163 mg, 0.81 mmol). Yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (dd, *J* = 7.0, 2.0 Hz, 9H), 3.77 (m, 3H), 4.74 (dd, *J* = 4.5, 2.0 Hz, 2H), 6.03 (dt, *J* = 16.0, 2.0 Hz, 1H), 6.88-7.05 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.0 (q), 38.8 (s), 51.7 (q), 62.4 (t), 121.3 (d), 141.9 (d), 166.3 (s), 177.7 (s). IR (cm^{-1}) ν: 2972, 2874, 1728, 1664, 1476, 1367, 1315, 1146. HRMS (ESI) *m/z* calcd for $C_{10}H_{16}NaO_4$ $[M+Na]^+$ 223.0941, found: 223.0935.

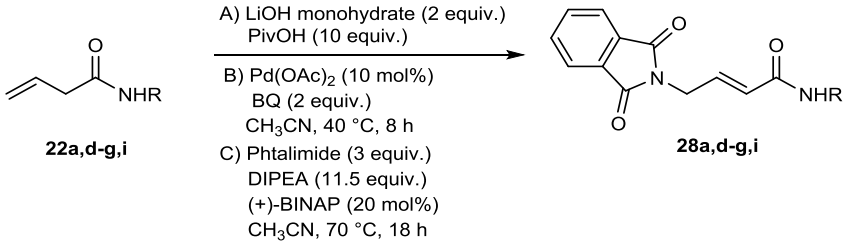
General procedure (GP19) for the Pd(0)-catalyzed amination.



27a **28a**

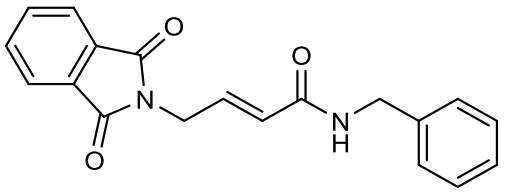
A sealed tube was charged with the amide **27a** (1 equiv., 50 mg, 0.18 mmol), and CH_3CN (900 μL, 0.2 M). Then, $Pd(OAc)_2$ (10 mol %, 4 mg, 0.018 mmol), (+)-BINAP (20 mol %, 22.4 mg, 0.036 mmol), phthalimide (3 equiv., 79.5 mg, 0.54 mmol) were added to the mixture. DIPEA was added last via a syringe (11.5 equiv., 352 mL, 2.07 mmol) and the mixture was stirred at reflux for the time required to complete the reaction (24 h). The solution was filtered through a small plug of silica gel, washed with AcOEt and concentrated at reduced pressure. The crude product was purified by silica gel column chromatography (eluent: AcOEt / CycloHexane 1:1) to afford **28a** in 83% yield (48 mg, 0.15 mmol).

General procedure (GP20) for the sequential Pd(II) / Pd(0) catalyzed amination.



A sealed tube was charged with $LiOH{\cdot}H_2O$ (2 equiv.) and t-$BuCO_2H$ (10 equiv.) and the mixture was heated at 40 °C for 10 minutes. Then BQ (2 equiv.), $Pd(OAc)_2$ (10 mol %) and CH_3CN (0.2 M) were added. The mixture was stirred for 15 minutes at rt, then the corresponding amide (**22a,d-g,i**) (1 equiv.) was added. The mixture was stirred at 40 °C for 8 hours. The completion of the reaction was monitored by TLC, and then DIPEA (11.5 equiv.), phtalimide (3 equiv.) and (+)-BINAP (20 mol %) were added and the mixture was stirred at 70 °C for 18 hours. After cooling to rt, the mixture was filtered through a SiO_2 pad and washed with AcOEt (20 mL for two times), then concentrated at reduced pressure. The crude product was purified by silica gel column chromatography to afford the corresponding aminated compounds **(28a,d-g,i)**.

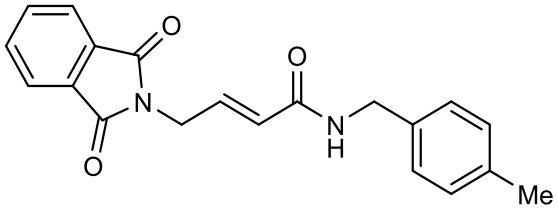
(*E*)-*N*-Benzyl-4-(1,3-dioxoisoindolin-2-yl)but-2-enamide (28a)



$C_{19}H_{16}N_2O_3$
M.W.: 320,1161

Following **GP20** with amide **22a** (1 equiv., 100 mg, 0.57 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **28a** in 90% yield (142 mg, 0.44 mmol). White solid, mp: 184-185 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.28 (d, J = 6.0 Hz, 2H), 4.33 (dd, J = 4.5, 2.0 Hz, 2H), 5.96 (dt, J = 15.5, 2.0 Hz, 1H), 6.68 (dt, J = 15.5, 4.5 Hz, 1H), 7.20-7.22 (m, 2H), 7.27-7.29 (m, 2H), 7.85-7.92 (m, 4H), 8.39 (t, J = 6.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ 38.0 (t), 42.1 (t), 123.2 (d), 124.4 (d), 126.8 (d), 127.4 (d), 128.3 (d), 131.6 (s), 134.5 (d), 136.3 (s), 139.1 (d), 164.0 (s), 1674.4 (s). IR (cm^{-1}) ν: 3282, 1771, 1701, 1629, 977, 720. HRMS (ESI) *m/z* calcd for $C_{19}H_{16}N_2NaO_3$ $[M+Na]^+$: 343.1059, found: 343.1053.

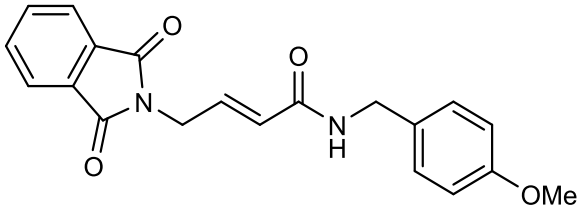
(*E*)-4-(1,3-Dioxoisoindolin-2-yl)-*N*-(4-methylbenzyl)but-2-enamide (28b)



$C_{20}H_{18}N_2O_3$
M.W.: 334,1317

Following **GP20** with amide **22b** (1 equiv., 100 mg, 0.52 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **28b** in 22% (38 mg, 0.11 mmol). Pale yellow solid, mp: 180-182 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (d, *J* = 4.5 Hz, 3H), 4.32-4.39 (m, 4H), 5.58 (br s, 1H), 5.82 (dt, *J* = 15.5, 1.5 Hz, 1H), 6.74-6.80 (m, 1H), 7.03-7.12 (m, 4H), 7.62-7.69 (m, 2H), 7.75-7.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.0 (q), 38.2 (t), 43.6 (t), 123.5 (d), 125.7 (d), 127.9 (d), 129.4 (d), 132.0 (d), 134.2 (s), 134.8 (d), 136.8 (s), 137.4 (d), 164.5 (s), 167.6 (s). IR (cm^{-1}) ν: 3274, 2923, 1771, 1713, 1666, 1623, 1547, 1458, 1351, 1218, 1118. . HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2NaO_3$ $[M+Na]^+$: 357.1210, found: 357.1222.

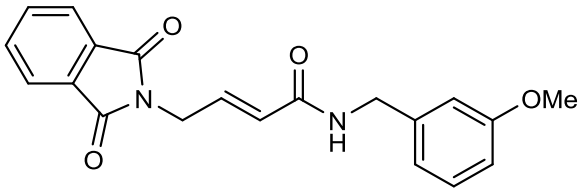
(*E*)-4-(1,3-Dioxoisoindolin-2-yl)-*N*-(4-methoxybenzyl)but-2-enamide (28c)



$C_{20}H_{18}N_2O_4$
M.W.: 350,1267

Following **GP20** with amide **22c** (1 equiv., 100 mg, 0.48 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **28c** in 53% (90 mg, 0.26 mmol). White solid, mp: 178-180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.71 (s, 3H), 4.32-4.36 (m, 4H), 5.61 (br s, 1H), 5.81 (td, *J* = 1.5, 15.5 Hz, 1H), 6.73-6.80 (m, 3H), 7.10-7.16 (m, 2H), 7.65-7.71 (m, 2H), 7.76-7.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2 (t), 43.4 (t), 55.3 (q), 114.1 (d), 123.5 (d), 125.7 (d), 129.3 (s), 129.9 (d), 131.9 (d), 134.2 (s), 136.8 (d), 159.1 (s), 164.4 (s), 167.6 (s). IR (cm^{-1}) ν: 3284, 2926, 1708, 1620, 1513, 1247. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2NaO_4$ $[M+Na]^+$: 373.1159, found: 373.1163.

(*E*)-4-(1,3-Dioxoisoindolin-2-yl)-*N*-(3-methoxybenzyl)but-2-enamide (28d)

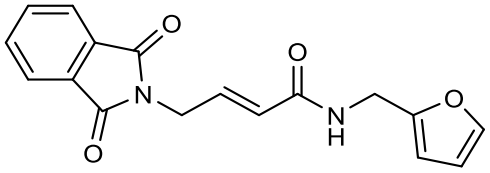


$C_{20}H_{18}N_2O_4$
M.W.: 350,1267

Following **GP20** with amide **22d** (1 equiv., 100 mg, 0.48 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **28d** in 76% yield (129 mg,

0.37 mmol). White solid, mp: 143-144 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.72 (d, *J* = 6.0 Hz, 3H), 4.31-4.43 (m, 4H), 5.66 (br s, 1H), 5.83 (dt, *J* = 15.5, 2.0 Hz, 1H), 6.70-6.84 (m, 4H), 7.10-7.18 (m, 1H), 7.62-7.75 (m, 2H), 7.75-7.84 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.2 (t), 43.7 (t), 55.2 (q), 113.1 (d), 113.4 (d), 120.1 (d), 123.5 (d), 125.5 (d), 129.8 (d), 131.9 (d), 134.2 (d), 136.9 (s), 139.4 (d), 159.9 (s), 164.4 (s), 167.6 (s). IR (cm^{-1}) ν: 3275, 2897, 1702, 1631, 1423, 1046, 718. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2NaO_4$ $[M+Na]^+$: 373.1159, found: 373.1157.

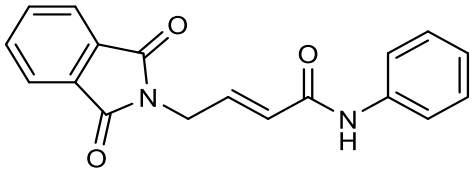
(*E*)-4-(1,3-Dioxoisoindolin-2-yl)-*N*-(furan-2-ylmethyl)but-2-enamide (28g)



$C_{17}H_{14}N_2O_4$
M.W.: 310,0954

Following **GP20** with amide **22g** (1 equiv., 85 mg, 0.51 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **28g** in 20% (30 mg, 0.097 mmol). Pale yellow solid, mp: 144-145 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.34 (dd, *J* = 2.0, 5.5 Hz, 2H), 4.39 (d, *J* = 5.5 Hz, 2H), 5.75 (br s, 1H), 5.82 (td, *J* = 1.5, 15.5 Hz, 1H), 6.14 (dd, *J* = 1.0, 3.5 Hz, 1H), 6.22 (dd, *J* = 2.0, 3.0 Hz, 1H), 6.76 (td, *J* = 5.5, 15.5 Hz, 1H), 7.25 (dd, *J* = 1.0, 2.0 Hz, 1H), 7.66 (dd, *J* = 3.0, 5.5 Hz, 2H), 7.78 (dd, *J* = 3.0, 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.5 (t), 38.2 (t), 107.7 (d), 110.5 (d), 123.5 (d), 125.4 (d), 131.9 (d), 134.2 (d), 137.1 (d), 142.2 (d), 150.8 (s), 164.3 (s), 167.6 (s). IR (cm^{-1}) ν: 3297, 2917, 1703, 1632, 1556, 1425, 1347, 716. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}N_2NaO_4$ $[M+Na]^+$: 333.0846, found: 333.0857.

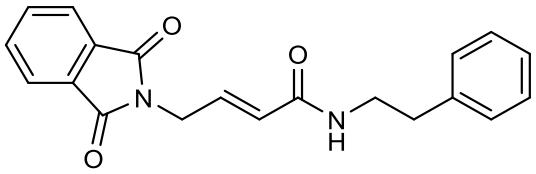
(*E*)-4-(1,3-Dioxoisoindolin-2-yl)-*N*-phenylbut-2-enamide (28h)



$C_{18}H_{14}N_2O_3$
M.W.: 306,1004

Following **GP20** with amide **22h** (1 equiv., 80 mg, 0.49 mmol) and with 1.5 equivalent of phthalimide (109 mg, 0.744 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **28h** in 32% yield (44 mg, 0.14 mmol). Pale yellow solid, mp: 173-174 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.48 (d, *J* = 5.5 Hz, 2H), 6.05 (d, *J* = 15.0 Hz, 1H), 6.95 (dt, *J* = 15.0, 5.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.19 (s, 1H), 7.31 (t, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 7.0 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.84-7.93 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.2 (t), 119.9 (d), 123.3 (d), 124.6 (d), 126.1 (d), 129.0 (d), 132.0 (d), 134.3 (s), 137.6 (s), 138.0 (d), 167.6 (s). IR (cm^{-1}) ν: 3366, 1769, 1706, 1388, 947, 756. HRMS (ESI) *m/z* calcd for $C_{18}H_{14}N_2NaO_3$ $[M+Na]^+$: 329.0897, found: 329.0901.

(*E*)-4-(1,3-Dioxoisoindolin-2-yl)-*N*-phenethylbut-2-enamide (28i)



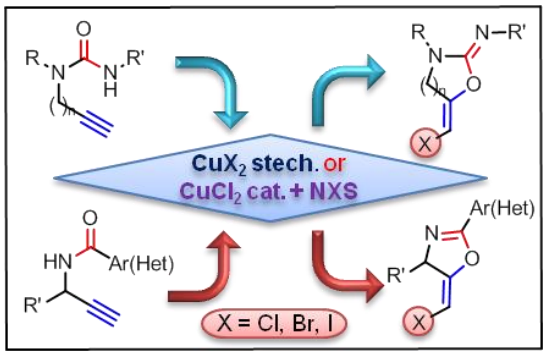
$C_{20}H_{18}N_2O_3$
M.W.: 334,1317

Following **GP20** with amide **22i** (1 equiv., 100 mg, 0.53 mmol). The crude product was purified by flash chromatography on silica gel (eluent: AcOEt / CycloHexane 1:1) to afford **28i** in 82% yield (145 mg, 0.43 mmol). Pale yellow solid, mp: 148-150 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (t, *J* = 7.0 Hz, 2H), 3.49 (dt, *J* = 6.0, 7.0 Hz, 2H), 4.33 (dd, *J* = 1.5, 6.0 Hz, 2H), 5.41 (br s, 1H), 5.76 (td, *J* = 1.5, 15.0 Hz, 1H), 6.71 (td, *J* = 6.0, 15.0 Hz, 1H), 7.09-7.25 (m, 5H), 7.66 (dd, *J* = 3.0, 5.5 Hz, 2H), 7.78 (dd, *J* = 3.0, 5.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 35.5 (t), 38.2 (t), 40.6 (t), 123.5 (d), 125.8 (d), 126.5 (d), 128.6 (d), 128.7 (d), 131.9 (d), 134.2 (s), 136.5 (s), 138.7 (d), 164.6 (s), 167.7 (s). IR (cm^{-1}) ν: 3284, 2929, 1711, 1391, 717. HRMS (ESI) *m/z* calcd for $C_{20}H_{18}N_2NaO_3$ $[M+Na]^+$: 357.1210, found: 357.1211.

General Conclusions

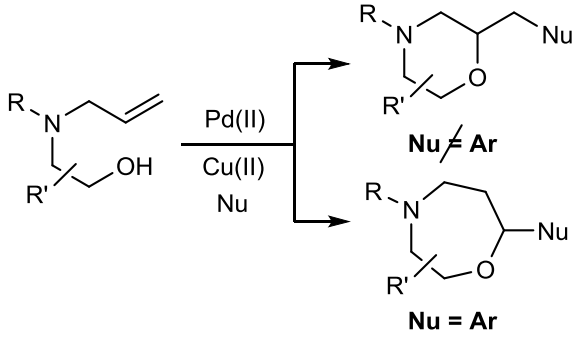
The main topic of my Ph.D. concerned the investigation of different transition metal-catalyzed reactions involving propargyl or allyl derivatives. Were obtained interesting results both with intramolecular alkoxylation sequences of terminal multiple C-C bonds and intermolecular allylic amination.

The first alkoxylation reaction proposed starts from a simple and accessible substrate like a propargyl urea or a secondary propargyl amide and by copper(II) catalysis permits to afford a wide range of variously substituted haloalkylidene heterocycles. The scope of the procedure was obtained working under two different reaction conditions, the former one employes a stoichiometric quantity of the proper copper salt, $CuCl_2$ or $CuBr_2$, the latter involves catalytic $CuCl_2$ and a stoichiometric amount of the suitable *N*-halosuccinimide (Scheme 57).



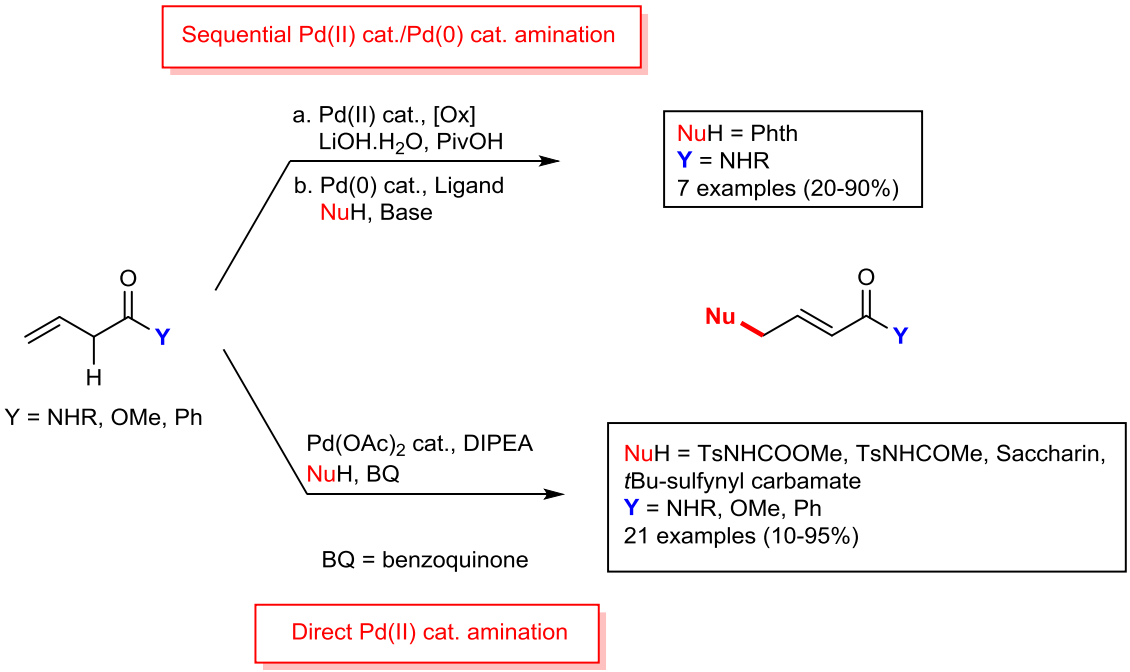
Scheme 57: Copper(II)-Catalyzed Alkoxyhalogenation of Alkynyl Ureas and Secondary Amides.

The second alkoxylation reaction studied involved a selective 7-*endo*-cyclization process palladium(II)-catalyzed in oxidative conditions of a particular range of substrates, 3-aza-5-alkenols. This mechanism was observable only when to the alkoxylation is related an arylation, confirming the uniqueness of the procedure (Scheme 58).



Scheme 58: Possible Pd-Catalyzed *exo*- and *endo*-Cyclization of 3-Aza-5-alkenols.

Lastly, an intermolecular process was investigated, a palladium(II)-catalyzed allylic amination of but-3-enoic derivatives (B3A).



Scheme 59: Complementary Routes for the Amination of B3A Derivatives.

To conclude, in this chapter we developed two complementary strategies for the palladium-catalyzed dehydrogenative amination of B3A derivatives, allowing to build-up various γ-AB2 products.

Based on this research work we published two scientific manuscripts:

1. ***Copper(II)-Catalyzed Alkoxyhalogenation of Alkynyl Ureas and Amides as a Route to Haloalkylidene-Substituted Heterocycle.***

S.Gazzola, E. Beccalli, T. Borelli, C. Castellano, M.A. Chiacchio, D. Diamante and G. Broggini *J. Org. Chem*. **2015**, *80*, 7226-7234.

DOI: 10.1021/acs.joc.5b01227

2. ***Dehydrogenative Allylic Amination of But-3-enoic Acid Derivatives***

D. Diamante, S. Gabrieli, T. Benincori, G. Broggini, J. Oble and G. Poli *Synthesis*, **2016**, *48*, 3400-3412.

DOI: 10.1055/s-0035-1562453

In addition, we have submitted to Organic Letters the third manuscript entitled:

3. ***Selective 7-endo-Cyclization of 3-Aza-5-alkenols through Oxidative Pd(II)-Catalyzed C-H Arylation and Intramolecular Alkoxylation***

S. Gazzola, G. Broggini, E. M. Beccalli, T. Borelli, C. Castellano and D. Diamante