UNIVERSITA' DEGLI STUDI DELL' INSUBRIA

Department of Science and High Technology

PhD in Chemical and Environmental Science (cv Chemical Science)

XXXV° Cycle

NOVEL TRANSITION METAL-CATALYZED C-H AND N-H CASCADES TOWARDS NITROGEN-CONTAINING TARGETS

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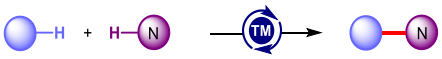
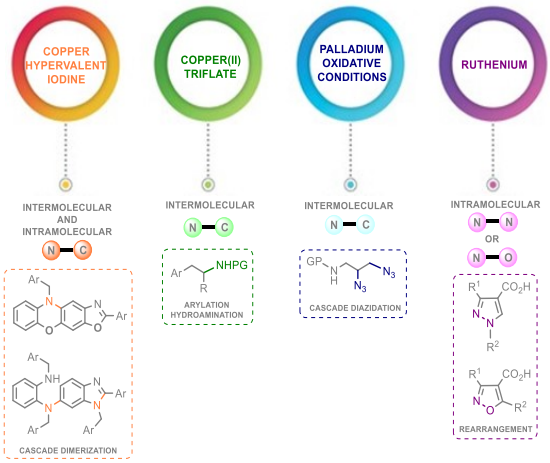
GENERAL INTRODUCTION

The interest for the development of innovative protocols that provide alternative conditions for the formation of nitrogen-containing bonds has grown over recent years. The nitrogen bond motif is found in many raw materials and fine chemicals, mainly in amine, amide and heterocyclic compounds, as well as in pharmaceuticals, smart materials and fertilizers.
As in many other synthetic transformations, the new challenges focus on the study of conditions that allow the use of unactivated substrates, in particular through C-H functionalization processes. Even in this type of procedure, transition metal catalysts furnish a powerful tool for building carbon-nitrogen and nitrogen-nitrogen bonds by assembling synthons which in their absence would be unreactive (Scheme 1).



Scheme 1. Four catalytic systems in nitrogen bond forming

Innovative and intriguing amination methodologies are often involved in cascade processes or in rearrangement reactions of easily accessible substrates. Domino reactions are increasingly being studied for the perspectives of green chemistry because they allow for a rapid increase in molecular complexity by reducing the number of synthetic steps, with consequent use of lower volume of solvent and reduced formation of waste.
In this PhD thesis four new synthetic procedures have been investigated, three of which involve the formation of C-N bonds in cascade reactions and one a rearrangement with formation of a N-N or O-N bond. The reaction conditions require the use of copper, palladium and ruthenium catalysts and allow access to acyclic or heterocyclic compounds (Scheme 2).



Scheme 2. Four catalytic systems in nitrogen bond forming

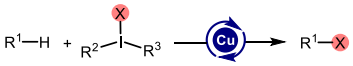
The first investigation allowed to set up the direct synthesis of oxazole-phenoxazine derivative by conversion of 2-benzylamino-phenol through a dimerization/cyclization reaction under oxidative copper catalysis (Chapter 1). The second synthetic procedure is related to the synthesis of 1-aryl-2-aminopropanes through a cascade of C-H functionalizations starting from allylic substrates and unactivated arenes promoted by $Cu(OTf)_2$ (Chapter 2). Inspired by the palladium-catalyzed oxidative conditions used for an amination/azidation process of aminoalkenes, a methodology for the diazidation of allyl sulfonylamides has been defined (Chapter 3). In addition to these cascade processes, the ruthenium-catalyzed rearrangement of suitable 4-alkylidene-isoxazol-5(4*H*)-ones was proven to be a useful procedure to access pyrazole- and isoxazole-4-carboxylic acids (Chapter 4).

CHAPTER 1

COPPER-CATALYZED/HYPERVALENT IODINE(III)-MEDIATED CASCADE DIMERIZATION/CYCLIZATION PROCESS

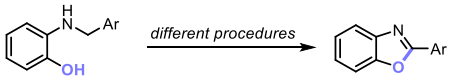
1.1 INTRODUCTION

In the field of C-H functionalization procedures, copper has emerged as a suitable alternative catalyst to the well-known palladium whose versatility has been widely proven due to its similar reactivity and chemoselectivity. In particular, the combination of a Cu-catalyst with a suitable oxidant could functionalize sp, sp^2 and sp^3 C-H groups forming C-C, C-N or C-O bonds.[1]
In literature are reported several copper-catalyzed procedures involving a hypervalent iodine(III) compound in the dual role of oxidant and source of functional groups (Scheme 3).[2]



Scheme 3. Cu-catalyzed procedure with hypervalent iodine(III) as oxidant and source of functional groups

However, copper-catalyzed reactions which involve the use of hypervalent iodine(III) exclusively as oxidant are reported in the literature.[3]
Among the natural and pharmaceutical compounds with interesting chemical and physical properties the benzoxazole nucleus is a frequently occurring motif which is useful in organic materials for optical applications.[4]
In this context, although the benzoxazole nucleus can be prepared through different cyclization procedures,[5] the most convenient approach to access 2-aryl-substituted benzoxazoles involves an intramolecular C-H functionalization of 2-benzylaminophenols (Scheme 4).[6]



Scheme 4. General procedure for intramolecular cyclization of 2-benzylaminophenols

Moreover, 2-aminophenols have the tendency to dimerize in the presence of an appropriate oxidant allowing the formation of the corresponding *o*-quinones, as shown in Scheme 5.[7]

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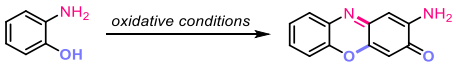
[4] a) H. Song, C. Rao, Z. Deng, Y. Yu, J. H. Naismith, The Biosynthesis of the Benzoxazole in Nataxazole Process via an Unstable Ester and has Synthetic Utility, *Angew. Chem. Int. Ed.* **2020**, *59*, 6054-6061; b) W.-R. Cui, C.-R. Zhang, R.-H. Xu, X.-R. Chen, R.-H. Yan, W. Jiang, R.-P. Liang, J.-D. Qiu, Low Band Gap Benzoxazole-Linked Covalent Organic Frameworks for Photo-Enhanced Target Uranium Recovery, *Small* **2021**, *17*, 2006882.

[5] a) Y. Endo, J.-E. Bäckvall, Biomimetic Oxidative Coupling of Benzylamines and 2-Aminophenols: Synthesis of Benzoxazoles, *Chem.-Eur. J.* **2012**, *18*, 13609-13613; b) H. Gan, Facile Preparation of Benzoxazoles from S8-Promoted Cyclization of 2-Nitrophenols with Arylmethyl Chloride, *ChemistrySelect* **2019**, *4*, 2858-2860.

[6] a) D.Xue, Y.-D. Long, Metal-Free TEMPO-Promoted C(sp^3)-H Amination To Afford Multisubstituted Benzimidazoles, *J. Org. Chem.* **2014**, *79*, 4727-4734; b) H. Gan, D. Miao, Q. Pan, R. Hu, X. Li, S. Han, S8-Mediated Cyclization of 2-Aminophenols/tiphenols with Arylmethyl Chloride: Approach to Benzoxazoles and Benzothiazoles, *Chem.-Asian J.* **2016**, *11*, 1770-1774.

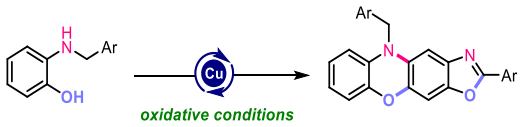
[7] a) Y. Yano, M. Ikuta, Y. Amamiya, T. Nabeshima, Isophenoxazine Synthase Model. Oxidation of *o*-Aminophenol by Oxidation-Active Flavin Mimic in an Aqueous Solution, *Chem. Lett.* **1991**, *20*, 461-464; b) F. Ferlin, A. Marini, N. Ascani, L. Ackermann, D. Lanari, L. Vaccaro, Heterogeneous Manganese-Catalyzed Oxidase C-H/C-O Cyclization to Access Pharmaceutically Active Compounds, *ChemCatChem*. **2020**, *12*, 449-454.



Scheme 5. General procedure for dimerization of 2-aminophenols

1.2 COPPER-CATALYZED CYCLIZATION/DIMERIZATION IN OXIDATIVE CONDITIONS

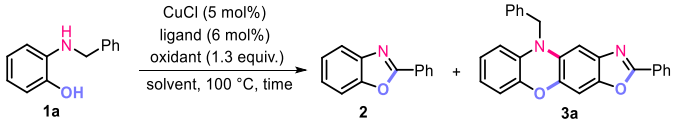
In this context, we envisaged a copper-catalyzed synthesis of a tetracyclic structure containing a phenoxazine moiety by dimerization/cyclization of 2-benzylaminophenols (Scheme 6).[8] It is well known that phenoxazine analogous structures are endowed with light-emitting properties, so in detail we expected fluorescent 5*H*-oxazolo[4,5,*b*]phenoxazines as reaction products.[9]



Scheme 6. Cu-Catalyzed synthesis of oxazolo-phenoxazines in oxidative conditions

Initially we analyzed the behaviour of 2-benzylamino-phenol **1a** in the presence of CuCl as catalyst and different oxidizing agents as shown in Table 1. The use of *t*-butyl-hydroperoxide or benzoquinone in combination of a copper-catalyst gave only the 2-phenyl-benzoxazole **2** (entries 1-3), whereas H_2O_2 as oxidant furnished only starting materials (entry 4). Only traces of compound **3a** were observed by adding 8-OH-quinoline or phenanthroline as ligands in the reaction medium (entries 5-6). Conversely, the benzoxazole formation was inhibited by the use of PIDA as oxidant in chlorobenzene (entry 7) and the combination of copper salt, PIDA and an *N*,*N*-bidentate ligands improved the yield of the oxazolo-phenoxazine **3a** (entry 8-9). PIFA, used as an alternative to PIDA, was found to be ineffective toward the cyclization and the dimerization/cyclization procedures (entry 10). Changing of solvent with DMF or acetonitrile in the presence of bathophenanthroline as ligand didn't allow the substrate conversion (entries 11-12). Finally, the combination CuCl, PIDA and bathophenanthroline in toluene (0.5 M) at 100 °C furnished the desired product **3a** with 72% yield (entry 13).

Table 1. Optimization of dimerization/cyclization of 2-benzylamino-phenol 1a



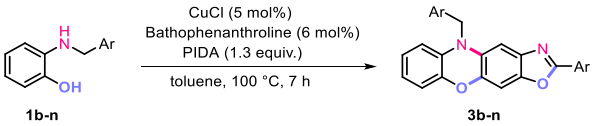
Entry	Oxidant	Ligand	Solvent	Time (h)	Product(s)
1	TBHP	-	1,4-Dioxane	4.0	**2** (10%)
2	TBHP	-	Chlorobenzene	4.0	**2** (44%)
3	BQ	-	Toluene	4 0	**2** (15%)
4	H_2O_2	-	Acetonitrile	4.0	**S.M.**
5	TBHP	8-OH quinoline	Chlorobenzene	1.0	**2** (66%) + **3a** (traces)

[8] C. Loro, L. Molteni, M. Papis, E. M. Beccalli, D. Nava, L. Lo Presti, S. Brenna, G. Colombo, F. Foschi, G. Broggini, Direct Synthesis of Fluorescent Oxazolo-phenoxazines by Copper-Catalyzed/Hypervalent Iodine(III)-Mediated Dimerization/Cyclization of 2-Benzylamino-phenols, *J. Org. Chem.* **2022**, *87*, 1032-1042.

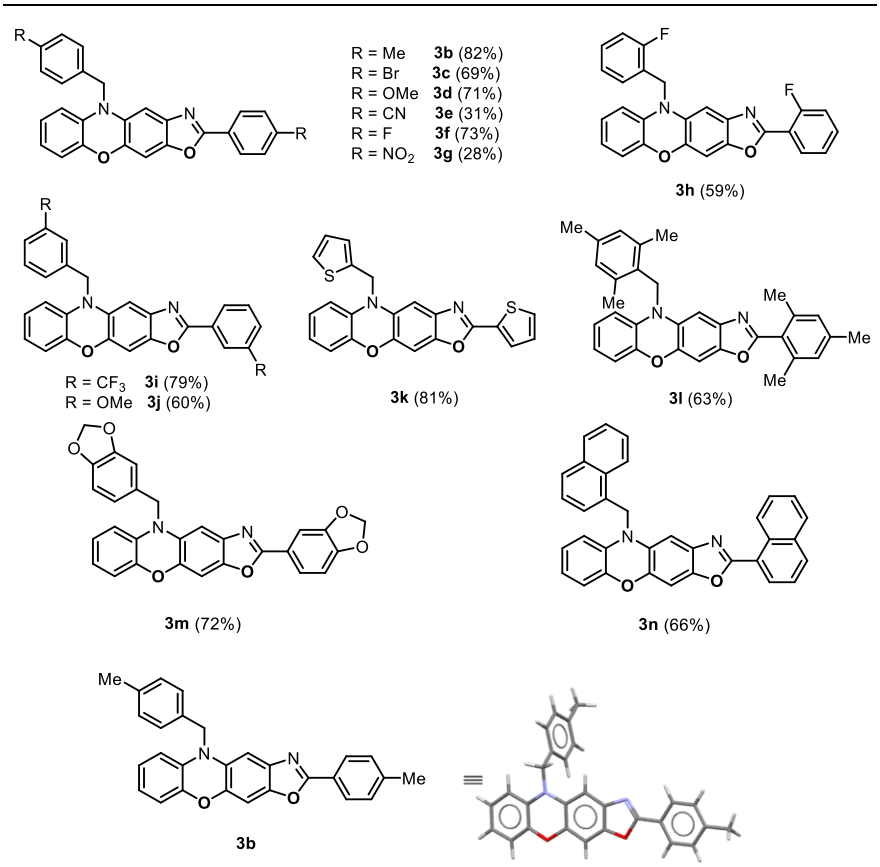
[9] a) A. M. Osman, S. A. M. Metwally, M. S. K. Youssef, Heterocyclic compounds. VIII. Studies on Oxazolophenoxazines, *Can. J. Chem.* **1976**, *54*, 37-43; b) T. Huang, D. Liu, J. Jiang, W. Jiang, Quinoxaline and Pyrido[x,y-*b*]pyrazine-Based Emitters: Tuning Normal Fluorescence to Thermally Activated Delayed Fluorescence and Emitting Color over the Entire Visible-Light Range, *Chem. Eur. J.* **2019**, *25*, 10926-10937; c) Y. Chen, Z. Peng, Y. Tao, Z. Wang, P. Lu, Y. Wang, Polymorphism-Dependent Emissions of Two Phenoxazine Derivatives, *Dyes Pigm.* **2019**, *161*, 44-50.

6	TBHP	Phen	Chlorobenzene	4.0	**2** (15%) + **3a** (traces)
7	PIDA	-	Chlorobenzene	4.0	**3a** (24%)
8	PIDA	Phen	Chlorobenzene	3.0	**3a** (58%)
9	PIDA	BPhen	Chlorobenzene	3.0	**3a** (53%)
10	PIFA	BPhen	Chlorobenzene	3.0	**S.M.**
11	PIDA	BPhen	DMF	3.0	**S.M.**
12	PIDA	BPhen	Acetonitrile	3.0	**S.M.**
13	PIDA	BPhen	Toluene	8.0	**3a** (72%)

At this point, 2-arylamino-phenols bearing highly diversified benzyl groups were tested as shown in Scheme 7. The presence of both electron-donating and electron-withdrawing substituents on the aromatic ring was tolerated furnishing the corresponding products **3b**-**j** in moderate to good yields. Also the presence of a heterocyclic group like thien-2-yl ring provided the desired compound **3k** in 81% yield. Otherwise, bulky substituents like mesityl, piperonal and naphthyl groups were suitable for the dimerization/cyclization procedure. Moreover, from the crude mixture of the reaction leading to product **3b**, a crystal suitable for X-ray diffraction analysis was obtained, permitting to have unambiguous evidence for the oxazolo-phenoxazine structure.[10]

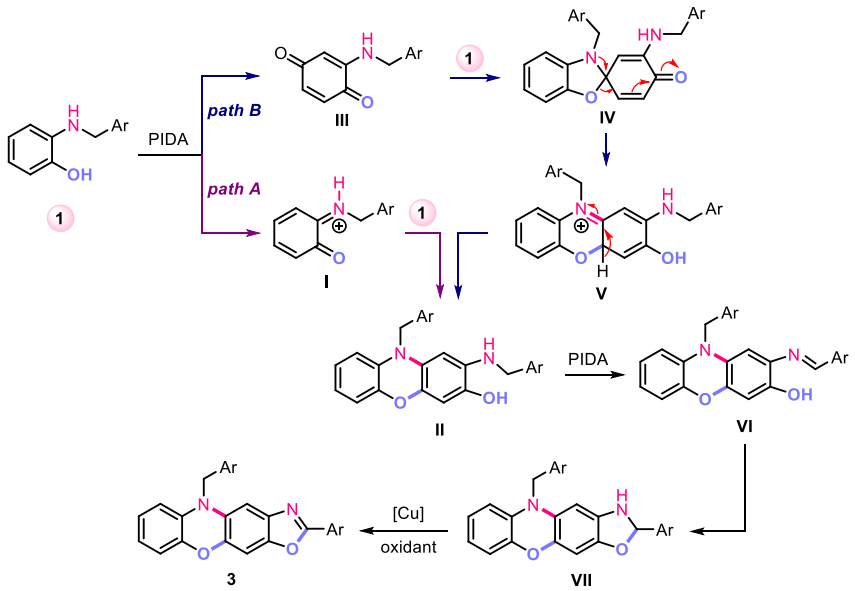


[10] X-Ray diffraction analysis of compound **3b** carried out by Prof. L. Lo Presti from Università degli Studi di Milano.



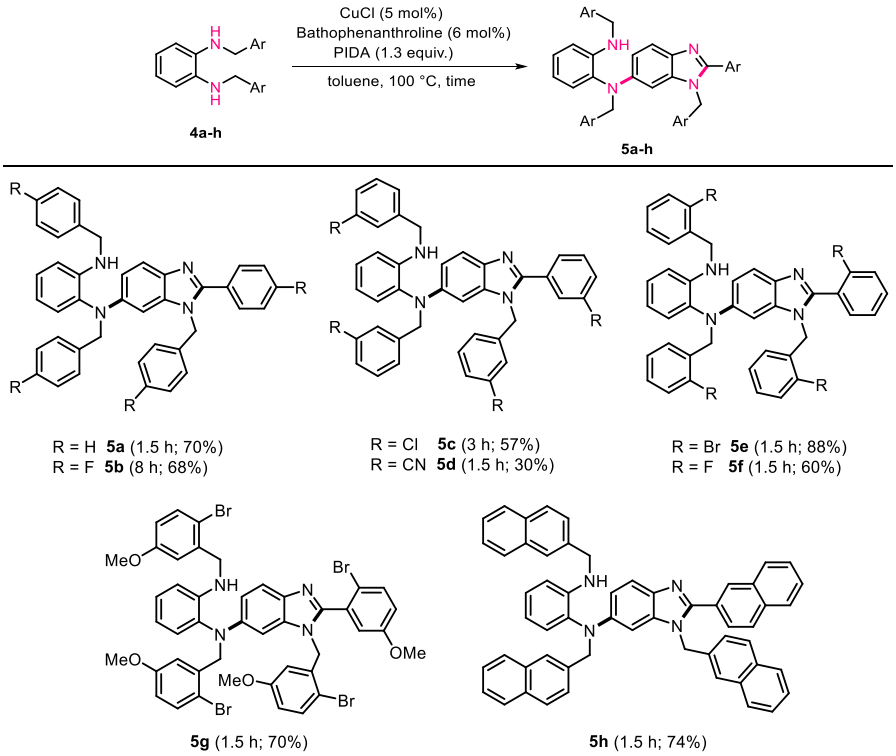
Scheme 7. Cu-Catalyzed synthesis of oxazolo-phenoxazines in oxidative conditions

A possible mechanism is proposed in Scheme 8. This proposal is speculative as the key intermediate **II** - which could result from the dimerization of 2-benzylamino-phenol **1** - has never been isolated. The first pathway involves the oxidation/dearomatization of the substrate induced by the hypervalent iodine(III), generating the *o*-quinone-type intermediate **I**. This latter interacts directly with **1** allowing the formation of **II**. Alternatively, **II** could be generated from the spiro-cyclohexandienone **IV** which arises from the coupling of **1** and the *p*-quinone **III**. The more stable phenoxazine **II** is formed through the rearrangement of intermediate **IV**. This took place through a regioselective ring expansion process favoured by the presence of acetate anion which captures the acidic H atom in intermediate **V**. At this point, the common intermediate **II** evolves through the oxidation to imine **VI** followed by the cyclization process. Finally, the copper-catalyzed oxidation of **VII** provided the oxazolo-phenoxazine **3**.



Scheme 8. Possible mechanism for cyclization/dimerization

At this point, due to their structural and electronic analogy with 2-aminophenols, we evaluated the reactivity of *N*,*N'*-dibenzyl-1,2-benzendiamines (Scheme 9). The compounds **4a-h** were treated with CuCl as catalyst, bathophenanthroline as bidentate ligand and an hypervalent iodine(III) in toluene at 100 °C. In all cases products **5a-h** were regioselectively obtained in good yields; in this case the formation of the five-membered ring took place, but the dimerization step was not operative toward the formation of the tetracyclic fused-ring.



Scheme 9. Cu-Catalyzed procedure on *N*,*N'*-dibenzyl-1,2-benzendiamines

The relative position of the substituents on the benzimidazole nucleus was determined with NMR studies and the selective substitution of the amino group at 6-position was assigned by NOESY experiment. The interaction between the aromatic proton at 6.35 ppm and the N1 benzylic signal at 5.19 ppm was diagnostic for the 6-substituted benzimidazole structure (Figure 1).

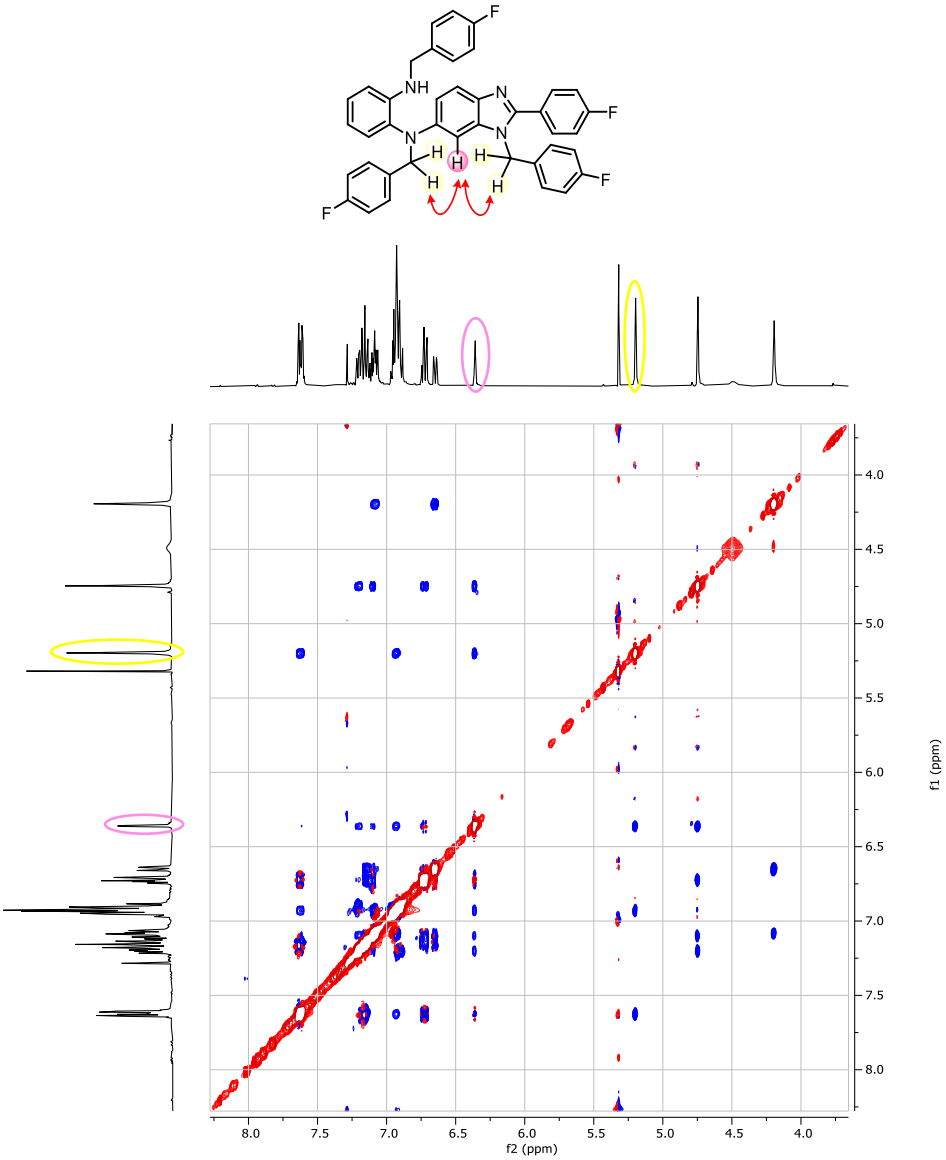
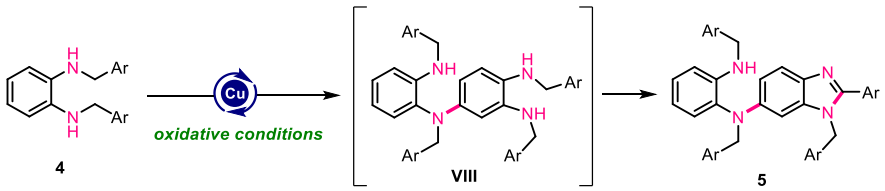


Figure 1. NOESY experiment on compound 5b

The formation of the benzimidazole products **5** suggests that plausibly the presence of a second benzylamino substituent – instead of a hydroxyl group - prevent the formation of a second C-N bond (Scheme 10). This reaction probably involves the oxidation of the intermediates **VIII** to imino derivatives which evolve to compounds **5** through oxidation of the first-formed 2,3-dihydrobenzimidazole derivatives.



Scheme 10. Possible procedure on *N,N'*-dibenzyl-1,2-benzendiamines

According to the fluorescent properties of oxazolo-phenoxazines,[9] we observed an intense fluorescence in solution which emission maxima differ depending on the substitution on the oxazole ring. In general, λ_{em} varies from blue to orange with decreasing the electron donating character of the substituent (*i.e.*, from 474

nm for compound **3k** to 584 nm for **3e**), as shown in Figure 2. The sole exception concerns compound **3g**, which was characterized by a feeble emission due to the quenching effect of the nitro groups.[11]

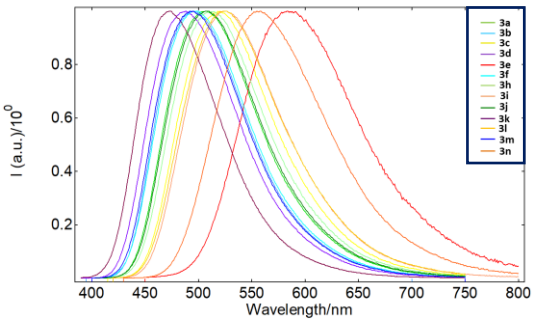
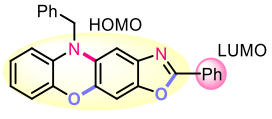


Figure 2. Normalized emission spectra of oxazolo-phenoxazines 3a-f, 3h-n (DCM, $5 \cdot 10^{-5}$ M)

In addition, TD-DFT calculations were performed on product **3a** and a great accordance between calculated and experimental UV-vis traces was observed, as shown in Figure 3.[12] Accordingly, the main absorption is a HOMO-LUMO transition (>98%): the HOMO is localized on the oxazolo-phenoxazine nucleus, whereas LUMO mainly involves the aromatic substituent at oxazole 2-position.



3a

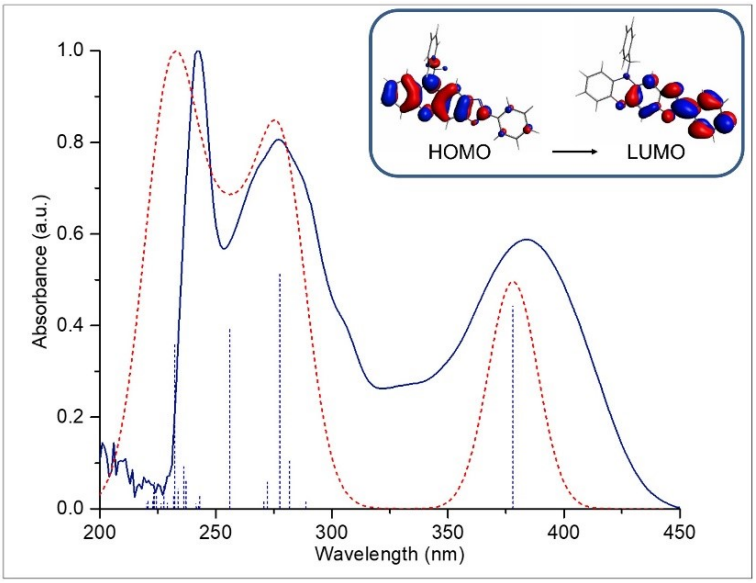


Figure 3. Calculated (dashed red) *vs* experimental (blue) UV-vis spectra of compound 3a

Preliminary experiments were carried out on 1-benzyl-2-phenyl-6-(aryl-benzyl)amino-benzimidazoles **5a-g** which were characterized by a fluorescence emission centered in the UV to the blue region (370nm-450nm), although less intense than the ones previously studied for the oxazolo-phenoxazine **3** (Figure 4).

[11] A. G. Ardizzoia, G. Colombo, B. Therrien, S. Brenna, Tuning the Fluorescence Emission and HOMO-LUMO Band Gap in Homoleptic Zinc(II) Complexes with N,O-Bidentate (Imidazo[1,5-*a*]pyrid-3-yl)phenols, *Eur. J. Inorg. Chem.* **2019**, *2019*, 1825-1831.

[12] DFT Calculation carried out by Prof. A. G. Ardizzoia from Università degli Studi dell'Insubria.

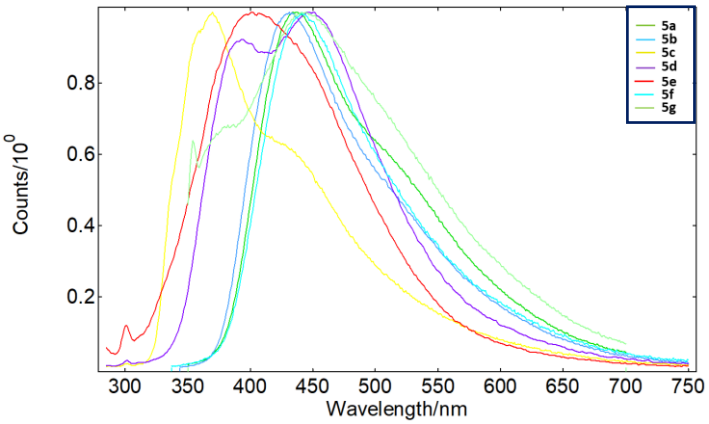


Figure 4. Normalized emission spectra of 1-benzyl-2-phenyl-6-(aryl-benzyl)amino-benzimidazoles (DCM, $5 \cdot 10^{-5}$ M)

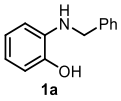
In conclusion, we performed an oxidative copper-catalyzed procedure for the cyclization/dimerization of 2-benzylamino phenols. A catalytic amount of CuCl combined with (diacetoxyiodo)benzene allowed the formation of two C-O bonds and one C-N in only one step in a regiospecific way. This synthetic protocol was extended also to *N*,*N'*-dibenzyl-1,2-diaminobenzenes which lead to 1-benzyl-2-phenyl-6-(aryl-benzyl)amino-benzimidazoles. In addition, the luminescence of oxazolo-phenoxazines **3** and 1-benzyl-2-phenyl-6-(aryl-benzyl)amino-benzimidazoles **5** could be modulated depending on the substituents on the aromatic ring leading to fluorescent organic dyes with a broad emission range.

1.3 EXPERIMENTAL SECTION

*Procedure for the synthesis of 2-benzylamino-phenols (**1**)*

In a solution of aminophenol (1.0 mmol) and MeOH (0.15 M), the appropriate benzaldehyde (1.0 mmol) was added, and the solution was stirred for 1 hour at room temperature. The mixture was cooled to 0 °C and then $NaBH_4$ or $NaBH(OAc)_3$ (2.0 mmol) was added portionwise. The resulting mixture was stirred for 1 hour and, after evaporation of the solvent, the solution was extracted with DCM (10 mL x2), washed with H_2O (10 mL x 2) and brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

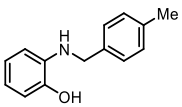
*N-Benzyl-2-aminophenol (**1a**)*



1a

FCC – AcOEt/hexane (1:9); **1a** (95%); white crystalline solid. The characterization of product **1a** is consistent with that reported in literature.[13]

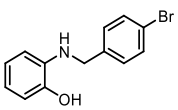
*N-(4-Methylbenzyl)-2-aminophenol (**1b**)*



1b

FCC – AcOEt/hexane (1:9); **1b** (91%); pale green crystalline solid. The characterization of product **1b** is consistent with that reported in literature.[14]

*N-(4-Bromobenzyl)-2-aminophenol (**1c**)*



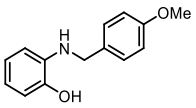
1c

FCC – AcOEt/hexane (1:4); **1c** (89%); light brown oil. The characterization of product **1c** is consistent with that reported in literature.[13]

[13] M. Xie, X. Liu, X. Zhu, X. Zhao, Y. Xia, L. Lin, X. Feng, Asymmetric Synthesis of Tetrahydroquinolines with Quaternary Stereocenters through the Povarov Reaction *Chem. Eur. J.* **2011**, *17*, 13800-13805.

[14] D. Ding, X. Lv, J. Li, L. Qiu, G. Xu, J. Sun A Pd-Catalyzed Cascade Reaction of N-H Insertion and Oxidative Dehydrogenative Aromatization: A New Entry to 2-Amino Phenols *Org. Biomol. Chem.* **2014**, *12*, 4084-4088.

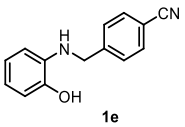
*N-(4-Methoxybenzyl)-2-aminophenol (**1d**)*



1d

FCC – AcOEt/hexane (1:9); **1d** (91%); white crystalline solid. The characterization of product **1d** is consistent with that reported in literature.[15]

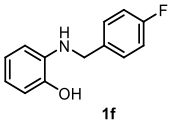
*N-(4-Cyanobenzyl)-2-aminophenol (**1e**)*



1e

FCC – AcOEt/hexane (1:9); **1e** (97%); light brown wax. The characterization of product **1e** is consistent with that reported in literature.[16]

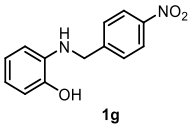
*N-(4-Fluorobenzyl)-2-aminophenol (**1f**)*



1f

FCC – AcOEt/hexane (1:9); **1f** (97%); pale green crystalline solid. The characterization of product **1f** is consistent with that reported in literature. [14]

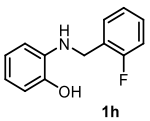
*N-(4-Nitrobenzyl)-2-aminophenol (**1g**)*



1g

FCC – AcOEt/hexane (3:7); **1g** (91%); beige solid; m.p.: 86-88 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.50 (s, 2H), 4.71 (bs, 1H), 6.50 (d, 1H, *J* = 9.4 Hz), 6.65 (t, 1H, *J* = 6.1 Hz), 6.75-6.82 (m, 2H), 7.54 (d, 2H, *J* = 8.7 Hz), 8.19 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 47.7, 112.1, 114.5, 118.2, 121.8, 123.9, 127.9, 136.1, 143.2, 147.2, 147.5. Anal. Calcd. For $C_{13}H_{12}N_2O_3$: C 63.93, H 4.95, N 11.47; found: C 64.15, H 5.09, N 11.30.

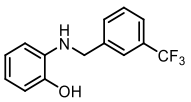
*N-(2-Fluorobenzyl)-2-aminophenol (**1h**)*



1h

FCC – AcOEt/hexane (1:9); **1h** (83%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.42 (s, 2H), 6.64-6.71 (m, 2H), 6.74-6.78 (m, 1H), 6.81-6.85 (m, 1H), 7.06-7.12 (m, 2H), 7.22-7.29 (m, 1H), 7.37 (t, 1H, *J* = 0 7.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 42.3, 112.9, 114.5, 115.3, 118.3, 121.6, 124.2, 126.4, 128.8, 129.5, 136.5, 143.9, 161.0. Anal. Calcd. For $C_{13}H_{12}FNO$: C 71.87, H 5.57, N 6.45; found: C 72.13, H 5.86, N 6.27.

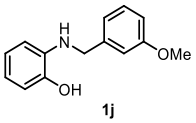
*N-[3-(Trifluoromethyl)benzyl]-2-aminophenol (**1i**)*



1i

FCC – AcOEt/hexane (1:4); **1i** (97%); brown solid; m.p.: 80-83 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.44 (s, 2H), 4.92 (bs, 1H), 6.66-6.75 (m, 3H), 6.88 (t, 1H, *J* = 7.4 Hz), 7.47 (t, 1H, *J* = 7.7 Hz), 7.59 (t, 2H, *J* = 7.4 Hz), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 48.2, 112.6, 114.6, 118.4, 121.8, 124.1, 124.2, 124.3, 129.1, 130.8, 131.3, 136.6, 140.5, 143.5. Anal. Calcd. For $C_{14}H_{12}F_3NO$: C 62.92, H 4.53, N 5.24; found: C 62.81, H 4.37, N 5.37.

*N-(3-Methoxybenzyl)-2-aminophenol (**1j**)*



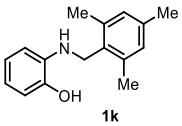
1j

FCC – AcOEt/hexane (1:4); **1j** (79%); beige oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.82 (s, 3H), 4.35 (s, 2H), 4.65 (bs, 1H), 6.63-6.75 (m, 3H), 6.84-6.86 (s, 2H), 6.98-7.01 (m, 2H), 7.29 (t, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 48.6, 55.3, 112.6, 112.7, 113.1, 114.5, 117.9, 119.9, 121.7, 129.6, 136.9, 141.1, 143.5, 159.9. Anal. Calcd. For $C_{14}H_{15}NO_2$: C 73.34, H 6.59, N 6.11; found: C 73.54, H 6.72, N 5.97.

[15] J. R. Bernardo, S. C. A. Sousa, P. R. Florindo, M. Wolff, B. Machura, A. C: Fernandes, Efficient and Chemoselective Direct Reductive Amination of Aromatic Alheydes Catalyzed by Oxo-Rhenium Complexes Containing Heterocyclic Ligands *Tetrahedron* **2013**, *69*, 9145-9154.

[16] B. Yadagiri, J. W. Lown, Selective Cleavage of Benzoxazoles to *o*-Hydroxy-*N*-Substituted Anilines with Sodium Borohydride-Acetic Acid *Synth. Commun.* **1990**, *20*, 175-181.

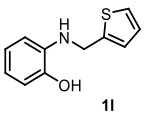
*N-(2,4,6-Trimethylbenzyl)-2-aminophenol (**1k**)*



1k

FCC – AcOEt/hexane (1:9); **1k** (98%); white solid; m.p.; 117-118 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (s, 3H), 2.40 (s, 6H), 4.25 (s, 2H), 6.70 (s, 2H), 6.88 (d, 1H, *J* = 7.8 Hz), 6.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.4, 21.0, 42.9, 112.3, 114.4, 117.8, 121.8, 129.2, 132.2, 137.4, 137.6, 143.7. Anal. Calcd. For $C_{16}H_{19}NO$: C 79.63, H 7.94, N 5.80; found: C 79.51, H 7.80, N 5.95.

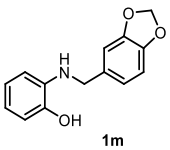
*N-(Thien-yl-methyl)-2-aminophenol (**1l**)*



1l

FCC – AcOEt/hexane (1:4); **1l** (83%); brown solid; m.p.; 81-84 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.38 (s, 2H), 4.79 (bs, 1H), 6.54-6.56 (m, 2H), 6.65 (d, 1H, *J* = 7.7 Hz), 6.71-6.76 (m, 1H), 6.83 (t, 1H, *J* = 5.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 43.9, 113.3, 114.8, 118.9, 121.6, 124.7, 125.3, 126.9, 136.3, 142.8, 144.1. Anal. Calcd. For $C_{11}H_{11}NOS$: C 64.36, H 5.40, N 6.82; found: C 64.27, H 5.29, N 6.90.

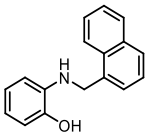
*N-(Benzo[d][1,3]dioxol-5-yl-methyl)-2-aminophenol (**1m**)*



1m

FCC – AcOEt/hexane (2:3); **1m** (88%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.26 (s, 2H), 5.95 (s, 2H), 6.63-6.69 (m, 2H), 6.72-6.79 (m, 2H), 6.80-6.85 (m, 2H), 6.89 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 48.6, 100.9, 108.2, 108.3, 112.9, 114.5, 118.3, 120.8, 121.7, 133.1, 136.4, 143.7, 146.8, 147.9. Anal. Calcd. For $C_{14}H_{13}NO_3$: C 69.12, H 5.39, N 5.76; found: C 69.36, H 5.56, N 5.62.

*N-(Naphthalen-1-yl-methyl)-2-aminophenol (**1n**)*



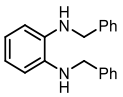
1n

FCC – AcOEt/hexane (1:9); **1n** (89%); beige solid; m.p.: 117-120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.58 (bs, 1H), 4.78 (s, 2H), 6.74-6.76 (m, 2H), 6.81 (d, 1H, *J* = 7.9 Hz), 6.91 (t, 1H, *J* = 10.5 Hz), 7.45 (, 1H, *J* = 8.2 Hz), 7.53-7.57 (m, 3H), 7.84 (d, 1H, *J* = 8.2 Hz), 7.91-7.94 (m, 1H), 8.10-8.13 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 46.6, 112.6, 114.5, 118.0, 121.9, 123.5, 125.6, 125.8, 125.9, 126.3, 128.1, 128.8, 131.6, 133.9, 134.4, 137.0, 43.6, 143.6. Calcd. For $C_{17}H_{15}NO$: C 81.90, H 6.06, N 5.62; found: C 81.77, H 5.90, N 5.73.

*Procedure for the synthesis of N,N'-dibenzylbenzene-1,2-diamines (**4**)*

In a solution of 1,2-phenylenediamine (1.0 mmol), the appropriate benzylbromide (2.0 mmol) in MeCN (0.15 M), the triethylamine (2.0 mmol) was added, and the solution was stirred for 3 hours at room temperature. The resulting mixture, after evaporation of the solvent, was extracted with DCM (10 mL x2), washed with H_2O (10 mL x 2) and brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

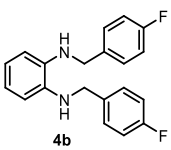
*N,N'-Dibenzylbenzene-1,2-diamine (**4a**)*



4a

FCC – AcOEt/hexane (1:9); **4a** (74%); light yellow crystalline solid. The characterization of product **4a** is consistent with that reported in literature.[17]

*N,N'-Di(4-fluorobenzyl)benzene-1,2-diamine (**4b**)*



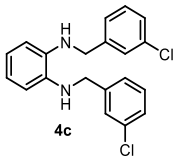
4b

FCC – AcOEt/hexane (1:4); **4b** (74%); light yellow crystalline solid. The characterization of product **4b** is consistent with that reported in literature.[18]

[17] C. Qian, W. Tang, A Versatile Synthesis of Vinyl-Substituted Heterocycles via Regio- and Enantioselective Pd-Catalyzed Tandem Allylic Substitution *Org. Lett.* **2020**, *22*, 4483-4488.

[18] P. Thapa, P. M. Palacios, T. Tran, B. S. Pierce, F. W. Jr. Foss, 1,2-Disubstituted Benzimidazoles by the Iron Catalyzed Cross-Dehydrogenative Coupling of Isomeric *o*-Phenylendiamine Substrates *J. Org. Chem*. **2020**, *85*, 1991-2009.

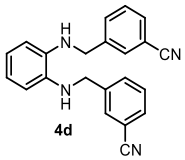
*N,N'-Di(3-chlorobenzyl)benzene-1,2-diamine (**4c**)*



4c

FCC – PE/DCM (7:3); **4c** (56%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.89 (bs, 2H), 4.33 (s, 4H), 6.72-6.76 (m, 2H), 6.85-6.89 (m, 2H), 7.28-7.33 (m, 6H), 7.46 (s, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 48.4, 112.6, 120.0, 125.9, 127.6, 127.9, 130.0, 134.6, 136.9, 141.7. Calcd. For $C_{20}H_{18}Cl_2N_2$: C 67.24, H 5.08, N 7.84; found: C 64.02, H 5.33, N 8.11.

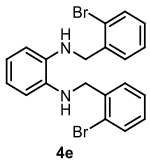
*N,N'-Bis(3-cianobenzyl)benzene-1,2-diamine (**4d**)*



4d

FCC – AcOEt/toluene (1:4); **4d** (39%); orange wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.02 (bs, 2H), 4.43 (s, 4H), 6.62-6.66 (m, 2H), 6.79-6.82 (m, 2H), 7.44-7.48 (m, 2H), 7.53 (d, 2H, *J* = 7.6 Hz), 7.67 (d, 2H, *J* = 7.6 Hz), 7.72 (s, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 47.8, 112.4, 112.5, 119.0, 119.9, 129.4, 130.9, 131.0, 132.1, 136.5, 141.3. Calcd. For $C_{20}H_{18}Cl_2N_2$: C 78.08, H 5.36, N 16.56; found: C 77.91, H 5.51, N 16.83.

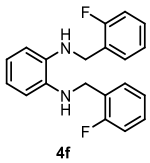
*N,N'-Di(2-bromobenzyl)benzene-1,2-diamine (**4e**)*



4e

FCC – AcOEt/hexane (7:3); **4e** (53%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.78 (bs, 2H), 4.29 (s, 4H), 6.51-6.56 (m, 2H), 6.64-6.69 (m, 2H), 7.02-7.05 (m, 2H), 7.16 (dd, 2H, *J* = 7.4, 7.4 Hz), 7.25-7.29 (m, 2H), 7.47 (d, 2H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 49.0, 113.1, 119.9, 123.7, 127.6, 128.8, 129.6, 132.9, 136.9, 138.3. Calcd. For $C_{20}H_{18}Br_2N_2$: C 53.84, H 4.07, N 6.28; found: C 54.07, H 4.36, N 6.02.

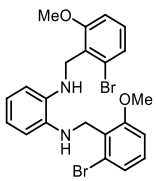
*N,N'-Di(2-fluorobenzyl)benzene-1,2-diamine (**4f**)*



4f

FCC – AcOEt/hexane (0.5:9.5); **4f** (32%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (bs, 2H), 4.44 (s, 4H), 6.70-6.75 (m, 2H), 6.83-6.88 (m, 2H), 7.11-7.17 (m, 4H), 7.28-7.34 (m, 2H), 7.40-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 42.4, 112.7, 115.4, 119.8, 124.2, 126.4, 128.8, 129.8, 137.2, 161.1. Calcd. For $C_{20}H_{18}F_2N_2$: C 74.06, H 5.59, N 8.64; found: C 73.85, H 5.92, N 8.39.

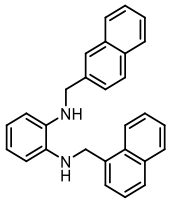
*N,N'-Di(2-bromo-5-methoxybenzyl)benzene-1,2-diamine (**4g**)*



4g

FCC – PE/DCM (1:9); **4g** (30%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.62 (s, 6H), 3.79 (bs, H), 4.25 (s, 4H), 6.53-6.62 (m, 5H), 6.68-6.72 (m, 2H), 6.87 (d, 1H, *J* = 3.0 Hz), 7.36 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 49.1, 55.5, 113.2, 113.8, 114.2, 115.4, 120.0, 133.4, 137.0, 139.4, 159.2. Calcd. For $C_{22}H_{22}Br_2N_2O_2$: C 52.20, H 4.38, N 5.53; found: C 52.67, H 4.56, N 5.78.

*N,N'-Di(naphthalen-2-yl-methyl)benzene-1,2-diamine (**4h**)*



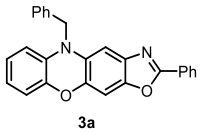
4h

FCC – AcOEt/hexane (0.5:9.5); **4h** (28%); orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.82 (bs, 2H), 4.52 (s, 4H), 6.82 (s, 4H), 7.44-7.49 (m, 4H), 7.54-7.56 (m, 2H), 7.75-7.92 (m, 8H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 49.1, 112.3, 119.6, 125.7, 126.1, 126.2, 126.3, 127.7, 127.8, 128.3, 132.8, 133.5, 136.9, 137.3. Calcd. For $C_{28}H_{24}N_2$: C 86.56, H 6.23, N 7.21; found: C 85.98, H 6.78, N 6.99.

Procedure for the dimerization/cyclization

In a solution of bathophenantroline (0.06 mmol) in toluene (0.25M), CuCl (0.05 mmol) was added, and the solution was stirred for 10 minutes. Then, the appropriate 2-benzylaminophenol or *N,N'*-disubstituted benzene-1,2-diamine (1.0 mmol) was added. The resulting mixture was magnetically stirred and heated at 100 °C for the appropriate time. The solution was extracted with DCM (10 mL x2), washed with H_2O (10 mL x 2), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

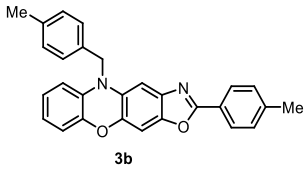
*5-Benzyl-2-phenyl-5H-oxazolo[4,5-b]phenoxazine (**3a**)*



3a

Reaction time: 7 hours. FCC – AcOEt/hexane (1:15); **3a** (72%); yellow solid; m.p.: 237-239 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.89 (s, 2H), 6.45 (d, 1H, *J* = 8.1 Hz), 6.70-6.81 (m, 4H), 6.98 (s, 1H), 7.28-7.37 (m, 5H), 7.47-7.51 (m, 3H), 8.11-8.16 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 50.2, 98.3, 102.2, 112.4, 115.4, 121.4, 124.2, 126.0, 126.9, 127.1, 127.3, 128.9, 129.0, 131.2, 132.4, 133.5, 135.6, 137.4, 144.5, 144.6, 145.6, 162.6. Calcd. For $C_{26}H_{18}N_2O_2$: C 79.98, H 4.65, N 7.17; found: C 79.85, H 4.49, N 7.34.

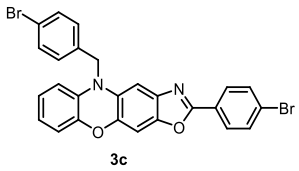
*5-(4-Methylbenzyl)2-(p-tolyl)-5H-oxazolo[4,5-b]phenoxazine (**3b**)*



3b

Reaction time: 7 hours. FCC – AcOEt/hexane (1:11); **3b** (82%); yellow solid; m.p.: 213-214 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H), 2.32 (s, 3H), 4.75 (s, 2H), 6.36 (d, 1H, *J* = 7.9 Hz), 6.58 (s, 1H), 6.62-6.71 (m, 3H), 6.85 (s, 1H), 7.06 (d, 2H, *J* = 8.2 Hz), 7.11 (d, 2H, *J* = 8.2 Hz), 7.18 (d, 2H, *J* = 8.3 Hz), 7.91 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.0, 21.6, 49.9, 98.2, 102.2, 112.3, 115.3, 121.2, 124.1, 124.3, 125.9, 127.0, 129.6, 129.7, 132.2, 132.6, 133.7, 136.9, 137.7, 141.5, 144.4, 144.6, 145.5, 162.8. Calcd. For $C_{28}H_{22}N_2O_2$: C 80.36, H 5.30, N 6.69; found: C 80.47, H 5.44, N 6.51.

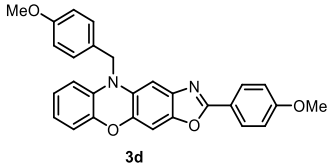
*5-(4-Bromobenzyl)2-(4-bromophenyl)-5H-oxazolo[4,5-b]phenoxazine (**3c**)*



3c

Reaction time: 7 hours. FCC – AcOEt/hexane (1:11); **3c** (69%); yellow solid; m.p.: 253-254 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.83 (s, 2H), 6.40 (d, 1H, *J* = 7.8 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 7.62 (d, 2H, *J* = 8.6 Hz), 7.99 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 45.4, 94.2, 97.8, 102.3, 107.9, 110.3, 111.2, 116.9, 117.4, 119.9, 121.4, 123.6, 124.1, 127.9, 128.9, 130.4, 133.5, 140.2, 140.4, 141.5, 155.1. Calcd. For $C_{26}H_{16}Br_2N_2O_2$: C 56.96, H 2.94, N 5.11; found: C 57.15, H 3.17, N 4.93.

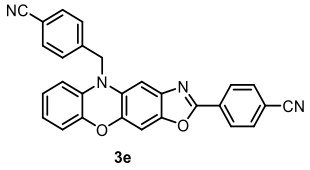
*5-(4-Methoxybenzyl)2-(4-methoxyphenyl)-5H-oxazolo[4,5-b]phenoxazine (**3d**)*



3d

Reaction time: 7 hours. FCC – AcOEt/hexane (1:3); **3d** (71%); yellow solid; m.p.: 242-243 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.79 (s, 3H), 3.88 (s, 3H), 4.83(s, 2H), 6.46 (s, 1H), 6.68 (s, 1H), 6.75-6.78 (m, 3H), 6.88 (d, 2H, *J* = 8.8 Hz), 6.94 (s, 1H), 6.99 (d, 2H, *J* = 10.0 Hz), 7.24 (d, 2H, *J* = 9.0 Hz), 8.06 (d, 2H, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 49.0 54.8, 54.9. 97.7, 101.6, 111.8, 113.8, 113.9, 114.8, 119.2, 120.7, 123.6, 126.7, 127.0, 128.3, 131.5, 133.3, 137.3, 143.6, 144.2, 144.9, 158.3, 158.4, 161.5. Calcd. For $C_{28}H_{22}N_2O_4$: C 74.65, H 4.92, N 6.22; found: C 74.89, H 5.19, N 6.01.

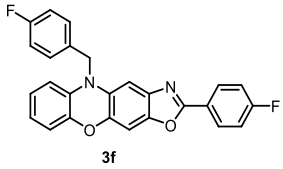
*4-(5-(4-Cyanobenzyl)-5H-oxazolo[4,5-b]phenoxazine-2-yl)-benzonitrile (**3e**)*



3e

Reaction time: 7 hours. FCC – AcOEt/hexane (1:3); **3e** (31%); brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.93 (s, 2H), 6.36 (d, 1H, *J* = 7.6 Hz), 6.58 (s, 1H), 6.78-6.82 (m, 3H), 7.01 (s, 1H), 7.46 (d, 2H, *J* = 8.2 Hz), 7.67 (d, 2H, *J* = 8.2 Hz), 7.76 (d, 2H, *J* = 8.3 Hz), 8.21 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 50.0, 98.8, 102.1, 111.6, 112.1, 114.2, 115.8, 118.2, 118.5, 122.1, 124.4, 126.9, 127.3, 130.9, 132.7, 132.9, 137.9, 141.5, 144.3, 145.3, 146.3, 160.7. Calcd. For $C_{28}H_{16}N_4O_2$: C 76.35, H 3.66, N 12.72; found: C 76.58, H 3.94, N 12.49.

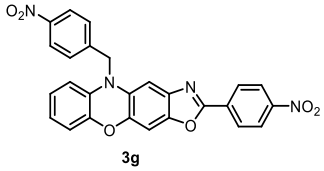
*5-(4-Fluorobenzyl)2-(4-fluorophenyl)-5H-oxazolo[4,5-b]phenoxazine (**3f**)*



3f

Reaction time: 7 hours. FCC – AcOEt/hexane (1:4); **3f** (73%); green solid; m.p.: 205-206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.76 (s, 2H), 6.32 (d, 1H, *J* = 7.7 Hz), 6.56 (s, 1H), 6.65-6.72 (m, 3H), 6.87 (s, 1H), 6.94- (m, 6H), 8.01-8.05 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 49.6, 98.4, 102.1, 112.2, 115.9, 116.0, 116.1, 116.3, 121.5, 123.4, 124.2, 127.7, 129.2, 132.2, 133.3, 137.6, 144.5, 145.7, 161.8, 162.1, 164.5. Calcd. For $C_{26}H_{16}F_2N_2O_2$: C 73.23, H 3.78, N 6.57; found: C 73.44, H 4.02, N 6.37.

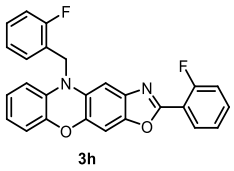
*5-(4-Nitrobenzyl)2-(4-nitrophenyl)-5H-oxazolo[4,5-b]phenoxazine (**3g**)*



3g

Reaction time: 7 hours. FCC – AcOEt/hexane (1:4); **3g** (28%); red solid; m.p.: 229-231 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.99 (s, 2H), 6.38 (d, 1H, *J* = 5.0 Hz), 6.61 (s, 1H), 6.82 (s, 3H), 7.05 (s, 1H), 7.54 (d, 2H, *J* = 7.2 Hz), 8.24-8.29 (m, 4H), 8.33-8.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 49.8, 98.8, 102.1, 112.1, 115.9, 122.2, 124.3, 124.4, 127.1, 127.7, 131.6, 134.7, 136.9, 139.5, 143.3, 146.4, 147.1, 150.2, 150.7, 151.9, 174.8. Calcd. For $C_{26}H_{16}N_4O_6$: C 65.00, H 3.36, N 11.66; found: C 65.13, H 3.58, N 11.49.

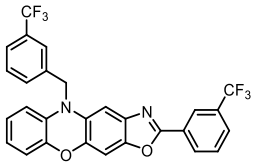
*5-(2-Fluorobenzyl)2-(2-fluorophenyl)-5H-oxazolo[4,5-b]phenoxazine (**3h**)*



3h

Reaction time: 7 hours. FCC – AcOEt/hexane (1:10); **3h** (59%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.93 (s, 2H), 6.42 (d, 1H, *J* =7.9 Hz), 6.71 (s, 1H), 6.72-6.80 (m, 3H), 7.01 (s, 1H), 7.04 (d, 1H, *J* = 7.4 Hz), 7.14-7.31 (m, 5H), 7.44-7.50 (m, 1H), 8.11 (dd, 1H, *J* = 7.5, 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 44.5, 98.4, 102.4, 112.2, 115.5, 115.8, 117.0, 122.2, 124.3, 124.4, 124.5, 127.5, 128.9, 9.8, 132.0, 132.5, 133.2, 133.7, 144.6, 144.9, 145.5, 158.9, 160.4, 160.9. Calcd. For $C_{26}H_{16}F_2N_2O_2$: C 73.23, H 3.78, N 6.57; found: C 73.12, H 3.62, N 6.72.

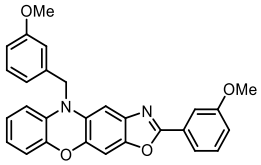
*5-((3-Trifluoromethyl)benzyl)2-((3-trifluoromethyl)phenyl)-5H-oxazolo[4,5-b]phenoxazine (**3i**)*



3i

Reaction time: 7 hours. FCC – DCM; **3i** (79%); yellow solid; m.p.: 209-210 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.92 (s, 2H), 6.39 (d,1H, *J* = 7.7 Hz), 6.61 (s, 1H), 6.78 (s, 3H), 6.99 (s, 1H), 7.45-7.52 (m, 2H), 7.56-7.62 (m, 3H), 7.72 (d, 1H, *J* = 7.9 Hz), 8.28 (d, 1H, *J* = 7.9 Hz), 8.38 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 50.2, 98.6, 102.1, 112.2, 115.6, 121.8, 122.5, 122.9, 123.8, 124.3, 124.4, 125.2, 127.4, 127.9, 129.3, 129.5, 129.6, 129.9, 131.4, 131.8, 132.2, 132.9, 137.0, 137.7, 144.4, 145.0, 145.9, 161.2. Calcd. For $C_{28}H_{16}F_6N_2O_2$: C 63.88, H 3.06, N 5.32; found: C 63.74, H 2.88, N 5.45.

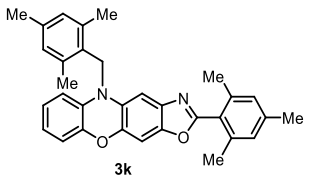
*5-(3-Methoxybenzyl)2-(3-methoxyphenyl)-5H-oxazolo[4,5-b]phenoxazine (**3j**)*



3j

Reaction time: 7 hours. FCC – AcOEt/hexane (1:4); **3j** (60%); green solid; m.p.: 220-222 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H), 3.78 (s, 3H), 4.74 (s, 2H), 6.35 (d, 1H, *J* = 7.8 Hz), 6.59-6.93 (m, 9H), 7.17 (dd, 1H, *J* = 6.9, 7.3 Hz), 7.28 (dd, 1H, *J* = 6.9, 7.3 Hz), 7.54 (s, 1H), 7.61 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 50.3, 55.2, 55.5, 98.3, 102.4, 111.2, 112.3, 112.4, 115.3, 117.9, 118.3, 119.5, 121.3, 124.2, 128.3, 129.9, 130.1, 132.3, 133.5, 137.5, 137.8, 144.6, 145.7, 159.9, 160.2, 162.5. Calcd. For $C_{28}H_{22}N_2O_4$: C 74.65, H 4.92, N 6.22; found: C 74.91, H 5.23, N 6.02.

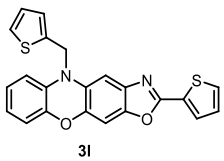
*5-(2,4,6-Trimethylbenzyl)2-(2,4,6-trimethylphenyl)-5H-oxazolo[4,5-b]phenoxazine (**3k**)*



3k

Reaction time: 7 hours. FCC – DCM/PE (1:1); **3k** (63%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.25 (s, 3H), 2.26 (s, 6H), 2.34 (s, 3H), 2.43 (s, 6H), 4.81 (s, 2H), 6.51 (d, 1H, *J* = 8.0 Hz), 6.71-6.75 (m, 1H), 6.79 (d, 2H, *J* = 7.8 Hz), 6.85 (d,3H, *J* = 6.9 Hz), 6.95 (s, 2H), 7.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.3, 20.7, 20.8, 21.3, 46.9, 98.6, 103.3, 113.5, 115.6, 120.2, 121.3, 123.9, 124.9, 128.6, 130.1, 132.9, 134.3, 136.5, 136.7, 137.2, 138.5, 140.1, 145.5, 145.7, 146.2, 162.7. Calcd. For $C_{32}H_{30}N_2O_2$: C 80.98, H 6.37, N 5.90; found: C 81.21, H 6.72, N 5.71.

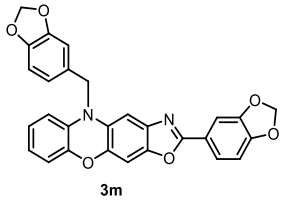
*2-(Thien-2-ul)-5-(thien-2-yl-methyl)-5H-oxazolo[4,5-b]phenoxazine (**3l**)*



3l

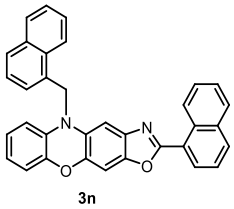
Reaction time: 7 hours. FCC – AcOEt/hexane (1:4); **3l** (81%); yellow solid; m.p.: 226-227 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.00 (s, 2H), 6.62 (d, 1H, *J* = 7.7 Hz), 6.76-6.78 (m, 2H), 6.82-6.86 (m, 2H), 6.94-6.96 (m, 2H), 6.99 (s, 1H), 7.16 (dd, 1H, *J* = 3.9, 4.9 Hz), 7.23 (d, 1H, *J* = 4.9 Hz), 7.49 (d, 1H, *J* = 4.9 Hz), 7.79 (d, 1H, *J* = 3.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 46.4, 93.3, 102.3, 121.6, 124.1, 124.7, 125.2, 127.2, 128.2, 129.1, 129.5, 129.6, 131.9, 132.9, 137.6, 138.9, 144.5, 144.6, 145.4, 158.7. Calcd. For $C_{22}H_{14}N_2O_2S_2$: C 65.65, H 3.51, N 6.96; found: C 65.90, H 3.84, N 6.75.

*2-(Benzo[1,3]dioxol-5-yl)-5-(benzo[1,3]dioxol-5-yl-methyl)-5H-oxazolo[4,5-b]phenoxazine (**3m**)*



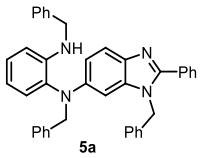
Reaction time: 7 hours. FCC – DCM/PE (9:1); **3m** (72%); yellow solid; m.p.: 264-265 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.96 (s, 2H), 6.05 (s, 2H), 6.19 (s, 2H), 6.68 (d, 1H, *J* = 8.0 Hz), 6.82-6.91 (m, 6H), 6.93-6.96 (m, 2H), 7.15 (d, 1H, *J* = 8.2 Hz), 7.55 (s, 1H), 7.68 (d, 1H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 47.4, 98.5, 100.9, 101.9, 102.1, 106.3, 106.8, 108.5, 108.9, 112.5, 115.1, 119.2, 120.3, 121.2, 124.4, 129.8, 131.5, 132.9, 137.5, 143.1, 143.5, 144.9, 147.6, 148.0, 150.1, 161.7. Calcd. For $C_{28}H_{18}N_2O_6$: C 70.29, H 3.79, N 5.86; found: C 70.49, H 4.06, N 5.72.

*2-(Naphthalen-1-yl)-5-(naphthalen-1-yl-methyl)-5H-oxazolo[4,5-b]phenoxazine (**3n**)*



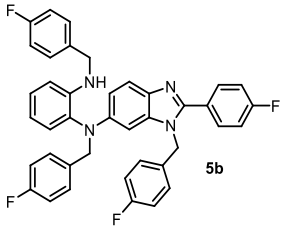
Reaction time: 7 hours. FCC – DCM/PE (9:1); **3n** (66%); yellow solid; m.p.: 240-242 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.27 (s, 2H), 6.30 (dd, 1H, *J* = 3.6, 5.7 Hz), 6.63 (s, 1H), 6.64-6.69 (m, 2H), 6.74 (dd, 1H, *J* = 3.6, 5.7 Hz), 6.98 (s, 1H), 7.26-7.39 (m, 2H), 7.40-7.68 (m, 5H), 7.74 (d, 1H, *J* = 7.8 Hz), 7.80 (d, 1H, *J* = 7.9 Hz), 7.89 (t, 2H, *J* = 8.2 Hz), 7.95 (d, 1H, *J* = 8.1 Hz), 8.24 (d, 1H, *J* = 7.3 Hz), 9.24 (d, 1H, *J* = 9.5 Hz);^{13}C NMR ($CDCl_3$, 101 MHz) δ 48.9, 98.2, 102.7, 112.6, 115.3, 121.3, 122.3, 123.1, 123.5, 124.2, 124.9, 125.6, 126.0, 126.2, 126.3, 126.4, 127.7, 127.9, 128.6, 128.7, 129.0, 129.2, 130.4, 130.8, 131.9, 132.2, 133.5, 133.9, 134.2, 138.2, 144.7, 144.8, 145.2, 162.3. Calcd. For $C_{34}H_{22}N_2O_2$: C 83.25, H 4.52, N 5.71 found: C 83.44, H 4.82, N 5.53.

*N,N'-Dibenzyl-N-(1-benzyl-2-phenyl-1H-benzo[d]imidazole-6-yl)-benzene-1,2-diamine (**5a**)*



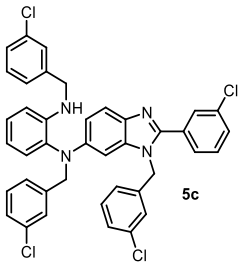
Reaction time: 1.5 hours. FCC – AcOEt/hexane (1:4); **5a** (70%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.09 (d, 2H, *J* = 3.7 Hz), 4.50 (bs, 1H), 4.66 (s, 2H), 5.12 (s, 2H), 6.37 (d, 1H, *J* = 2.1 Hz), 6.52-6.61 (m, 3H), 6.84-6.89 (m, 2H), 7.03-7.05 (m, 4H), 7.08-7.14 (m, 11H), 7.28-7.33 (m, 3H), 7.50-7.56 (m, 3H);^{13}C NMR ($CDCl_3$, 101 MHz) δ 47.7, 48.4, 56.7, 95.3, 111.6, 112.7, 117.6, 120.1, 126.3, 126.9, 127.0, 127.1, 127.3, 127.6, 127.7, 128.4, 128.5, 128.6, 128.7, 129.0, 129.2, 129.5, 130.4, 133.8, 136.3, 136.4, 137.1, 138.9, 139.4, 144.9, 145.5, 152.6. Calcd. For $C_{40}H_{34}N_4$: C 84.18, H 6.00, N 9.82; found: C 84.63, H 5.91, N 9.69.

*N,N'-Di(4-fluorobenzyl)-N-(1-(4-fluorobenzyl)-2(4-fluorophenyl)-1H-benzo[d]imidazole-6-yl)-benzene-1,2-diamine (**5b**)*



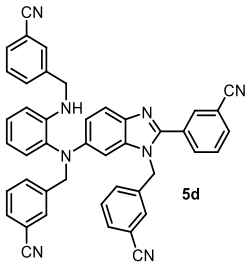
Reaction time: 8 hours. FCC – AcOEt/hexane (1:4); **5b** (68%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.18 (d, 2H, *J* = 2.8 Hz), 4.48 (bs, 1H), 4.74 (s, 2H), 5.19 (s, 2H), 6.36 (d, 1H, *J* = 1.9 Hz), 6.65 (d, 1H, *J* = 8.0 Hz), 6.70-6.73 (m, 2H), 6.90-6.96 (m, 8H), 7.06-7.11 (m, 5H), 7.15-7.21 (m, 3H), 7.60-7.63 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 47.0, 47.7, 55.8, 95.3, 111.7, 112.8, 115.3, 115.9, 116.0, 117.9, 120.2, 127.8, 128.5, 128.6, 128.7, 130.9, 131.7, 133.5, 134.3, 134.8, 136.8, 144.7, 145.4, 151.6, 160.8, 161.9, 162.2, 163.6. Calcd. For $C_{40}H_{30}F_4N_4$: C 74.75, H 4.71, N 8.72; found: C 75.06, H 5.14, N 9.21.

*N,N-'Di(3-chlorobenzyl)-N-(1-(3-chlorobenzyl)-2(3-chlorophenyl)-1H-benzo[d]imidazole-6-yl)-benzene-1,2-diamine (**5c**)*



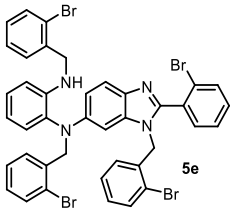
Reaction time: 3 hours. FCC – AcOEt/hexane (3:7); **5c** (57%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (s, 2H), 4.42 (bs, 1H), 4.69 (s, 2H), 5.14 (s, 2H), 6.24 (d, 1H, *J* = 2.0 Hz), 6.53 (d, 1H, *J* = 7.9 Hz), 6.62-6.69 (m, 2H), 6.74 (d, 1H, *J* = 2.0 Hz), 6.92 (s, 1H), 6.96 (s, 1H), 7.00-7.15 (m, 9H), 7.19 (s, 2H), 7.31 (d, 1H, *J* = 7.7 Hz), 7.37 (d, 1H, *J* = 8.3 Hz), 7.42 (d, 1H, *J* = 7.3 Hz), 7.56-7.64 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 47.2, 48.0, 56.5, 94.8, 111.8, 113.1, 118.2, 120.4, 124.2, 125.1, 125.1, 126.3, 127.0, 127.1, 127.1, 127.3, 127.4, 128.0, 128.3, 128.4, 128.9, 129.3, 129.9, 129.9, 130.2, 130.4, 133.1, 134.5, 134.5,135.0, 135.1, 136.7, 136.7, 137.6, 137.7, 140.8, 141.4, 144.3, 145.6, 153.9. Calcd. For $C_{40}H_{30}Cl_4N_4$: C 67.81, H 4.27, N 7.91; found: C 66.89, H 4.91, N 7.69.

*N,N'-Di(3-cianobenzyl)-N-(1-(3-cianobenzyl)-2(3-cianophenyl)-1H-benzo[d]imidazole-6-yl)-benzene-1,2-diamine (**5d**)*



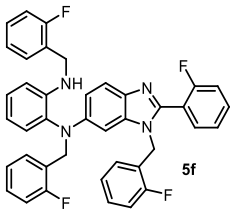
Reaction time: 1.5 hours. FCC – AcOEt/hexane (1:1); **5d** (30%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.33 (s, 2H), 4.56 (bs, 1H), 4.87 (s, 2H), 5.31 (s, 2H), 6.22 (s, 1H), 6.57 (d, 1H, *J* = 8.0 Hz), 6.76 (d, 1H, *J* = 7.5 Hz), 6.80 (d, 1H, J = 7.6 Hz), 7.11 (d, 1H, *J* = 7.7 Hz), 7.14 (d, 1H, *J* = 8.0 Hz), 7.18 (d, 2H, *J* = 3.4 Hz), 7.21 (d, 1H, *J* = 6.7 Hz), 7.38 (d, 4H, *J* = 6.4 Hz), 7.40-7.48 (m, 4H), 7.51-7.63 (m, 2H), 7.71 (d, 1H, *J* = 8.8 Hz), 7.76 (d, 1H, J = 7.5 Hz), 7.85 (d, 1H, J = 6.7 Hz), 7.96 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 46.9, 47.8, 55.9, 94.7, 112.7, 112.7, 113.4, 117.8, 118.1, 118.6, 118.8, 128.4, 128.5, 129.5, 129.5, 129.5, 129.9, 130.1, 130.2, 130.4, 130.5, 131.0, 131.1, 131.3, 131.5, 131.9, 132.5, 133.0, 133.2, 136.4, 136.8, 137.2, 140.0, 140.9, 143.9, 145.6, 150.1. Calcd. For $C_{44}H_{30}N_8$: C 78.79, H 4.51, N 16.71; found: C 78.23, H 4.91, N 16.04.

*N,N'-Di(2-bromobenzyl)-N-(1-(2-bromobenzyl)-2(2-bromophenyl)-1H-benzo[d]imidazole-6-yl)-benzene-1,2-diamine (**5e**)*



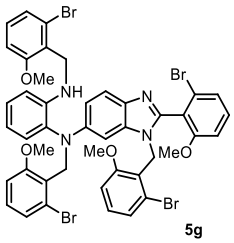
Reaction time: 1.5 hours. FCC – AcOEt/hexane (3:7); **5e** (88%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.16 (d, 2H, *J* = 5.6 Hz),4.62 (bs, 1H), 4.70 (s, 2H), 5.05 (s, 2H), 6.20-6.35 (m, 1H), 6.43 (d, 1H, *J* = 8.0 Hz), 6.49-6.66 (m, 3H), 6.83-6.90 (m, 2H), 6.91-6.98 (m, 5H), 7.01 (d, 1H, *J* = 7.2 Hz), 7.05 (d, 1H, *J* = 7.1 Hz), 7.14-7.28 (m, 4H), 7.31 (d, 1H, *J* = 7.6 Hz), 7.32-7.45 (m, 2H), 7.51-7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 47.8, 48.2, 56.9, 95.4, 111.8, 112.6, 117.9, 120.6, 122.7, 123.1, 123.2, 124.2, 127.4, 127.5, 127.6, 127.7, 127.9, 128.4, 128.5, 128.6, 128.7, 129.1, 129.2, 131.4, 132.5, 132.7, 132.8, 132.9, 133.0, 133.2, 134.7, 135.8, 136.4, 136.9, 138.0, 144.6, 145.3, 151.9. Calcd. For $C_{40}H_{30}Br_4N_4$: C 54.21, H 3.41, N 6.32; found: C 54.63, H 3.91, N 6.59.

*N,N'-Di(2-fluorobenzyl)-N-(1-(2-fluorobenzyl)-2(2-fluorophenyl)-1H-benzo[d]imidazole-6-yl)-benzene-1,2-diamine (**5f**)*



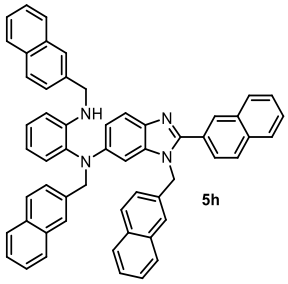
Reaction time: 1.5 hours. FCC – AcOEt/hexane (2:3); **5f** (60%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.32 (s, 2H), 4.65 (bs, 1H), 4.86 (s, 2H), 5.21 (s, 2H), 6.51 (d, 1H, *J* = 1.9 Hz), 6.64-6.81 (m, 4H), 6.86-6.95 (m, 3H), 6.95-7.05 (m, 3H), 7.08 (d, 1H, *J* = 7.5 Hz), 7.13 (d, 1H, *J* = 7.6 Hz), 7.15-7.25 (m, 5H), 7.26-7.36 (m, 2H), 7.44-7.53 (m, 1H), 7.60-7.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 41.0, 42.1, 50.0, 95.1, 111.6, 112.5, 115.1, 115.3, 115.4, 116.0, 117.8, 118.7, 120.3, 122.8, 124.0, 124.1, 124.3, 124.7, 125.4, 126.2, 127.8, 128.6, 128.7, 128.8, 128.9, 129.4, 129.5, 131.9, 132.4, 133.2, 136.3, 136.7, 144.8, 145.4, 147.7, 160.1, 160.2, 160.6, 160.7. Calcd. For $C_{40}H_{30}F_4N_4$: C 74.75, H 4.71, N 8.72; found: C 74.11, H 5.03, N 8.96.

*N,N'-Di(2-bromo-5-methoxybenzyl)-N-(1-(2-bromo-5-methoxybenzyl)-2(2-bromo-5-methoxyphenyl)-1H-benzo[d]imidazole-6-yl)-benzene-1,2-diamine (**5g**)*



Reaction time: 1.5 hours. FCC – AcOEt/hexane (2:3); **5g** (70%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.14 (s, 3H), 3.43 (s, 3H), 3.54 (s, 3H), 3.62 (s, 3H), 4.17 (d, 2H, *J* = 3.7 Hz), 4.58 (bs, 1H), 4.70 (s, 2H), 5.05 (s, 2H), 6.12 (d, 1H, *J* = 2.8 Hz), 6.33 (d, 1H, *J* = 1.7 Hz), 6.46 (dd, 1H *J* = 2.9, 8.8 Hz), 6.50 (d, 2H, *J* = 7.2 Hz), 6.54 (dd, 1H, *J* = 3.0, 8.8 Hz), 6.56-6.66 (m, 2H), 6.69 (d, 1H, *J* = 2.8 Hz), 6.75-6.84 (m, 2H), 6.88 (d, 1H, *J* = 2.9 Hz), 7.02 (t, 1H, *J* = 7.7 Hz),7.08 (d, 1H, *J* = 7.3 Hz), 7.14 (d, 1H, *J* = 8.8 Hz), 7.23-7.30 (m, 2H), 7.45 (d, 1H, *J* = 8.9 Hz), 7.50 (d, 1H, *J* = 8.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 48.0, 48.2, 55.2, 55.3, 55.4, 55.6, 57.1, 95.3 ,111.9, 112.4, 112.9, 113.0, 113.1, 113.2, 114.1, 114.2, 114.3, 114.3, 115.1, 117.4, 117.9, 118.0, 120.5, 127.9, 128.5, 132.7, 133.1, 133.2, 133.3, 133.4, 133.7, 135.7, 135.8, 136.3, 137.9, 139.0, 144.5, 145.0, 150.8, 158.8, 158.9, 159.0, 159.2. Calcd. For $C_{44}H_{38}Br_4N_4O_4$: C 52.51, H 3.81, N 5.57; found: C 52.73, H 4.22, N 5.79.

*N,N'-Di(naphthalen-2-yl-methyl)-N-(1-(naphthalen-2-yl-methyl)-2(naphthalen-2-yl)-1H-benzo[d]imidazole-6-yl)-benzene-1,2-diamine (**5h**)*



Reaction time: 1.5 hours. FCC – AcOEt/hexane (2:3); **5h** (74%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.22 (d, 2H, *J* = 2.2 Hz), 4.67 (bs, 1H), 4.96 (s, 2H), 5.42 (s, 2H), 6.60 (d, 1H, *J* = 2.0 Hz), 6.63 (d, 1H, *J* = 8.1 Hz), 6.66-6.73 (m, 1H), 6.86 (dd, 1H, *J* = 2.2, 8.9 Hz), 7.05-7.12 (m, 2H), 7.15 (d, 1H, *J* = 8.4 Hz), 7.20 (d, 1H, *J* = 7.6 Hz), 7.31-7.39 (m, 2H), 7.40-7.46 (m, 6H), 7.48 (d, 1H, *J* = 6.7 Hz), 7.50-7.59 (m, 7H), 7.63 (d, 1H, *J* = 8.4 Hz), 7.70 (d, 1H, *J* = 4.8 Hz), 7.72-7.81 (m, 5H), 7.82-7.89 (m, 2H), 7.91 (d, 1H, *J* = 8.7 Hz), 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 47.7, 48.8, 57.0, 95.4, 111.7, 112.8, 117.7, 120.3, 124.1, 125.1, 125.3, 125.4, 125.5, 125.6, 125.7, 125.9, 126.0, 126.1, 126.3, 126.4, 126.6, 127.0, 127.6, 127.6, 127.6, 127.7, 127.8, 127.9, 128.2, 128.2, 128.4, 128.5, 128.6, 128.8, 132.6, 132.6, 132.8, 133.0, 133.3, 133.4, 133.6, 133.7, 134.0, 136.5, 136.8, 137.5, 144.8, 145.5, 152.8. Calcd. For $C_{56}H_{42}N_4$: C 87.24, H 5.49, N 7.27; found: C 87.63, H 5.91, N 6.69.

*Photophysical data for products **3***

Table E.P.1. Photophysical data for products 3 recorded in dichloromethane solution ($5 \cdot 10^{-5}$ M)

Compounds	λ_{ab} (nm)	λ_{exc} (nm)	λ_{em} (nm)	Stokes shift(s) (eV)	τ (ns)
3a	384	386	507	0.77	5.3
3b	382	385	495	0.72	5.1
3c	391	397	519	0.73	5.0
3d	379	380	488	0.72	4.5
3e	414	420	584	0.83	3.9
3f	380	380	498	0.77	5.4
3h	382	385	510	0.79	5.6
3i	393	394	526	0.79	5.6
3j	385	387	508	0.76	5.4
3k	351	351	474	0.92	4.3
3l	389	391	524	0.81	5.7
3m	381	381	495	0.75	5.0
3n	398	397	558	0.90	5.8

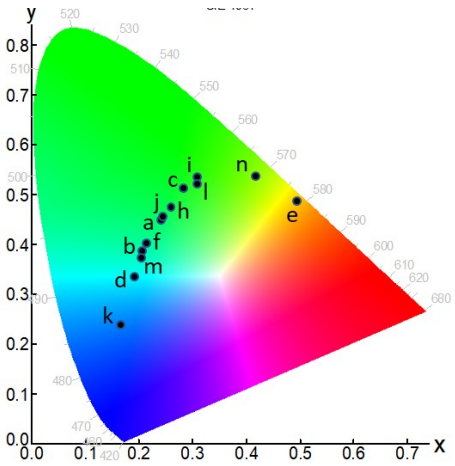


Figure E.P.1. CIE 1931 chromaticity plot for compounds 3 in dichloromethane solution ($5 \cdot 10^{-5}$ M)

CHAPTER 2

COPPER(II) TRIFLATE IN FRIEDEL-CRAFTS ARYLATION AND HYDROAMINATION SEQUENCES

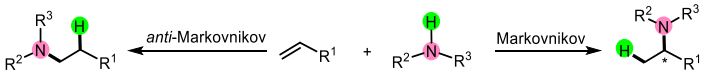
2.1 INTRODUCTION

2.1.1 Friedel-Crafts for C-H functionalization of arenes

The Friedel-Craft (FC) reaction plays an important role in the selective functionalization of aromatic C-H bonds. The interest of Charles Friedel and James Mason Craft in the $AlCl_3$ catalytic activity allowed to develop an efficient and reproducible method for the formation of C-C bonds between aliphatic and aromatic compounds by exploiting the formation of carbocation intermediates.[19]
Reactions involving carbocations have been in use since long before the discovery of carbocations themselves, first identified by Norris in 1901 and still integral part of industrial and academic organic chemistry. This great discovery revolutionized the history of organic chemistry and it contributed to the rise of several reactions based on rearrangements and eliminations.[20]
Still nowadays, innovative methodologies for the construction of C-C bonds to develop new compounds or procedures involving more than one bond formation or asymmetric processes continue to emerge.[21]

2.1.2 The role of copper in hydroamination reactions of alkenes

Hydroamination reactions are extremely attractive procedures to obtain nitrogen-containing compounds. Uncatalyzed reactions are prohibited by large activation energy barrier especially with non-activated alkenes. Moreover, the presence of a catalyst allows to control the chemo-, regio- and stereoselectivity of the procedure. Among them, one of the most intriguing aspects – related to alkene functionalization - is the regiochemical outcome: *anti*-Markovnikov if the amino group is installed on the less substituted carbon or Markovinikov if it is on the more substituted one. This last outcome of amination opens the way to the possible introduction of a stereocenter (Scheme 11).

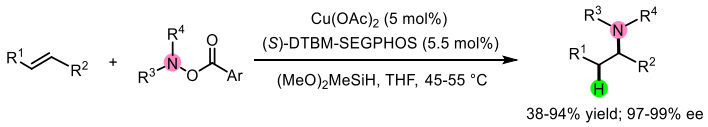


Scheme 11. Regiochemistry in hyroamination procedure

Earth-abundant metals – such as iron and copper – have less catalytic properties compared to noble ones like Pd, Au, Pt, Ru and Ag, but they represent the future due to the possible environmental friendly approach. In this field, copper was broadly used to promote or catalyze the C-N bond formation through intermolecular functionalization.[22] One of the first copper-catalyzed hydroamination reactions carried out in the presence of a phosphine ligand is an intramolecular procedure which leads to five- and six-termed nitrogen rings.[23] This combination has been widely exploited also by Buchwald group in intermolecular hydroamination

[19] a) G. A. Olah, in Friedel–Crafts Chemistry, Wiley, New York, **1973**.; b) G. A. Olah, in 100 Years of Carbocations and Their Significance in Chemistry, ed. G. A. Olah and G. K. Surya Prakash, John Wiley and Sons, **2004**, 7-41.
[20] R. R,Naredla, D. A. Klumpp, Contemporary Carbocation Chemistry: Applications in Organic Synthesis, *Chem. Rev.* **2013**, *113*, 6905-6948.
[21] T. B. Poulsen, K. A. Jørgensen, Catalystic Asymmetric Friedel-Crafts Alkylation Reactions-Copper Showed the Way, *Chem. Rev.* **2008**, *108*, 2903-2915.
[22] a) R. Y. Liu, S. L. Buchwald, CuH-Catalyzed Olefin Functionalization: from Hydroamination to Carbonyl Addition, *Acc. Chem. Res.* **2020**, *53*, 1229-1243; b) S. Bezzenine-Lafollée, R. Gil, D. Prim, J. Hannedouche, First-Row Late Transition Metals for Catalytic Alkene Hydrofunctionalisation: Recent Advances in C-N, C-O and C-P Bond Formation, *Molecules* **2017**, *22*, 1901.
[23] H. Ohmiya, T. Moriya, M. Sawamura, Cu(I)-Catalyzed Intramolecular Hydroamination of Unactivated Alkenes Bearing a Primary or Secondary Amino Group in Alcoholic Solvents, *Org. Lett.* **2009**, *11*, 2145-2147.

processes.[24] A significant example is the regio and enantioselective reaction performed on internal unactivated olefins with $Cu(OAc)_2$ and (*S*)-DTBM-SEGPHOS (Scheme 12).[25]

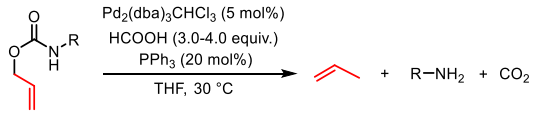


Scheme 12. Hydroamination of unactivated alkenes with a diphosphinic ligand

This type of procedure, especially in the presence of copper(II) catalysts, remains a challenge to synthesize products containing an amino group with regio- and stereoselective outcomes.

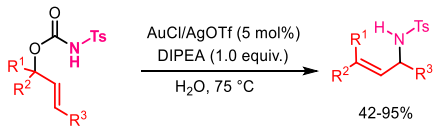
2.2 COPPER(II) TRIFLATE-PROMOTED CASCADE FRIEDEL-CRAFT ARYLATION OF *O*-ALLYL CARBAMATES

The development of new synthetic methodologies that could lead to variously functionalized products - in compliance with the atom economy and the optimization of working times - has always been one of the primary objectives in organic synthesis. This justifies the increase in investigations on the C-H activation - intrinsically non-activated groups - and on the use of easily accessible substrates. Among the latter, the *O*-allyl carbamates deserve to be included because they play an important role as intermediates in organic chemistry and in peptide synthesis. Indeed, the presence of an allyl group linked to the oxygen atom of the carbamate unit makes these compounds susceptible to various reactions, among which cyclizations or rearrangement reactions stand out. *O*-Allyl carbamates have been used in various conditions, although the most interesting behaviours have been observed with the use of transition metals.
One of the first examples of the reactivity of this substrate dates to 1986, when Tsuji proposed a Pd-catalyzed process for the deprotection of *O*-allyl carbamates in the presence of formic acid as a source of hydride (Scheme 13).[26]



Scheme 13. Palladium deallylation of *O*-allyl carbamates

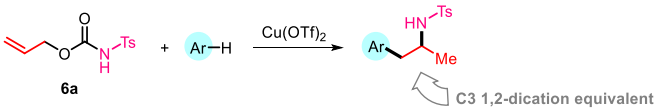
Subsequently, the decarboxylation of *N*-protected *O*-allyl carbamates has been widely studied in different conditions. Among all, the study carried out in 2010 by Yang and coworkers on the Au(I) triflate-catalyzed aza-Claisen rearrangement of *N*-tosyl carbamates is worth of noting (Scheme 14).[27] This gold catalyst is behave also as a mild Lewis acid which can coordinate and activate unsaturated carbon-carbon bonds allowing intramolecular nucleophilic attack.



Scheme 14. AgOTf-Catalyzed rearrangement of *N*-tosyl carbamates

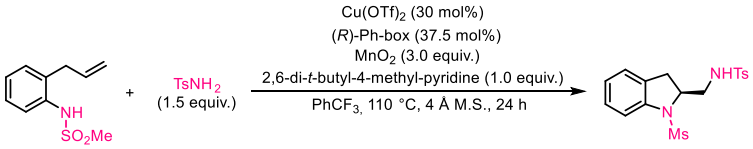
[24] a) N. Niljianskul, S. Zhu, S. L. Buchwald, Enantioselective Synthesis of a-Aminosilanes by Copper-Catalyzed Hudroamination of Vinylsilanes, Angew. Chem. Int. Ed. 2015, 54, 1638-1641; b) J. S. Bandar, M. T. Pirnot, S. L. Buchwald, Mechanistic Studies Lead to Dramatically Improved Reaction Conditions for the Cu-Catalyzed Asymmetric Hydroamination of Olefins, *J. Am. Chem. Soc.* **2015**, *137*, 14812-14818.
[25] Y. Yang, S.-L. Shi, D. Niu, P. Liu, S. L. Buchwald, Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines, *Science* **2015**, *349*, 62-66.
[26] J. Tsuji, New general synthetic methods involving π-allylpalladium complexes as intermediates and neutral reaction conditions, *Tetrahedron* **1986**, *42*, 4361-4401.
[27] D. Xing, D. Yang, Gold(I)-Catalyzed Highly Regio- and Stereoselective Decarboxylative Amination of Allylic *N*-Tosylcarbamates via Base-Induced Aza-Claisen Rearrangement in Water, *Org. Lett.* **2010**, *12*, 1068-1071.

In this context and given the interest of our research group on the reactivity of *N*-substituted carbamates,[28] we started the study reacting *N*-tosyl *O*-allyl carbamate **6a** - which behave as C3 1,2-dication equivalents with an aromatic reaction partner in the presence of $Cu(OTf)_2$ (Scheme 15).



Scheme 15. *O*-Allyl carbamate as C3 1,2-dication equivalent with $Cu(OTf)_2$

Copper(II) triflate is an additive used both for its ability as catalyst - especially in hydroamination and carboamination processes - but also exploited as Lewis acid in various synthetic procedures.[29] Concerning the first point, Chemler and co-workers reported different intramolecular procedures to access variously *N*-containing rings also with the insertion of an amine group. A significant example of an asymmetric reaction carried out with $Cu(OTf)_2$, (*R*,*R*)-Ph-box, MnO_2, which was the first catalytic enantioselective procedure in the presence of this kind of catalyst, is reported in Scheme 16.[30]



64% yield; 71% *ee*

Scheme 16. $Cu(OTf)_2$ enantioselective diamination procedure

Like all metal triflate, also $Cu(OTf)_2$ plays a crucial role as Lewis acid in different procedures, thus it was proven to be an alternative more safer source of triflic acid.[31]
The *in situ* formation of TfOH is due to the reduction of $Cu(OTf)_2$ with a compound which could behave as hydrogen donor (Scheme 17). These milder conditions avoid the use of this acid itself which was qualified as superacid (pKa – 14.7) and dangerous for humans (its inhalation is toxic, and it promotes tissue destructions).

Scheme 17. *In situ* formation of TfOH from $Cu(OTf)_2$

Our study began reacting *O*-allyl *N*-tosyl carbamate **6a** in mesitylene in the presence of a stoichiometric amount of $Cu(OTf)_2$ (Table 2, entry 1).[32] Under these conditions, the reaction provided a mixture containing 1-mesityl-2-tosylaminopropane **7** and tosylamide arising from the degradation of carbamate. Since the arylation/hydroamination product was isolated in moderate yield (36%), a wide optimization study, of which only the most significant conditions are reported here, was undertaken. First of all, the reaction does not proceed with a catalytic amount of copper(II) triflate, while an excess of it increased the yield of **7** (entries 2,3). The use of other metal triflate, such as AgOTf, $Yb(OTf)_3$ and $Zn(OTf)_2$, gave unsatisfactory results (entries 4-6). Conversely, the TMSOTf disclosed a new reactivity involving the double arylation of the allyl moiety (entry 7). In fact, after 4 hours under reflux, the crude mixture contained 1,2-diarylpropane **8** as the only product of functionalization of the allyl residue, isolated 89% yield.

[28] a) S. Giofrè, R. Sala, E. M. Beccalli, L. Lo Presti, G. Broggini, Iodoamination of Alkenyl Sulfonamides by Potassium Iodide and Hydrogen Peroxide in Aqueous Medium, *Helv. Chim. Acta* **2019**, *102*, e1900088; b) S. Giofrè, C. Loro, L. Molteni, C. Castellano, A. Contini, D. Nava, G. Broggini, E. M. Beccalli, Copper(II)-Catalyzed Aminohalogenation of Alkynyl Carbamates, *Eur. J. Org. Chem.* **2021**, 1750-1757.

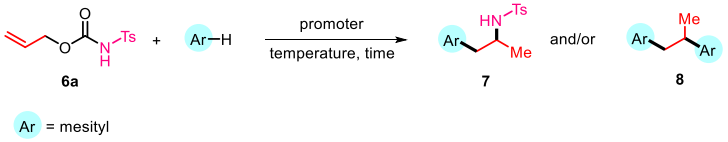
[29] S. R. Chemler, Evolution of copper(II) as new alkene amination promoter and catalyst, *J. Organomet. Chem.* **2011**, *696*, 150-158.

[30] F. C. Sequeira, B. W. Turnpenny, S. R. Chemler, Copper-Promoted and Copper-Catalyzed Intermolecular Alkene Diamination, *Angew. Chem. Int. Ed.* **2010**, *122*, 6509-6512.

[31] a) W. Fang, M. Presset, A Guérinot, C. Bour, S. Bezzenine-Lefollée, V. Gandon, Silver-Free Two Component Approach in Gold Catalysis: Activation of [LAuCl] Complexes with Derivatives of Copper, Zinc, Indium, Bismuth, and Other Lewis Acids, *Chem. Eur. J.* **2014**, *20*, 5439-5446; b) W. Rao, P. Kothandaraman, C: B. Koh, P. W. H. Chan, Copper(II) Triflate-Catalyzed Intramolecular Hydroamination of Homoallylic Amino Alcohols as an Expedient Route to trans-2,5-Dihydro-1*H*-pyrroles and 1,2-Dihydroquinolines, *Adv. Synth. Catal.* **2010**, *352*, 2521-2530.

[32] C. Loro, J. Oble, F. Foschi, M. Papis, E. M. Beccalli, S. Giofrè, G. Poli, G. Broggini, Acid-mediated decarboxylative C-H coupling between arenes and *O*-allyl carbamates, *Org. Chem. Front.* **2022**, *9*, 1711-1718.

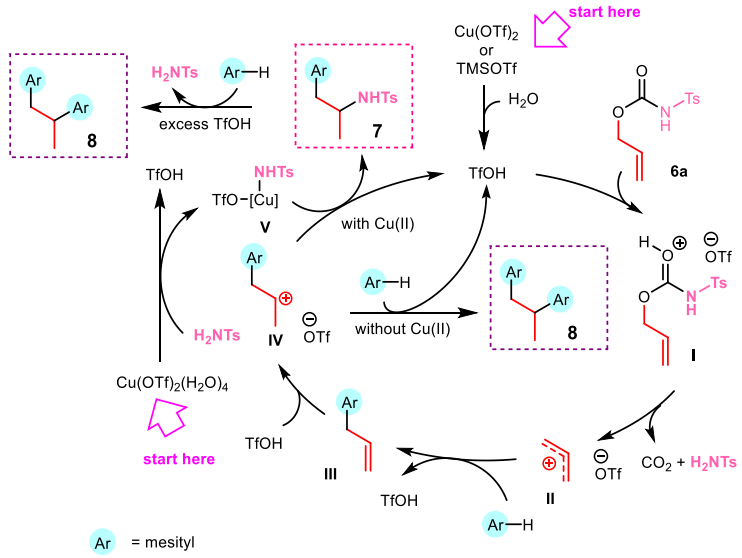
Table 2. Optimization of arylation/hydroamination of *O*-allyl *N*-tosyl carbamate 6a



Entry	Promoter (equiv.)	Temperature (°C)	Time (h)	Product(s)
1	$Cu(OTf)_2$ (1.0)	100	6.0	**7** (36%) + $TsNH_2$ (43%)
2	$Cu(OTf)_2$ (0.1)	100	24	**S.M.**
3	$Cu(OTf)_2$ (4.0)	130	3 0	**7** (85%) + $TsNH_2$ (11%)
4	$Zn(OTf)_2$ (4.0)	130	3.0	**S.M.**
5	$Yb(OTf)_3$ (1.0)	100	1.0	**S.M.**
6	AgOTf (4.0)	130	1.5	**7** (25%) + $TsNH_2$ (31%)
7	TMSOTf (4.0)	130	3.0	**8** (89%)

For these double coupling reactions, we hypothesized the following mechanism shown in Scheme 18. First, we assume that triflic acid is formed *in situ* from $Cu(OTf)_2$ or TMSOTf, leading to the protonation at the carbonyl oxygen atom of the carbamate function which generates the activated *O*-allyl carbamate **I**.[33] This intermediate undergoes a decarboxylative/deamidative Friedel-Crafts alkylation by attack of the aromatic partner on the allyl carbenium ion **II** to give intermediate **III**. Subsequent Markovnikov protonation of **III** generates the carbocation intermediate **IV**. At this stage, the nature of the promoter directs the reaction path. In the presence of $Cu(OTf)_2$, the extruded *N*-tosylamide can coordinate the copper, generating the amido copper-complex **V**, which selectively attacks the intermediate **IV**, providing the 1-aryl-2-tosylaminopropane **7**.[34] Otherwise, in the presence of TMSOTf, carbenium ion **IV** undergoes a second Friedel-Crafts alkylation, affording the 1,2-diarylpropane **8**. Moreover, in the presence of excess trifilc acid hydroaminated product **7** suffers a deamidative substitution by mesitylene via an incipient or discrete carbenum ion, to afford the diarylated product **8**.

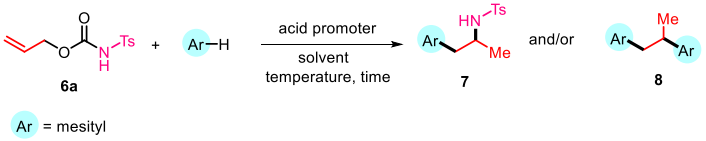
[33] C. Michon, F. Medina, F. Capet, P. Roussel, F. Agbossou-Niedercorn, Inter- and intramolecular hydroamination of unactivated alkenes catalysed by combination of copper and silver salts: the unveiling of Brønsted acid catalyst, *Adv. Synth. Catal.* **2010**, *352*, 3293-3305.
[34] J. G. Taylor, N. Whittall, K. K. Hii, Copper-catalysed intremolecular hydroamination of alkenes, *Org. Lett.* **2006**, *8*, 3561-3564.



Scheme 18. Possible reaction mechanisms

Having hypothesized the role of triflic acid as the effective promoter of the reaction,[35] we performed some experiments directly using triflic acid in various solvents and different catalytic amount. Working in mesitylene with triflic acid (5 mol%), the process was completely selective for the arylation/hydroamination pathway, although obtained in lower yield than the reaction promoted by $Cu(OTf)_2$ (Table 3, entry 1). The reaction carried out in different solvents didn't provide fruitful results. While the use of DMF at 130 °C led solely to a mixture of degradation products, the use of DCE as a solvent at 80 °C showed a lack of selectivity towards the two different difunctionalization processes (entries 2,3). Finally, the quantity of triflic acid in chlorobenzene was decisive for the course of the process: working with 5 mol% of TfOH it is possible to access 1-mesityl-2-tosylaminopropane **7** in 58% yield, while increasing the quantity of the catalyst the process loss selectivity (entries 4,5). Other acidic promoters were tested, but *p*-toluenesulfonic acid and H_2SO_4 behaved analogously to $Cu(OTf)_2$ without improvement of the yield (entries 6,7).

Table 3. Study of the difunctionalization of *O*-allyl *N*-tosyl carbamate 1a with different acids

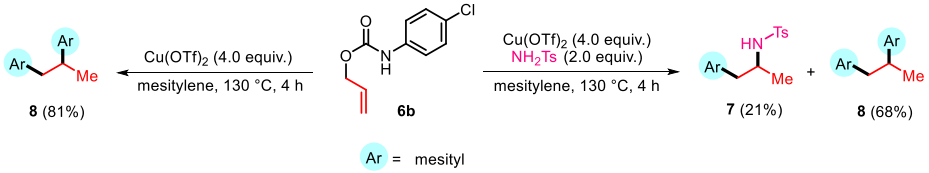


Entry	Acid promoter (equiv.)	Solvent [0.25M]	Temperature (°C)	Time (h)	Product(s)
1	TfOH (0.05)	-	130	4.0	**7** (69%) + $TsNH_2$ (26%)
2	TfOH (0.05)	DMF	130	4.0	**degr. products**
3	TfOH (0.05)	DCE	80	4 0	**7** (23%) + **8** (11%)
4	TfOH (0.05)	Chlorobenzene	130	4.0	**7** (58%) + $TsNH_2$ (41%)
5	TfOH (0.2)	Chlorobenzene	130	4.0	**7** (18%) + **8** (34%)
6	PTSA (4.0)	-	130	1.5	**7** (59%) + $TsNH_2$ (18%)

[35] a) M. Tschan, C. M. Thomas, H. Strub, J.-F. Carpentier, Copper(II) triflate as source of triflic acid: effective, green catalyst of hydroalkoxylation reactions, *Adv. Synth. Catal.* **2009**, *351*, 2496-2505; b) T. T. Dang, F. Boeck, L. Hinterman, Hidden Brønsted acid catalysis pathways of accidental or deliberate generation of triflic acid from metal triflates, *J. Org. Chem.* **2011**, *76*, 9353-9361.

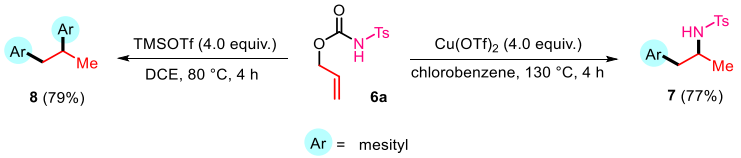
7	H_2SO_4 (1.0)	-	130	4.0	**7** (25%) + $TsNH_2$ (14%)

Corollary experiments using the *O*-allyl *N*-4-chlorophenyl carbamate **6b** were carried out next (Scheme 19). The diarylated product **8** was obtained in the presence of $Cu(OTf)_2$ as the promoter without formation of the corresponding aniline derivative. However, carrying out the same reaction with exogenous tosylamine (2.0 equiv.) afforded a mixture of the 1-aryl-2-aminoproapane **7** and the diarylated derivative **8**. These results corroborate the above proposed mechanism which show that H_2NTs is a suitable nitrogen nucleophile to trap the carbenium ion **IV** when copper(II) triflate is used as the promoter.



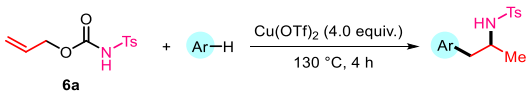
Scheme 19. Corollary experiments with *O*-allyl *N*-4-chlorophenyl carbamate 6b

To allow the use of various types of arenes, including the solid ones, these difunctionalization reactions have also been studied in different solvents (Scheme 20). Concerning the $Cu(OTf)_2$ promoted arylation/hydroamination sequence, the best result was obtained with chlorobenzene as the solvent at 130 °C. Conversely, the diarylation process – totally selective employing TMSOTf as additive – was proven to be efficient working in DCE at 80 °C. Although these two protocols do not represent an improvement in terms of yields, they demonstrate that it is possible to work in the presence of a solvent other than the aromatic reaction partner itself.

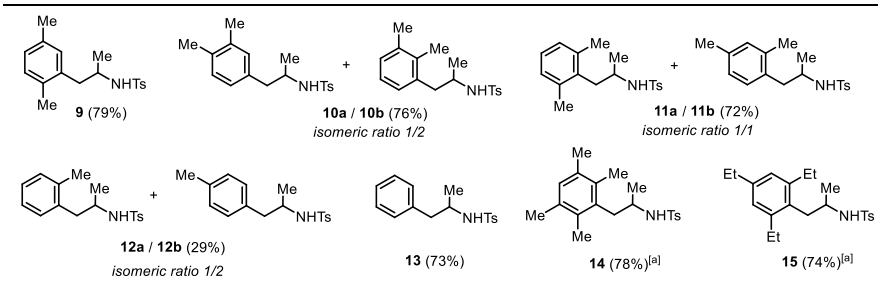


Scheme 20. Different solvents for the double difunctionalisation of *O*-allyl *N*-4-tosyl carbamate 6a

Among the range of branched amines, *N*-substituted phenethylamine derivatives have been widely studied in recent years for their value in organic, bioorganic, and medicinal chemistry.[36] For this reason, we test the decarboxylative arylation/hydroamination sequence with other aromatic hydrocarbons.
We started reacting *O*-allyl carbamate **6a** in *p*-xylene with 4.0 equivalents of $Cu(OTf)_2$ at 130 °C, 4.0 h which afforded the corresponding arylated 2-tosylaminopropane **9** as the sole product in good yield (Scheme 21). When the reaction was carried out in *o*-xylene, *m*-xylene, or toluene this gave the corresponding arylation/hydroamination products as mixtures of two regioisomers **10a**/**10b**, **11a**/**11b**, and **12a**/**12b**. Also, the less electron-rich benzene provided the expected cascade products **13** in acceptable yield. Finally, the arylated/hydroamination compounds **14**-**15** were obtained in good yields from heavily alkylated arenes like durene and 1,3,5-triethylbenzene.



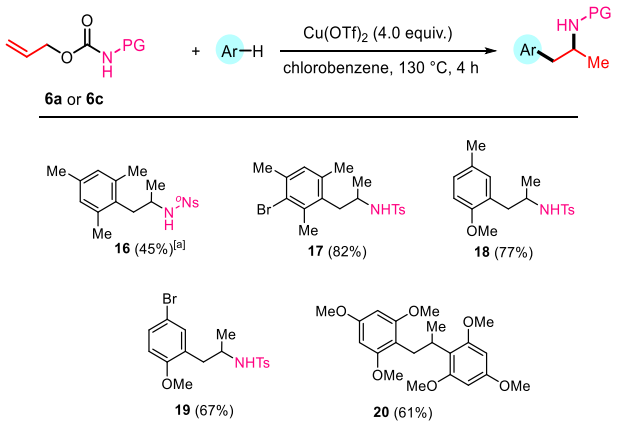
[36] a) T. Hasegawa, H. Yamamoto, Development of new chiral auxiliary derived from (*S*)-(-)-phenylethylamine for a synthesis of enantiopure (*R*)-2-propyloctanoic acid, *Synthesis* **2003**, *8*, 1181-1186; b) M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, Asymmetric synthesis of isoquinoline alkaloids: 2004-2015, *Chem. Rev.* **2016**, *116*, 12369-12465.



[a] With chlorobenzene as solvent (0.25 M) and 5.0 equiv. of arene

Scheme 21. Arylation/hydroamination of *O*-allyl *N*-tosyl carbamate 6a with different hydrocarbons

The scope of the reaction was evaluated next, keeping $Cu(OTf)_2$ as promoter changing the carbamate and the nature of the arene. For this reason, *O*-allyl *N*-2-nosylcarbamate **6c** was treated with mesitylene (Scheme 22), whereas the reaction carried out on *N*-tosyl carbamate **6a** with mesityl bromide, 4-methylanisole, 4-bromoanisole in chlorobenzene as solvent gave the corresponding hydroaminated products **17**-**19** in fair to good yields. If the hydroamination process is ineffective with deactivated arenes, only the diarylation products were obtained with strongly activated arenes. Thus, using 1,3,5-trimethoxybenzene the diarylated product **20** was solely formed.

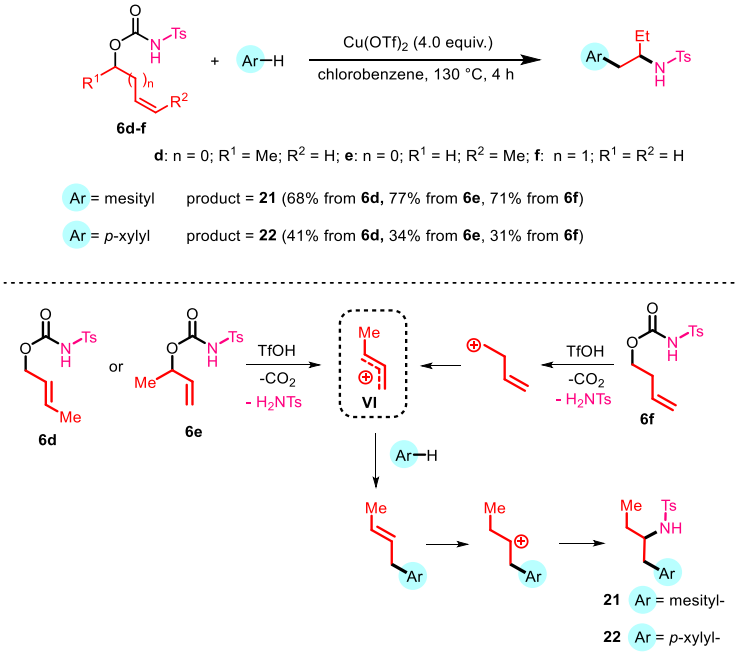


[a] The reaction was carried out in mesitylene as solvent (0.25M)

Scheme 22. Variation in arylation/hydroamination of *O*-allyl *N*-substituted carbamates

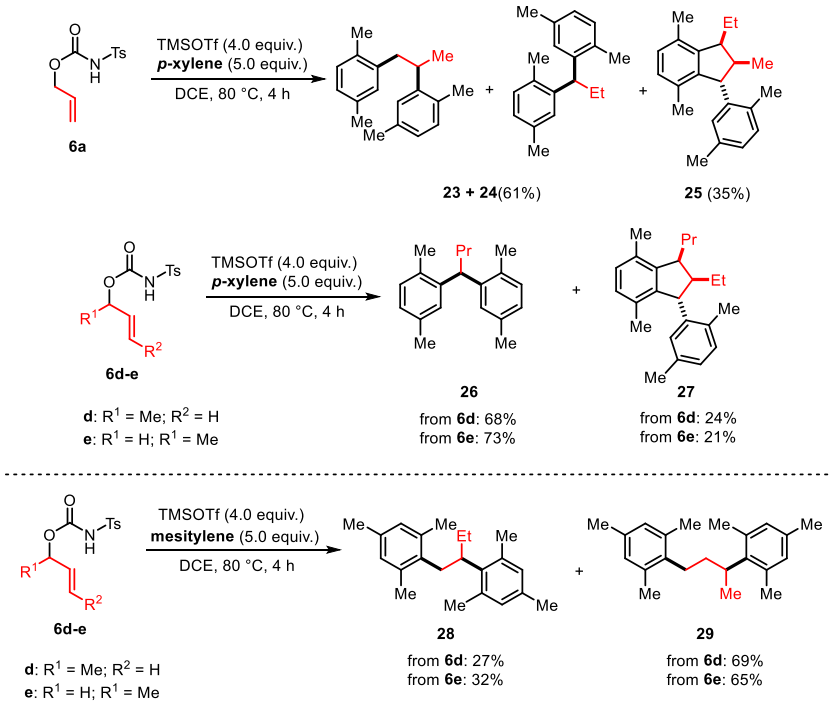
To obtain more information on the generality of allyl structures capable of undergoing this cascade process, *O*-alkenyl *N*-tosyl carbamates **6d**-**f** were treated with $Cu(OTf)_2$ in mesitylene or *p*-xylene (Scheme 23). The expected products were isolated in all cases, although formation and isolation of the reaction products in *p*-xylene was more difficult.

The analogous course of the reactions on the three different substrates indicates a convergence in the formation of carbocation **VI** which, after the FC reaction, undergoes regioselectively the hydroamination promoted by copper.



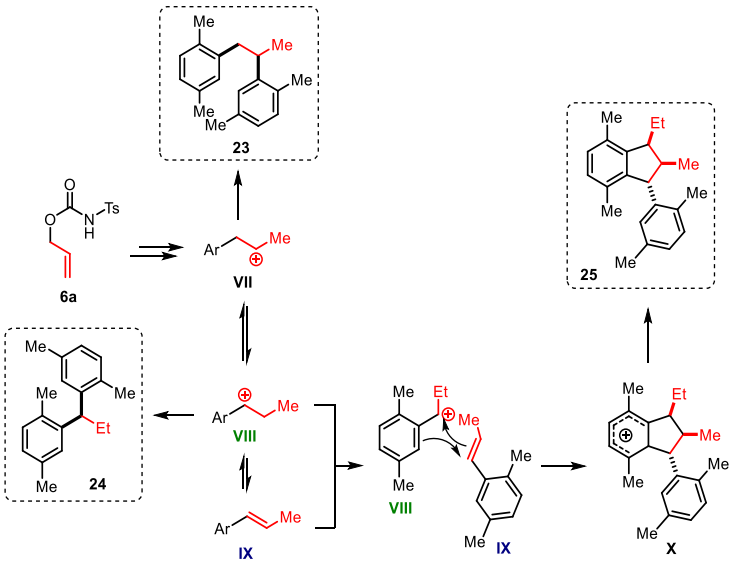
Scheme 23. Arylation/hydroamination of *N*-tosyl carbamate with substituents on the allylic chain

At this point we have dedicated to the evaluation of the generality of the diarylation process which took place with success starting from carbamate **1a** with mesitylene in the presence of TMSOTf. The reactions in this case were carried out in DCE as a solvent with 5 equivalents of arene since in these conditions it is possible to work at 80 instead of 130 °C with similar results. If the reaction in mesitylene provided only one product, operating in *p*-xylene a mixture difficultly separable containing the 1,2-diarylated product **23**, the 1,1-diarylated product **24**, and indane **25** was obtained (Scheme 24). The *O*-butenyl substituted carbamates **6d** and **6e** - as already observed in the arylation/hydroamination reactions - lead to the same products, namely 1,1-diarylated compound **26** and indane **27** toward a mixture of the 1,2-diarylated product **28** and 1,3-diarylated product **29** when reacted with mesitylene.



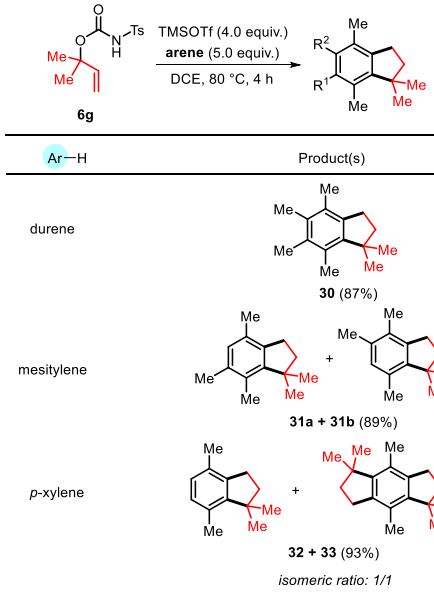
Scheme 24. TMSOTf promoted diarylation of *N*-tosyl carbamates

The formation of **23**, **24** and **25** can be rationalized in the way proposed in Scheme 25: after the first FC allylation, a Markovnikov protonation take place with a second molecule of *p*-xylene which intercepts the carbocation **VII** to give **23**. On the other hand, *p*-xylene - less nucleophilic than mesitylene - allows a competitive 1,2 shift of the hydride ion which leads to carbocation **VIII** precursor of **24**. At this point, the benzyl carbocation **VIII** and styrene **IX** react together allowing a [3 + 2] formal cycloaddition giving rise to the intermediate **X** which evolves into the indane product **25**.[37]
The mechanism of formation of indane **27** is similar to that described for **25**.



Scheme 25. Possible mechanism for diarylation process with *p*-xylene

N-Tosyl carbamate α,α-dimethyl substituted **6g** was then treated under the standard conditions with durene, affording the indane **30** in 87% yield (Scheme 26). The same behaviour was observed working with mesitylene, resulting however in an inseparable mixture of the isomeric indanes **31a** and **31b** or *p*-xylene yielding a mixture of indane **32** and hydrindacene **33** in a 1:1 ratio.

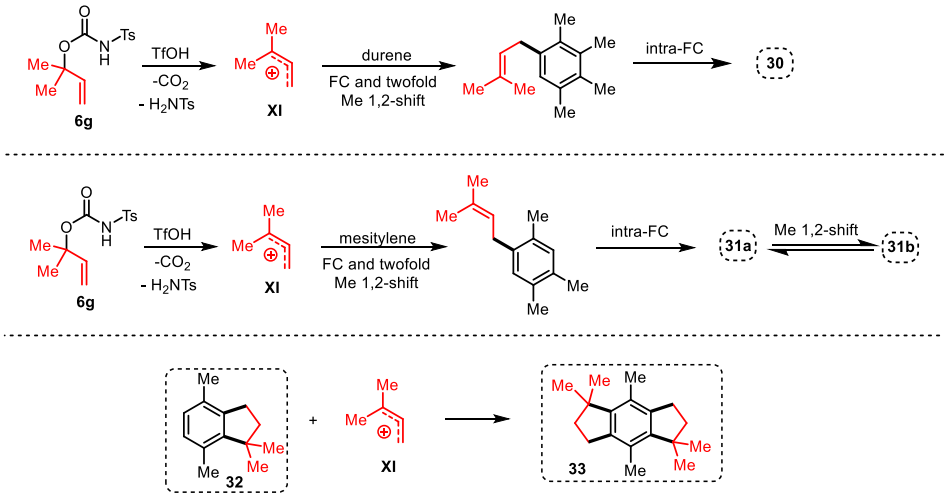


Scheme 26. TMSOTf promoted diarylation of the *N*-tosyl carbamate α,α-dimethyl substituted 6g

This behaviour can be reasonably explained with a second intramolecular FC reaction on the intermediate **XI** resulting from the intermolecular FC on the less substituted carbon (Scheme 27). It should be emphasized

[37] E. J. Eisenbraun, J. R. Mattox, R. C. Bansal, M. A. Wilhelm, P. W. K. Flanagan, A. B. Carel, R. E. Laramy, M. C. Hamming, Polyalkyl aromatic hydrocarbons. II. Cyclialkylation of benzoid hydrocarbons with isoprene, *J. Org. Chem.* **1968**, *33*, 2000-2008.

that - in the case of mesitylene and durene – a 1,2-migrations of methyl take place before or after the first reaction of FC allowing the intramolecular FC.[38]
However, in the case of *p*-xylene a second carbocation specie **XI** could attack the highly reactive indane **32** affording the hydrindacene **33**.

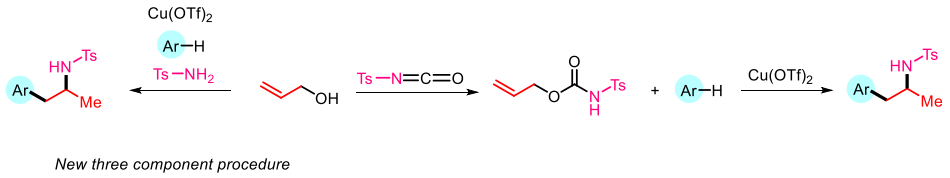


Scheme 27. Possible mechanism for the formation of indane structures

This work evidences that *O*-allyl *N*-sulfonyl carbamates are ideal C3 dication species. According to the nature of the aromatic partner and the allyl moiety, the mechanisms can take different paths - arylation/hydroamination *vs* diarylation sequences – which gave a palette of synthetic opportunities.

2.3 COPPER(II) TRIFLATE-CATALYZED THREE COMPONENT REACTION FOR HYDROAMINATION PROCEDURES

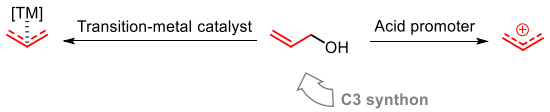
Among the cascade reactions developed, the arylation/hydroaminations are the most intriguing due to the wide interest that 1-aryl-2-aminopropanes in organic synthesis and in the pharmaceutical field.[18] This prompted us to investigate the feasibility of this reaction starting from substrates more easily accessible and possibly working under milder and more sustainable conditions. Thus, we thought to start directly from allyl alcohol as possible C3 synthon precursor (Scheme 28).



Scheme 28. Arylation/hydroamination procedure starting from different *O*-allylic residues

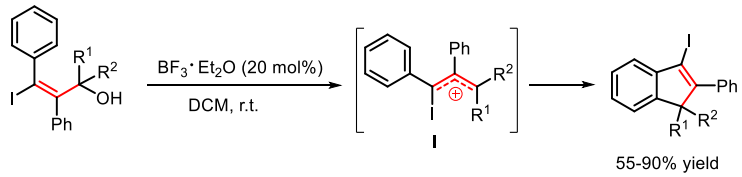
Alcohols bearing an allyl residue have been used in various procedures as precursors of C3 synthons through either the formation of π-allyl intermediates in the presence of metal catalysts or the generation of carbocation intermediates by an acid promoter (Scheme 29).

[38] a) G. K. Surya, Y. Zhang, L. Chen, T. Lu, A copper(II) triflate-catalyzed tandem Friedel-Crafts alkylation/cyclization process towards dihydroindenes, *Adv. Synth. Catal.* **2011**, *353*, 1055-1060; b) G. A. Olah, A. Molnár, in *Hydrocarbon Chemistry*, John Wiley and Sons, **2003**, 160-214; c) R. H: Allem, L. D. Yats, Kinetics of the three-compound equilibrations. II. The isomerization of xylene, *J. Am. Chem. Soc.* **1959**, *81*, 5289-5292; d) H. C. Brown, H. Jungk, The isomerization of *o*- and *p*-xylenes and some related alkylbenzenes under the influence of hydrogen bromide and aluminium bromide; the relative isomerization aptitudes of alkyl groups, *J. Am. Chem. Soc.* **1955**, *77*, 5579-5584; e) D. A. McCaulay, A. P. Lien, Isomerization of the methylbenzenes, *J. Am. Chem. Soc.* **1952**, *74*, 6246-6250.



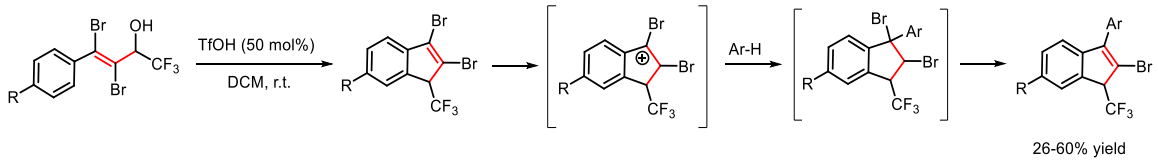
Scheme 29. Allyl alcohol as C3 synthon

Allyl alcohols have attracted considerable interest also in the field of Friedel-Crafts alkylation, above all to introduce an allyl group into aromatic systems.[39]
In 2008, Li and coworkers reported an innovative way to synthesize 3-iodoindenes through an intramolecular Friedel-Crafts arylation of iodinated allyl alcohols with a Lewis acid (Scheme 30).[40] Key intermediate was the allyl cation **I** which could be obtained by the carbon-oxygen bond cleavage.



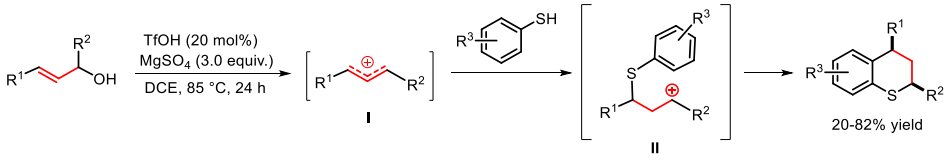
Scheme 30. Lewis-acid catalyzed intramolecular Friedel-Crafts arylation of iodinated allyl alcohols

Although they are suitable substrates, only a restricted number of examples in which allyl alcohols are used as C3 dicationic equivalents are known in the literature. In this regard, an example concerns the arylation of brominated allyl alcohols which could behave as highly reactive multicentered electrophile.[41] This reaction, promoted by triflic acid, allowed the synthesis of arylated indenes through an intra/intermolecular arylation sequence (Scheme 31).



Scheme 31. Triflic acid promoted synthesis of indenes

One year later, Pullarkat and co-workers proposed the synthesis of polysubstituted thiochroman derivatives (Scheme 32).[42] In this work copper(II) triflate was used as hidden source of triflic acid, for this reason a catalytic amount of the acid itself was alternatively used. At the beginning the nucleophilic addition of thiol take place on the carbocationic specie **I** and then the intermediate **II** – formed through protonolysis – paved the way for an intramolecular cyclization.



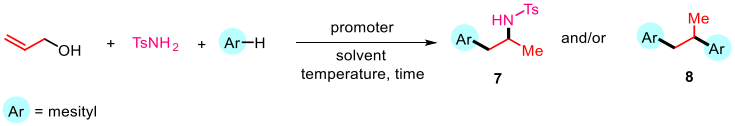
Scheme 32. Triflic acid catalyzed cascade reaction of allyl alcohols

Our work began by treating the allyl alcohol and the tosylamide in the conditions previously used with the *O*-allyl carbamates (*i.e.* mesitylene as solvent, 4.0 equiv. of $Cu(OTf)_2$ at 130 °C for 3.0 hours) (Table 4, entry 1).

[39] M. Bandini, M. Tragni, π-Activated alcohols: an emerging class of alkylating agents for catalytic Friedel-Crafts reactions, *Org. Biomol. Chem.* **2009**, *7*, 1501-1507.
[40] X. Zhou, H. Zhang, X. Xie, Z. Li, Efficient Synthesis of 3-Iodoindenes via Lewis-Acid Catalyzed Friedel-Crafts Cyclization of Iodinated Allylic Alcohols, *J. Org. Chem.* **2008**, *73*, 3958-3960.
[41] A. N. Kazakova, R. O. Iakovenko, I. A. Boyarskaya, A. Y. Ivanov, M. S. Avdontceva, A. A. Zolotarev, T. L. Panikorovsky, G. L. Starova, V. G. Nenajdenko, A. V. Vasilyev, Brominated CF_3-allyl alcohols as multicentered electrophiles in TfOH promoted reactions with arenes, *Org. Chem. Front.* **2017**, *4*, 255-265.
[42] M. Duy Vu, C. Qing Foo, A. Sadeer, S. S. Shand, Y. Li, S. A. Pullarkat, Triflic-Acid-Catalyzed Tandem Allylic Substitution-Cyclization Reaction of Alcohols with Thiophenols – Facile Access to Polysubstituted Thiochromans, *ACS Omega* **2018**, *3*, 8945-8951.

These reaction conditions gave a mixture of arylation/hydroamination and diarylation products **7** and **8**, respectively. The low selectivity and the moderate yields prompted us to optimize the conditions.
First, the reaction solvent was changed to chlorobenzene combined with 5 equivalents of mesitylene (entry 2). These conditions were found to be selective for the formation of the *N*-tosyl 1-aryl-2-aminopropane **7**. Then, the reaction was proven to be effective working with 1.0 equivalent of copper(II) triflate (entry 3). For evidence of the role of triflic acid, we worked with 5 mol% of this acid (entry 4). After 4 hours the expected hydroamination product **7** was recovered from a mixture with compound **8**, demonstrating once again how triflic acid promotes the reaction, even if not selectively. Gratifyingly, we found that the process can be more sustainable in terms of amount of copper(II) triflate and temperature. To facilitate the release of triflic acid from $Cu(OTf)_2$, we investigated the effect of a ligand that could coordinate copper ensuring milder and more favorable conditions for the cascade process. Thus, xanthphos was chosen as phosphine ligand and was used at 100 °C or at 75 °C - as shown in entries 5-6 – giving in both cases the expected hydroaminated product **7** in high yield. However lower reaction temperatures at 50 °C led exclusively to the starting substrate (entry 7).

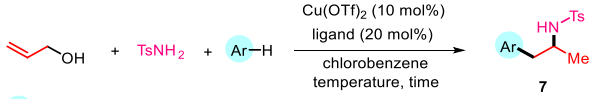
Table 4. Optimization of arylation/hydroamination on allyl alcohol



Entry	Promoter (equiv.)	Ligand (20 mol%)	Solvent [0.25M]	Temperature (°C)	Time (h)	Product(s)
1	$Cu(OTf)_2$ (4.0)	-	Mesitylene	130	3.0	**7** (34%) + **8** (22%)
2	$Cu(OTf)_2$ (4.0)	-	Chlorobenzene	130	4.0	**7** (63%)
3	$Cu(OTf)_2$ (1.0)	-	Chlorobenzene	130	6 0	**7** (60%)
4	TfOH (0.05)	-	Chlorobenzene	130	4.0	**7** (71%) + **8** (12%)
5	$Cu(OTf)_2$ (0.1)	Xanthphos	Chlorobenzene	100	24	**7** (78%)
6	$Cu(OTf)_2$ (0.1)	Xanthpos	Chlorobenzene	75	24	**7** (81%)
7	$Cu(OTf)_2$ (0.1)	Xantphos	Chlorobenzene	50	24	-

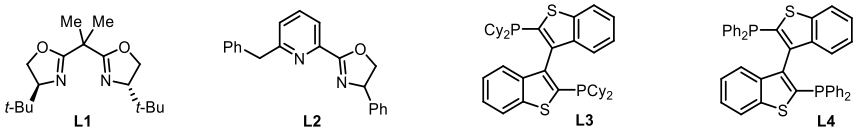
Given the possibility of carrying out the reaction in the presence of a catalytic amount of $Cu(OTf)_2$ in the presence of xantphos, we investigated the feasibility of a stereoselective outcome combining a suitable bidentate ligand. The first trials employing the bis(oxazoline) ligand **L1** and the pyrido-oxazoline **L2** take only to mixtures of tarry products (Table 5, entries 1-2). A small amount of the arylated/hydroaminated product **7** was observed working with (*R*)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthalene ((*R*)-BINAP) (entry 3). The obtainment of the desired product, although in low yield, prompted us to work with diphosphine ligand at lower temperatures for longer times. More consistent results have been obtained using phanephos as ligand both the enantiomers were tested at 100 °C for 24 hours and the best result was observed with the (*S*)-one reaching the 1-aryl-2-tosylaminopropane **7** with 54% yield (entries 4-5).
On the other hand, the use of more electron rich benzothiophene-phosphine ligands **L3** and **L4** at 75 °C gave the best results in arylation/hydroamination sequences (entries 6-7). In both cases compound **7** was obtained but the use of enantiomeric pure ligands (such as (*S*)-phanephos, (*R*)-phanephos or **L3**) gave only a racemic mixture of enantiomers, which was determined through a chiral HPLC analysis. Failure to obtain enantiomeric excesses can be plausibly due - as suggested by Hii and coworkers - to the reversibility of C-N bond formation.[34] Indeed, a diphosphine ligand lowers the energy barrier of the process catalyzed making it reversible at 75 °C.

Table 5. Optimization of arylation/hydroamination of allyl alcohol with $Cu(OTf)_2$ as catalyst

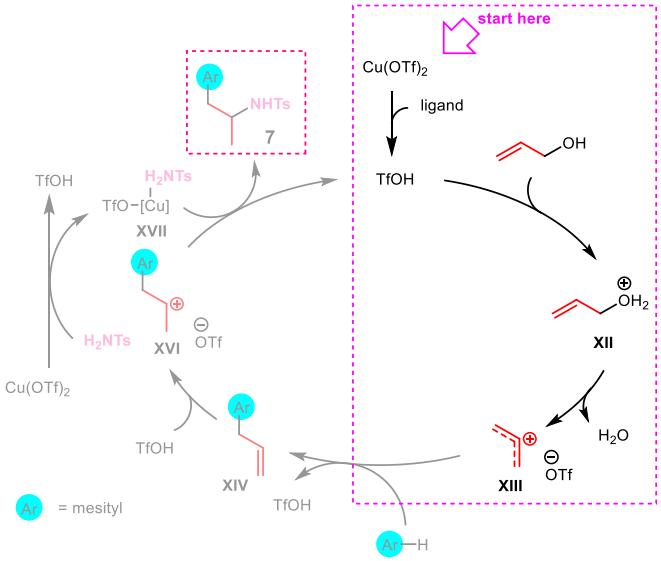


Ar = mesityl

Entry	Ligand (20 mol%)	Temperature (°C)	Time (h)	Product(s)
1	**L1**	130	6	-
2	**L2**	130	6	-
3	(*R*)-BINAP	110	24	**7** (trace)
4	(*R*)-Phanephos	100	24	**7** (31%)
5	(*S*)-Phanephos	100	24	**7** (54%)
6	**L3**	80	24	**7** (75%)
7	**L4**	80	24	**7** (87%)



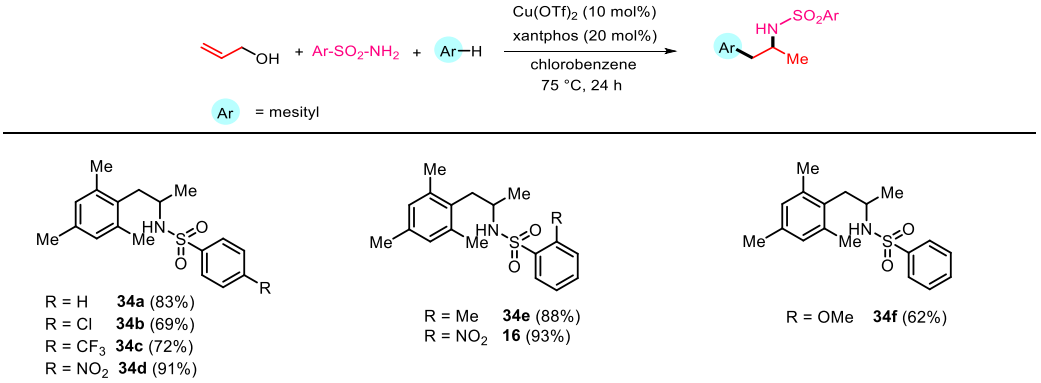
For the arylation/hydroamination coupling reactions, we hypothesized the mechanism shown in Scheme 33. As for the difunctionalization of *O*-allyl carbamates, we assume that triflic acid is formed *in situ* from $Cu(OTf)_2$ leading to protonation at the oxygen atom of alcohol generation of the activated allyl alcohol **XII**.[43] This latter gave the allyl carbenium ion **XIII** through the loss of a molecule of water and then undergoes a Friedel-Crafts alkylation by attack of the aromatic partner. At this point the outcome of the reaction proceeds through a Markovnikov protonation of **XIV,** which generates the carbocation intermediate **XV**. At this stage, the amido copper-complex **XVI** selectively attacks the intermediate **XVII** providing the 1-aryl-2-tosylaminopropane **7**.



Scheme 33. Possible reaction mechanisms on allyl alcohol

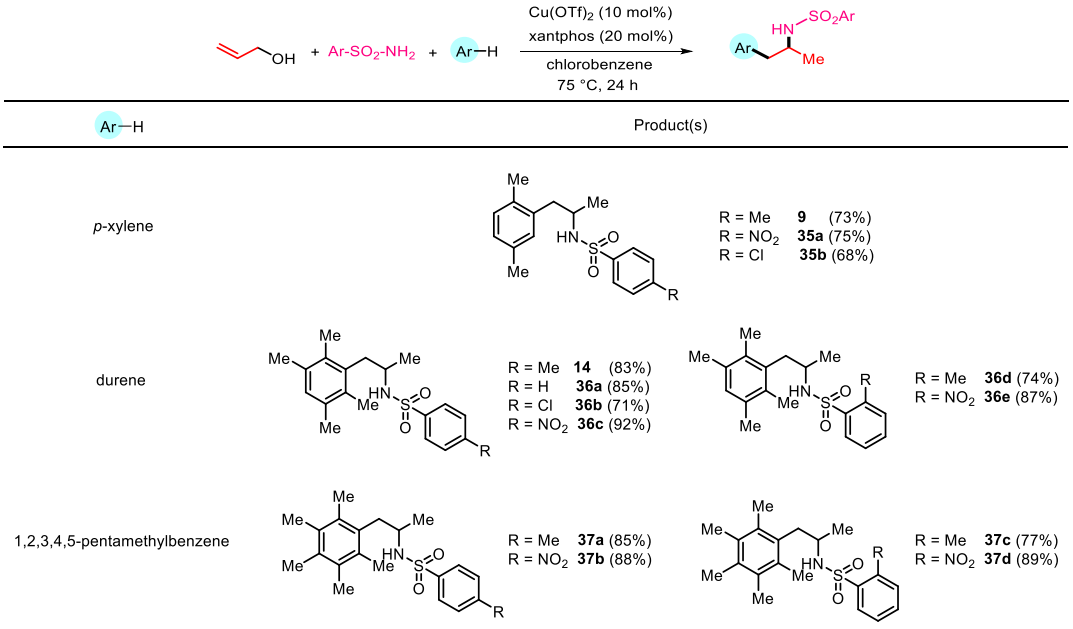
[43] W. Rao, P. Kothandaraman, C. Boon Koh, P. Wai Hong Chan, Copper(II) Triflate-Catalyzed Intramolecular Hydroamination of Homoallylic Amino Alcohols as an Expedient Route to trans-2,5-Dihydro-*1H*-pyrroles and 1,2-Dihydroquinolines, *Adv. Synth. Catal.* **2010**, *352*, 2521-2530.

The good results obtained by working with xantphos at 75 °C (Table 5, entry 9) led us to investigate these conditions based on the presence of mesitylene with different sulfonamides (Scheme 34).
The aryl sulfonamides tested have electron-donor and withdrawing, groups on the phenyl ring and all the reactions proceed in good to excellent yields, with the exception of benzenesulfonamide which led to the product **34a** more difficulty than the others.



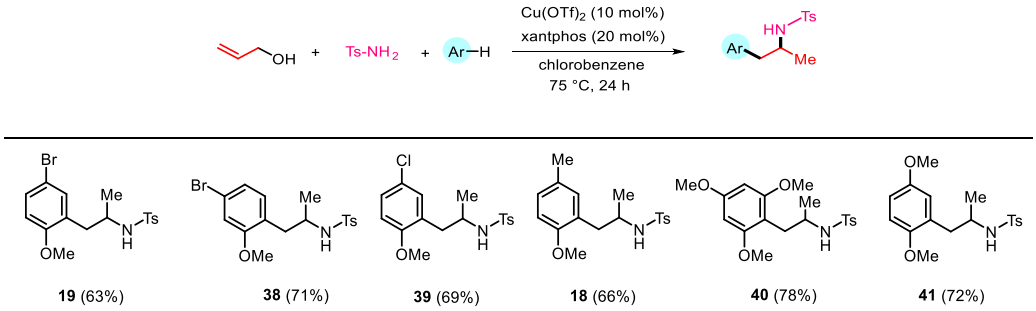
Scheme 34. Cu-Catalyzed arylation/hydroamination sequence reaction with sulfonamides and mesitylene

The next step involved the use of different kind of hydrocarbons to analyze the outcome of the reaction in the presence of aromatics with various electronic availability (Scheme 35). Starting from *p*-xylene, the arylation/hydroamination products **9**, **35a-b** were obtained in good yields. On the other hand, more electron-rich hydrocarbons – such as durene and 1,2,3,4,5-pentamethylbenzene – lead to the desired products **14**, **36a-e** and **37a-d** despite the greater steric hindrance than mesitylene.



Scheme 35. Scope of arylation/hydroamination sequence reaction with sulfonamides and hydrocarbons

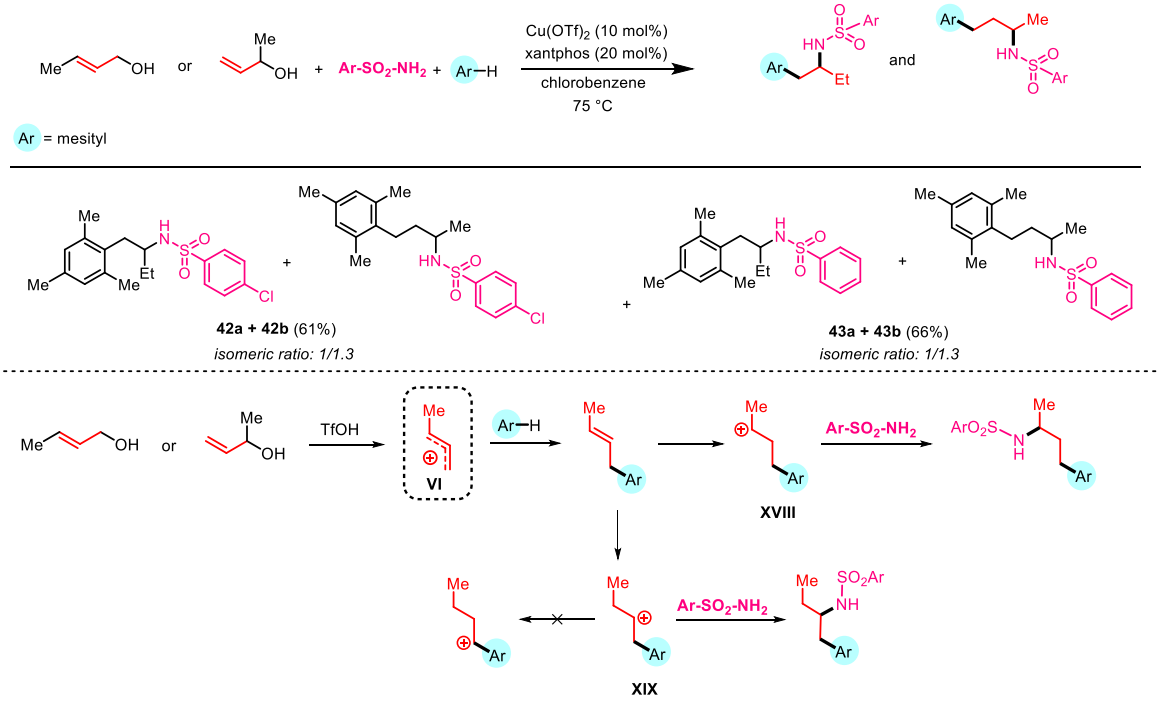
A wider scope of the reaction was evaluated next, keeping the promoting system $Cu(OTf)_2$/xanthphos in chlorobenzene at 75 °C (Scheme 36). Reacting the allyl alcohol with 2 equivalents of tosylamide as nitrogen nucleophile with 5 equivalents of 4-bromoanisole, 3-bromoanisole, 4-chloroanisole and 4-methylanisole the *N*-tosyl 1-aryl-2-aminopropane **19, 38-39, 18** were achieved. It is worth noting that this approach is complementary to the one starting from *O*-allyl carbamates because in this case strongly activated arenes, such as 1,4-dimethoxybenzene and 1,3,5-trimethoxybenzene, selectively led to the arylation/hydroamination products rather than diarylation.



Scheme 36. Cu-Catalyzed procedure on variously substituted arenes

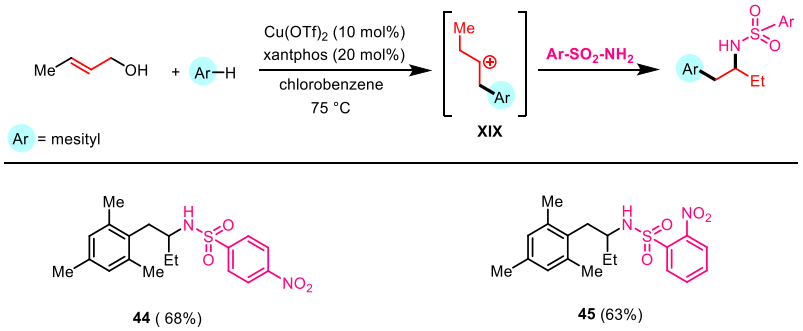
To have a better knowledge of the behaviour of this C–H cascade protocol, other tests were undertaken. Accordingly, the C–H coupling between variously substituted *N*-tosyl carbamates in the presence of a catalytic amount of $Cu(OTf)_2$ and 5.0 equivalents of mesitylene was next investigated (Scheme 37). In this case, each isomeric alcohol – like crotyl alcohol and 3-buten-2-ol – furnished mixtures of two different type of hydroaminated compounds, due to the double behaviour of the alcohols to act as C3 1,2- and 1,3-dication equivalents.

This result suggests that – when the allyl alcohol have a longer chain – the highly nucleophilic sulfonamide intercepts the carbenium ions **XVIII** and **XIX** giving the mixture of **42a** and **42b** when the reaction was carried out with the benzenesulfonamide or **43a** and **43b** working with 4-chlorobenzenesulfonamide. It is plausible that the very reactive sulfonamide doesn't let the time for a homobenzylic to benzylic cation 1,2-hydride shift.



Scheme 37. Arylation/hydroamination products with substituents on the allylic chain

Conversely, the use of 2-nitrobenzenesulfonamide or 4-nitrobenzenesulfonamide gave selectively the 1-aryl-2-sulfonylaminobutanes **44** and **45** (Scheme 38).



Scheme 38. The selective arylation/hydroamination products with substituents on the allylic chain

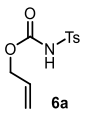
In conclusion, allyl alcohols proved to be useful C3 synthons for the cascade FC arylation/hydroamination process. The copper catalyzed three-component process makes it possible to use milder conditions and to use commercially available substrates by reducing unnecessary synthetic steps.

2.4 EXPERIMENTAL SECTION

*Procedure for the synthesis of O-allyl N-substituted carbamates (**6**)*

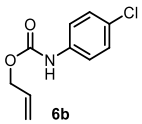
In a solution of the appropriate allyl alcohol (10.0 mmol) in DCE (15 mL), the suitable isocyanate (10.0 mmol) was added. The resulting reaction mixture is magnetically stirred at room temperature for 24 hours. After the evaporation of the solvents, the desired compound was obtained.

*O-Allyl-N-tosylcarbamate (**6a**)*



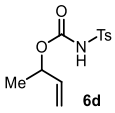
6a (99%); white solid. The characterization of product **6a** is consistent with that reported in literature.[44]

*O-Allyl-N-(4-chlorophenyl)carbamate (**6b**)*



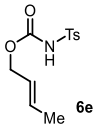
6b (89%); yellow wax. The characterization of product **6b** is consistent with that reported in literature.[45]

*O-But-3-en-2-yl-N-tosylcarbamate (**1d**)*



1d (94%); white solid. The characterization of product **6d** is consistent with that reported in literature.[44]

*O-But-2-en-1-yl-N-tosylcarbamate (**6e**)*



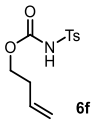
6e (96%); yellow oil. The characterization of product **6e** is consistent with that reported in literature.[46]

[44] S. Nicolai, C. Piemontesi, J. Waser, A palladium-catalyzed aminoalkynylation strategy towards bicyclic heterocycles: synthesis of (±)-trachelanthamidine, *Angew. Chem. Int. Ed.* **2011**, *50*, 4680-4683.

[45] Y. Sabesan, M. Scott, *N*-Methylimidazole-catalyzed synthesis of carbamates from hydroxamic acids via the Lossen rearrangement, *Org. Lett.* **2013**, *15*, 602-605.

[46] D. Xing, D. Yang, Gold(I)-catalyzed highly regio- and stereoselective decarboxylative amination of allylic *N*-tosylcarbamates via base-induced aza-Claisen rearrangement in water, *Org. Lett.* **2010**, *12*, 1068-1071.

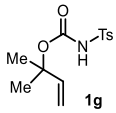
*O-But-3-en-1-yl-N-tosylcarbamate (**6f**)*



6f

6f (96%); yellow oil. The characterization of product **6f** is consistent with that reported in literature.[47]

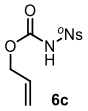
*O-2-Methylbut-3-en-2-yl-N-tosylcarbamate (**6g**)*



1g

6g (95%); yellow oil. The characterization of product **6g** is consistent with that reported in literature.[46]

*Procedure for the synthesis of O-allyl N-(o-nosyl)-carbamate (**6c**)*



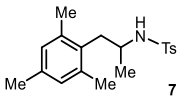
6c

In a solution of allyl chloroformate (1.1 mmol), DMAP (0.1 mmol) and *o*-nosylsulfonamide (1.0 mmol) in DCM (20 mL), triethylamine (1.1 mmol) was added at 0 °C. The resulting reaction mixture is allowed to warm to room temperature and it's magnetically stirred for 24 hours. The resulting solution is diluted with DCM (10 mL) and washed with HCl 10% solution (2 x 5 mL), saturated $NaHCO_3$ solution (2 x 10 mL) and brine (10 mL), dried over $MgSO_4$ and filtered. After the evaporation of the solvents, the desired compound **6c** was obtained with 70% yield as yellow wax. The characterization of product **6c** is consistent with that reported in literature.[32]

Procedure for the arylation/hydroamination procedure

In a sealed tube, in a solution of the appropriate *O*-allyl carbamate (1.0 mmol), arene (5.0 mmol) in chlorobenzene (0.4 M), $Cu(OTf)_2$ (4.0 mmol) and H_2O (100 μL) were added. The resulting reaction mixture was heated at 130 °C and it's magnetically stirred for 4 hours. The resulting solution was filtered and the solvent was evaporated under reduced pressure. The residue was purified through FCC.

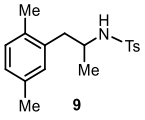
*1-(2,4,6-Trimethylphenyl)-2-tosylamino-propane (**7**)*



7

FCC – AcOEt/hexane (1:1); **7** (77%); light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (d, 3H, *J* = 6.5 Hz), 2.14 (s, 6H), 2.23 (s, 3H), 2.41 (s, 3H), 2.64 (dd, 1H, *J* = 8.0, 14.1 Hz), 2.79 (dd, 1H, *J* = 7.4, 14.1 Hz), 3.41-3.50 (m, 1H), 4.33 (d, 1H, *J* = 6.6 Hz), 6.74 (s, 2H), 7.19 (d, 2H, *J* = 8.2 Hz), 7.56 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.3, 20.8, 21.4, 21.5, 36.9, 49.9, 127.0, 129.2, 129.5, 131.5, 135.8, 136.6, 137.5, 143.1. IR ν_{max} 2926, 1321, 1154 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{26}NO_2S$ $[M+H]^+$ 332.1679; found: 332.1679.

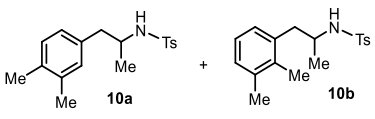
*1-(2,5-Dimethylphenyl)-2-tosylamino-propane (**9**)*



9

FCC – AcOEt/hexane (2:3); **9** (79%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (d, 3H, *J* = 6.4 Hz), 2.09 (s, 3H), 2.24 (s, 3H), 2.41 (s, 3H), 2.59 (dd, 1H, *J* = 7.4, 13.7 Hz), 2.73 (dd, 1H, *J* = 6.9, 13.7 Hz), 3.41-3.48 (m, 1H), 4.72 (d, 1H, *J* = 6.7 Hz), 6.76 (s, 2H), 6.89-6.95 (m, 2H), 7.20 (d, 2H, *J* = 8.1 Hz), 7.59 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 18.9, 20.9, 21.5, 21.7, 41.1, 50.1, 126.9, 127.5, 129.5, 130.5, 130.9, 133.2, 135.4, 135.5, 137.5, 143.0. IR ν_{max} 2934, 1324, 1151 cm^{-1}. Anal. Calcd. For $C_{18}H_{23}NO_2S$: C 68.11, H 7.30, N 4.41; found: C 68.31, H 7.17, N 4.39.

*1-(3,4-Dimethylphenyl)-2-tosylamino-propane (**10a**) and 1-(2,3-dimethylphenyl)-2-tosylamino-propane (**10b**)*



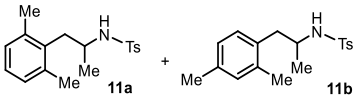
10a **10b**

FCC – AcOEt/hexane (1:4); **10a** + **10b** (76%; isomeric ratio after purification: 1/1.4); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) major isomer **10a**: δ 1.13 (d, 3H, *J* = 6.5 Hz), 2.17 (s, 3H), 2.24 (s, 3H), 2.42 (s, 3H), 2.55-2.64 (m, 2H), 3.45-.3.51 (m, 1H), 4.26 (d, 1H, *J* = 6.9 Hz), 6.73-6.74 (m, 2H), 6.96-7.00 (m, 1H), 7.21 (d, 2H, *J* = 8.7 Hz), 7.59 (d, 2H, *J* = 8.4 Hz); minor isomer **10b**: δ 1.19 (d,

[47] J. Rajabi, M. M. Lorion, V. L. Ly, F. Liron, J. Oble, G. Prestat, G. Poli, Dormant versus evolving aminopalladated intermediates: toward a unified mechanistic scenario in Pd^{II}-catalyzed aminations, *Chem. Eur. J.* **2014**, *20*, 1539-1546.

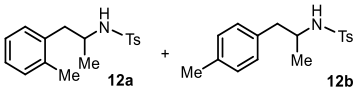
2H, *J* = 6.4 Hz), 1.19 (s, 3H), 2.17 (s, 3H), 2.41 (s, 3H), 2.71 (d, 2H, *J* = 7.2 Hz), 3.35-3.41 (m, 1H), 4.34 (d, 1H, *J* = 6.2 Hz), 6.83-6.84 (m, 1H), 6.96-7.00 (m, 2H), 7.16 (d, 2H, *J* = 7.8 Hz), 7.48 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 15.1, 19.3, 19.7, 20.6, 21.5, 22.0, 41.9, 42.9, 49.9, 50.9, 125.5, 126.7, 126.9, 127.0, 128.3, 128.7, 129.4, 129.5, 129.8, 130.6, 134.3, 134.9, 136.7, 137.4, 137.6, 142.9, 143.0. IR ν_{max} 2934, 1324, 1151 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{18}H_{24}NO_2S$ $[M+H]^+$: 318.1528; found: 318.1522.

*1-(2,6-Dimethylphenyl)-2-tosylamino-propane (**11a**) and 1-(2,4-dimethylphenyl)-2-tosylamino-propane (**11b**)*



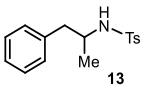
FCC – DCM; **11a** + **11b** (72%; isomeric ratio after purification: 1/1); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) mixture of two isomer **11a** + **11b**: δ 1.14 (d, 6H, *J* = 6.5 Hz), 2.09 (s, 4H), 2.19 (s, 4H), 2.28 (s, 4H), 2.41 (s, 3H), 2.42 (s, 3H), 2.58-2.73 (m, 3H), 2.85 (dd, 1H, J = 7.0, 13.9 Hz), 3.38-.3.54 (m, 2H), 4.37 (t, 2H, *J* = 7.5 Hz), 6.82-6.88 (m, 4H), 6.92 (d, 1H, *J* = 7.5 Hz),6.98-7.02 (m, 1H), 7.19 (d, 4H, *J* = 8.1 Hz), 7.56 (d, 2H, *J* = 9.0 Hz), 7.57 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.2, 20.4, 20.9, 21.4, 21.5, 21.6, 21.7, 37.2, 40.8, 49.8, 50.1, 126.9, 127.0, 128.5, 129.5, 130.1, 131.4, 132.4, 134.4, 136.0, 136.1, 136.4, 137.3, 137.4, 143.0, 143.1. IR ν_{max} 2925, 1325, 1159 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{18}H_{24}NO_2S$ $[M+H]^+$: 318.1528; found: 318.1522.

*1-(2-Methylphenyl)-2-tosylamino-propane (**12a**) and 1-(4-methylphenyl)-2-tosylamino-propane (**12b**)*



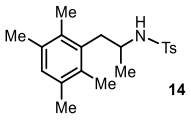
FCC – DCM; **12a** + **12b** (29%); yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) major isomer **12a**: δ 1.14 (d, 3H, *J* = 4.9 Hz), 2.15 (s, 3H), 2.41 (s, 3H), 2.62-2.67 (m, 1H), 2.77 (dd, 1H, *J* = 5.2, 10.3 Hz), 3.43-.3.52 (m, 1H), 4.32 (d, 1H, *J* = 4.7 Hz), 6.99 (d, 1H, *J* = 13.4 Hz), 7.01-7.13 (m, 3H), 7.19-7.23 (m, 2H), 7.56-7.62 (m, 2H); minor isomer **12b**: δ 1.11 (d, 3H, *J* = 4.9 Hz), 2.31 (s, 3H), 2.43 (s, 3H), 2.62-2.67 (m, 2H), 3.43-.3.52 (m, 1H), 4.24 (d, 1H, *J* = 5.5 Hz), 6.89 (d, 1H, *J* = 5.9 Hz), 7.01-7.13 (m, 2H), 7.19-7.23 (m, 2H), 7.56-7.62 (m, 2H);^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.3, 21.4, 21.5, 21.7, 41.2, 42.9, 49.9, 50.9, 126.0, 126.8, 126.9, 127.1, 129.2, 129.6, 130.2, 130.6, 135.5, 136.3, 136.4, 137.4, 143.9, 143.1. IR ν_{max} 2917, 1378, 1157 cm^{-1}. Anal. Calcd. For $C_{17}H_{21}NO_2S$: C 67.30, H 6.98, N 4.62; found: C 67.44, H 7.21, N 7.27.

*1-Phenyl-2-tosylamino-propane (**13**)*



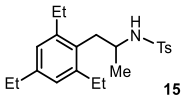
FCC – AcOEt/hexane (1:4); **13** (73%); light brown oil. The characterization of product **9** is consistent with that reported in literature.[48]

*1-(2,3,5,6-Tetramethylphenyl)-2-tosylamino-propane (**14**)*



FCC – AcOEt/hexane (4:1); **14** (78%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, 3H, *J* = 6.5 Hz), 2.04 (s, 6H), 2.16 (s, 6H), 2.41 (s, 3H), 2.77 (dd, 1H, *J* = 7.5, 14.3 Hz), 2.90 (dd, 1H, *J* = 7.8, 14.3 Hz), 3.38-3.45 (m, 1H), 4.51 (d, 1H, *J* = 6.7 Hz), 6.82 (s, 1H), 7.15 (d, 2H, *J* = 8.2 Hz), 7.49 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.1, 20.7, 21.5, 21.9, 37.2, 50.3, 126.9, 129.3, 130.2, 132.5, 133.9, 134.1, 137.2, 142.9. IR ν_{max} 2925, 1378, 1155 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{20}H_{28}NO_2S$ $[M+H]^+$: 346.1835; found: 346.1835.

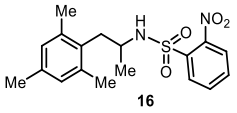
*1-(2,4,6-Triethylphenyl)-2-tosylamino-propane (**15**)*



FCC – AcOEt/hexane (4:1); **15** (74%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09-1.15 (m, 9H), 1.25-1.27 (m, 3H), 2.41 (s, 3H), 2.43-2.54 (m, 4H), 2.55-2.61 (m, 2H), 2.69 (dd, 1H, *J* = 8.4, 14.1 Hz), 2.82 (dd, 1H, *J* = 7.2, 14.1 Hz), 3.36-3.43 (m, 1H), 4.48 (s, H), 6.81 (s, 2H), 7.19 (d, 2H, *J* = 8.3 Hz), 7.57 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 15.4, 15.5, 21.4, 21.5, 26.1, 28.5, 35.4, 50.6, 126.0, 127.1, 129.5, 129.8, 137.3, 142.6, 142.7, 143.0. IR ν_{max} 2931, 1321, 1161 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{22}H_{32}NO_2S$ $[M+H]^+$: 374.2148; found: 374.2149.

[48] C. Michon, F. Medina, F. Capet, P. Roussel, Inter- and intramolecular hydroamination of unactivated alkenes catalysed by a combination of copper and silver salts: the unveiling of a Brønsted acid catalysis, *Adv. Synth. Catal.* **2010**, *352*, 3293-3305.

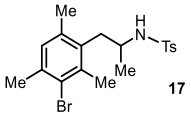
*1-Mesityl-2-(o-nosylamino)-propane (**16**)*



16

FCC – AcOEt/hexane (1:4); **16** (45%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, *J* = 7.5 Hz), 2.16 (s, 3H), 2.19 (s, 6H), 2.72 (dd, 1H, *J* = 7.5, 14.2 Hz), 2.85 (dd, 1H, *J* = 8.0, 14.2 Hz), 3.78-3.85 (m, 1H), 5.31 (t, 1H, *J* = 3.4 Hz), 6.62 (s, 2H), 7.61-7.68 (m, 2H), 7.79 (d, 1H, *J* = 7.6 Hz), 7.98 (d, 1H, *J* = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.3, 22.4, 36.6, 51.2, 125.4, 125.4, 129.2, 130.4, 131.1, 132.8, 134.8, 135.7, 136.4, 136.5. IR ν_{max} 2919, 1537, 1347, 1162 cm^{-1}. Anal. Calcd. For $C_{18}H_{22}N_2O_4S$: C 59.65, H 6.12, N 7.73; found: C 58.52, H 5.91, N 7.56.

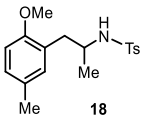
*1-(3-Bromo-2,4,6-trimethylphenyl)-2-tosylamino-propane (**17**)*



17

FCC – AcOEt/hexane (1:4); **17** (82%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, 3H, *J* = 6.5 Hz), 2.18 (s, 3H), 2.19 (s, 3H), 2.34 (s, 3H), 2.42 (s, 3H), 2.71 (dd, 1H, *J* = 7.3, 14.3 Hz), 2.87 (dd, 1H, *J* = 7.9, 14.3 Hz), 3.39-3.46 (m, 1H), 4.35 (d, 1H, *J* = 7.5 Hz), 6.83 (s, 1H), 7.15 (d, 2H, *J* = 8.1 Hz), 7.49 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.5, 20.7, 21.6, 22.1, 23.9, 37.9, 50.1, 126.6, 126.8, 129.4, 130.3, 133.5, 135.2, 136.3, 139.9, 143.2. IR ν_{max} 2925, 1328, 1157 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{25}BrNO_2S$ $[M+H]^+$: 410.0784; found: 410.0783.

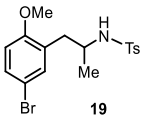
*1-(2-Methoxy-5-methylphenyl)-2-tosylamino-propane (**18**)*



18

FCC – DCM; **18** (77%); light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, 3H, *J* = 6.6 Hz), 2.18 (s, 3H), 2.38 (s, 3H), 2.51 (dd, 1H, *J* = 4.9, 13.6 Hz), 2.69 (dd, 1H, *J* = 8.9, 13.6 Hz), 3.38-3.45 (m, 1H), 3.74 (s, 3H), 4.99 (d, 1H, *J* = 5.3 Hz), 6.63-6.66 (m, 2H), 6.94 (s, 1H, *J* = 8.3 Hz), 7.08 (d, 2H, *J* = 8.1 Hz), 7.42 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.4, 22.8, 27.1, 37.3, 51.2, 55.4, 110.4, 125.7, 126.8, 128.2, 129.2, 130.0, 131.8, 137.2, 142.4, 169.4. IR ν_{max} 2925, 2851, 1319, 1157 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{18}H_{24}NO_3S$ $[M+H]^+$: 334.1471; found: 334.1471.

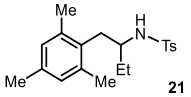
*1-(5-Bromo-2-methoxyphenyl)-2-tosylamino-propane (**19**)*



19

FCC – AcOEt/hexane (1:4); **19** (67%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, *J* = 3.6 Hz), 2.40 (s, 3H), 2.49 (dd, 1H, *J* = 4.9, 13.6 Hz), 2.71 (dd, 1H, *J* = 10.7, 13.6 Hz), 3.39-3.47 (m, 1H), 3.77 (s, 3H), 4.79 (d, 1H, *J* = 6.2 Hz), 6.95 (s, 1H, *J* = 2.3 Hz), 7.11 (d, 2H, *J* = 8.1 Hz), 7.20-7.23 (m, 1H), 7.43 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.5, 23.0, 37.1, 51.2, 55.6, 112.1, 113.1, 126.7, 128.4, 129.4, 130.5, 133.5, 136.9, 142.8, 156.2. IR ν_{max} 2927, 2853, 1323, 1157 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{17}H_{21}BrNO_3S$ $[M+H]^+$: 398.0420; found: 398.0418.

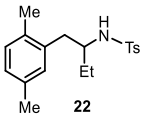
*1-(2,4,6-Trimethylphenyl)-2-tosylamino-butane (**21**)*



21

FCC – AcOEt/hexane (1:4); **21** (77%); yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84 (t, 3H, *J* = 7.4 Hz), 1.45-1.55 (m, 2H), 2.15 (s, 6H), 2.23 (s, 3H), 2.40 (s, 3H), 2.66 (dd, 1H, *J* = 7.6, 14.1 Hz), 2.78 (dd, 1H, *J* = 7.8, 14.1 Hz), 3.29-3.36 (m, 1H), 4.26 (d, 1H, *J* = 7.5 Hz), 6.71 (s, 2H), 7.15 (d, 2H, *J* = 8.3 Hz), 7.52 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.1, 20.3, 20.8, 21.5, 34.9, 55.5, 126.9, 129.2, 129.3, 135.7, 136.5, 137.6, 142.8. IR ν_{max} 2916, 1318, 1153 cm^{-1}. Anal. Calcd. For $C_{17}H_{21}NO_2S$: C 69.53, H 7.88, N 4.05; found: C 69.72, H 8.09, N 4.28.

*1-(2,5-Dimethylphenyl)-2-tosylamino-butane (**22**)*



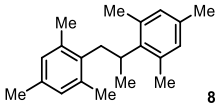
22

FCC – AcOEt/hexane (1:4); **22** (41%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, 3H, *J* = 7.4 Hz), 1.43-1.63 (m, 2H), 2.11 (s, 3H), 2.23 (s, 3H), 2.40 (s, 3H), 2.63-2.68 (m, 2H), 3.27-3.36 (m, 1H), 4.36 (d, 1H, *J* = 6.9 Hz), 6.73 (s, 1H), 6.88-6.93 (m, 2H), 7.17 (d, 2H, *J* = 8.0 Hz), 7.55 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 9.7, 18.9, 20.9, 21.5, 27.7, 38.7, 55.6, 126.9, 127.4, 129.4, 130.5, 130.9, 133.2, 135.3, 135.6, 137.5, 142.9. IR ν_{max} 2921, 1323, 1155 cm^{-1}. Anal. Calcd. For $C_{17}H_{21}NO_2S$: C 68.85, H 7.60, N 4.23; found: C 68.66,H 7.68, N 4.42.

Procedure for the diarylation procedure

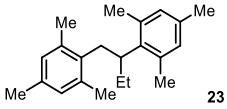
In a sealed tube, in a solution of the appropriate *O*-allyl carbamate (1.0 mmol), arene (5.0 mmol) in chlorobenzene (0.4 M), TMSOTf (4.0 mmol) was added. The resulting reaction mixture was heated at 130 °C and it was magnetically stirred for 4 hours. The resulting solution was diluted with DCM (10 mL), washed with saturated $NaHCO_3$ solution (2 x 10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

*1,2-Bis(2,4,6-trimethylphenyl)-propane (**8**)*



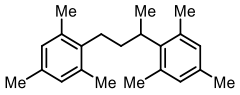
FCC – AcOEt/hexane (1:1); **8** (79%); brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.48 (d, 3H, *J* = 7.4 Hz), 2.18 (s, 2H), 2.35 (s, 7H), 2.39 (s, 5H), 2.72 (s, 2H), 3.12 (dd, 1H, *J* = 6.3, 13.6 Hz), 3.26 (dd, 1H, *J* = 7.7, 13.6 Hz), 3.49-3.58 (m, 1H), 6.96 (s, 4H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.2, 20.6, 20.8, 21.2, 34.2, 36.0, 76.7, 77.0, 77.3, 126.9, 128.9, 134.9, 135.0, 135.8, 136.5, 137.7, 140.2. Anal. Calcd. For $C_{21}H_{28}$: C 89.94, H 10.06; found: C 90.13, H 9.96.

*1,2-Bis(2,4,6-trimethylphenyl)-butane (**23**)*



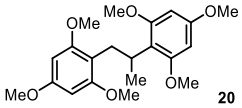
FCC – AcOEt/hexane (1:4); **23** (32%); brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (t, 3H, *J* = 7.6 Hz), 1.72-1.83 (m, 1H), 1.92 (s, 2H), 1.96-2.04 (m, 1H), 2.15 (s, 6H), 2.25 (s, 6H), 2.54 (s, 3H), 3.02 (d, 1H, *J* = 7.8 Hz), 3.18-3.26 (m, 1H), 6.72 (s, 1H), 6.79 (s, 2H), 6.82 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.0, 20.2, 20.7, 20.8, 21.5, 21.6, 26.8, 33.6, 42.9, 128.9, 129.0, 131.1, 134.9, 135.6, 136.4, 137.5, 137.8. Anal. Calcd. For $C_{22}H_{30}$: C 89.73, H 10.27; found: C 89.99, H 10.18.

*1,3-Bis(2,4,6-trimethylphenyl)-butane (**24**)*



FCC – AcOEt/hexane (1:4); **24** (69%); brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.41 (d, 3H, *J* = 7.4 Hz), 1.78-1.91 (m, 2H), 2.26 (s, 9H), 2.27 (m, 3H), 2.38 (s, 3H), 2.41 (s, 3H), 2.46 (dd, 1H, *J* = 5.4, 12.1 Hz), 2.61-2.68 (m, 1H), 3.29-3.38 (m, 1H), 6.79-6.86 (m, 4H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.1, 19.6, 20.7, 20.8, 28.8, 35.2, 35.5, 134.8, 134.9, 135.8, 136.1, 136.4, 139.9. Anal. Calcd. For $C_{22}H_{30}$: C 89.73, H 10.27; found: C 89.76, H 10.48.

*Synthesis of 1,2-bis(2,4,6-trimethoxyphenyl)-propane (**20**)*

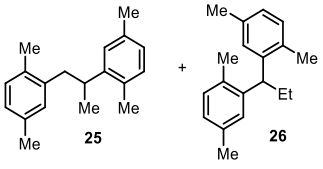


In a sealed tube, in a solution of the appropriate *O*-allyl *N*-tosyl carbamate (1.0 mmol), 1,3,5-trimethoxybenzene (5.0 mmol) in chlorobenzene (0.4 M), $Cu(OTf)_2$ (4.0 mmol) and H_2O (100 μL) are added. The resulting reaction mixture is heated at 130 °C and it's magnetically stirred for 4 hours. The resulting solution is filtered, and the solvent is evaporated under reduced pressure. Compound **20** is isolated with 61% as white wax; FCC – hexane. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, 3H, *J* = 5.4 Hz), 2.88 (dd, 1H, *J* = 5.4, 9.5 Hz), 3.00 (dd, 1H, *J* = 5.7, 9.5 Hz), 3.56-3.65 (m, 1H), 3.71 (s, 12H), 3.79 (s, 6H), 6.09 (d, 4H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 95 MHz) δ 18.4, 27.8, 29.5, 55.2, 55.3, 55.6, 90.4, 91.5, 112.1, 116.9, 158.3, 158.7, 158.8. IR ν_{max} 2854 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{21}H_{29}O_6$ $[M+H]^+$: 377.1959; found: 377.1959.

Procedure for the diarylation procedure with p-xylene

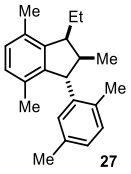
In a sealed tube, in a solution of the appropriate *O*-allyl carbamate (1.0 mmol), *p*-xylene (5.0 mmol) in chlorobenzene (0.4 M), TMSOTf (4.0 mmol) was added. The resulting reaction mixture was heated at 130 °C and it was magnetically stirred for 4 hours. The resulting solution was diluted with DCM (10 mL), washed with saturated $NaHCO_3$ solution (2 x 10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

*1,2-Bis(2,5-dimethylphenyl)-propane (**25**) + 1,1-bis(2,5-dimethylphenyl)-propane (**26**)*



FCC – AcOEt/hexane (0.05:9.95); **25** + **26** (61%); white wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, 3H, *J* = 7.3 Hz), 1.19 (d, 3H, *J* = 6.8 Hz), 1.92-1.99 (m, 2H), 2.19-2.35 (m, 24H), 2.74 (dd, 1H, *J* = 9.2, 13.4 Hz), 2.86 (dd, 1H, *J* = 5.3, 13.4 Hz), 3.17-3.24 (m, 1H), 4.08 (t, 1H, *J* =7.4 Hz), 6.87-6.95 (m, 7H), 7.01-7.03 (m, 4H), 7.14 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.0, 19.0, 19.1, 19.2, 20.6, 21.0, 21.2, 21.3, 28.9, 35.4, 41.4, 44.4, 126.2, 126.4, 126.6, 127.8, 130.0, 130.1, 130.2, 130.8, 132.0, 133.0, 133.2, 134.9, 135.1, 135.5, 139.1, 142.5, 145.5. Anal. Calcd. For $C_{19}H_{24}$: C 90.42, H 9.58; found: C 91.18, H 9.39.

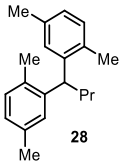
*1,2-(2,5-Dimethylphenyl)-3-ethyl-2,4,7-trimethyl-indane (**27**)*



27

FCC – hexane; **27** (35%); white wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, 3H, *J* = 7.6 Hz), 1.11 (d, 3H, *J* = 6.9 Hz), 1.53-1.57 (m, 1H), 1.60 (s, 3H), 1.72-1.83 (m, 1H), 2.18 (s, 3H), 2.34 (s, 3H), 2.41 (s, 3H), 2.48-2.54 (m, 1H), 6.89-6.95 (m, 2H), 7.06 (d, 1H, *J* = 7.1Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.9, 13.5, 18.9, 19.0, 19.8, 21.0, 22.6, 47.2, 50.3, 51.6, 126.4, 127.9, 128.1, 128.5, 129.6, 130.6, 131.6, 132.8, 135.6, 143.4, 144.8, 147.2. Anal. Calcd. For $C_{22}H_{28}$: C 90.35, H 9.65; found: C 90.08, H 9.81.

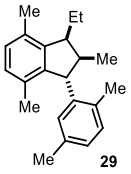
*1,2-Bis(2,5-dimethylphenyl)-butane (**28**)*



28

FCC – AcOEt/hexane (0.05:9.95); **28** (73%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, 3H, *J* = 7.3 Hz), 1.34-1.44 (m, 2H), 1.88-1.93 (m, 2H), 2.25 (s, 6H), 2.30 (s, 6H), 4.21 (t, 1H, *J* = 7.4 Hz), 6.92 (d, 2H, *J* =7.2 Hz), 6.97 (s, 2H), 7.20 (d, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.2, 19.2, 21.2, 21.3, 38.2, 42.2, 126.4, 127.9, 130.1, 133.1, 135.1, 142.7. Anal. Calcd. For $C_{20}H_{26}$: C 90.16, H 9.84; found: C 89.94 H 10.09.

*1,2-(2,5-Dimethylphenyl)-3-ethyl-2,4,7-trimethyl-indane (**29**)*



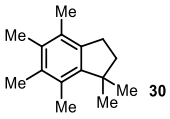
29

FCC – hexane; **29** (24%); white wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87-0.92 (m, 6H), 1.18-1.33 (m, 2H), 1.36-1.47 (m, 2H), 1.55 (s, 3H), 1.58-1.73 (m, 2H), 2.18 (s, 3H), 2.23-2.29 (m, 1H), 2.35 (s, 3H), 2.40 (s, 3H), 3.33-3.38 (m, 1H), 4.28 (d, 1H, *J* = 10.5 Hz), 6.67 (s, 1H), 6.79 (d, 1H, *J* = 7.5 Hz), 6.91 (d, 2H, *J* = 7.8 Hz), 7.04 (d, 1H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.2, 14.9, 19.1, 19.2, 19.9, 20.4, 21.0, 21.0, 32.2, 43.0, 49.9, 58.5, 126.4, 127.8, 128.1, 128.6, 129.5, 130.4, 131.7, 132.9, 135.6, 143.6, 145.0, 147.4. Anal. Calcd. For $C_{24}H_{32}$: C 89.94, H 10.06; found: C 89.70, H 10.25.

Procedure for the synthesis of indane products

In a sealed tube, in a solution of the appropriate α,α-dimethyl substituted *O*-allyl carbamate (1.0 mmol), *p*-xylene (5.0 mmol) in chlorobenzene (0.4 M), TMSOTf (4.0 mmol) was added. The resulting reaction mixture was heated at 130 °C and it was magnetically stirred for 4 hours. The resulting solution was diluted with DCM (10 mL), washed with saturated $NaHCO_3$ solution (2 x 10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

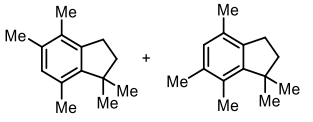
*1,1,4,5,6,7-Hexamethyl-2,3-dihydro-indane (**30**)*



30

FCC – AcOEt/hexane (3:7); **30** (87%); light yellow oil. The characterization of product **30** is consistent with that reported in literature.[49]

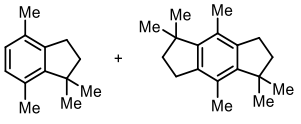
*1,1,4,5,7-Pentamethyl-2,3-dihydro-indane (**31a**) and 1,1,4,6,7-pentamethyl-2,3-dihydro-indane (**31b**)*



31a **31b**

FCC – AcOEt/hexane (3:7); **31a** + **31b** (89% isomeric ratio after purification: 1/1.4); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) major isomer: δ 1.29 (s, 6H), 1.94 (t, 2H, *J* = 7.1Hz), 2.21-2.33 (m, 9H), 2.86 (t, 2H, *J* = 7.1 Hz), 6.87 (s, 1H); minor isomer: δ 1.41 (s, 6H), 1.94 (t, 2H, *J* = 7.1 Hz), 2.21-2.33 (m, 9H), 2.76 (t, 2H, *J* = 7.3 Hz), 6.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.9, 15.3, 16.4, 18.7, 20.0, 21.1, 27.8, 27.9, 28.9, 28.2, 41.2, 43.1, 120.9, 128.9, 129.4, 129.5, 130.7, 132.2, 132.8, 134.7, 135.3, 139.4, 139.9, 148.8, 149.4. Anal. Calcd. For $C_{14}H_{20}$: C 89.29, H 10.71; found: C 89.03, H 10.82.

*1,1,4,5,6,7-Hexamethyl-2,3-dihydro-indane (**32**) and 1,1,4,5,5,8-hexamethyl-hyndrindacene (**33**)*



32 **33**

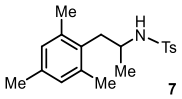
FCC – hexane; **32** + **33** (93% isomeric ratio after purification: 3/2); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 18H), 1.91-1.93 (m, 4H), 2.21 (s, 3H), 2.24 (s, 6H), 2.37 (s, 3H), 2.72-2.78 (m, 4H), 6.83-6.88 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.2, 17.7, 18.0,26.3, 26.8, 27.4, 27.5, 41.4, 41.9, 42.5, 45.4, 126.3, 128.2, 129.8, 130.3, 131.5, 141.8, 144.4, 145.8, 147.7.

[49] Y. Zhang, L. Chen, T. Lu, A copper(II) triflate-catalyzed tandem Friedel-Crafts alkylation/cyclization process towards dihydroindenes, *Adv. Synth Catal.* **2011**, *353*, 1055-1060.

Procedure for the arylation/hydroamination procedure starting from allyl alcohols

In a Schlenk, a mixture of $Cu(OTf)_2$ (10 mol%) and xantphos (20 mol%) in chlorobenzene (0.4 M) was heated at 50 °C for 15. Then, the allyl alcohol (1.0 mmol), the aromatic partner (5.0 mmol) and the appropriate solfonamide (2.0 mmol) were added and the resulting mixture was heated at 75 °C overnight. The resulting solution was diluted with DCM (10 mL), washed with saturated $NaHCO_3$ solution (2 x 10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

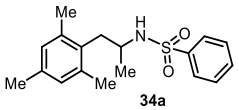
*1-(2,4,6-Trimethylphenyl)-2-tosylamino-propane (**7**)*



7

FCC – AcOEt/hexane (1:1); **7** (81%); light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.14 (d, 3H, *J* = 6.5 Hz), 2.14 (s, 6H), 2.23 (s, 3H), 2.41 (s, 3H), 2.64 (dd, 1H, *J* = 8.0, 14.1 Hz), 2.79 (dd, 1H, *J* = 7.4, 14.1 Hz), 3.41-3.50 (m, 1H), 4.33 (d, 1H, *J* = 6.6 Hz), 6.74 (s, 2H), 7.19 (d, 2H, *J* = 8.2 Hz), 7.56 (d, 2H, *J* = 8.2 Hz).

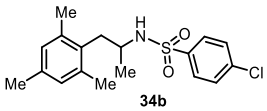
*1-(2,4,6-Trimethylphenyl)-2-phenylamino-propane (**34a**)*



34a

FCC – AcOEt/hexane (1.5:8.5); **34a** (83%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, 3H, *J* = 6.5 Hz), 2.14 (s, 6H), 2.23 (s, 3H), 2.64 (dd, 1H, *J* = 7.9, 14.0 Hz), 2.79 (dd, 1H, *J* = 7.3, 14.0 Hz), 3.44-3.51 (m, 1H), 4.42 (d, 1H, *J* = 6.8 Hz), 6.74 (s, 2H), 7.40 (t, 2H, *J* = 7.5 Hz), 7.52 (t, 1H, *J* = 7.4 Hz), 7.68 (d, 2H, *J* = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.2, 20.8, 21.8, 36.8, 49.9, 126.9, 128.8, 129.3, 131.2, 132.3, 135.8, 136.5, 140.3. IR ν_{max} 2926, 1326, 1158 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{18}H_{22}NO_2S$ [M-H]$^-$: 316.1377; found: 316.1377.

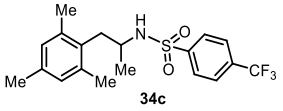
*1-(2,4,6-Trimethylphenyl)-2-(4-chlorophenyl)amino-propane (**34b**)*



34b

FCC – AcOEt/hexane (3:7); **34b** (69%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (d, 3H, *J* = 6.4 Hz), 2.14 (s, 6H), 2.25 (s, 3H), 2.64 (dd, 1H, *J* = 6.9, 14.2 Hz), 2.76 (dd, 1H, *J* = 8.2, 14.1 Hz), 3.44-3.53 (m, 1H), 4.49 (d, 1H, *J* = 7.3 Hz), 6.71 (s, 2H), 7.30 (d, 2H, *J* = 8.4 Hz), 7.53 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.2, 20.8, 22.4, 36.6, 50.3, 128.2, 128.9, 129.3, 131.2, 136.1, 136.3, 138.6, 138.8. IR ν_{max} 2923, 1321, 1163 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{18}H_{21}ClNO_2S$ [M-H]$^-$: 350.0987; found: 350.0977.

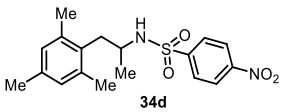
*1-(2,4,6-Trimethylphenyl)-2-(4-trifluoromethyl-phenyl)amino-propane (**34c**)*



34c

FCC – AcOEt/hexane (1:9); **34c** (72%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 3H, *J* = 6.0 Hz), 2.12 (s, 6H), 2.23 (s, 3H), 2.65 (dd, 1H, *J* = 6.6, 14.2 Hz), 2.75 (dd, 1H, *J* = 8.6, 14.2 Hz), 3.48-3.55 (m, 1H), 4.56 (d, 1H, *J* = 7.4 Hz), 6.68 (s, 2H), 7.58 (d, 2H, *J* = 8.3 Hz), 7.69 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.2, 20.6, 22.6, 36.5, 50.4, 125.7, 125.8, 125.8, 125.9, 127.2, 129.3, 131.0, 133.6, 133.9, 136.0, 136.2, 143.7, 143.8. IR ν_{max} 2922, 1339, 1125, 1018 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{21}F_3NO_2S$ [M-H]$^-$: 384.1251; found: 384.1240.

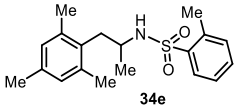
*1-(2,4,6-Trimethylphenyl)-2-(p-nosylamino)-propane (**34d**)*



34d

FCC – AcOEt/hexane (3:7); **34d** (91%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32 (d, 3H, *J* = 6.4 Hz), 2.13 (s, 6H), 2.19 (s, 3H), 2.65 (dd, 1H, *J* = 5.8, 14.4 Hz), 2.73 (dd, 1H, *J* = 9.2, 14.2 Hz), 3.55-3.62 (m, 1H), 4.49 (d, 1H, *J* = 7.8 Hz), 6.64 (s, 2H), 7.69 (d, 2H, *J* = 8.7 Hz), 8.12 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.2, 20.6, 23.1, 36.5, 123.8, 127.8, 129.3, 131.1, 136.2, 136.4, 146.0, 149.5. IR ν_{max} 2918, 1342, 1158 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{18}H_{21}N_2O_4S$ [M-H]$^-$: 361.1228; found: 361.1216.

*1-(2,4,6-Trimethylphenyl)-2-(2-methylphenyl)amino-propane (**34e**)*

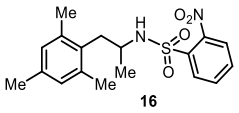


34e

FCC – AcOEt/hexane (1:4); **34e** (88%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (d, 3H, *J* = 6.4 Hz), 2.01 (s, 6H), 2.14 (s, 3H), 2.31 (s, 3H), 2.56 (dd, 1H, *J* = 8.3, 14.0 Hz), 2.69 (dd, 1H, *J* = 7.4, 14.0 Hz), 3.28-3.39 (m, 1H), 4.46 (d, 1H, *J* = 7.1 Hz), 6.64 (s, 2H), 7.10 (d, 1H, *J* = 7.6 Hz), 7.17 (t, 1H, *J* = 6.6 Hz), 7.33 (t, 1H, *J* = 7.4 Hz), 7.85 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.0, 20.2, 20.8, 21.8, 36.7, 49.7, 125.9, 129.3 ,129.6, 131.2, 132.4,

132.7, 135.9, 136.6, 137.2, 137.9. IR ν_{max} 2917, 1299, 1157cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{24}NO_2S$ [M-H]$^-$: 330.1533; found: 330.1532.

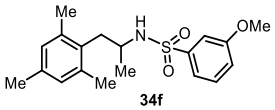
*1-(2,4,6-Trimethylphenyl)-2-(o-nosylamino)-propane (**16**)*



16

FCC – AcOEt/hexane (1:4); **16** (93%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, *J* = 7.5 Hz), 2.16 (s, 3H), 2.19 (s, 6H), 2.72 (dd, 1H, *J* = 7.5, 14.2 Hz), 2.85 (dd, 1H, *J* = 8.0, 14.2 Hz), 3.78-3.85 (m, 1H), 5.31 (t, 1H, *J* = 3.4 Hz), 6.62 (s, 2H), 7.61-7.68 (m, 2H), 7.79 (d, 1H, *J* = 7.6 Hz), 7.98 (d, 1H, *J* = 7.4 Hz).

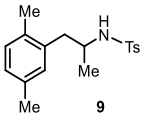
*1-(2,4,6-Trimethylphenyl)-2-(2-methylphenyl)amino-propane (**34f**)*



34f

FCC – AcOEt/hexane (2:3); **34f** (88%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (d, 3H, *J* = 6.5 Hz), 2.09 (s, 6H), 2.16 (s, 3H), 2.59 (dd, 1H, *J* = 8.3, 13.9 Hz), 2.78 (dd, 1H, *J* = 7.0, 13.9 Hz), 3.38-3.46 (m, 1H), 3.75 (s, 3H), 4.81 (d, 1H, *J* = 6.9 Hz), 6.67 (s, 2H), 6.99 (d, 1H, *J* = 7.3 Hz), 7.19 (s, 1H), 7.23-7.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.3, 20.8, 21.6, 36.8, 50..0, 55.5, 111.4, 118.9, 119.2, 129.3, 129.9, 131.3, 135.8, 136.5, 141.6, 159.8. IR ν_{max} 2968, 1309, 1155 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{24}NO_3S$ [M-H]$^-$: 346.1482; found: 346.1468.

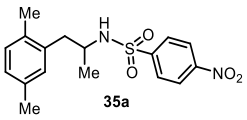
*1-(2,5-Dimethylphenyl)-2-tosylamino-propane (**9**)*



9

FCC – AcOEt/hexane (2:3); **9** (73%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (d, 3H, *J* = 6.4 Hz), 2.09 (s, 3H), 2.24 (s, 3H), 2.41 (s, 3H), 2.59 (dd, 1H, *J* = 7.4, 13.7 Hz), 2.73 (dd, 1H, *J* = 6.9, 13.7 Hz), 3.41-3.48 (m, 1H), 4.72 (d, 1H, *J* = 6.7 Hz), 6.76 (s, 2H), 6.89-6.95 (m, 2H), 7.20 (d, 2H, *J* = 8.1 Hz), 7.59 (d, 2H, *J* = 8.2 Hz).

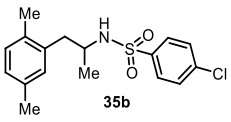
*1-(2,5-Dimethylphenyl)-2-(p-nosylamino)-propane (**35a**)*



35a

FCC – AcOEt/hexane (1:2); **35a** (75%); light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.31 (d, 3H, *J* = 6.4 Hz), 2.09 (s, 3H), 2.19 (s, 3H), 2.58 (dd, 1H, *J* = 8.9, 14.0 Hz), 2.72 (dd, 1H, *J* = 5.5, 14.0 Hz), 3.48-3.58 (m, 1H), 4.49 (d, 1H, *J* = 7.4 Hz), 6.69 (s, 1H), 6.84-6.88 (m, 2H), 7.69 (d, 2H, *J* = 8.8 Hz), 8.13 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 18.8, 20.8, 23.0, 40.9, 51.1, 123.9, 127.8, 130.6, 130.8, 135.1, 135.6, 146.1, 149.6. IR ν_{max} 2921, 1377, 1161 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{17}H_{19}N_2O_4S$ [M-H]$^-$: 347.1071; found: 347.1055.

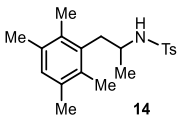
*1-(2,5-Dimethylphenyl)-2-(4-chlorophenyl)amino-propane (**35b**)*



35b

FCC – MeOH/DCM (0.1:9.9); **35b** (68%); light brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.23 (d, 3H, *J* = 6.4 Hz), 2.10 (s, 3H), 2.23 (s, 3H), 2.41 (s, 3H), 2.62 (d, 2H, *J* = 7.2 Hz), 3.43-3.51 (m, 1H), 4.68 (d, 1H, *J* = 6.9 Hz), 6.73 (s, 1H), 6.92 (s, 2H), 7.32 (d, 2H, *J* = 8.6 Hz), 7.54 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 18.8, 20.8, 22.3, 41.0, 50.5, 127.6, 128.2, 129.1, 130.6, 130.8, 132.9, 135.3, 135.4, 138.7, 138.9. IR ν_{max} 2924, 1322, 1159 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{17}H_{19}ClNO_2S$ [M-H]$^-$: 336.0831; found: 336.0828.

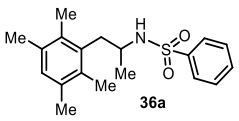
*1-(2,3,5,6-Tetramethylphenyl)-2-tosylamino-propane (**14**)*



14

FCC – AcOEt/hexane (1:4); **14** (78%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, 3H, *J* = 6.5 Hz), 2.04 (s, 6H), 2.16 (s, 6H), 2.41 (s, 3H), 2.77 (dd, 1H, *J* = 7.5, 14.3 Hz), 2.90 (dd, 1H, *J* = 7.8, 14.3 Hz), 3.38-3.45 (m, 1H), 4.51 (d, 1H, *J* = 6.7 Hz), 6.82 (s, 1H), 7.15 (d, 2H, *J* = 8.2 Hz), 7.49 (d, 2H, *J* = 8.3 Hz).

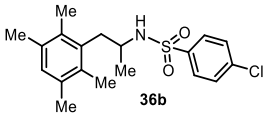
*1-(2,3,5,6-Tetramethylphenyl)-2-phenylamino-propane (**36a**)*



36a

FCC – MeOH/DCM (0.1:9.9); **36a** (85%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, 3H, *J* = 6.5 Hz), 2.03 (s, 6H), 2.16 (s, 6H), 2.78 (dd, 1H, *J* = 7.5, 14.2 Hz), 2.90 (dd, 1H, *J* = 7.9, 14.2 Hz), 3.38-3.45 (m, 1H), 4.44 (d, 1H, *J* = 6.7 Hz), 6.82 (s, 1H), 7.37 (t, 2H, *J* = 7.9 Hz), 7.49 (t, 1H, *J* = 7.4 Hz), 7.60 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 6.1, 20.7, 21.9, 37.2, 50.3, 126.9, 128.8, 130.4, 132.2, 132.5, 133.9, 134.0, 140.1. IR ν_{max} 2920, 1379, 1135 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{24}NO_2S$ [M-H]$^-$: 330.1533; found: 330.1530.

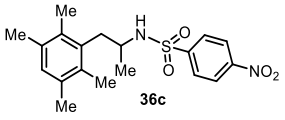
*1-(2,3,5,6-Tetramethylphenyl)-2-(4-chlorophenyl)amino-propane (**36b**)*



36b

FCC – AcOEt/hexane (1:4); **36b** (71%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.29 (d, 3H, *J* = 6.4 Hz), 2.02 (s, 6H), 2.15 (s, 6H), 2.75 (dd, 1H, *J* = 6.2, 14.5 Hz), 2.86 (dd, 1H, *J* = 8.9, 14.5 Hz), 3.39-3.46 (m, 1H), 4.32 (d, 1H, *J* = 7.2 Hz), 6.82 (s, 1H), 7.25 (d, 2H, *J* = 8.6 Hz), 7.41 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.1, 20.6, 22.7, 36.9, 50.7, 128.0, 128.8, 130.3, 132.3, 133.8, 134.1, 138.5, 138.6. IR ν_{max} 2917, 1381, 1135 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{23}ClNO_2S$ [M-H]$^-$: 364.1144; found: 364.1129.

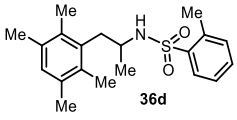
*1-(2,3,5,6-Tetramethylphenyl)-2-(p-nosylamino)-propane (**36c**)*



36c

FCC – AcOEt/hexane (1:4); **36c** (92%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37 (d, 3H, *J* = 6.4 Hz), 2.02 (s, 6H), 2.09 (s, 6H), 2.74 (dd, 1H, *J* = 5.5, 14.8 Hz), 2.85 (dd, 1H, *J* = 9.6, 14.5 Hz), 3.48-3.58 (m, 1H), 4.53 (d, 1H, *J* = 7.8 Hz), 6.73 (s, 1H), 7.59 (d, 2H, *J* = 8.7 Hz), 8.08 (d, 2H, *J* = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.1, 20.5, 23.3, 36.8, 51.4, 123.6, 127.5, 130.3, 133.9, 134.1, 145.8, 149.5. IR ν_{max} 2920, 1345, 1160 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{23}N_2O_4S$ [M-H]$^-$: 375.1384; found: 375.1368.

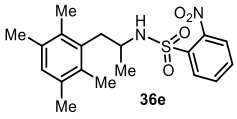
*1-(2,3,5,6-Tetramethylphenyl)-2-(2-methylphenyl)amino-propane (**36d**)*



36d

FCC – AcOEt/hexane (1:4); **36d** (74%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.24 (d, 3H, *J* = 6.5 Hz), 1.97 (s, 6H), 2.15 (s, 6H), 2.26 (s, 3H), 2.76 (dd, 1H, *J* = 7.4, 14.3 Hz), 2.88 (dd, 1H, *J* = 8.2, 14.3 Hz), 3.22-3.39 (m, 1H), 4.36 (d, 1H, *J* = 6.2 Hz), 6.82 (s, 1H), 7.14 (d, 1H, *J* = 7.4 Hz), 7.23-7-25 (m, 1H), 7.40 (t, 1H, *J* = 9.0 Hz), 7.90 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.0, 19.8, 20.6, 22.1, 37.1, 50.0, 125.8, 129.7, 130.4, 132.4, 132.5, 132.6, 133.8, 134.1, 137.1, 137.5. IR ν_{max} 2918, 1315, 1125 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{20}H_{26}NO_2S$ [M-H]$^-$: 344.1690; found: 344.1686.

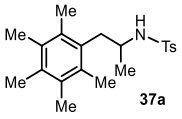
*1-(2,3,5,6-Tetramethylphenyl)-2-(o-nosylamino)-propane (**36e**)*



36e

FCC – AcOEt/hexane (1:4); **36e** (87%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (d, 3H, *J* = 6.5 Hz), 2.07 (s, 6H), 2.08 (s, 6H), 2.84 (dd, 1H, *J* = 6.9, 14.5 Hz), 2.97 (dd, 1H, *J* = 8.6, 14.6 Hz), 3.69-3.79 (m, 1H), 5.33 (d, 1H, *J* = 6.4 Hz), 6.66 (s, 1H), 7.607.65 (m, 2H), 7.76-7.79 (m, 1H), 7.91-7.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.2, 20.6, 22.8, 36.9, 51.9, 125.5, 130.3, 130.3, 132.5, 132.6, 132.8, 133.8, 133.9, 134.6. IR ν_{max} 2920, 1344, 1163 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{23}N_2O_4S$ [M-H]$^-$: 375.1384; found: 375.1375.

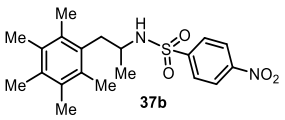
*1-(2,3,4,5,6-Pentamethylphenyl)-2-tosylamino-propane (**37a**)*



37a

FCC – DCM; **37a** (85%); white solid; m.p.: 169-170 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (d, 3H, *J* = 6.4 Hz), 2.08 (s, 6H), 2.15 (s, 6H), 2.14 (s, 3H), 2.40 (s, 3H), 2.78 (dd, 1H, *J* = 7.3, 14.5 Hz), 2.91 (dd, 1H, *J* = 7.9, 14.5 Hz), 3.33-3.41 (m, 1H), 4.29 (d, 1H, *J* = 6.4 Hz), 7.12 (d, 2H, *J* = 8.0 Hz), 7.46 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.8, 16.9, 17.1, 21.5, 21.9, 37.5, 50.5, 126.9, 129.2, 131.2, 132.1, 132.8, 133.3, 137.1, 142.8. IR ν_{max} 2919, 1319, 1135 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{21}H_{28}NO_2S$ [M-H]$^-$: 358.1846; found: 358.1835.

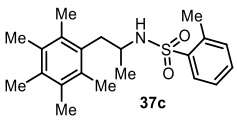
*1-(2,3,4,5,6-Pentamethylphenyl)-2-(p-nosylamino)-propane (**37b**)*



37b

FCC – AcOEt/hexane (2:3); **37b** (88%); orange solid; m.p.: 183-185 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.38 (d, 3H, *J* = 6.4 Hz), 2.07 (s, 12H), 2.15 (s, 3H), 2.76 (dd, 1H, *J* = 5.2, 14.9 Hz), 2.86 (dd, 1H, *J* = 9.8, 14.8 Hz), 3.48-3.59 (m, 1H), 4.46 (d, 1H, *J* = 8.2 Hz), 7.57 (d, 2H, *J* = 8.7 Hz), 8.03 (d, 2H, *J* = 8.7Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.7, 16.8, 17.1, 23.4, 37.1, 51.7, 123.4, 127.6, 131.1, 131.7, 132.9, 133.8, 145.8, 149.2. IR ν_{max} 2920, 1349, 1165 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{20}H_{25}N_2O_4S$ [M-H]$^-$: 389.1541; found: 389.1530.

*1-(2,3,4,5,6-Pentamethylphenyl)-2-(2-methylphenyl)amino-propane (**37c**)*

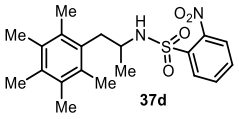


37c

FCC – AcOEt/hexane (2:3); **37c** (77%); yellow solid; m.p.: 115-117 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (d, 3H, *J* = 6.4 Hz), 2.06 (s, 6H), 2.15 (s, 6H), 2.23 (s, 3H), 2.28 (s, 3H), 2.81 (dd, 1H, *J* = 7.3, 14.5 Hz), 2.92 (dd, 1H, *J* = 8.2, 14.5 Hz), 3.32-3.40 (m, 1H), 4.50 (d, 1H, *J* = 6.4 Hz), 7.12 (d, 1H, *J* = 7.5 Hz), 7.26 (d, 1H, *J* = 7.6 Hz), 7.42 (t, 1H, *J* = 7.4 Hz), 7.92 (d, 1H, *J* = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.9, 16.9, 17.0, 22.2, 37.4, 50.4, 125.7, 129.7, 131.2,

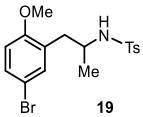
132.1, 132.2, 132.8, 133.4, 137.1, 137.6. IR ν_{max} 2932, 1347, 1126 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{21}H_{28}NO_2S$ $[M-H]^-$: 358.1846; found: 358.1835.

*1-(2,3,4,5,6-Pentamethylphenyl)-2-(o-nosylamino)-propane (**37d**)*



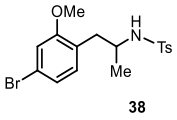
FCC – AcOEt/hexane (2:3); **37d** (89%); yellow solid; m.p.: 130-132 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (d, 3H, *J* = 6.5 Hz), 2.04 (s, 6H), 2.11 (s, 3H), 2.12 (s, 6H), 2.86 (dd, 1H, *J* = 6.6, 14.8 Hz), 2.98 (dd, 1H, *J* = 8.9, 14.8 Hz), 3.70-3.79 (m, 1H), 5.35 (d, 1H, *J* = 6.3 Hz), 7.57-7.64 (m, 2H), 7.74 (d, 1H, *J* = 9.4 Hz), 7.92 (d, 1H, *J* = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 16.9, 17.2, 22.9, 37.1, 130.4, 131.1, 132.1, 132.5, 132.7, 133.1, 134.6, 146.7. IR ν_{max} 2922, 1346, 1128 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{20}H_{25}N_2O_4S$ $[M-H]^-$: 389.1541; found: 389.1530.

*1-(5-Bromo-2-methoxyphenyl)-2-tosylamino-propane (**19**)*



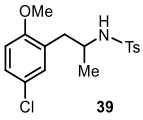
FCC – DCM; **19** (63%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, *J* = 3.6 Hz), 2.40 (s, 3H), 2.49 (dd, 1H, *J* = 4.9, 13.6 Hz), 2.71 (dd, 1H, *J* = 10.7, 13.6 Hz), 3.39-3.47 (m, 1H), 3.77 (s, 3H), 4.79 (d, 1H, *J* = 6.2 Hz), 6.95 (s, 1H, *J* = 2.3 Hz), 7.11 (d, 2H, *J* = 8.1 Hz), 7.20-7.23 (m, 1H), 7.43 (d, 2H, *J* = 8.2 Hz).

*1-(4-Bromo-2-methoxyphenyl)-2-tosylamino-propane (**38**)*



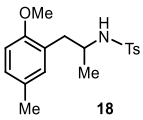
FCC – AcOEt/hexane (1:4); **38** (71%); light brown oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.21 (d, 3H, *J* = 6.5 Hz), 2.39 (s, 3H), 2.73 (d, 2H, *J* = 7.2 Hz), 3.55-3.63 (m, 1H), 3.77 (s, 3H), 4.39 (d, 1H, *J* = 6.2 Hz), 6.67 (d, 1H, *J* = 11.1 Hz), 6.93 (d, 2H, *J* = 7.8 Hz), 7.15 (d, 2H, *J* = 8.3 Hz), 7.54 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.4, 22.3, 42.3, 50.5, 55.4, 113.5, 118.1, 124.7, 126.9, 129.4, 131.6, 137.4, 142.8, 158.9. IR ν_{max} 2918, 1378, 1199 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{17}H_{19}BrNO_3S$ $[M-H]^-$: 396.0275; found: 396.0261.

*1-(5-Chloro -2-methoxyphenyl)-2-tosylamino-propane (**39**)*



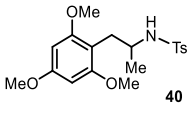
FCC – MeOH/DCM (0.5:9.5); **39** (69%); light yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, *J* = 5.9 Hz), 2.39 (s, 3H), 2.49 (dd, 1H, *J* = 5.0, 13.7 Hz), 2.71 (dd, 1H, *J* = 9.3, 13.5 Hz), 3.40-3.47 (m, 1H), 3.77 (s, 3H), 4.79 (d, 1H, *J* = 5.9 Hz), 6.65 (d, 1H, *J* = 8.7 Hz), 6.80 (d, 1H, *J* = 2.2 Hz), 7.06-7.09 (m, 1H), 7.11 (d, 2H, *J* = 7.9 Hz), 7.44 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.5, 22.9, 37.1, 51.1, 55.7, 111.6, 125.7, 126.7, 127.5, 127.7, 129.3, 130.7, 142.8, 144.3, 155.7 IR ν_{max} 2918, 1326, 1157 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{17}H_{19}ClNO_3S$ $[M-H]^-$: 352.0780; found: 352.0778.

*1-(5-Methyl -2-methoxyphenyl)-2-tosylamino-propane (**18**)*



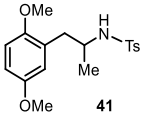
FCC – AcOEt/hexane (1:4); **18** (66%); yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25 (d, 3H, *J* = 6.6 Hz), 2.18 (s, 3H), 2.38 (s, 3H), 2.51 (dd, 1H, *J* = 4.9, 13.6 Hz), 2.69 (dd, 1H, *J* = 8.9, 13.6 Hz), 3.38-3.45 (m, 1H), 3.74 (s, 3H), 4.99 (d, 1H, *J* = 5.3 Hz), 6.63-6.66 (m, 2H), 6.94 (s, 1H, *J* = 8.3 Hz), 7.08 (d, 2H, *J* = 8.1 Hz), 7.42 (d, 2H, *J* = 8.2 Hz).

*1-(2,4,6-Trimethoxyphenyl)-2-tosylamino-propane (**40**)*



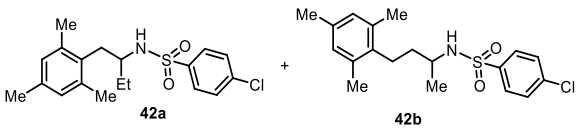
FCC – DCM; **40** (78%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (d, 3H, *J* = 6.4 Hz), 2.37 (s, 3H), 2.49-2.61 (m, 2H), 3.26-3.33 (m, 1H), 3.69 (s, 6H), 3.80 (s, 3H), 5.09 (d, 1H, *J* = 5.4 Hz), 5.93 (s, 2H), 7.00 (d, 2H, *J* = 8.0 Hz), 7.34 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.4, 23.5, 23.4, 50.8, 55.2, 55.5, 106.6, 126.6, 128.9, 137.1, 141.9, 158.4, 160.0. IR ν_{max} 2920, 1379, 1207, 1160 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{24}NO_5S$ $[M-H]^-$: 378.1381; found: 378.1359.

*1-(2,5-Dimethoxyphenyl)-2-tosylamino-propane (**41**)*



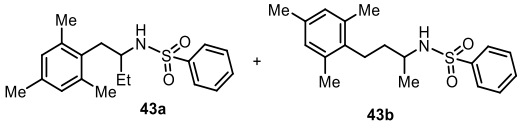
FCC – DCM; **41** (72%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (d, 3H, *J* = 6.6 Hz), 2.37 (s, 6H), 2.49 (dd, 1H, *J* = 4.9, 13.6 Hz), 2.73 (dd, 1H, *J* = 9.0, 13.6 Hz), 3.36-3.45 (m, 1H), 3.69 (s, 3H), 3.74 (s, 3H), 5.06 (d, 1H, *J* = 5.4 Hz), 6.41 (s, 1H), 6.68 (s, 2H), 7.08 (d, 2H, *J* = 8.0 Hz), 7.43 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.4, 22.8, 37.4, 51.2, 55.6, 55.9, 111.5, 112.2, 116.7, 126.8, 127.0, 129.2, 137.1, 142.5, 151.2, 153.7. IR ν_{max} 2929, 1319, 1223, 1155 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{18}H_{22}NO_4S$ $[M-H]^-$: 348.1275; found: 348.1273.

*1-(2,4,6-Trimethylphenyl)-2-(4-chlorophenyl)amino-butane and 1-(2,4,6-trimethylphenyl)-3-(4-chlorophenyl)amino-butane 1-(2,4,6-trimethylphenyl)-(4-chlorophenyl)amino-butane (**42a** + **42b**)*



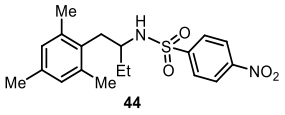
FCC – DCM; ***42a*** *+* ***42b*** (61% isomeric ratio after purification: 1/1.3); colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) compound **42a** δ 0.93 (t, 3H, *J* = 7.9 Hz), 1.57-1.67 (m, 2H), 2.14 (s, 6H), 2.31 (s, 3H), 2.66-2.75 (m, 2H), 3.34-3.41 (m, 1H), 4.31 (d, 1H, *J* = 7.8 Hz), 6.90 (s, 2H), 7.44-7.44 (m, 2H), 7.73 (d, 2H, *J* = 8.5 Hz); compound **42b** δ 1.16 (d, 3H, *J* = 6.6 Hz), 1.40-1.54 (m, 2H), 2.19 (s, 6H), 2.24 (s, 3H), 2.40-2.49 (m, 1H), 2.51-2.53 (m, 1H), 3.42-3.49 (m, 1H), 4.37 (d, 1H, *J* = 8.3 Hz), 6.81 (s, 2H), 7.49 (d, 2H, *J* = 8.4 Hz), 7.84 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 19.5, 20.3, 20.8, 21.0, 21.7, 22.8, 25.5, 29.1, 34.4, 36.8, 50.8, 55.9, 127.7, 128.0, 128.4, 128.8, 128.9, 129.2, 129.4, 131.3, 132.3, 134.8, 135.3, 135.6, 136.0, 136.3, 139.0, 140.1, 142.1, 143.7. IR ν_{max} 2919, 1314, 1155 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{23}ClNO_2S$ $[M-H]^-$: 364.1144; found: 364.1128.

*1-(2,4,6-Trimethylphenyl)-2-phenylamino-butane and 1-(2,4,6-trimethylphenyl)-3-phenylamino-butane 1-(2,4,6-trimethylphenyl)-(4-chlorophenyl)amino-butane (**43a** + **43b**)*



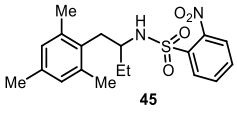
FCC – MeOH/DCM (1:50); ***43a*** *+* ***43b*** (66% isomeric ratio after purification: 1/1.3); colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) compound **43a** δ 0.84 (t, 3H, *J* = 7.3 Hz), 1.39-1.66 (m, 2H), 2.18 (s, 6H), 2.23 (s, 3H), 2.38-2.46 (m, 1H), 2.49-2.58 (m, 1H), 3.43-3.50 (m, 1H), 4.38 (d, 1H, *J* = 8.7 Hz), 6.80 (s, 2H), 7.36 (t, 1H, *J* = 7.8 Hz), 7.48-7.52 (m, 2H), 7.92 (d, 2H, *J* = 9.0 Hz); compound **43b** δ 1.14 (d, 3H, *J* = 6.6 Hz), 1.39-1.66 (m, 2H), 2.15 (s, 6H), 2.22 (s, 3H), 2.68 (dd, 1H, *J* = 7.6, 14.2 Hz), 2.78 (dd, 1H, *J* = 7.8, 14.1 Hz) 3.33-3.39 (m, 1H), 4.33 (d, 1H, *J* = 7.7 Hz), 6.70 (s, 2H), 7.48-7.52 (m, 3H), 7.63 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.0, 19.6, 20.3, 20.7, 20.7, 21.8, 25.5, 28.2, 34.8, 36.8, 50.7, 55.6, 126.8, 126.9, 128.7, 128.9, 129.1, 129.3, 131.4, 132.1, 132.6, 134.9, 135.2, 135.6, 135.7, 136.5, 140.5, 141.2. IR ν_{max} 2965, 1322, 1158 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{24}NO_2S$ $[M-H]^-$: 330.1533; found: 330.1531.

*1-(2,4,6-Trimethylphenyl)-(p-nosyl)butane (**44**)*



FCC – AcOEt/PE (1:4); ***44*** (68%); yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, 3H, *J* = 7.5 Hz), 21.66-1.73 (m, 2H), 2.12 (s, 6H), 2.18 (s, 3H), 2.68 (d, 2H, *J* = 7.6 Hz), 3.49-3.51 (m, 1H), 4.35 (d, 1H, *J* = 7.8 Hz), 6.59 (s, 2H), 7.62 (d, 2H, *J* = 8.2 Hz), 8.08 (d, 2H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.8, 20.3, 20.6, 29.7, 29.7, 34.2, 56.6, 123.7, 123.9, 127.5, 129.2, 133.8, 136.3, 136.4, 146.2, 146.5, 152.4. IR ν_{max} 2918, 1347, 1155 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{23}N_2O_4S$ $[M-H]^-$: 375.1384; found: 375.1379.

*1-(2,4,6-Trimethylphenyl)-2-(o-nosyl)-butane (**45**)*



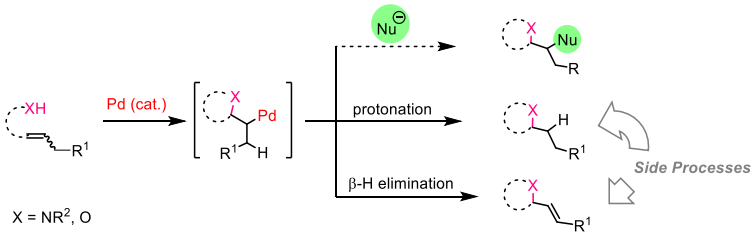
FCC – AcOEt/PE (1:4); ***45*** (63%); yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.97 (t, 3H, *J* = 7.4 Hz), 1.58-1.72 (m, 2H), 2.13 (s, 3H), 2.18 (s, 6H), 2.75 (dd, 1H, *J* = 6.9, 14.4 Hz), 2.80 (dd, 1H, *J* = 8.8, 14.4 Hz), 3.71-3.80 (m, 1H), 5.26 (d, 1H, *J* = 7.9 Hz), 6.54 (s, 2H), 7.54-7.64 (m, 2H), 7.76-7.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.3, 20.4, 20.7, 29.3, 29.7, 34.8, 56.9, 125.3, 129.1, 129.1, 129.9, 131.2, 131.2, 132.4, 132.8, 135.5, 136.5, 144.4. IR ν_{max} 2916, 1356, 1164 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{19}H_{23}N_2O_4S$ $[M-H]^-$: 375.1384; found: 375.1382.

CHAPTER 3

PALLADIUM-CATALYZED AZIDATION PROCEDURES OF UNACTIVATED ALKENES

3.1 INTRODUCTION

Palladium-catalyzed couplings have become an invaluable tool for the organic chemist, because they allow to synthesize a number of complex products via an amazing number of different mechanisms. This transition metal is greatly used in synthetic procedures for the preparation of fine chemicals, pharmaceutically active compounds, agrochemicals and advanced materials. In the context of palladium-catalyzed procedures, difunctionalization of unactivated alkenes had recently become a powerful tool to prepare vicinal disubstituted products.[50] Various combination of functional groups had been installed on hydrocarbons, also in intra/intermolecular procedures resulting in differently functionalized heterocyclic systems. The success in these reactions depends on the nature of the palladium intermediate and on the reaction conditions to prevent undesired side reactions of protonation and β-hydride elimination (Scheme 39). Generally, palladium appears in three oxidation states: Pd(0), Pd(II) and Pd(IV) where the first combination - Pd(0)/Pd(II) - typically occurs in classical coupling reactions like Heck, Suzuki, Stille, Sonogashira reactions and, more recently, in C-C bond formation through C-H activation.[51] On the other hand, already at the end of the last century it was known that the use of appropriate oxidants such as hypervalent iodine compounds (e.g. PIFA and PIDA), oxone, H_2O_2 and Selectfluor®, favour the catalytic cycle Pd(II)/Pd(IV).[52]



Scheme 39. Possible procedures on alkyl-palladium intermediate

In this scenario, reactions involving the introduction of an azido group in both inter and intramolecular procedures are rather rare, and this was true in particular for aminoazidation procedures, despite organoazides are versatile intermediates valuable for a wide range of application in organic synthesis.[53] Recently, we reported a new palladium-catalyzed procedure to convert aminoalkenes into azidomethyl substituted nitrogen-containing heterocycles.[54] This synthetic protocol provides five-, six-, and seven-membered heterocyclic rings through a selective *exo*-cyclization/azidation of unactivated terminal alkenes (Scheme 40). The conditions involved the use of H_2O_2 as inexpensive oxidant which was essential to generate a Pd(IV) specie as the key-intermediate for the reaction.

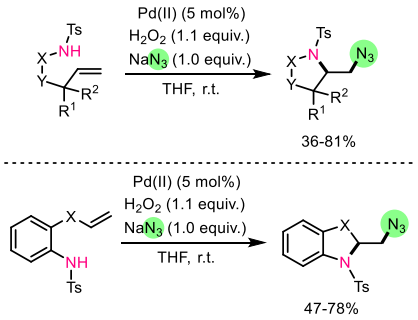
[50] G. Yin, X. Mu, G. Li, Palladium(II)-Catalyzed Oxidative Difunctionalization of Alkenes: Bond Forming at a High-Valent Palladium Center, *Acc. Chem. Res*. **2016**, *49*, 2413-2423.

[51] a) S. Jagtap, Heck Reaction – State of the Art, *Catalysts* **2017**, *7*, 267; b) X. Chen, K. M. Engle, H. Wang, J.-Q. Yu, Palladium(II)-Catalyzed C-H Activation/C-C Cross-Coupling Reactions: Versatility and Practicality, *Angew. Chem. Int. Ed.* **2009**, *48*, 5094-5115.

[52] E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, C-C, C-O, C-N Bond Formation on sp^2 Carbon by Pd(II)-Catalyzed Reactions Involving Oxidant Agents, *Chem. Rev.* **2007**, *107*, 5318-5365.

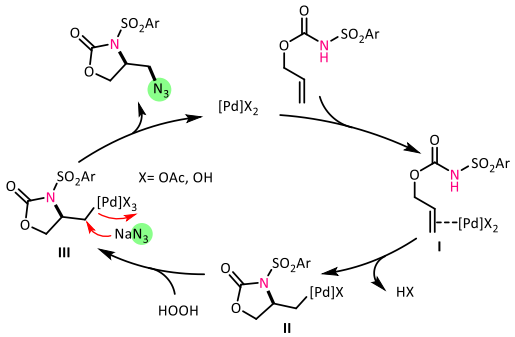
[53] R. Sala, C. Loro, F. Foschi, G. Broggini, Transition Metal Catalyzed Azidation Reactions, *Catalyst* **2020**, *10*, 1173.

[54] F. Foschi, C. Loro, R. Sala, J. Oble, L. Lo Presti, E. M. Beccalli, G. Poli, G. Broggini, Intramolecular Aminoazidation of Unactivated Terminal Alkenes by Palladium-Catalyzed Reactions with Hydrogen Peroxide as the Oxydant, *Org. Lett.* **2020**, *22*, 1402-1406.



Scheme 40. Pd-Catalyzed aminoazidation of unactivated terminal alkenes

The possible mechanism, reported in Scheme 4, starts with the exocyclic nucleopalladation of complex **I** to generate the π-alkyl-palladium(II) intermediate **II**. The subsequent substitution of the azide anion of the C-Pd(IV) bond affords the final amination/azidation product with the regeneration of the catalyst.



Scheme 41. Possible mechanism Pd(II)/Pd(IV)

Following our interest in azidation procedures, we proposed a new method for the palladium-catalyzed diazidation of aminoalkenes. 1,2-Diazide compounds are ideal precursors for vicinal primary diamines which were proven to be important motifs in biological active products.[55] Different approaches starting from alkenes to afford 1,2-diazides are reported in the literature. Some of them involve electrochemical activation, often combined with a transition-metal catalyst.[56]

Concerning the classical transition-metal procedures, iron and copper catalysts are the most used for the generation of an azido radical which activates an appropriate carbon-carbon double bond for a cascade difunctionalization.

In 1962, Minisci and Galli reported the pioneering work for the radical diazidation of alkenes promoted by a Fe(II)/Fe(III) system in the presence of H_2O_2 as the oxidant.[57]

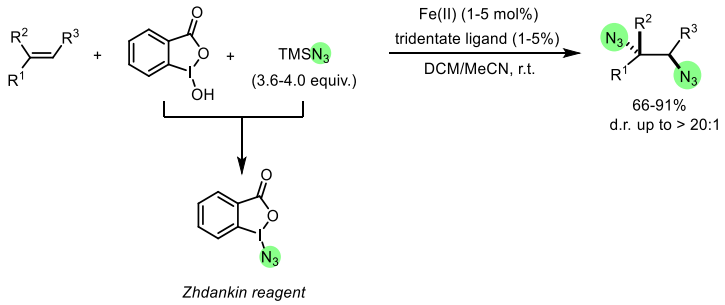
About fifty years later, Xu *et al.* focused their attention on iron-catalyzed *trans*-diazidation of unactivated olefins.[58] The reaction involves the *in situ* formation of the Zhdankin reagent (ABX) which was generated from $TMSN_3$ and a benziodoxole (Scheme 42).

[55] E. T. Michalson, J. Szmuszkovicz, Medicinal agents incorporating the 1,2-diamine functionality, *Prog. Drug Res.* **1989**, *33*, 135-149.

[56] a) C.-Y. Cai, Y.-T. Zheng, J.-F. Li, H.-C. Xu, Cu-Electrocatalytic Diazidation of Alkenes at ppm Catalyst Loading, *J. Am. Chem. Soc.* **2022**, *144*, 11980-11985; b) G. S. Sauer, S. Lin, An Electrocatalytic Approach to the Radical Difunctionalization of Alkenes, *ACS Catal.* **2018**, *8*, 5175-5187; c) N. Ahmed, S. Khatoon, B. Shirinfar, Radical Diazidation of Alkenes: Cu/Fe/Mn Catalysis and Electrochemical Support, *ChemElectroChem* **2018**, *5*, 1245-1248; d) N. Fu, G. S. Sauer, A. Saha, A. Loo, S. Lin, Metal-catalyzed electrochemical diazidation of alkenes, *Science* **2017**, *357*, 575-579.

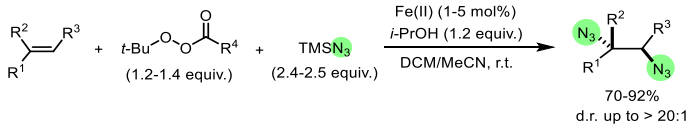
[57] F. Minisci, R. Galli, Reactivity of hydroxy and alkoxy radicals in presence of olefins and oxidation-reduction systems. Introduction of azido, chloro and acyloxy groups in allylic position and azido-chlorination of olefins. Tetrahedron Lett. **1963**, *6*, 357-360.

[58] Y.-A. Yuan, D.-F. Lu, Y.-R. Chen, H. Xu, Iron-Catalyzed Direct Diazidation for a Broad Range of Olefins, *Angew. Chem. Int. Ed.* **2016**, *128*, 534-538.



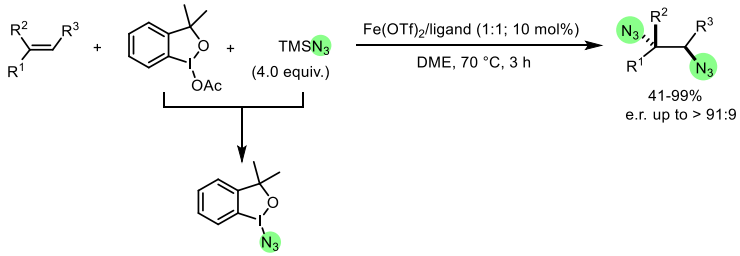
Scheme 42. Fe-Catalyzed diazidation of unactivated alkenes with the *in situ* formation of Zhdankin reagent

The same group proposed a new Fe(II)-catalyzed diazidation of alkenes via activation of peroxyesters promoted by nitrogen-based ligands.[59] In this method, the iron-ligand complex reductively cleaves the O-O bond of the peroxyester to generate the corresponding radical which facilitates the formation of the azide radical (Scheme 43).



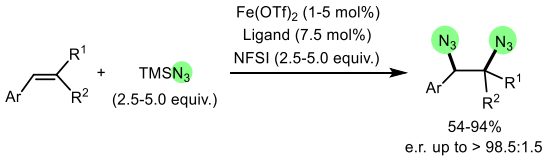
Scheme 43. Diazidation of unactivated alkenes via peroxyester activation

In 2021 Liu, Wu, Feng and co-workers reported a Fe-catalyzed enantioselective synthesis of 1,2-diazides starting from α,β-unsaturated carbonyl compounds.[60] The *in situ* formation of an azide-containing cyclic hypervalent iodine(III) species allowed the generation an azido radical in the easiest way (Scheme 44).



Scheme 44. Enantioselective diazidation of α,β-unsaturated carbonyl compounds

The same year Bao *et al.* proposed an asymmetric diazidation of styrenes with the same type of iron catalyst (Scheme 45).[61] In this case, the *N*-fluorobenzenesulfonamide was used as *N*-radical precursor to generate radical species through a single electron transfer process, with the iron catalyst as the promoter for the radical procedure.



Scheme 45. Iron-catalyzed asymmetric diazidation of styrenes

Moving on the copper-catalyzed reactions, Loh and co-workers reported new conditions to obtain alkyl azides from styrenes using CuI as catalyst and Zhdankin reagent as azide source (Scheme 46, eq. A).[62] This latter,

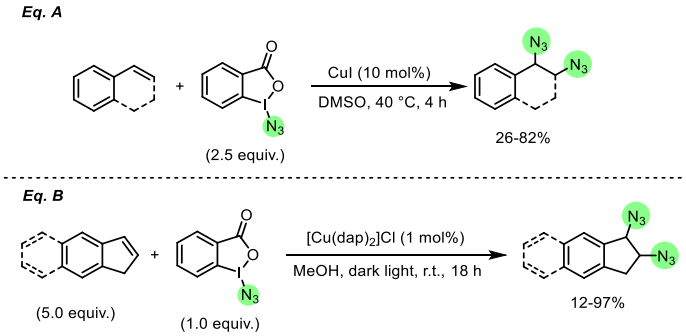
[59] S.-J. Shen, C.-L. Zhu, D.-F. Lu, H. Xu, Iron-Catalyzed Direct Olefin Diazidation via Peroxyester Activation Promoted by Nitrogen-Based Ligand, *ACS Catal.* **2018**, *8*, 4473-4482.

[60] W. Liu, M. Pu, J. He, T. Zhang, S. Dong, X. Liu, Y.-D. Wu, X. Feng, Iron-Catalyzed Enantioselective Radical Carboazidation and Diazidation of α,β-Unsaturated Carbonyl Compounds, *J. Am. Chem. Soc.* **2021**, *143*, 11856-11863.

[61] D. Lv, Q. Sun, H. Zhou, L. Ge, Y. Qu, T. Li, X. Ma, Y. Li, H. Bao, Iron-Catalyzed Radical Asymmetric Aminoazidation and Diazidation of Styrenes, *Angew Chem. Int. Ed.* **2021**, *60*, 12455-12460.

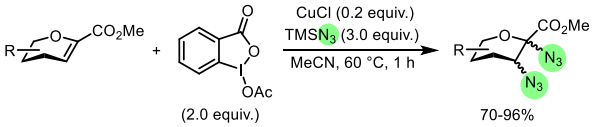
[62] M.-Z. Lu, C.-Q. Wang, T.-P. Loh, Copper-Catalyzed Vicinal Oxyazidation and Diazidation of Styrenes under Mild Conditions: Access to Alkyl Azides, *Org. Lett.* **2015**, *17*, 6110-6113.

combined with $[Cu(dap)_2]Cl$ (a copper complex bearing two phenanthroline ligands) as catalyst in absence of visible light, was used for the diazidation of styrene-type double bonds (Scheme 46, eq. B).[63]



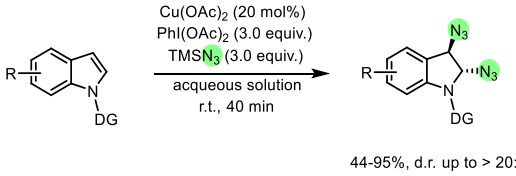
Scheme 46. Copper-catalyzed diazidation of styrenes-type double bond with ABX

In 2021, Qin used a copper-catalyzed synthetic protocol to generate 2,3-diazidation sugar acid derivatives through a radical pathway involving the *in situ* generation of the ABX compound, as shown in Scheme 47.[64]



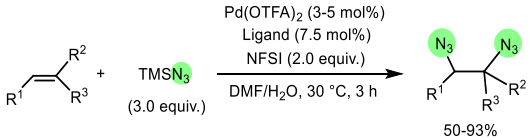
Scheme 47. Copper-catalyzed glycal diazidation

A Cu-catalyzed procedure which didn't involve the use of the Zhdankin reagent as azide source was the diastereoselective 2,3-diazidation of indoles.[65] In this case the combination of $TMSN_3$ and (diacetoxyiodo)benzene as oxidant allowed the obtainment of the azido radical, which was rapidly inserted into the indole C2-position (Scheme 48).



Scheme 48. Diasteroselective Cu(II)-catalyzed 2,3-diazidation of indoles

To the best of our knowledge, the sole example of diazidation reactions catalyzed by palladium has been proposed by Liu and co-workers in 2017 (Scheme 49).[66] The Pd(II)/Pd(IV) procedure, which involves a Pd(III) species, was promoted by *N*-fluorobenzenesulfonamide as oxidant in the presence of $TMSN_3$ as azide source. Working with cyclic alkenes, the authors observed that the diasteroselectivity rapidly increased simply using water as co-solvent.



Scheme 49. Pd-catalyzed diazidation of alkenes with NFSI and $TMSN_3$

[63] G. Fumagalli, P. T. G. Rabet, S. Boyd, M. F. Greaney, Three-Component Azidation of Styrene-Type Double-Bonds: Light-Switchable Behavior of a Copper Photoredox Catalyst, *Angew. Chem. Int Ed.* **2015**, *54*, 11481-11484.

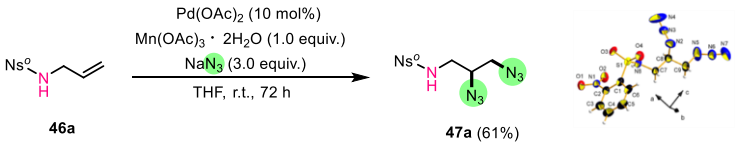
[64] R. Cao, H. He, C. Zhang, X.-Y. Liu, Y. Qin, An improved glycal diazidation protocol with copper catalyst, *Tetrahedron Lett.* **2021**, *70*, 153010.

[65] R.J. Liu, Z. Fang, X. Liu, Y. Dou, J. Jiang, F. Zhang, J. Qu, Q. Zhu, Diasteroselective 2,3-diazidation of indoles *via* copper(II)-catalyzed dearomatization, *Chin. Chem. Lett.* **2020**, *31*, 1332-1336.

[66] H. Peng, Z. Yuan, P. Chen, G. Liu, Palladium-Catalyzed Intermolecular Oxidative Diazidation of Alkenes, *Chin. J. Chem.* **2017**, *35*, 876-880.

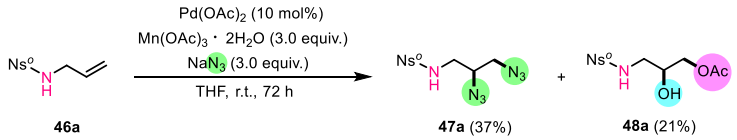
3.2 PALLADIUM-CATALYZED DIFUNCTIONALIZATION OF UNACTIVATED ALKENES

In order to investigate new azidation reactions, we choose the *N*-allyl *o*-nosylsulfonamide **46a** as initial model substrate and - after some preliminary experimentations - we found that working with $Pd(OAc)_2$ (10 mol%), $Mn(OAc)_3{\cdot}2H_2O$ (1.0 equiv.) and NaN_3 (3.0 equiv.) in THF at room temperature, 72 h afforded the 2,3-diazidation product **47a** in 61% yield (Scheme 50). The single-crystal X-ray structure analysis of compound **47a** gave unambiguous proof for the formation of this product.[67]



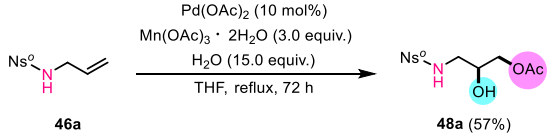
Scheme 50. Pd-Catalyzed diazidation of *N*-allyl *o*-nosylsulfonamide

The reactions carried out in acetonitrile or dichloromethane gave only unreacted substrate. The product **47a** was achieved using a co-catalytic quantity of $Mn(OAc)_3{\cdot}2H_2O$, even if in lower yield than that obtained with a stoichiometric amount of the oxidant.
It is worth noting that the substrate **46a** treated with a larger quantity of Mn(III) species (*i.e.* 3.0 equivalents) gave also a regioselective hydroxylation/alkoxylation process furnishing compound **48a**, as showed in Scheme 51.



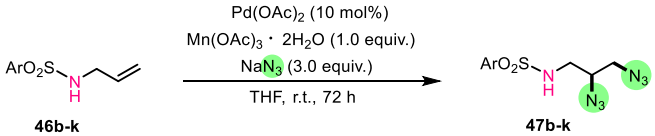
Scheme 51. Pd-Catalyzed hydroxylation/alkoxylation of *N*-allyl *o*-nosylsulfonamide

The compound **48a** was obtained selectively carrying out the reaction overnight at reflux without azide sources. Also in this case, other solvents inhibited the conversion of the substrates and only the addition of 15.0 equivalents of water in the reaction medium increased the yield to 57% (Scheme 52).

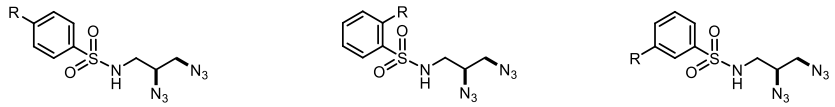


Scheme 52. Pd-Catalyzed hydroxylation/alkoxylation of *N*-allyl *o*-nosylsulfonamide

Focusing on the diazidation procedure, the reaction conditions were tested on *N*-allyl sulfonamides bearing different groups on the aromatic ring. Substrates bearing electron-withdrawing and electron-donating groups furnished the expected products in good yields (Scheme 53).



[67] X-Ray diffraction analysis of compound **47a** carried out by Prof. L. Lo Presti from Università degli Studi di Milano.



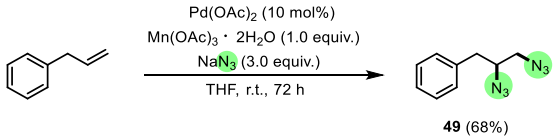
R = Me **47b** (67%)
R = H **47c** (58%)
R = Cl **47d** (61%)
R = CF_3 **47e** (56%)
R = NO_2 **47f** (65%)

R = Me **47g** (60%)
R = OCF_3 **47j** (54%)

R = OMe **47k** (66%)

Scheme 53. Pd-Catalyzed diazidation procedure on different *N*-allyl sulfonamides

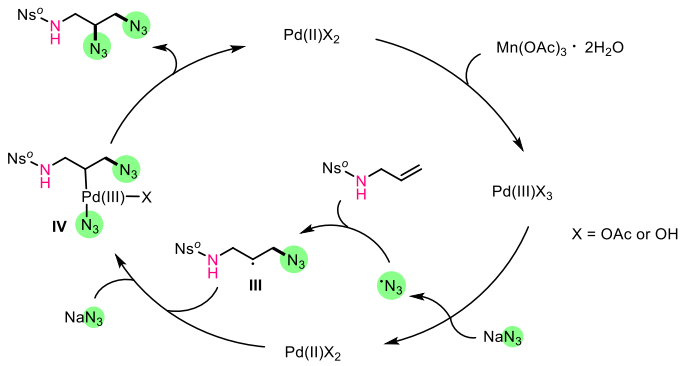
To further test the scope of this behaviour, the reaction conditions were applied to the allyl benzene and, gratifyingly, the corresponding 2,3-diazidation product **49** was isolated in good yields (Scheme 54).



49 (68%)

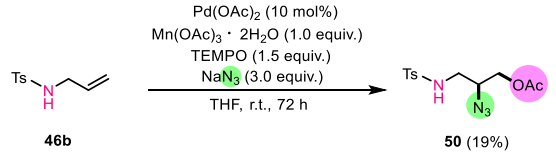
Scheme 54. Pd-Catalyzed diazidation on allyl benzene

Being reported in the literature that manganese(III) acetate could mediate radical reactions acting as one-electron oxidant, we propose the mechanism shown in Scheme 55.[68] After the initial oxidation of the catalyst, the palladium species could generate the azido radical. This latter undergoes a quick addition to the alkene giving the carbon radical **III** which is probably trapped by the palladium species. The subsequent ligand exchange on the so-obtained intermediate **IV** through a reductive elimination provides the vicinal diazidation product.



Scheme 55. Hypothesized reaction mechanism for the diazidation procedure

To have experimental evidence of the radical pathway, we add 1.5 equivalents of the radical scavenger TEMPO in the reaction mixture. In these conditions, we observed the formation of the 3-acetoxy-2-azido product **50** (Scheme 56).

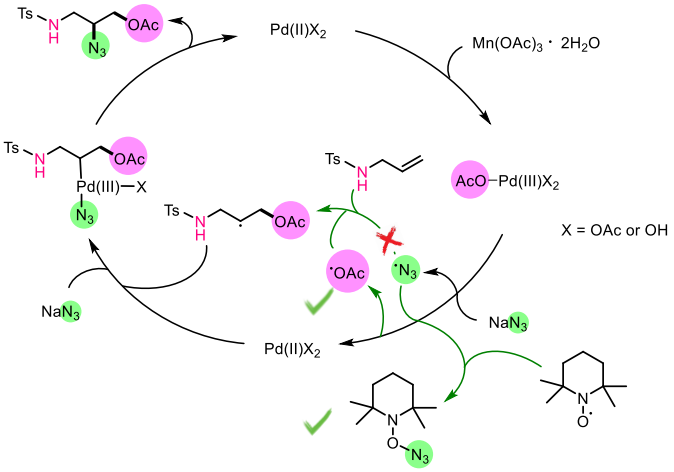


46b **50** (19%)

Scheme 56. Reaction with 1.5 equivalents of radical scavenger TEMPO

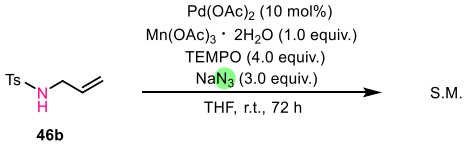
[68] M. Mondal, U. Bora, Recent advances in manganese(III) acetate mediated organic synthetis, *RCS Adv.* **2013**, *3*, 18716-18754.

The formation of compound **50** could be justified by the mechanism proposed in Scheme 57. Under these conditions, TEMPO can trap half of the azide radicals thus allowing the acetoxy radicals to trigger the radical mechanism.[69]



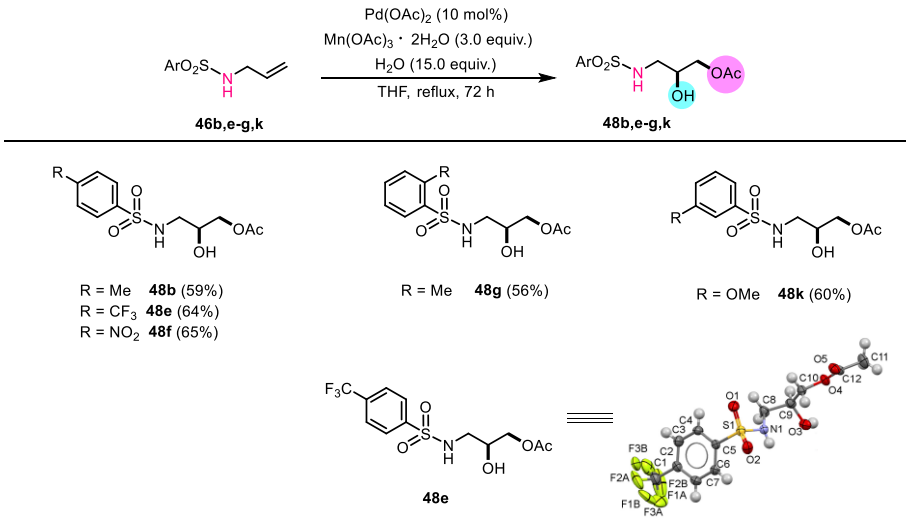
Scheme 57. Mechanism with radical scavenger TEMPO

Indeed, the reaction conditions are not operative working with 4.0 equivalents of TEMPO which could trap all the free radical in the reaction mixture (Scheme 58).



Scheme 58. Reaction with 4.0 equivalents of radical scavenger TEMPO

At this point, we carried out the scope for the acetoxy/hydroxylation procedure (Scheme 59). The optimized reaction conditions were tested on *N*-allyl sulfonamides bearing different groups on the aromatic ring. All these substrates furnished the desired products in good yield and the single-crystal X-ray structure analysis of compound **48e** gave unambiguous proof for the formation of this acetoxy/hydroxylation product.[70]

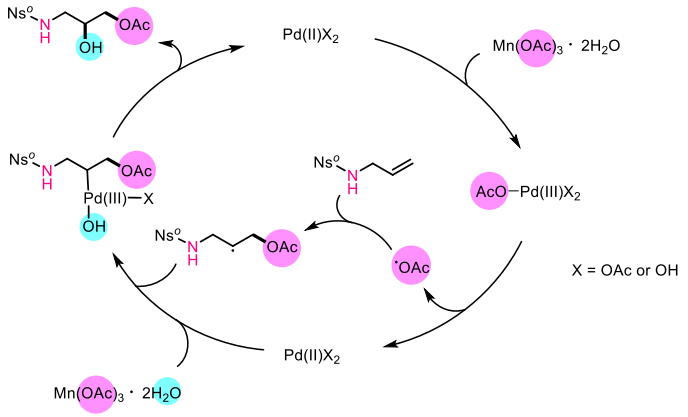


Scheme 59. Pd-Catalyzed acetoxy/hydroamination of allyl sulfonamides

[69] M. Shee, N. D. Pradeep Singh, Chemical versatility of azide radical: journey from a transient species to synthetic accessibility in organic transformations, *Chem. Soc. Rev.* **2022**, *51*, 2255-2312.

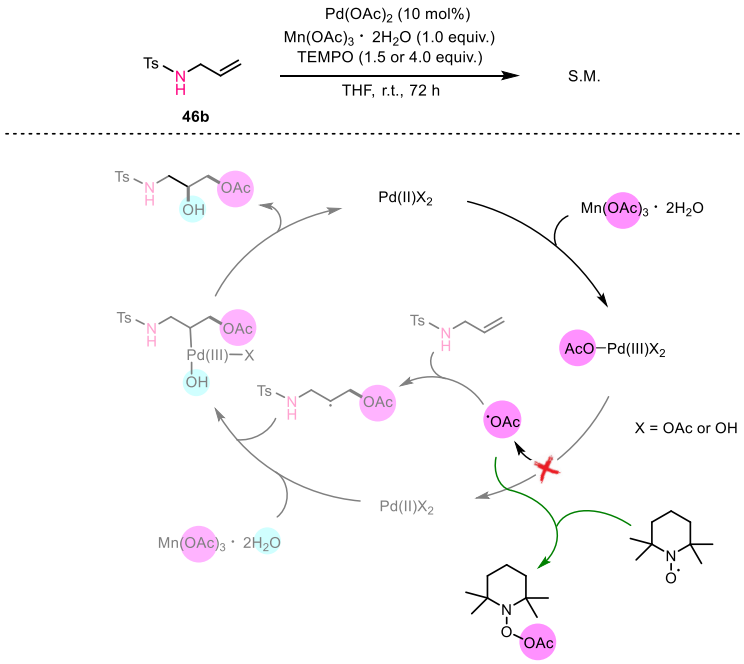
[70] X-Ray diffraction analysis of compound **48e** carried out by Prof. L. Lo Presti from Università degli Studi di Milano.

Also in the case of the acetoxy/hydroxylation process a radical mechanism which involves the initial attack of the acetoxy radical followed by the hydroxylation step has been proposed (Scheme 60).



Scheme 60. Pd-Catalyzed acetoxy/hydroamination mechanism

For this reason, the reaction was repeated adding in the reaction mixture 1.5 and 4.0 equivalents of the radical scavenger TEMPO in the reaction mixture. Conversely to what observed in the diazidation procedure, also in the case of the reaction performed with 1.5 equivalents of TEMPO, unreacted substrate was recovered, probably due to the trapping of the acetoxy radical which could not trigger the supposed mechanism (Scheme 61).



Scheme 61. Acetoxy/hydroxylation procedure with 1.5 or 4.0 equivalents of radical scavenger TEMPO

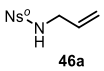
In conclusion, with this work new palladium-catalyzed conditions for diazidation or acetoxy/hydroxylation processes were found through functionalization of non-activated C-C double bonds. Reasonably these reactions take place through a radical process which involves the generation of a Pd(III) intermediate. However, this hypothesis will have to be confirmed by searching for new evidence.

3.3 EXPERIMENTAL SECTION

*Procedure for the synthesis of N-allyl sulfonamides (**46a,b,f**)*

In a round bottom flask, the appropriate sulfonyl chloride (1.0 mmol) was added to a solution allyl amine (1.1 mmol) and triethylamine (1.0 mmol) in DCM (7 mL) at 0°C. The resulting reaction mixture was magnetically stirred at room temperature for 2 hours. The resulting solution was diluted with DCM (10 mL), washed with saturated $NaHCO_3$ solution (2 x 10 mL), brine (10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure.

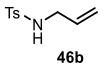
*N-Allyl-2-nitrobenzenesulfonamide (**46a**)*



46a

46a (94%); white solid. The characterization of product **46a** is consistent with that reported in literature.[71]

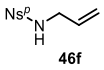
*N-Allyl-4-methylbenzenesulfonamide (**46b**)*



46b

46b (96%); colourless oil. The characterization of product **46b** is consistent with that reported in literature.[72]

*N-Allyl-4-nitrobenzenesulfonamide (**46f**)*



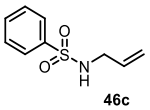
46f

46f (93%); light yellow solid. The characterization of product **46f** is consistent with that reported in literature.[71]

*Procedure for the synthesis of N-allyl sulfonamides (**46c-e, g-k**)*

In a round bottom flask, the allyl bromide (1.0 mmol) in MeCN (1.5 mL) was added to a solution of the appropriate sulfonamide (2.0 mmol), KI (0.1 mmol) and K_2CO_3 (2.0 mmol) in MeCN (1.5 mL). The resulting reaction mixture was magnetically stirred at 80 °C for 48 hours. The resulting solution was filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

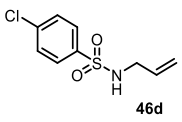
*N-Allyl-benzenesulfonamide (**46c**)*



46c

FCC – AcOEt/hexane (3:7); **46c** (54%); colorless oil. The characterization of product **46c** is consistent with that reported in literature.[71]

*N-Allyl-4-chlorobenzenesulfonamide (**46d**)*



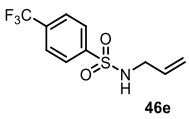
46d

FCC – AcOEt/hexane (3:7); **46d** (52%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.63 (t, 2H, *J* = 6.0 Hz), 4.45 (s, 1H), 5.12-5.21 (m. 2H), 5.68-5.78 (m, 1H), 7.51 (d, 2H, *J* = 8.6 Hz), 7.81 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 45.8, 118.1, 128.6, 129.4, 132.7, 138.6, 139.3 . IR ν_{max} 3278, 1321,985 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_9H_9ClNO_2S$ $[M-H]^-$: 230.0048; found: 230.0047.

[71] D. D. Pickford, J. Nugent, B. Owen, J. J. Mousseau, R. C. Smith, E. A. Anderson, Twofold Radical-Based Synthesis of *N*,*C*-Difunctionalized Bicyclo[1.1.1]pentanes, *J. Am. Chem. Soc.* **2021**, *143*, 9729-9736.

[72] A. Banerjee, S. Sarkar, J. A. Shah, N. C. Frederiks, E. A. Bazan-Bergamino, C. J. Johnson, M.-Y. Ngai, Excited-State Copper Catalysis for the Synthesis of Heterocycles, *Angew. Chem. Int. Ed.* **2022**, *61*, e202113841.

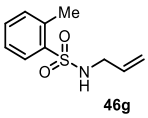
*N-Allyl-4-trifluoromethylbenzenesulfonamide (**46e**)*



46e

FCC – AcOEt/hexane (3:7); **46e** (51%); yellow oil. The characterization of product **46e** is consistent with that reported in literature.[73]

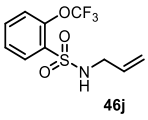
*N-Allyl-2-methylbenzenesulfonamide (**46g**)*



46g

FCC – AcOEt/hexane (3:7); **46g** (48%); colorless oil. The characterization of product **46g** is consistent with that reported in literature.[71]

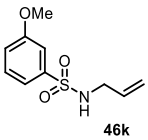
*N-Allyl-2-trifluoromethoxybenzenesulfonamide (**46j**)*



46j

FCC – AcOEt/hexane (3:7); **46j** (55%); pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.64 (t, 2H, *J* = 6.1 Hz), 4.68 (s, 1H), 5.10-5.21 (m, 2H), 5.67-5.77 (m, 1H), 7.41-7.44 (m, 2H), 7.64 (t, 1H, *J* = 7.9 Hz), 8.05 (d, 1H, *J* = 9.9 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 45.9, 118.1, 119.9, 131.0, 132.6, 134.4. IR ν_{max} 3308, 1338, 1247, 1208, 1156, 992 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{10}H_9F_3NO_3S$ $[M-H]^-$: 280.0261; found: 280.0259.

*N-Allyl-4-trifluoromethylbenzenesulfonamide (**46k**)*



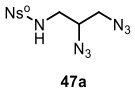
46k

FCC – AcOEt/hexane (3:7); **46k** (62%); pale yellow oil. The characterization of product **46k** is consistent with that reported in literature.[74]

*General procedure for the synthesis of diazidation compounds (**47** and **49**)*

In a round bottom flask, the NaN_3 (3.0 mmol) was added to a solution of the appropriate alkene (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $Mn(OAc)_3$ $2H_2O$ (1.0 equiv.) in THF (7 mL). The resulting reaction mixture was magnetically stirred at room temperature for 72 hours. The resulting solution was diluted with DCM (10 mL), washed with brine (2 x 10 mL), water (10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

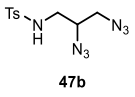
*N-(2,3-Diazidopropyl)-2-nitrobenzenesulfonamide (**47a**)*



47a

FCC- DCM; **47a** (61%); pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.13-3.19 (m, 1H), 3.29-3.36 (m, 1H), 3.46-3.58 (m, 2H), 3.71-3.77 (m, 1H), 5.71 (t, 1H, *J* = 5.6 Hz), 7.79 (t, 2H, *J* = 4.2 Hz), 7.92 (t, 1H, *J* = 5.2 Hz), 8.15 (t, 1H, *J* = 4.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 44.6, 52.2, 60.9, 125.7, 130.9, 133.0, 133.5, 133.9. IR ν_{max} 3323, 2104, 1376 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_9H_8N_8O_4S$ $[M-H]^-$: 325.0473; found: 311.0814.

*N-(2,3-Diazidopropyl)-4-methylbenzenesulfonamide (**47b**)*



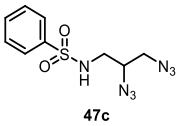
47b

FCC- DCM; **47b** (67%); pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.45 (s, 3H), 2.95-3.01 (m, 1H), 3.10-3.17 (m, 1H), 3.43 (dd, 1H, *J* = 6.6, 12.8 Hz), 3.48 (dd, 1H, *J* = 4.6, 12.8 Hz), 3.65-3.70 (m, 1H), 4.90 (t, 1H, *J* = 6.3 Hz), 7.34 (d, 2H, *J* = 8.0 Hz), 7.76 (d, 2H, *J* = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 21.5, 44.1, 52.3, 60.8, 127.0, 129.9, 136.5, 144.1. IR ν_{max} 3268, 2098, 1374 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{10}H_{12}N_7O_2S$ $[M-H]^-$: 294.0779; found: 311.0814.

[73] A. Gheorghe, B. Quiclet-Sire, X. Vila, S. Z. Zard, Synthesis of 3-Arylpiperidines by a Radical 1,4-Aryl Migration, *Org. Lett.* **2005**, *7*, 1653-1656.

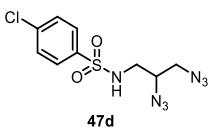
[74] A. Gheorghe, B. Quiclet-Sire, X. Vila, S. Z. Zard, Synthesis of 3-arylpiperidines by a radical 1,4- and 1,2-aryl migrations, *Tetrahedron* **2007**, *63*, 7187-7212.

*N-(2,3-Diazidopropyl)-benzenesulfonamide (**47c**)*



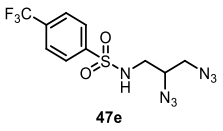
FCC- DCM/MeOH (9.5:0.5); **47c** (58%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97-3.04 (m, 1H), 3.14-3.19 (m, 1H), 3.44 (dd, 1H, *J* = 6.6, 12.7 Hz), 3.50 (dd, 1H, J = 4.6, 12.8 Hz), 3.70-3.71 (m, 1H), 4.89 (t, 1H, *J* = 6.6 Hz), 7.55-7.65 (m, 3H), 7.88 (d, 2H, *J* = 9.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 44.1, 52.3, 60.8, 126.9, 129.4, 133.2, 139.5. IR ν_{max} 3277, 2098, 1325 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_9H_{10}N_7O_2S$ [M-H]$^-$: 280.0622; found: 280.0619

*N-(2,3-Diazidopropyl)-4-chlorobenzenesulfonamide (**47d**)*



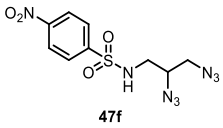
FCC- DCM; **47d** (61%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97-3.04 (m, 1H), 3.13-3.19 (m, 1H), 3.46 (dd, 1H, *J* = 6.5, 12.8 Hz), 3.51 (dd, 1H, *J* = 4.9, 12.8 Hz), 3.67-3.73 (m, 1H), 4.91 (t, 1H, *J* = 5.4 Hz), 7.53 (d, 2H, *J* = 8.5 Hz), 7.81 (d, 2H, *J* = 11.2 Hz);^{13}C NMR ($CDCl_3$, 101 MHz) δ 44.1, 52.2, 60.8, 128.5, 129.7, 138.1, 139.7. IR ν_{max} 3282, 2101, 1330, cm^{-1}. HRMS(ESI): *m/z* calc. for $C_9H_9N_7ClO_2S$ [M-H]$^-$: 314.0232; found: 314.0231.

*N-(2,3-Diazidopropyl)-4-trifluoromethylbenzenesulfonamide (**47e**)*



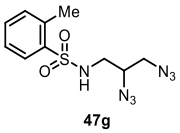
FCC- DCM; **47e** (56%); colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.03 (dd, 1H, *J* = 6.6, 13.4 Hz), 3.19 (dd, 1H, *J* = 4.8, 13.7 Hz), 3.47 (dd, 1H, *J* = 6.4, 12.7 Hz), 3.52 (dd, 1H, *J* = 4.9, 12.8 Hz), 3.69-3.75 (m, 1H), 5.10 (s, 1H), 7.83 (d, 2H, *J* = 8.3 Hz), 8.01 (d, 2H, *J* = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 44.2, 52.2, 60.8, 121.8, 124.5, 126.4, 126.5, 126.6, 126.6, 127.5, 134.6, 135.0, 143.2. IR ν_{max} 3284, 2101, 1320, 1162, 1128, 1094 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{10}H_9F_3N_7O_2S$ [M-H]$^-$: 348.0496; found: 348.0484.

*N-(2,3-Diazidopropyl)-4-nitrobenzenesulfonamide (**47f**)*



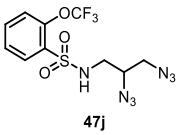
FCC- DCM; **47f** (65%); colourless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.06 (dd, 1H, *J* = 7.2, 13.8 Hz), 3.23 (dd, 1H, *J* = 4.4, 18.2 Hz), 3.48 (dd, 1H, *J* = 6.2, 12.8 Hz), 3.2 (dd, 1H, *J* = 5.1, 12.8 Hz), 3.69-3.76 (m, 1H), 5.13 (s, 1H), 8.07 (d, 2H, *J* = 8.8 Hz), 8.40 (d, 2H, *J* = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 44.2, 52.1, 60.7, 124.6, 128.3, 145.5, 150.3. IR ν_{max} 3282, 2094, 1345 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_9H_9N_8O_4S$ [M-H]$^-$: 325.0473; found: 325.0469.

*N-(2,3-Diazidopropyl)-2-methylbenzenesulfonamide (**47g**)*



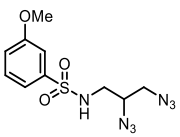
FCC- DCM; **47g** (60%); white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.67 (s, 3H), 2.93-3.00 (m, 1H), 3.12-3.18 (m, 1H), 3.41 (dd, 1H, *J* = 6.6, 12.8 Hz), 3.46 (dd, 1H, *J* = 4.8, 12.8 Hz), 3.62-3.68 (m, 1H), 4.84 (t, 1H, *J* = 5.6 Hz), 7.33-7.37 (m, 2H), 7.51 (t, 1H, *J* = 7.6 Hz), 7.97 (d, 1H, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 43.9, 52.4, 60.9, 126.4, 129.4, 132.8, 133.2, 136.9, 137.4. IR ν_{max} 3284, 1318, 2098 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{10}H_{12}N_7O_2S$ [M-H]$^-$: 294.0779; found: 311.0814.

*N-(2,3-Diazidopropyl)-2-trifluoromethoxybenzenesulfonamide (**47j**)*



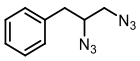
FCC- AcOEt/hexane (3:7); **47j** (54%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.99-3.06 (m, 1H), 3.16-3.22 (m, 1H), 3.46 (dd, 1H, *J* = 6.6, 12.8 Hz), 3.53 (dd, 1H, *J* = 4.7, 12.9 Hz), 3.67-3.71 (m, 1H), 5.02 (s, 1H), 7.46 (d, 2H, *J* = 7.5 Hz), 7.68 (t, 1H, *J* = 6.9 Hz), 8.05 (d, 1H, *J* = 9.8 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 44.2,52.3, 60.9, 120.1, 126.7, 130.9, 134.8. IR ν_{max} 3296, 2104, 1340, 1250, 1210, 1160 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{10}H_9F_3N_7O_3S$ [M-H]$^-$: 364.0445; found: 364.0432.

*N-(2,3-Diazidopropyl)-3-methoxybenzenesulfonamide (**47k**)*



FCC- AcOEt/hexane (3:7); **47k** (66%); colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97-3.04 (m, 1H), 3.14-3.21 (m, 1H), 3.45 (dd, 1H, *J* = 6.6, 12.8 Hz), 3.51 (dd, 1H, *J* = 4.6, 12.8 Hz), 3.66-3.71 (m, 1H), 3.88 (s, 3H), 4.79 (t, 1H, *J* = 6.8 Hz), 7.13-7.16 (m, 1H), 7.37 (s, 1H), 7.43-7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 44.2, 52.3, 55.7, 60.8, 111.8, 119.0, 119.4, 130.5, 140.6, 160.2 IR ν_{max} 3280, 2099, 1317 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{10}H_{12}N_7O_3S$ [M-H]$^-$: 310.0728; found: 310.0724

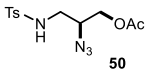
*2,3-Diazidopropyl-benzene (**49**)*



49

FCC- DCM; **49** (68%); pale yellow oil. The characterization of product **49** is consistent with that reported in literature.[75]

*General procedure for the diazidation with TEMPO (**50**)*



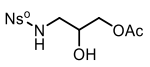
50

In a round bottom flask, the NaN_3 (3.0 mmol) was added to a solution of the appropriate alkene (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $Mn(OAc)_3$ $2H_2O$ (1.0 equiv.), TEMPO (1.5 equiv.) in THF (7 mL). The resulting reaction mixture was magnetically stirred at room temperature for 72 hours. The resulting solution was diluted with DCM (10 mL), washed with brine (2 x 10 mL), water (10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. Compound **50** was isolated with 19% as colorless oil; FCC – AcOEt/hexane (3:7). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (s, 3H), 2.45 (s, 3H), 2.91-2.98 (m, 1H), 3.01-3.15 (m, 1H), 3.75-3.81 (m, 1H), 4.15 (dd, 1H, *J* = 6.5, 11.8 Hz), 4.19 (dd, 1H, *J* = 4.9, 11.7 Hz), 4.92 (t, 1H, *J* = 6.5 Hz), 7.34 (d, 2H, *J* = 8.2 Hz), 7.75 (d, 2H, *J* = 8.3 Hz); ^{13}C NMR ($CDCl_3$, 95 MHz) δ 20.21.5, 43.4, 59.8, 63.8, 127.0, 129.9, 136.6, 143.9, 170.4. IR ν_{max} 3272, 2108, 1741, 1368, 1156 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{12}H_{15}N_4O_4S$ $[M-H]^-$: 311.0819; found: 311.0814.

*General procedure for the synthesis of acetoxy/hydroxylated compounds (**48**)*

In a round bottom flask, the NaN_3 (3.0 mmol) was added to a solution of the appropriate alkene (1.0 mmol), $Pd(OAc)_2$ (10 mol%), $Mn(OAc)_3$ $2H_2O$ (1.0 equiv.) in THF (7 mL). The resulting reaction mixture was magnetically stirred at room temperature for 72 hours. The resulting solution was diluted with DCM (10 mL), washed with brine (2 x 10 mL), water (10 mL), dried over $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

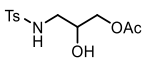
*N-(2-Hydroxy-3-acetoxy)-2-nitrobenzenesulfonamide (**48a**)*



48a

FCC- AcOEt/hexane (4:1); **48a** (57%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.10 (s, 3H), 2.59 (d, 1H, *J* = 3.6 Hz), 3.09-3.16 (m, 1H), 3.28-3.34 (m, 1H), 4.06 (dd, 1H, *J* = 5.8, 11.7 Hz), 4.17 (dd, 1H, *J* = 4.4, 11.6 Hz), 5.84 (t, 1H, *J* = 6.2 Hz), 7.75-7.77 (m, 2H), 7.88-7.91 (m, 1H), 8.14-8.15 (m, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.7, 46.0, 65.9, 68.6, 125.5, 131.0, 132.8, 133.5, 133.8, 148.1, 171.2. IR ν_{max} 3326, 2921, 1727 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{11}H_{13}N_2O_7S$ $[M-H]^-$: 317.0449; found: 317.0445.

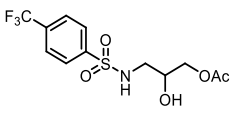
*N-(2-Hydroxy-3-acetoxy)-4-methylbenzenesulfonamide (**48b**)*



48b

FCC- MeOH/DCM (1:9); **48b** (59%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.08 (s, 3H), 2.44 (s, 3H), .2.72 (d, 1H, J = 2.5 Hz), 2.92-2.98 (m, 1H), 3.08-3.15 8 (m, 1H), 3.92-3.98 (m, 1H), 4.07 (dd, 1H, *J* = 5.9, 11.8 Hz), 4.12 (dd, 1H, *J* = 4.8, 11.7 Hz), 5.05 (t, 1H, *J* = 6.4 Hz), 7.33 (d, 2H, *J* = 8.0 Hz), 7.75 (d, 2H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.7, 21.5, 45.4, 65.8, 68.6, 121.1, 129.8, 136.5, 143.8, 171.2. IR ν_{max} 3269, 2924, 1722 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{12}H_{16}NO_5S$ $[M-H]^-$: 286.0755; found: 286.0752.

*N-(2-Hydroxy-3-acetoxy)-4-trifluoromethylbenzenesulfonamide (**48e**)*

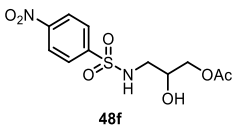


48e

FCC- AcOEt/hexane (4:1); **48e** (64%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (s, 3H), 2.57 (bs, 1H), 2.97-3.03 (m, 1H), 3.14-3.21 (m, 1H), 3.96-4.00 (m, 1H), 4.08 (dd, 1H, *J* = 9.6, 15.5 Hz), 4.15 (dd, 1H, *J* = 4.5, 11.7 Hz), 5.11 (t, 1H, *J* = 6.2 Hz), 7.81 (d, 2H, *J* = 8.0 Hz), 8.01 (d, 2H, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.7, 45.4, 65.8, 68.6, 114.8, 126.4, 126.4, 127.6, 143.3, 171.3. IR ν_{max} 3479, 3165, 2921, 1720 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{12}H_{13}F_3NO_5S$ $[M-H]^-$: 340.0472; found: 340.0456.

[75] Y.A. Yuan, D.-F. Lu, Y.-R. Chen, H. Xu, Iron-Catalyzed Direct Diazidation for a Broad Range of Olefins, *Angew. Chem. Int. Ed*. **2016**, *55*, 534-538.

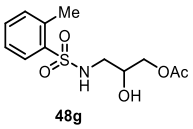
*N-(2-Hydroxy-3-acetoxy)-4-nitrobenzenesulfonamide (**48f**)*



48f

FCC- AcOEt/hexane (4:1); **48f** (65%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (s, 3H), 2.55 (d, 1H, *J* = 4.1 Hz), 2.99-3.03 (m, 1H), 3.18-3.24 (m, 1H), 3.95-4.00 (m, 1H), 4.09 (dd, 1H, J = 9.8, 11.7 Hz), 4.15 (dd, 1H, J = 4.5, 11.8 Hz), 5.18 (t, 1H, J = 5.5 Hz), 8.07 (d, 2H, J = 8.7 Hz), 8.39 (d, 2H, J = 8.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.7, 45.4, 66.8, 68.6, 124.5, 128.3, 134.3, 145.6, 171.3. IR ν_{max} 3496, 3274, 2944, 1722 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{11}H_{13}N_2O_7S$ $[M-H]^-$: 317.0449; found: 317.0447.

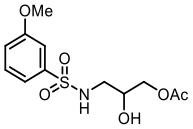
*N-(2-Hydroxy-3-acetoxy)-2-methylobenzenesulfonamide (**48g**)*



48g

FCC- AcOEt/hexane (4:1); **48g** (56%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.07 (s, 3H), 2.62 (d, 1H, *J* = 4.6 Hz), 2.67 (s, 3H), 2.91-2.97 (m, 1H), 3.09-3.14 (m, 1H), 3.91-3.97 (m, 1H), 4.06 (dd, 1H, J = 5.8, 11.7 Hz), 4.11 (dd, 1H, J = 4.7, 11.8 Hz), 5.08 (t, 1H, J = 7.2 Hz), 7.32-7.35 (m, 2H), 7.49 (t, 1H, J = 7.4 Hz), 7.97 (d, 1H, J = 9.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.2, 20.8, 45.2, 65.8, 68.6, 126.2, 129.4, 132.7, 132.9, 137.1, 137.4, 171.3. IR ν_{max} 3288, 2927, 1722 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{12}H_{16}NO_5S$ $[M-H]^-$: 286.0755; found: 286.0759.

*N-(2-Hydroxy-3-acetoxy)-3-methoxybenzenesulfonamide (**48k**)*



48k

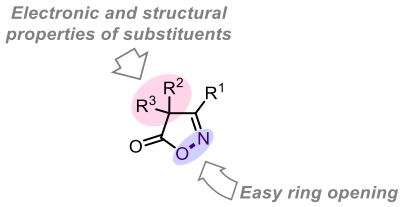
FCC- AcOEt/hexane (4:1); **48k** (60%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.09 (s, 3H), 2.75 (d, 1H, *J* = 15.9 Hz), 2.95-3.01 (m, 1H), 3.14-3.18 (m, 1H), 3.87 (s, 3H), 3.94-3.99 (m, 1H), 4.08 (dd, 1H, *J* = 5.6, 11.7 Hz), 4.13 (dd, 1H, *J* = 4.8, 11.7 Hz), 5.12 (t, 1H, *J* = 6.7 Hz), 7.09-7.15 (m, 1H), 7.37-7.38 (m, 1H), 7.43-7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 20.8, 45.5, 55.7, 65.8, 68.6, 111.8, 119.1, 119.2, 130.3, 140.6, 160.1, 171.3. IR ν_{max} 3496, 3274, 2944, 1722 cm^{-1}. HRMS(ESI): *m/z* calc. for $C_{12}H_{16}NO_6S$ $[M-H]^-$: 302.0704; found: 302.0703.

CHAPTER 4

RUTHENIUM-CATALYZED NON-DECARBOXYLATIVE REARRANGEMENT OF 4*H*-ISOXAZOL-5-ONES

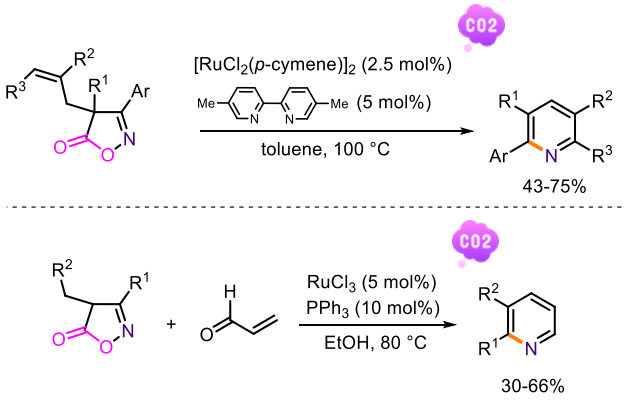
4.1 INTRODUCTION

It is well established that ruthenium complexes have a great interest in organic synthesis, above all due to their high ability to coordinate heteroatoms. In recent years, among the various typologies of reactions in which ruthenium catalysts are used, they have been successfully applied in the rearrangement of 4*H*-isoxazol-5-ones, which could be considered as useful building blocks to access acyclic and heterocyclic compounds.[76] These kinds of substrates were characterized by high stability and easy ring opening at the nitrogen-oxygen bond, but the different type of products obtained depends on the reaction conditions and on the structural and electronic properties of the substituent at the C4 position of the ring (Scheme 62).



Scheme 62. Structure of 4*H*-isoxazol-5-ones

In this context, ruthenium-catalyzed transformation of 4*H*-isoxazol-5-ones could give the rise to nitrogen-containing heterocycles such as pyridines, aziridines and benzo-fused indole derivatives.
In 2016, Okamoto and Ohe reported the conversion of 4-allyl-isoxazol-5-ones into the corresponding pyridines and later Jurberg's group developed a new method to access 2,3-disubstituted pyridines using acrolein and $RuCl_3$ as catalyst (Scheme 63).[77]



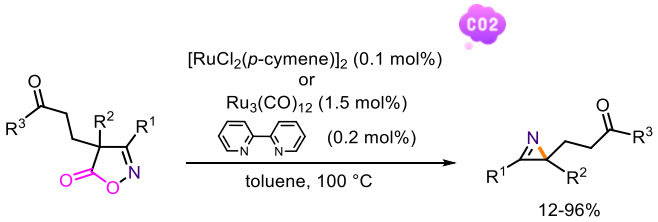
Scheme 63. Two ruthenium-catalyzed methods to access pyridines

In 2017, 2*H*-aziridines were synthesized from the corresponding isoxazol-5-ones using $[RuCl_2(p\text{-cymene})]_2$ or $Ru_3(CO)_{12}$ as catalyst and a bipyridine ligand (Scheme 64).[78]

[76] a) E. M. Beccalli, D. Pocar, C. Zoni, Recent developments in the chemistry of isoxazole-5-ones, *Target Heterocyclic Systems* **2003**, *7*, 31-63; b) A. A. G. Fernandes, A. F. da Silva, S. Thurow, C. Y. Jr. Okada, I. D. Jurberg; Isoxazol-5-ones: Unusual Heterocycles with Great Synthetic Potential, *Target Heterocyclic Systems* **2018**, *22*, 409-435; c) A. F. da Silva, I. A. A. G. Fernandes, S. Thurow, M. L. Stivanin, I. D. Jurberg, Isoxazol-5-ones as Strategic Building Blocks in Organic Synthesis, *Synthesis* **2018**, *50*, 2473-2489.

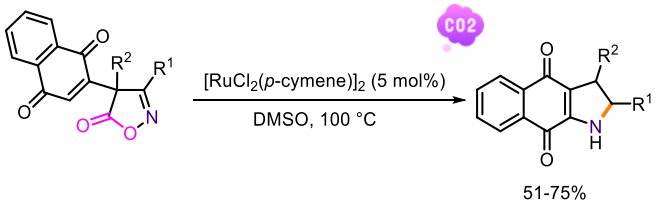
[77] a) K. Okamoto, K. Sasakura, T. Shimbayashi, K. Ohe, Ruthenium-catalyzed Decarboxylative and Dehydrogenative Formation of Highly Substituted Pyridines from Alkene-tethered Isoxazol-5(4*H*)-ones *Chem. Lett.* **2016**, *45*, 988-990; b) A. A. G. Fernandes, M. L. Stivanin, I. D. Jurberg, $RuCl_3/PPh_3$ – Catalyzed Direct Conversion of Isoxazol-5-ones to 2,3-Disubstituted Pyridines, *ChemistrySelect* **2019**, *4*, 3360-3365.

[78] S. Rieckhoff, M. Titze, W. Frey, R. Peters, Ruthenium-Catalyzed Synthesis of 2*H*-Aziridines from Isoxazolinones *Org. Lett.* **2017**, *19*, 4436-4439.



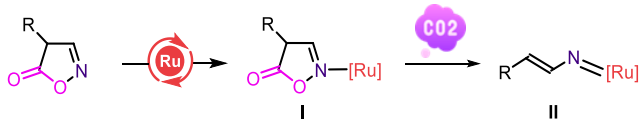
Scheme 64. Rearrangement into 2*H*-aziridines

Our research group contributed in this field through a divergent conversion of isoxazole-5-ones bearing a 1,4-napthoquinone moiety at the 4-position four of the starting materials. The use of $[RuCl_2(p\text{-cymene})]_2$ in DMSO at 100 °C allowed the conversion into benzo-fused indole derivatives through the C-H functionalization of the napthoquinone nucleus (Scheme 65).[79]



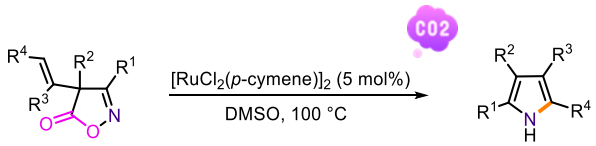
Scheme 65. Ru-Catalyzed divergent conversion into benzo-fused indole derivatives

As showed in Scheme 66, all these reactions involve a decarboxylative step on the ruthenium-iminocarboxylic complex **I** which generates the vinyl ruthenium-nitrenoid species **II** as key intermediate.[80]



Scheme 66. Classical ruthenium-catalyzed decarboxylative rearrangement

Following our interest in this kind of rearrangement, we focalized our attention on a different ruthenium-catalyzed decarboxylative process of 4-alkenyl-isoxazol-5-ones as a new method to access pyrroles, which are structural core in a wide range of natural compounds and synthetic products.[81] This procedure furnished tri- and tetrasubstituted 1*H*-pyrrole products in good to excellent yields without the use of additional additives (Scheme 67). [82]



Scheme 67. Ruthenium-catalyzed decarboxylative synthesis of 1*H*-pyrroles

In Scheme 68 the possible mechanism which start with the oxidative addition of the ruthenium complex to the substrate with the generation of intermediate **III** is described. The latter evolves, after the decarboxylative

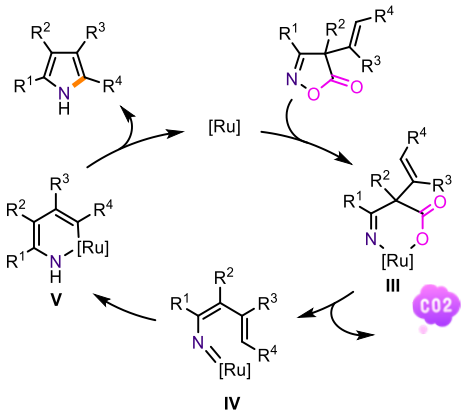
[79] M. S. Christodoulou, S. Giofrè, E. M. Beccalli, F. Foschi, G. Broggini, Divergent Conversion of 4-Napthoquinone-substituted 4*H*-Isoxazolones to Different Benzo-fused Indole Derivatives, *Org. Lett.* **2020**, *22*, 2735-2739.

[80] T. Shimbayashi, K. Sasakura, A. Eguchi, K. Okamoto, K. Ohe, Recent Progress on Cyclic Nitrenoid Precursors in Transition-Metal-Catalyzed Nitrene-Transfer Reactions *Chem. Eur. J.* **2019**, *25*, 3156-3180.

[81] a) Y. Geng, A. Tang, K. Tajima, Q. Zeng, E. Zhou, Conjugated materials containing dithieno[3,2-*b*:2',3'-*d*]pyrrole and its derivatives for organic and hybrid solar cell applications, *J. Mater. Chem. A* **2019**, *7*, 64-96; b) S. Peng, Q. He, G. I. Vargas-Zúñiga, L. Qin, I. Hwang, S. Kuk Kim, N. Jung Heo, C.-H. Lee, R. Dutta, J. L. Sessler, Strapped calix[4]pyrroles: from syntheses to applications, *Chem. Soc. Rev.* **2020**, *49*, 865-907; c) A. N. Bismillah, I. Aprahamian, Fundamental studies to emerging applications of pyrrole-BF_2 (BOPHY) fluorophores, *Chem. Soc. Rev.* **2021**, *50*, 5631-5649.

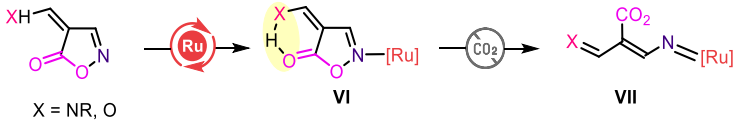
[82] L. Molteni, C. Loro, M. S. Christodoulou, M. Papis, F. Foschi, E. M. Beccalli, G. Broggini, Ruthenium-Catalyzed Decarboxylative Rearrangement of 4-Alkenyl-isoxazol-5-ones to Pyrrole Derivatives, *Eur. J. Org. Chem.* **2022**, e202200496.

step, into the corresponding vinyl ruthenium nitrenoid species **IV** affording the ruthenacycle **V** by an electrocyclic reaction. Finally, the 1*H*-pyrrole is obtained through the reductive elimination of **V** with the regeneration of the active ruthenium-catalyst.



Scheme 68. Possible ruthenium-catalyzed decarboxylative mechanism

The ruthenium-catalyzed conversion of the 4-alkenyl-isoxazol-5-ones into 1*H*-pyrrole products confirmed the tendency of these substrates to give decarboxylation processes.
Since the vinylruthenium-nitrenoid species is the key intermediate in which the decarboxylation process takes place, we thought that isoxazol-5-ones bearing an enamine or enol moiety in 4-position could deflect the classical behavior given the possibility of establishing intramolecular hydrogen bonds with the carboxyl group, avoiding the loss of carbon dioxide (Scheme 69).

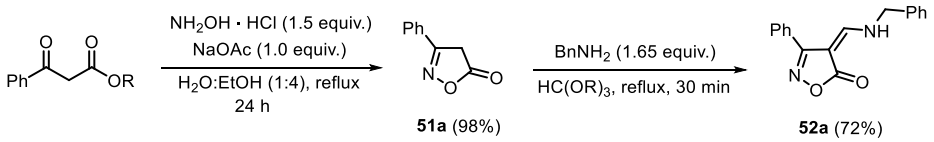


Scheme 69. Supposed ruthenium-catalyzed non-decarboxylative rearrangement

4.2 NON-DECARBOXYLATIVE REARRANGEMENT OF 4*H*-ISOXAZOL-5-ONES

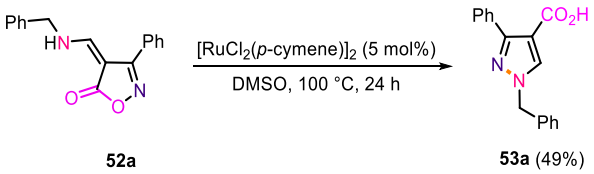
In this context, we investigate the behaviour of isoxazol-5-ones differently substituted at the position 4 with 2-hydroaminoalkylidenyl and 2-hydroxyalkylidenyl groups to access pyrazole- and isoxazole-4-carboxylic acids.[83]
The pyrazole and isoxazole motifs are part of the structure of many products in pharmaceuticals and agriculture, as well as in the design of new materials.[84] It should be evidenced that no direct syntheses of 1,2-diheteroatom five-membered rings with a carboxylic acid group in 4-position are known in the literature, being accessible solely by transformation of functional groups already present on the heterocycles.[85]
To analyze the behaviour of 4-(2-hydroaminoalkylidenyl)-isoxazol-5-ones, compound **52a** was chosen as model substrate. The latter was synthesized starting from the corresponding β-ketoester and hydroxylamine, functionalizing the 4-position of the obtained isoxazolone ring (**51a**) by heating with orthoester and benzylamine (Scheme 70).

[83] C. Loro, L. Molteni, M. Papis, L. Lo Presti, F. Foschi, E. M. Beccalli, G. Broggini, Non-Decarboxylative Ruthenium-Catalyzed Rearrangement of 4-Alkylidene-isoxazol-5-ones to Pyrazole- and Isoxazole-4-carboxylic acids, *Org. Lett.* **2022**, *24*, 3092-3096.
[84] a) M. Khan, M. Alam, G. Verma, W. Akhtar, M. Akhter, M. Shaquiquzzaman, The therapeutic voyage of pyrazole and its analogs: a review, *Eur. J. Med. Chem.* **2016**, *120*, 170-201; b) S. Mishra, S. Patel, C. G. Halpani, Recent updates in curcumin pyrazole and isoxazole derivatives: synthesis and biological application, *Chem. Biodiversity* **2019**, *16*, e1800366; c) G. C. Arya, K. Kaur, V. Jaitak, Isoxazole derivatives as anticancer agent: A review on synthetic strategies, mechanism of action and SAR studies, *Eur. J. Med. Chem.* **2021**, *221*, 113511; d) G. Mercuri, G. Giambastiani, C. Di Nicola, C. Pettinari, S. Galli, R. Vismara, R. Viviani, F. Costantino, M. Taddei, C. Atzori, F. Bonino, S. Bordiga, B. Civalleri, A. Rossin, Metal-Organic Frameworks in Italy: From synthesis and advanced characterization to theoretical modelling and applications, *Coord. Chem. Rev.* **2021**, *437*, 213861.
[85] a) Z. Chen, Y. Zheng, J.-A. Ma, Use of Traceles Activating and Directing Group for the Construction of Trifluoromethylpyrazoles: One-Pot Transformation of Nitroolefins and Trigluorodiazoethane *Angew. Chem. Int. Ed.* **2017**, *56*, 4569-4574; b) D. R. Fandrick, S. Sanyal, K. Kaloko, J. A. Mulder, Y. Wang, L. Wu, H. Lee, M. Roschangar, C. H. Hoffman, A. Senanayake, A Michael Equilibration Model to Control Site Selectivity in the Condensation toward Aminopyrazoles *Org. Lett*. **2015**, *17*, 2964-2967; c) N. M. Padial, E. Quartapelle Procopio, C. Montoro, E. López, E. Oltra, V. Colombo, A. Maspero, N. Masciocchi, S. Galli, I. Senkovska, S. Kaskel, E. Barea, J. A: R. Navarro, Highly hydrophobic isoreticular porous metal-organic compounds *Angew. Chem. Int. Ed.* **2013**, *52*, 8290-8294.



Scheme 70. Synthesis of the 2-hydroaminoalkylidenyl substituted isoxazol-5-one 52a

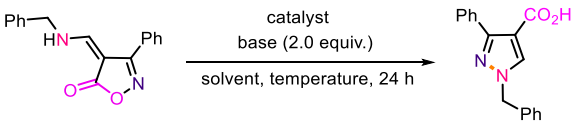
At this point, compound **52a** was tested in the conditions used in a previous work [82] (*i.e.* $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), DMSO, 100 °C) and, gladly, after 24 hours the pyrazole-4-carboxylic acid **53a** was obtained with 49% yields (Scheme 71).



Scheme 71. Rearrangement of 52a into pyrazole-4-carboxylic acid 53a

This preliminary result validated our initial hypothesis. Changing of the solvent to acetonitrile at 70 °C raised the yield of **53a** to 68% yield (Table 6, entry 1). On the other hand, the use of a Ru(0) specie such as $Ru_3(CO)_{12}$ didn't allow for the substrate rearrangement (entry 2). The use of 10 mol% of Ru-catalyst alone or in the presence of a base such as Na_2CO_3 or TEA did not increase the yield of the pyrazole-4-carboxylic acid **53a** (entries 3-5). Moreover, catalysts based on different transition metals [$Pd(OAc)_2/PPh_3$, $Pd(PPh_3)_4$ and $FeCl_2$)] were proven to be ineffective giving back the unreacted substrate or a mixture of degradation products (entries 6-8).

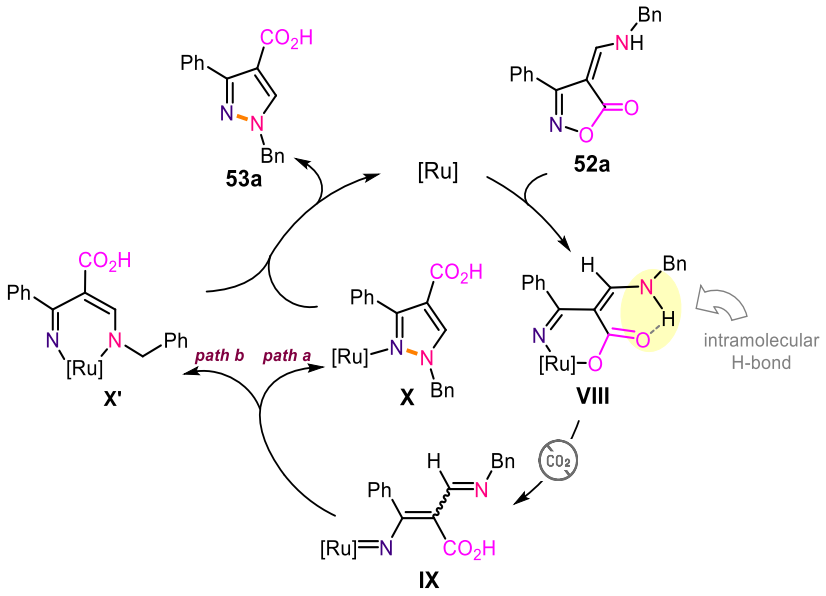
Table 6. Optimization for the rearrangement of substrate 52a



Entry	Catalyst (mol%)	Base	Solvent	Temperature (°C)	Product(s)
1	$[RuCl_2(p\text{-cymene})]_2$ (5)	-	Acetonitrile	70	**53a** (68%)
2	$Ru_3(CO)_{12}$ (5)	-	DMSO	100	-
3	$[RuCl_2(p\text{-cymene})]_2$ (10)	-	Acetonitrile	70	**53a** (70%)
4	$[RuCl_2(p\text{-cymene})]_2$ (5)	Na_2CO_3	Acetonitrile	70	**53a** (11%)
5	$[RuCl_2(p\text{-cymene})]_2$ (5)	TEA	Acetonitrile	70	**53a** (7%)
6	$Pd(OAc)_2$ (5) + PPh_3 (10)		Acetonitrile	70	**S.M.**
7	$Pd(PPh_3)_4$ (5)		Acetonitrile	70	**S.M.**
8	$FeCl_2$ (5)		Acetonitrile	70	**degr. products**

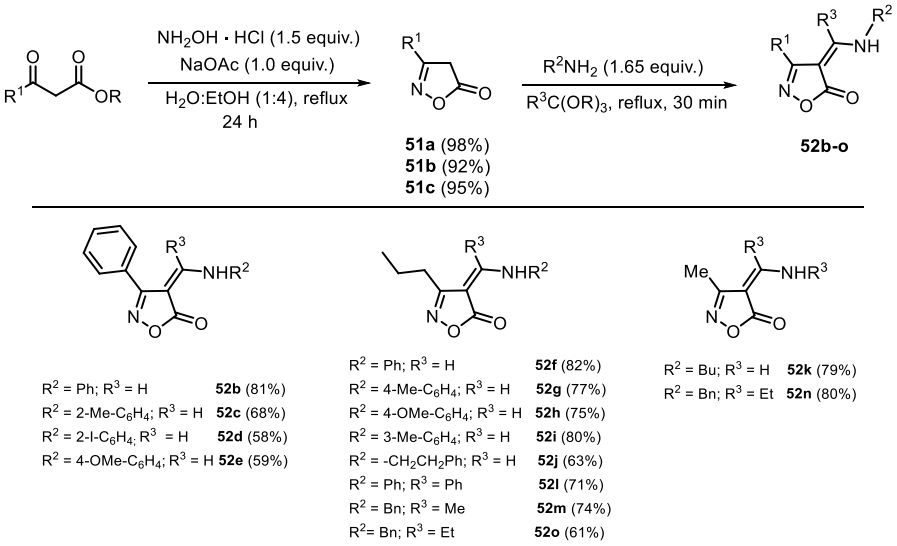
A plausible mechanism for the non-decarboxylative process was reported in Scheme 72. The catalytic process, very similar to those proposed in Scheme 68, starts with the oxidative addition of the metal to the isoxazol-5-one **52a**. The generation of the intermediate **VIII** and its ring opening results in the vinyl ruthenium-nitrenoid specie **IX** without loss of carbon dioxide. In this case, the driving force to hamper the

decarboxylative process during the ring-opening step should be the presence of an intramolecular hydrogen-bond between the NH group and the oxygen of the carboxylic group. Then intermediate **IX** evolves to either **X** (directly, *path a*) or **X'** (by previous addition to the metal, *path b*) affording the pyrazole-4-carboxylic acid **53a**. The final product is obtained by deligandation or reductive elimination of the metal.



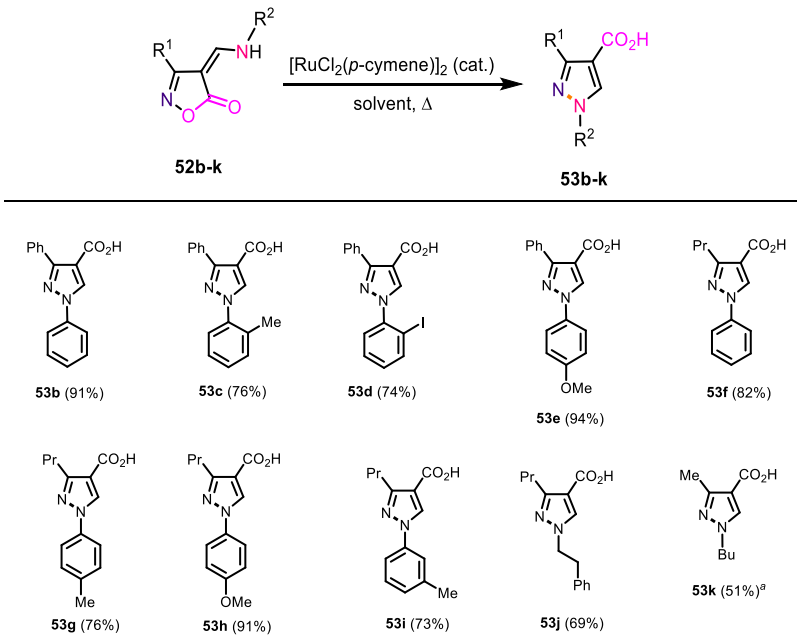
Scheme 72. Supposed mechanism for the ruthenium-catalyzed non-decarboxylative rearrangement

The scope of the reaction was tested on isoxazol-5-ones differently substituted at the C3 and C4 positions. For this reason, the 4-(2-hydroaminoalkylidenyl)-substituted isoxazol-5-ones **52b-o** were synthesized following the known procedure showed in the Scheme 73, through the functionalization of the compounds **51a-c**.



Scheme 73. Preparation of the isoxazol-5-ones 52b-o

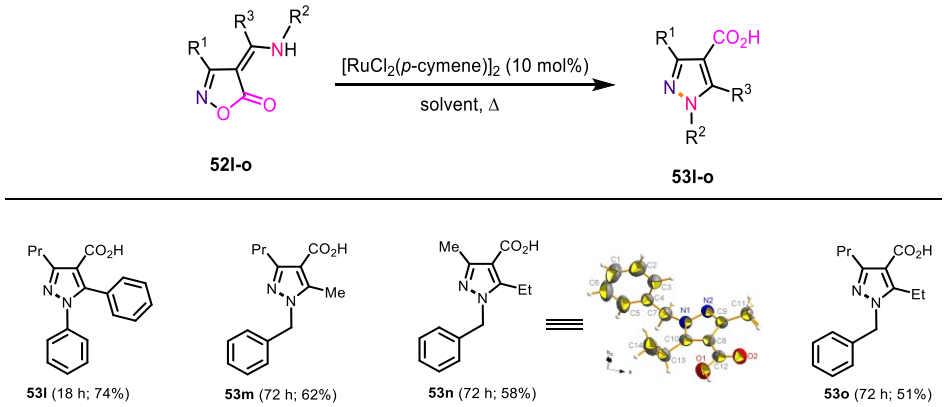
At the beginning we tested the rearrangement of isoxazolones incorporating α-unsubstituted secondary enamines **52b-k** in the presence of a catalytic amount of $[RuCl_2(p\text{-cymene})]_2$ in acetonitrile at 70 °C or in DMSO at 120 °C, as depicted in Scheme 74. After 24 hours, all substrates rearranged into the corresponding 1,3-disubstituted pyrazole-4-carboxylic acids **53b-k** in fair to good yields. Aryl enamines gave better yields than alkyl ones.



[a] Reaction carried out in DMSO at 120 °C for 48 hours with 10% of $[RuCl_2(p\text{-cymene})]_2$

Scheme 74. Synthesis of 1,3-disubstituted pyrazole-4-carboxylic acids 53b-k

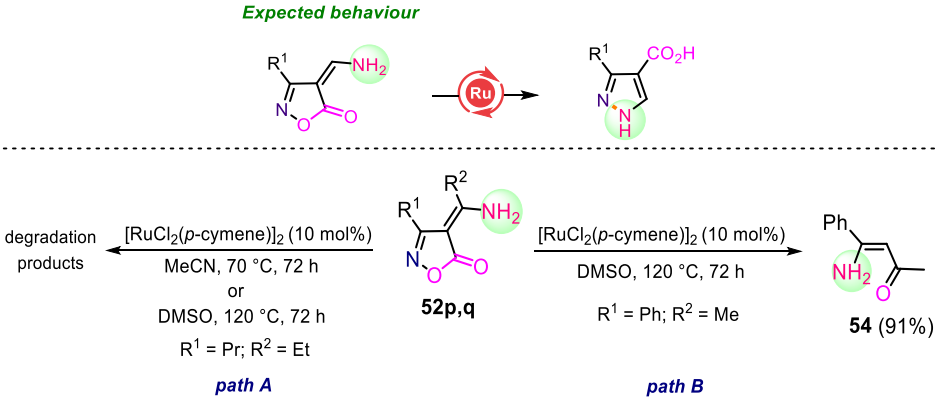
Also the isoxazolones bearing α-substituted secondary enamines **52l-o** rearranged with 10 mol% of $[RuCl_2(p\text{-cymene})]_2$ in DMSO at 120 °C (Scheme 75). In this case 1,3,5-trisubstituted pyrazole-4-carboxylic acids **53l-o** were achieved in 51-74% yields. Moreover, the X-ray crystal structure analysis of compound **53n** gave unambiguous proof for the formation of such compounds.[86]



Scheme 75. Synthesis of 1,3,5-trisubstituted pyrazole-4-carboxylic acids 53l-o

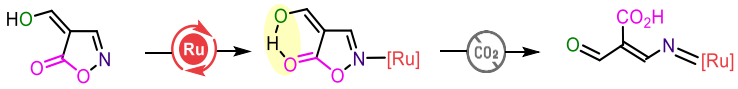
Otherwise, isoxazol-5-ones bearing primary enamines did not rearrange into the corresponding NH-pyrazole-4-carboxylic acids. Indeed, substrate **52p** – treated with 10 mol% of $[RuCl_2(p\text{-cymene})]_2$ in acetonitrile at 70 °C or in DMSO at 120 °C – gave a mixture of degradation products (Scheme 76, *path A*). On the other hand, the isoxazolone **52q** led to (*Z*)-1-amino-1-phenyl-1-buten-3-one **54** under the same reaction conditions (Scheme 76, *path B*). These results confirmed the inability of isoxazol-5-ones bearing primary enamines to rearrange into the corresponding pyrazole-4-carboxylic acids.

[86] X-Ray diffraction analysis of compound **53n** carried out by Prof. L. Lo Presti from Università degli Studi di Milano.



Scheme 76. Behaviour of isoxazol-5-ones bearing primary enamines

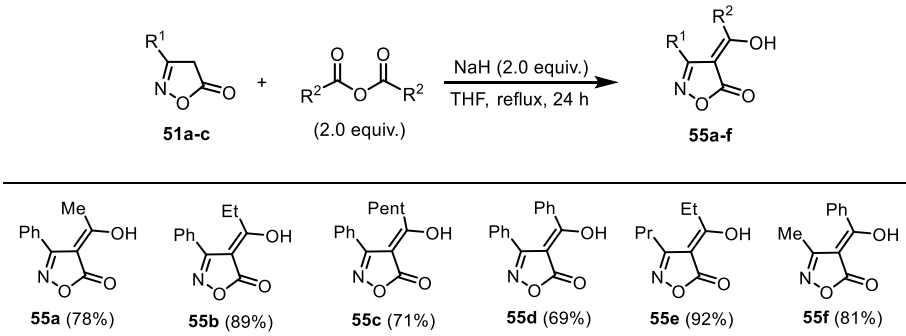
Then, we reasoned that isoxazolones bearing 2-hydroxyalkylidenyl groups linked at the C4 position could analogously deflect the ruthenium-catalyzed decarboxylative pathway into the non-decarboxylative one. Indeed, these substrates could lead to the corresponding isoxazole-4-carboxylic acids exploiting the intramolecular hydrogen bond between the enol and the carboxylic group (intermediate **XI**), as depicted in Scheme 77.



XI

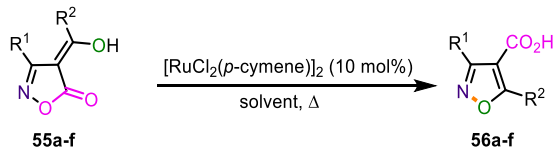
Scheme 77. Supposed ruthenium non-decarboxylative rearrangement of isoxazolones bearing 2-hydroxyalkylidenyl groups

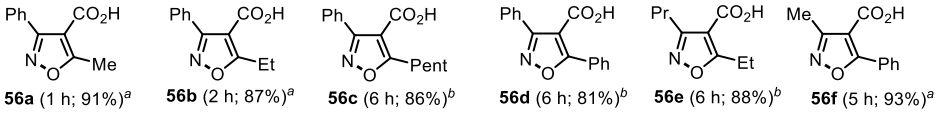
For this reason, enol substrates **55a-f** were prepared by functionalization of isoxazol-5-ones **51a-c** with the corresponding anhydrides in the presence of NaH in THF at reflux as showed in Scheme 78.



Scheme 78. Synthesis of the 2-hydroxyalkylidenyl substituted isoxazol-5-one 55a-f

These latter treated in the standard conditions (*i.e.* with 10 mol% of $[RuCl_2(p\text{-cymene})]_2$ in acetonitrile at 70 °C or in DMSO at 120 °C) afforded the expected isoxazole-4-carboxylic acids **56a-f** through the intramolecular N-O bond formation (Scheme 79). All the products were obtained in good to excellent yields.





56a (1 h; 91%)[a] **56b** (2 h; 87%)[a] **56c** (6 h; 86%)[b] **56d** (6 h; 81%)[b] **56e** (6 h; 88%)[b] **56f** (5 h; 93%)[a]

[a] Reaction carried out in MeCN at 70 °C
[b] Reaction carried out in DMSO at 120 °C

Scheme 79. Ru-Catalyzed synthesis of isoxazole-4-carboxylic acids 56a-f

In conclusion, these non-decarboxylative rearrangements of isoxazol-5-ones pave the way to useful alternative procedures to obtain different heterocycles with a carboxylic group. The access to pyrazole- and isoxazole-4-carboxylic acids is plausibly due to the intramolecular H bond which is established in the key intermediate of the reaction avoiding the loss of carbon dioxide. Finally, this synthetic protocol allows for a wider access to these compounds, boosting their use in pharmaceutical and new material research.

4.1 EXPERIMENTAL SECTION

*Procedure for the synthesis of 3-substituted isoxazole-5-ones (**51**)*

In a solution of the appropriate β-ketoester (1.0 mmol) in EtOH (14.6 mL), a solution of hydroxylamine hydrochloride (1.5 mmol), sodium acetate (1.5 mmol) in H_2O (3.7 mL) was added dropwise, and the solution was stirred for 24 hours at reflux. After the evaporation of the solvent, the solution was extracted with AcOEt (15 mL x3), washed with H_2O (10 mL x 2), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure.

*3-Phenyl-isoxazol-5(4H)-one (**51a**)*

51a

51a (98%); pink solid. The characterization of product **51a** is consistent with that reported in literature.[87]

*3-Propyl-isoxazol-5(4H)-one (**51b**)*

51b

51b (92%); red oil. The characterization of product **51b** is consistent with that reported in literature. [87]

*3-Methyl-isoxazol-5(4H)-one (**51c**)*

51c

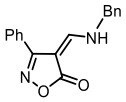
51c (95%); colorless oil. The characterization of product **51c** is consistent with that reported in literature. [87]

*Procedure for the synthesis of 3-substituted isoxazol-5-ones (**52**)*

In a solution of the appropriate 3-substituted isoxazole-5-ones (1.0 mmol) in the suitable orthoester (2.0 mL), the appropriate primary amine (1.1 mmol) was added, and the solution was stirred for 90 minutes at reflux. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

[87] R. Torán, C. Vila, A. Sanz-Marco, M.C. Munoz, J. R. Pedro, G. Blay, Organocatalytic Enantioselective 1,6-aza-Micheal Addition of Isoxazolin-5-ones to *p*-Quinone Methides *Eur. J. Org. Chem.* **2020**, *5*, 627-630.

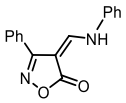
*(Z)-4-((Benzylamino)methylene)-3-phenylisoxazol-5(4H)-one (**52a**)*



52a

FCC – AcOEt/DCM (1:4); **52a** (72%); yellow solid; m.p.: 131-133 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.63 (s, 2H), 7.26-7.31 (m, 2H), 7.35-7.38 (m, 3H), 7.40-7.49 (m, 3H), 7.54-7.57 (m, 2H), 7.67 (s, 1H), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 53.7, 90.1, 127.6, 127.8, 128.6, 128.7, 129.2, 129.3, 130.4, 135.0, 153.5, 161.4, 174.9. IR ν_{max} 3091, 1678 cm^{-1}. Anal. Calcd. For $C_{17}H_{14}N_2O_2$: C 73.37, H 5.07, N 10.07; found: C 73.21, H 5.31, N 9.89.

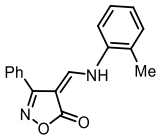
*(Z)-3-Phenyl-4-((phenylamino)methylene)isoxazol-5(4H)-one (**52b**)*



52b

FCC – AcOEt/DCM (1:4); **52b** (81%); yellow solid. The characterization of product **52b** is consistent with that reported in literature.[88]

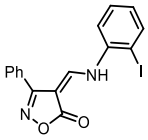
*(Z)-3-Phenyl-4-((2-tolylamino)methylene)isoxazol-5(4H)-one (**52c**)*



52c

FCC – methanol/hexane (1:9); **52c** (68%); orange wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.46 (s, 3H), 7.18-7.22 (m, 2H), 7.26-7.32 (m, 2H), 7.53-7.57 (m, 3H), 7.63-7.66 (m, 2H), 8.09 (d, 1H, *J* = 12.7 Hz), 11.04 (d, 1H, *J* = 12.7 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 17.2, 92.9, 116.0, 126.7, 127.6, 127.7, 128.3, 128.4, 129.2, 130.6, 131.6, 136.4, 146.1, 161.1, 174.8. IR ν_{max} 3087, 1675 cm^{-1}. Anal. Calcd. For $C_{17}H_{14}N_2O_2$: C 73.37, H 5.07, N 10.07; found: C 73.19, H 4.98, N 10.21.

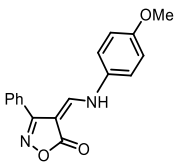
*(Z)-4-((2-Iodophenylamino)methylene)-3-phenylisoxazol-5(4H)-one (**52d**)*



52d

FCC – methanol/hexane (18:1); **52d** (58%); orange wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00 (t, 1H, *J* = 7.8 Hz), 7.22 (d, 1H, *J* = 8.1 Hz), 7.42 (t, 1H, *J* = 7.6 Hz), 7.50-7.57 (m, 3H), 7.60-7.67 (m, 2H), 7.90 (d, 1H, *J* = 7.9 Hz), 7.98 (d, 1H, *J* = 12.3 Hz), 11.00 (d, 1H, *J* = 12.3 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 89.7, 94.2, 116.9, 127.7, 127.8, 128.2, 129.3, 129.8, 130.7, 9.2, 140.4, 145.4, 161.2, 173.9. IR ν_{max} 3113, 1684 cm^{-1}. Anal. Calcd. For $C_{16}H_{11}IN_2O_2$: C 49.25, H 2.84, N 7.18; found: C 49.38, H 2.71, N 7.42.

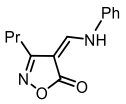
*(Z)-4-((4-Methoxyphenylamino)methylene)-3-phenylisoxazol-5(4H)-one (**52e**)*



52e

FCC – AcOEt/DCM (1:4); **52e** (59%); orange wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.69 (s, 3H), 6.82 (d, 2H, *J* = 8.9 Hz), 7.04 (d, 2H, *J* = 8.9 Hz), 7.32-7.28 (m, 1H), 7.38-7.42 (m, 3H), 7.48-7.56 (m, 2H), 7.84 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 55.6, 91.7, 115.3, 119.6, 126.3, 127.8, 128.4, 128.5, 129.3, 129.4, 130.6, 131.1, 146.2, 158.5, 161.3, 174.7. IR ν_{max} 3113, 1684 cm^{-1}. Anal. Calcd. For $C_{17}H_{14}N_2O_3$: C 69.38, H 4.79, N 9.52; found: C 69.64, H 4.60, N 9.83.

*(Z)-4-((Phenylamino)methylene)-3-propylisoxazol-5(4H)-one (**52f**)*

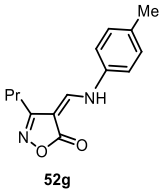


52f

FCC – AcOEt/DCM (1:4); **52f** (82%); pale brown solid; m.p.: 122-123 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, 3H, *J* = 7.3 Hz), 1.59-1.69 (m, 2H), 2.49 (t, 2H, *J* = 7.4 Hz), 7.12-7.19 (m, 3H), 7.30 (t, 2H, *J* = 7.8 Hz), 7.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.6, 20.3, 27.4, 93.0, 117.4, 126.2, 129.8, 137.6, 144.4, 162.1, 174.0. IR ν_{max} 3085, 1679 cm^{-1}. Anal. Calcd. For $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17; found: C 68.08, H 5.93, N 10.24.

[88] C. Wentrup, H. Briehl, P. Lorencak, U. J. Vogelbacher, H.-W. Winter, A. Maquestiau, R. Flammang, Primary Ethynamines (HC≡CNH$_2$, PhC≡ CNH$_2$), Aminopropadienone (H$_2$NCH=C=C=O), and Imidoylketene (HN=CHCH=C=O). Preparation and Identification of Molecules of Cosmochemical Interest *J. Am. Chem. Soc.* **1988**, *110*, 1337-1343.

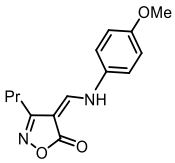
*(Z)-3-Propyl-4-((4-tolylamino)methylene)isoxazol-5(4H)-one (**52g**)*



52g

FCC – AcOEt/hexane (2:3); **52g** (77%); orange solid; m.p.; 122-123 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, 3H, *J* = 7.4 Hz), 1.71-1.80 (m, 2H), 2.37 (s, 3H), 2.58 (t, 2H, *J* = 7.4 Hz), 7.11 (d, 2H, *J* = 8.3 Hz), 7.23 (d, 2H, *J* = 8.2 Hz), 7.88 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.8, 20.6, 20.8, 27.7, 93.0, 117.5, 130.5, 135.4, 136.6, 144.1, 162.0, 174.3. IR ν_{max} 3105, 1687 cm^{-1}. Anal. Calcd. For $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47; found: C 69.11, H 6.38, N 11.62.

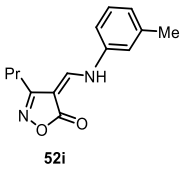
*(Z)-4-((4-Methoxyamino)methylene)-3-propylisoxazol-5(4H)-one (**52h**)*



52h

FCC – AcOEt/hexane (3:2); **52h** (75%); red wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, 3H, *J* = 7.3 Hz), 1.60-1.70 (m, 2H), 2.48 (t, 2H, *J* = 7.4 Hz), 3.73 (s, 3H), 6.85 (d, 2H, *J* = 8.8 Hz), 7.08 (d, 2H, *J* = 8.8 Hz), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.8, 20.5, 27.6, 55., 92.4, 115.1, 119.3, 131.1, 144.6, 158.2, 162.0, 174.3 IR ν_{max} 3086, 1673 cm^{-1}. Anal. Calcd. For $C_{14}H_{16}N_2O_3$: C 64.60, H 6.20, N 10.76; found: C 64.86, H 5.94, N 10.60.

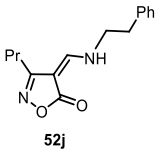
*(Z)-3-Propyl-4-((3-tolylamino)methylene)isoxazol-5(4H)-one (**52i**)*



52i

FCC – AcOEt/hexane (1:1); **52i** (80%); orange wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, 3H, *J* = 7.3 Hz), 1.62-1.71 (m, 2H), 2.30 (s, 3H), 2.50 (t, 2H, *J* = 7.5 Hz), 6.92-6.98 (m, 3H), 7.20-7.24 (m, 1H), 7.85 (s, 1H), 10.45 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.9, 20.7, 21.4, 27.8, 93.3, 114.7, 118.3, 127.3, 129.9, 7.8, 140.4, 144.2, 162.2, 174.3. IR ν_{max} 3097, 1682 cm^{-1}. Anal. Calcd. For $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47; found: C 68.57, H 6.83, N 11.04.

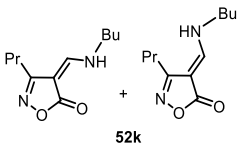
*(Z)-4-((Phenethylamino)methylene)-3-propylisoxazol-5(4H)-one (**52j**)*



52j

FCC – AcOEt/hexane (1:1); **52j** (63%); brown wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (t, 3H, *J* = 7.4 Hz), 1.37-1.48 (m, 2H), 2.26 (t, 2H, *J* = 7.5 Hz), 2.87 (t, 2H, *J* = 6.7 Hz), 3.60 (q, 2H, *J* = 6.4 Hz), 7.01-7.24 (m, 5H), 8.97 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.8, 19.8, 26.6, 35.9, 50.5, 88.7, 126.0, 127.9, 128.1, 136.0, 151.5, 161.3, 173.7 IR ν_{max} 3105, 1686 cm^{-1}. Anal. Calcd. For $C_{15}H_{18}N_2O_2$: C 69.74, H 7.02, N 10.84; found: C 69.52, H 7.23, N 10.60.

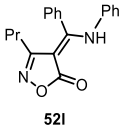
*4-((Butylamino)methylene)-3-methylisoxazol-5(4H)-one (**52k**)*



52k

FCC – AcOEt/hexane (3:2); **52k** (79%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89-0.97 (m, 3H), 1.33-1.44 (m, 2H), 1.60-1.69 (m, 2H), 2.13 (s, 3H), 3.43 (q, 2H, *J* = 6.7 Hz), 7.35-7.41 (m, 1H), 8.86 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.8, 13.5, 19.6, 32.3, 49.9, 152.2, 158.6, 158.7, 174.4. IR ν_{max} 3270, 1694 cm^{-1}. Anal. Calcd. For $C_9H_{14}N_2O_2$: C 59.32, H 7.74, N 15.37; found: C 59.51, H 7.96, N 15.79.

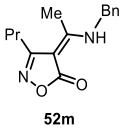
*(Z)-4-(Phenyl(phenylamino)methylene)3-propylisoxazol-5(4H)-one (**52l**)*



52l

FCC – AcOEt/hexane (2:3); **52l** (71%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.60 (t, 3H, *J* = 7.3 Hz), 1.15-1.25 (m, 2H), 1.84 (t, 2H, *J* = 7.6 Hz), 6.81 (d, 2H, *J* = 7.7 Hz), 7.09-7.19 (m, 3H), 7.28-7.32 (m, 2H), 7.44 (t, 2H, *J* = 7.8 Hz), 7.48-7.53 (m, 1H), 11.90 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.7, 20.3, 29.8, 91.9, 124.4, 126.7, 128.5, 128.9, 129.1, 130.6, 131.0, 136.8, 162.0, 163.0. IR ν_{max} 2994, 1632 cm^{-1}. Anal. Calcd. For $C_{19}H_{18}N_2O_2$: C 74.49, H 5.92, N 9.14; found: C 74.67, H 5.69, N 10.37.

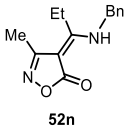
*(Z)-4-(1-(Benzylamino)ethylidene)3-propylisoxazol-5(4H)-one (**52m**)*



52m

FCC – AcOEt/hexane (3:2); **2m** (74%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (t, 3H, *J* = 7.4 Hz), 1.59-1.69 (m, 2H), 2.26 (s, 3H), 2.53 (t, 2H, *J* = 7.4 Hz), 4.56 (d, 2H, *J* = 6.2 Hz), 7.19 (d, 2H, *J* = 8.8 Hz), 7.24-7.33 (m, 3H), 10.73 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.9, 15.8, 20.5, 30.9, 47.3, 89.6, 126.9, 128.3, 129.3, 135.4, 161.2, 165.3, 175.7. IR ν_{max} 3090, 1675 cm^{-1}. Anal. Calcd. For $C_{15}H_{18}N_2O_2$: C 69.74, H 7.02, N 10.84; found: C 69.90, H 6.86, N 10.62.

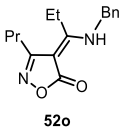
*(Z)-4-(1-(Benzylamino)propylidene)3-methylisoxazol-5(4H)-one (**52n**)*



52n

FCC – AcOEt/hexane (3:2); **52n** (80%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (t, 3H, *J* = 7.7 Hz), 2.23 (s, 3H), 2.62 (q, 2H, *J* = 7.7 Hz), 4.58 (d,2H, *J* = 6.2 Hz), 7.21 (d, 2H, *J* = 7.1 Hz), 7.25-7.33 (m, 3H), 10.6 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.6, 14.6, 22.1, 46.9, 89.1, 127.0, 128.4, 129.2, 135.5, 157.5, 170.5, 175.9. IR ν_{max} 3291, 1679 cm^{-1}. Anal. Calcd. For $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47; found: C 69.05, H 6.42, N 11.04.

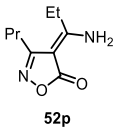
*(Z)-4-(1-(Benzylamino)propylidene)3-propylisoxazol-5(4H)-one (**52o**)*



52o

FCC – AcOEt/hexane (2:3); **52o** (80%); orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (t, 3H, *J* = 7.4 Hz), 1.17 (t, 3H, *J* = 7.7 Hz), 1.61-1.71 (m, 2H), 2.50 (t, 2H, *J* = 7.4 Hz), 2.59 (q, 2H, *J* = 7.7 Hz), 4.56 (d, 2H, *J* = 6.1 Hz), 7.17-7.30 (m, 5H), 10.7 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.6, 14.0, 20.3, 22.2, 30.6, 46.9, 88.2, 127.0, 128.3, 129.2, 135.6, 160.9, 170.5, 176.1. IR ν_{max} 3091, 1673 cm^{-1}. Anal. Calcd. For $C_{16}H_{20}N_2O_2$: C 70.56, H 7.40, N 10.29; found: C 70.37, H 7.61, N 10.58.

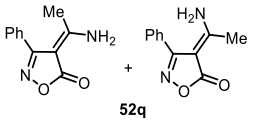
*(Z)-4-(1-Aminopropylidene)3-propylisoxazol-5(4H)-one (**52p**)*



52p

FCC – AcOEt/hexane (1:1); **52p** (71%); orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, 3H, *J* = 7.4 Hz), 1.35 (t, 3H, *J* = 7.5 Hz), 1.70-1.80 (m, 2H), 2.60 (t, 2H, *J* = 7.4 Hz), 2.70 (q, 2H, *J* = 7.6 Hz), 6.51 (bs, 1H), 9.80 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.6, 14.0, 20.3, 26.3, 30.8, 89.0, 161.2, 170.4, 175.6. IR ν_{max} 3098, 1664 cm^{-1}. Anal. Calcd. For $C_9H_{14}N_2O_2$: C 59.32, H 7.74, N 15.37; found: C 59.55, H 7.58, N 15.11.

*4-(1-Aminoethylidene)3-phenylisoxazol-5(4H)-one (**52q**)*



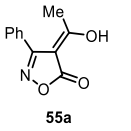
52q

FCC – AcOEt/hexane (1:1); **52q** (63%); orange solid; m.p.: 201-203 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.86 (s, 3H), 2.18 (s, 3H), 7.12 (bs, 2H), 7.28-7.34 (m, 3H), 7.46-7.55 (m, 7H), 9.45 (bs, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ 20.0, 27.4, 87.8, 90.2, 127.0, 127.8, 128.5, 128.7, 128.9, 129.6, 131.0, 133.4, 162.4, 162.6, 167.9, 173.8, 17.4, 188.4. IR ν_{max} 3102, 1671 cm^{-1}. Anal. Calcd. For $C_{11}H_{10}N_2O_2$: C 65.34, H 4.98, N 13.85; found: C 65.52, H 4.68, N 13.60.

*Procedure for the synthesis of 4-hydroxyalkyliden-isoxazol-5-ones (**55**)*

In a solution of the appropriate 3-substituted isoxazole-5-ones (1.0 mmol) in THF dry (10.0 mL), NaH (2.0 mmol) and the appropriate anhydride (2.0 mmol) were added. The resulting solution was stirred for 30 minutes at 0 °C and at reflux for 24 hours. The solvent was evaporated under reduced pressure, and it was quenched with a 2M acqueous solution of HCl (5.0 mL) and extracted with DCM (5 mL x 3), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

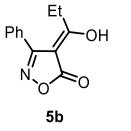
*(Z)-4-(1-Hydroxyethylidene)-3-phenylisoxazol-5(4H)-one (**55a**)*



55a

FCC – AcOEt/hexane (2:3); **55a** (80%); red solid; m.p.: 98-101 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.11 (s, 3H), 7.48-7.55 (m, 4H), 7.63-7.68 (m, 1H), 9.38 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 34.0, 98.0, 126.6, 128.6, 128.7, 128.9, 129.2, 130.7, 132.2, 161.5, 163.2, 174.8. IR ν_{max} 3198, 1712 cm^{-1}. Anal. Calcd. For $C_{11}H_9NO_3$: C 65.02, H 4.46, N 6.89; found: C 65.27, H 4.29, N 7.31.

*(Z)-4-(1-Hydroxypropylidene)-3-phenylisoxazol-5(4H)-one (**55b**)*

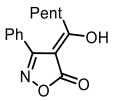


5b

55b (89%); red oil. The characterization of product **55b** is consistent with that reported in literature.[89]

[89] S. Biju, M. L. Reddy, A. H. Cowley, K. V. Vasudevan 3-Phenyl-4-acyl-5-isoxazolonate complex of Tb3+ doped into poly-β-hydroxydutyrate matrix as a promising light-conversion molecular device *J. Mater. Chem.* 2009, *19*, 5179-5187.

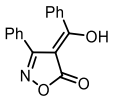
*(Z)-4-(1-Hydroxyhexylidene)-3-phenylisoxazol-5(4H)-one (**55c**)*



55c

FCC – AcOEt/hexane (2:3); **55c** (71%); yellow wax. ^{1}H NMR (CD_3OD, 400 MHz) δ 0.78 (t, 3H, *J* = 6.6 Hz), 1.11-1.25 (m, 4H), 1.31-1.45 (m, 2H), 2.53-2.57 (m, 2H), 7.15-7.33 (m, 3H), 7.38-7.50 (m, 2H); ^{13}C NMR (CD_3OD, 101 MHz) δ 14.4, 23.6, 26.4, 32.9, 40.6, 93.2, 127.7, 128.7, 129.8, 130.0, 130.8, 133.9, 165.9, 179.0, 197.5. IR ν_{max} 3214, 1661 cm^{-1}. Anal. Calcd. For $C_{15}H_{17}NO_3$: C 69.48, H 6.61, N 5.40; found: C 69.36, H 6.80, N 5.57.

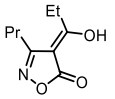
*(Z)-4-(1-Hydroxy(phenyl)methylidene)-3-phenylisoxazol-5(4H)-one (**55d**)*



55d

FCC – AcOEt/hexane (2:3); **55d** (71%); orange solid; m.p.: 145-147 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11-7.20 (m, 6H), 7.28-7.35 (m, 3H), 7.38-7.48 (m, 1H), 10.33 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 95.9, 128.0, 128.3, 128.4, 128.5, 129.6, 130.1, 130.8, 133.1, 161.2, 177.9, 180.3. IR ν_{max} 3062, 1633 cm^{-1}. Anal. Calcd. For $C_{16}H_{11}NO_3$: C 72.45, H 4.18, N 5.28; found: C 72.66, H 3.92, N 4.96.

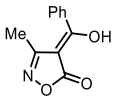
*(Z)-4-(1-Hydroxypropylidene)-3-propylisoxazol-5(4H)-one (**55e**)*



55e

FCC – AcOEt/hexane (2:3); **55e** (92%); orange solid; m.p.: 99-103 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.97 (t, 3H, *J* = 7.5 Hz), 1.15 (t, 3H, *J* = 7.5 Hz), 1.65-1.75 (m, 2H), 2.79-2.85 (m, 4H), 13.3 (bs,1 H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 8.8, 13.6, 19.9, 29.3, 31.2, 95.8, 164.1, 172.8, 173.0. IR ν_{max} 3107, 1666 cm^{-1}. Anal. Calcd. For $C_9H_{13}NO_3$: C 59.00, H 7.15, N 7.65; found: C 59.16, H 7.03, N 7.92.

*(Z)-4-(1-Hydroxy(phenyl)methylene)-3-methylisoxazol-5(4H)-one (**55f**)*



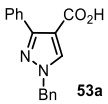
55f

FCC – AcOEt/hexane (3:7); **55f** (81%); orange oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.03 (s, 3H), 7.54-7.58 (m, 2H), 7.60-7.69 (m, 3H), 11.0 (bs, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.4, 97.9, 128.7, 131.5, 133.3, 157.7, 177.5, 179.8. IR ν_{max} 3068, 1654 cm^{-1}. Anal. Calcd. For $C_{11}H_9NO_3$: C 65.02, H 4.46 N 6.89; found: C 65.20, H 4.25, N 6.12.

General procedure for the synthesis of pyrazole 4-carboxylic acids and isoxazole 4-carboxylic acids

In a sealed tube, to a solution of the appropriate 4-alkylidene-isoxazole-5-ones (1.0 mmol) in MeCN or DMSO (3.0 mL), $[RuCl_2(p\text{-cymene})]_2$ (5 or 10 mol%) was added. The resulting solution was stirred at reflux overnight. The solvent was evaporated under reduced pressure, and the resulting mixture was washed with brine (10 mL x 3) and extracted with AcOEt (5 mL x 3), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. The residue was purified through FCC.

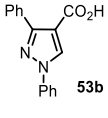
*1-Benzyl-3-phenyl-1H-pyrazole-4-carboxylic acid (**53a**)*



53a

FCC – AcOEt/hexane (1:1); **53a** (68%); brown solid; m.p.: 150-153 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.35 (s, 2H), 7.32-7.47 (m, 8H), 7.79 (d, 2H, *J* = 9.3 Hz), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 56.6, 111.0, 127.9, 128.2, 128.5, 128.6, 9.1, 129.3, 132.0, 134.9, 135.9, 153.7, 167.0. IR ν_{max} 3125, 1724 cm^{-1}. Anal. Calcd. For $C_{17}H_{14}N_2O_2$: C 73.37, H 5.07, N 10.07; found: C 73.69, H 4.86, N 10.41.

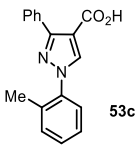
*1,3-Diphenyl-1H-pyrazole-4-carboxylic acid (**53b**)*



53b

FCC – AcOEt/hexane (2:3); **53b** (91%); orange solid; m.p.: 204-206 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.54 (m, 6H), 7.74-7.80 (m, 2H), 7.83-7.90 (m, 2H), 8.58 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 112.7, 119.6, 119.7, 127.7, 128.0, 128.8, 129.4, 129.6, 131.8, 133.4, 139.1, 154.5, 167.6. IR ν_{max} 3156, 1664 cm^{-1}. Anal. Calcd. For $C_{16}H_{12}N_2O_2$: C 72.72, H 4.58, N 10.60; found: C 72.56, H 4.79, N 10.38.

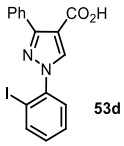
*3-Phenyl-1-(2-tolyl)-1H-pyrazole-4-carboxylic acid (**53c**)*



53c

FCC – AcOEt/hexane (2:3); **53c** (76%); brown solid; m.p.: 128-132 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.36 (s, 3H), 7.31-7.48 (m, 7H), 7.90 (d, 2H, *J* = 9.3 Hz), 8.28 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 18.1, 111.6, 126.0, 126.8, 127.9, 128.7, 129.2, 129.4, 131.5, 131.8, 133.6, 137.4, 138.8, 153.9, 168.3. IR ν_{max} 3181, 1674 cm^{-1}. Anal. Calcd. For $C_{17}H_{14}N_2O_2$: C 73.37, H 5.07, N 10.07; found: C 73.52, H 4.78, N 10.32.

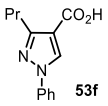
*1-(2-Iodophenyl)-3-phenyl-1H-pyrazole-4-carboxylic acid (**53d**)*



53d

FCC – AcOEt/hexane (2:3); **53d** (74%); grey solid; m.p.: 169-172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.19-7.23 (m, 1H), 7.43-7.54 (m, 5H), 7.90 (d, 2H, *J* = 7.5 Hz), 8.00 (d, 1H, *J* = 7.9 Hz), 8.39 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 93.9, 111.8, 127.9, 128.9, 129.2, 129.5, 130.9, 131.6, 138.0, 140.3, 142.3, 154.3, 167.8. IR ν_{max} 3190, 1677 cm^{-1}. Anal. Calcd. For $C_{16}H_{11}IN_2O_2$: C 49.25, H 2.84, N 7.18; found: C 49.46, H 2.58, N 7.32.

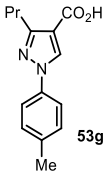
*1-Phenyl-3-propyl-1H-pyrazole-4-carboxylic acid (**53f**)*



53f

FCC – AcOEt/hexane (1:1); **53f** (82%); brown solid; m.p.: 137-138 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, 3H, *J* = 7.4 Hz), 1.76-1.86 (m, 2H), 2.98 (t, 2H, *J* = 7.5 Hz), 7.33 (t, 1H, *J* = 7.4 Hz), 7.47 (t, 2H, *J* = 7.6 Hz), 7.69 (d, 2H, *J* = 7.9 Hz), 8.43 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.0, 22.3, 29.6, 112.9, 119.5, 127.3, 129.5, 132.3,c139.2, 157.0, 168.9. IR ν_{max} 3162, 1682 cm^{-1}. Anal. Calcd. For $C_{13}H_{14}N_2O_2$: C 67.81, H 6.13, N 12.17; found: C 67.53, H 6.25, N 12.36.

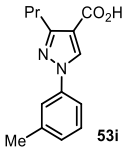
*3-Propyl-1-(4-tolyl)-1H-pyrazole-4-carboxylic acid (**53g**)*



53g

FCC – AcOEt/hexane (2:3); **53g** (76%); grey solid; m.p.: 141-143 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.95 (t, 3H, *J* = 7.3 Hz), 1.67-1.76 (m, 2H), 2.30 (s, 3H), 2.88 (t, 2H, *J* = 7.5 Hz), 7.17 (d, 2H, *J* = 8.2 Hz), 7.48 (d, 2H, *J* = 8.4 Hz), 8.29 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.0, 20.9, 22.3, 29.6, 112.8, 119.4, 130.0, 132.1, 137.0, 137.2, 156.8, 168.8. IR ν_{max} 3158, 1634 cm^{-1}. Anal. Calcd. For $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47; found: C 68.60, H 6.81, N 11.19.

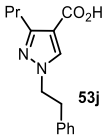
*3-Propyl-1-(4-tolyl)-1H-pyrazole-4-carboxylic acid (**53i**)*



53i

FCC – AcOEt/hexane (9:1); **53i** (73%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (t, 3H, *J* = 7.3 Hz), 1.77-1.86 (m, 2H), 2.44 (s, 3H), 2.98 (t, 2H, *J* = 7.6 Hz), 7.16 (d, 1H, *J* = 7.7 Hz), 7.36 (t, 1H, *J* = 7.7 Hz), 7.47 (d, 2H, *J* = 8.0 Hz), 7.55 (s, 1H), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.0, 21.5, 22.4, 29.6, 112.7, 116.6, 120.3, 128.2, 129.3, 132.3, 139.2, 139.8, 157.0, 168.7. IR ν_{max} 3175, 1682 cm^{-1}. Anal. Calcd. For $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47; found: C 68.96, H 6.48, N 11.19.

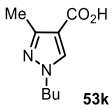
*1-Phenethyl-3-propyl-1H-pyrazole-4-carboxylic acid (**53j**)*



53j

FCC – AcOEt/hexane (1:1); **53j** (73%); brown soild; m.p.: 147-148 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (t, 3H, *J* = 7.4 Hz), 1.69-1.80 (m, 2H), 2.90 (t, 2H, J = 6.8 Hz), 3.18 (t, 2H, *J* = 7.1 Hz), 4.30 (t, 2H, *J* = 7.0 Hz), 7.08 (d, 2H, *J* = 8.1 Hz), 7.23-7.33 (m, 3H), 7.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.9, 22.5, 29.5, 36.5, 53.9, 110.4, 126.9, 128.6, 128.7, 135.1, 137.5, 156.2, 168.2. IR ν_{max} 3182, 1694 cm^{-1}. Anal. Calcd. For $C_{15}H_{18}N_2O_2$: C 69.74, H 7.02, N 10.84; found: C 69.96, H 6.86, N 10.61.

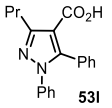
*1-Butyl-3-methyl-1H-pyrazole-4-carboxylic acid (**53k**)*



53k

FCC – AcOEt/hexane (1:1); **53k** (51%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, 3H, *J* = 7.4 Hz), 1.29-1.40 (m, 2H), 1.81-1.90 (m, 2H), 2.30 (s, 3H), 4.05 (t, 2H, *J* = 7.6 Hz), 7.84 (s, 1H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.1, 15.5, 29.7, 32.0, 52.2, 106.3, 133.8, 160.6, 176.2. IR ν_{max} 3295, 1717 cm^{-1}. Anal. Calcd. For $C_9H_{14}N_2O_2$: C 59.32, H 7.74, N 15.37; found: C 59.47, H 7.56, N 15.18.

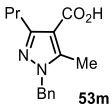
*1,5-Diphenyll-3-propyl-1H-pyrazole-4-carboxylic acid (**53l**)*



53l

FCC – AcOEt/hexane (2:3); **53l** (74%); green solid; m.p.: 177-180 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (t, 3H, *J* = 7.4 Hz), 1.78-1.87 (m, 2H), 2.99 (t, 2H, *J* = 7.6 Hz), 7.15-7.17 (m, 2H), 7.24-7.27 (m, 5H), 7.29-7.38 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 14.2, 22.4, 30.2, 110.2, 120.3, 125.4, 127.7, 128.0, 128.7, 129.0, 129.6, 130.5, 139.2, 147.0, 156.5, 168.0. IR ν_{max} 3167, 1671 cm^{-1}. Anal. Calcd. For $C_{19}H_{18}N_2O_2$: C 74.49, H 5.92, N 9.14; found: C 74.71, H 5.79, N 9.31.

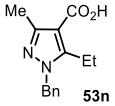
*1-Benzyl-5-methyl-3-propyl-1H-pyrazole-4-carboxylic acid (**53m**)*



53m

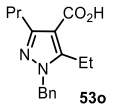
FCC – AcOEt/hexane (2:3); **53m** (62%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, 3H, *J* = 7.3 Hz), 1.61-1.70 (m, 3H), 2.39 (s, 3H), 2.80 (t, 2H, *J* = 7.5 Hz), 5.22 (s, 2H), 7.02 (d, 2H, *J* = 8.6 Hz), 7.19-7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 10.5, 12.9, 21.4, 29.0, 51.9, 107.7, 125.6, 126.8, 127.8, 135.0, 144.4, 154.6, 168.5. IR ν_{max} 3186, 1671 cm^{-1}. Anal. Calcd. For $C_{15}H_{18}N_2O_2$: C 69.74, H 7.02, N 10.84; found: C 69.96, H 6.87, N 10.63.

*1-Benzyl-5-ethyl-3-methyl-1H-pyrazole-4-carboxylic acid (**53n**)*


53n

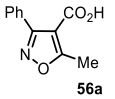
FCC – AcOEt/hexane (2:3); **53n** (58%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.99 (t, 3H, *J* = 7.5 Hz), 2.41 (s, 3H), 2.84 (q, 2H, *J* = 7.5 Hz), 5.21 (s, 2H), 7.04 (d, 2H, *J* = 7.7 Hz), 7.17-7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.2, 14.3, 18.9, 52.7, 108.5, 126.7, 127.9, 128.8, 136.4, 150.9, 151.8, 169.5. IR ν_{max} 3063, 1690 cm^{-1}. Anal. Calcd. For $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47; found: C 68.95, H 6.42, N 11.61.

*1-Benzyl-5-ethyl-3-propyl-1H-pyrazole-4-carboxylic acid (**53o**)*


53o

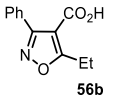
FCC – AcOEt/hexane (2:3); **53o** (51%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, 3H, *J* = 7.4 Hz), 1.06 (t, 3H, *J* = 7.4 Hz), 1.69-1.78 (m, 2H), 2.85-2.93 (m, 4H), 5.29 (s, 2H), 7.10 (d, 2H, *J* = 8.6 Hz), 7.27-7.33 (m, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 13.2, 14.0, 18.9, 22.4, 30.1, 52.8, 107.7, 126.6, 127.8, 128.8, 136.6, 150.9, 155.7, 168.6. IR ν_{max} 3173, 1679 cm^{-1}. Anal. Calcd. For $C_{16}H_{20}N_2O_2$: C 70.56, H 7.40, N 10.29; found: C 70.82, H 7.15, N 10.44.

*5-Methyl -3-phenylisoxazole-4-carboxylic acid (**56a**)*


56a

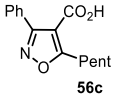
FCC – AcOEt/hexane (2:3); **56a** (91%); white solid. The characterization of product **56a** is consistent with that reported in literature.[90]

*5-Ethyl -3-phenylisoxazole-4-carboxylic acid (**56b**)*


56b

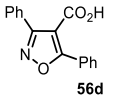
FCC – AcOEt/hexane (2:3); **56b** (87%); grey solid; m.p.: 149-151 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (t, 3H, *J* = 7.6 Hz), 3.20 (q, 2H, *J* = 7.6 Hz), 7.43-7.52 (m, 3H), 7.60-.7.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.4, 21.5, 106.6, 128.1, 128.2, 129.4, 129.9, 162.8, 167.4, 182.1. IR ν_{max} 2984, 1680 cm^{-1}. Anal. Calcd. For $C_{12}H_{11}NO_3$: C 66.35, H 5.10, N 6.45; found: C 66.57, H 4.97, N 6.67.

*5-Pentyl -3-phenylisoxazole-4-carboxylic acid (**56c**)*


56c

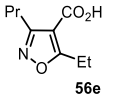
FCC – AcOEt/hexane (3:7); **56c** (86%); yellow wax. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, 3H, *J* = 9.9 Hz), 1.35-1.42 (m, 4H), 1.78-1.85 (m, 2H), 3.15 (t, 2H, *J* = 7.6 Hz), 7.43-7.48 (m, 3H), 7.62-7.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.8, 21.2, 25.9, 26.6, 30.3, 105.8, 7.0, 127.1, 128.4, 128.9, 161.7, 165.0, 180.2. IR ν_{max} 2960, 1682 cm^{-1}. Anal. Calcd. For $C_{13}H_{17}NO_3$: C 69.48, H 6.61, N 5.40; found: C 69.27, H 6.76, N 5.65.

*3,5-Diphenylisoxazole-4-carboxylic acid (**56d**)*


56d

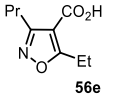
FCC – AcOEt/hexane (2:3); **56d** (81%); yellow oil. The characterization of product **56d** is consistent with that reported in literature.[91]

*5-Ethyl -3-propylisoxazole-4-carboxylic acid (**56e**)*


56e

FCC – AcOEt/hexane (3:7); **56e** (88%); yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (t, 3H, *J* = 7.5 Hz), 1.34 (t, 3H, *J* = 7.6 Hz), 1.71-1.83 (m, 2H), 2.86 (t, 2H, *J* = 7.5 Hz), 3.13 (q, 2H, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 11.3, 13.9, 20.9, 21.2, 27.9, 106.4, 163.7, 166.5, 181.3. IR ν_{max} 2829, 1666 cm^{-1}. Anal. Calcd. For $C_9H_{13}NO_3$: C 59.00, H 7.15, N 7.65; found: C 58.73, H 7.33, N 7.83.

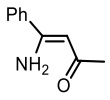
*5-Methyl -3-phenylisoxazole-4-carboxylic acid (**56f**)*


56e

FCC – AcOEt/hexane (3:7); **56f** (93%); white solid; m.p.: 151-153 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.55 (s, 3H), 7.48-7.57 (m, 3H), 7.90-7.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 12.3, 107.3, 126.7, 128.4, 129.4, 131.5, 161.3, 166.9, 174.4. IR ν_{max} 3136, 1714 cm^{-1}. Anal. Calcd. For $C_{11}H_9NO_3$: C 65.02, H 4.46, N 6.89; found: C 65.29, H 4.28, N 6.51.

[90] J. H. Kalin, H. Zhang, S. Gaudrel-Grosay, G. Vistoli, A. P. Kozikowski Chiral Mercaptoacetamides Display Enantioselective Inhibition of Histone Deacetylase 6 and Exhibit Neuroprotection in Cortical Neuron Models of Oxidative Stress *ChemMedChem* **2012**, *7*, 425-439.
[91] P. Vitale, S. Tacconelli, M. G. Perrone, P. Malerba, L. Simone, A. Scilimati, A. Lavecchia, M. Dovizio, E. Marcantoni, A. Bruno, P. Patrignani Synthesis, Pharmacological Characterization, and Docking Analysis of a Novel Family of Diarylisoxazoles as Highly Selective Cyclooxygenase-1 (COX-1) Inhibitors. *J. Med. Chem.* **2013**, *56*, 4277-4299.

*Procedure for the synthesis of (Z)-1-amino-1-phenyl-1-buten-3-one (**54**)*



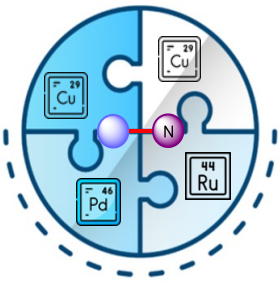
54

In a sealed tube, to a solution of the appropriate 4-alkylidene-isoxazole-5-ones (1.0 mmol) in DMSO (3.0 mL), $[RuCl_2(p\text{-cymene})]_2$ (5 or 10 mol%) was added. The resulting solution was stirred at 120 °C for 72 hours. The solvent was evaporated under reduced pressure, and the resulting mixture was washed with brine (10 mL x 3) and extracted with AcOEt (5 mL x 3), dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure. Compound **54** was afforded as yellow wax (91%) after FCC- AcOEt/hexane (3:2). The characterization of product **54** is consistent with that reported in literature.[92]

[92] L. Di Nunno, A. Scilimati, P. Vitale Reaction of 3-phenylisoxazole with alkyllithiums. *Tetrahedron* 2005, *61*, 2623-2630.

GENERAL CONCLUSIONS

In this PhD thesis various goals related to the preparation of nitrogen-containing heterocyclic and acyclic compounds were achieved by methodologies based on catalytic systems containing copper, palladium and ruthenium (Scheme 80). The value of the results achieved is supported by the fact that the proposed synthetic procedures only involve the functionalization of unactivated bonds, not pre-functionalized and therefore easily accessible and cheap.



Scheme 80. Four transition metal catalyst in nitrogen bond forming

In the first part, a copper catalyzed cyclization/dimerization of benzyl aminophenols is developed to afford products which showed an interesting fluorescent property.
Subsequently a domino procedure for the synthesis of 1-aryl-2-aminopropanes is reported starting either from carbamates or allyl alcohols in the presence of copper(II) triflate, in excess in the former case and in catalytic amount in the latter.
Following our interest in azidation reactions, the third part of the thesis focuses on a new palladium catalyzed procedure for the synthesis of diazidation compounds.
Finally, the first non-decarboxylative rearrangement of suitably 4-substituted isoxazol-5-ones is analyzed in the presence of a ruthenium(II) catalyst.
It's worth noting that the four transition metal-catalyzed methodologies allowed the obtainment of nitrogenated targets which interest go from materials to fine chemical and pharmaceutical fields.

GENERAL EXPERIMENTAL INFO

All chemicals and solvents were purchased from commercial sources.
Thin layer chromatography (TLC) was performed using 0.25 mm silica gel precoated plates Si 60-F254 (Merck, Darmstadt, Germany) visualized by UV-254 light and CAM staining.
Purification by flash column chromatography (FCC) was conducted by using silica gel Si 60, 230-400 mesh, 0.040-0.063 mm (Merck).
Melting points were determined on a Stuart Scientific SMP3 and are corrected.
^{1}H, ^{13}C NMR and NOESY spectra were recorded on a Bruker Avance 400 (400 and 101 MHz, respectively) or Bruker Avance 300 (300 and 75 MHz, respectively); chemical shifts are indicated in parts per million downfield from $SiMe_4$. Coupling constants values J are given in Hz.
The UV-vis, excitation and emission spectra were measured using a fluorescence spectrometer (Edinburgh Instruments FS5) equipped with a 150 W continuous Xenon lamp as a light source and were corrected for the wavelength response of the instrument. Lifetime measurements were performed on the same FS5 Edinburgh Instruments equipped with an EPLED-320 (Edinburgh Instruments) pulsed source. Analysis of the lifetime decay curve was done using Fluoracle® Software package (Ver. 1.9.1), which runs the FS5 instrument.
FT-IR spectra were recorded on a Tensor 27 (ATR Diamond) Bruker infrared spectrophotometer and are reported in frequency of absorption (cm^{-1}).
Elemental
s were executed on Perkin-Elmer CHN Analyzer Series II 2400.
High-resolution mass spectra (HRMS) were recorded using a mass spectrometer MicroTOF from Bruker with an electron spray ion source (ESI) and a TOF detector or using a mass spectrometer from Thermo Fisher Scientific with an electron spray ion source (ESI) and a LTQ Orbitrap as detector at Institut Parisien de Chimie Moléculaire (France) or at Università degli Studi dell'Insubria (Italy).