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Efficient and mild Ullmann-type N-arylation of amides, carbamates, and azoles in water.

Maud Bollenbach,^{[a]#} Pedro G. V. Aquino,^{[a,b]#} João Xavier de Araújo-Júnior,^[b] Jean-Jacques Bourguignon,^[a] Frédéric Bihel,^[a] Christophe Salomé,^[a,c] Patrick Wagner^[a] and Martine Schmitt*^[a]

Abstract: A simple, sustainable, efficient, mild, and low-cost protocol was developed for D-glucose-assisted Cu-catalyzed Ullmann reactions in water for amides, carbamates, and nitrogen-containing heterocycles. The reaction was compatible with diverse aryl/heteroaryl iodides, giving highly substituted pyridine, indole, or indazole rings. This method offers an attractive alternative to the existing protocols, because the reaction proceeds in aqueous media, occurs at or near ambient temperature, and provides the N-arylated products in good-to-high yields.

Introduction

The formation of transition-metal-catalyzed C–N bonds via cross-coupling reactions plays an important role in the preparation of numerous important products in biological, pharmaceutical, and material sciences.^[1] Formation of C–N bonds by Ullmann and Goldberg coupling reactions provides a powerful tool to prepare these nitrogen-containing compounds on both laboratory and industrial scales.^[2] However, the classic Ullmann and Goldberg coupling reactions suffer from drawbacks such as harsh reaction conditions, including high reaction temperatures (160–200 °C), extended reaction times, and the use of large amounts of Cu, and low tolerance of functional groups.^[3] In 2001, an important breakthrough was achieved by two research groups with the discovery of efficient and versatile Cu/ligand systems that enable these cross-coupling reactions to occur under much milder conditions (90–110 °C).^[4,5] Since the last decade, the formation of C–N bonds by Cu-mediated cross-coupling approaches has led to a spectacular resurgence of interest.^[6–8]

From economic and environmental point of view, water as a solvent is a good alternative to organic solvents;^[9] wide applications of N-arylated compounds in many fields have stimulated the development of new strategies for their synthesis in water. However, reactions in water suffer from the poor solubility of organic reagents in aqueous media. A micellar system can improve the solubility of components, thereby accelerating the reaction rate owing to the aggregation of reactants in the unique micellar environment.^[10] Very recently, our group

highlighted the efficiency of D-glucose to generate Cu(I) species from a Cu(II) source for conducting the N-arylation of primary amines in water at 25 °C.^[11] However, this new catalytic system (Cu(OTf)₂/D-glucose, dipivaloylmethane, NaOt-Bu) failed when other classes of amines were used. N-arylamides represent an important class of compounds found in numerous bioactive products^[13] such as top-selling medicines (e.g., Lipitor®, Liloderm®, and Vyvanse®)^[14] as well as biological and synthetic polymers (e.g., proteins and nylons);^[15,16] they also serve as versatile building blocks in the preparation of pharmaceuticals, agrochemicals, polymers, etc.^[17] Therefore, we continued our efforts to develop Cu-catalyzed cross-couplings in aqueous media for that class of amine.^[12] Herein, we report a simple, practical, and efficient D-glucose-assisted Cu-catalyzed N-arylation of amides, carbamates, and nitrogen-containing heterocycles. Our approach includes i) use of an inexpensive Cu(II) catalyst, ii) presence of renewable feedstocks (D-glucose

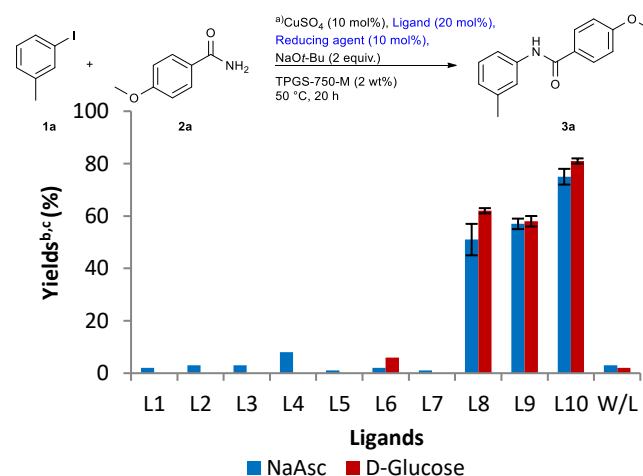
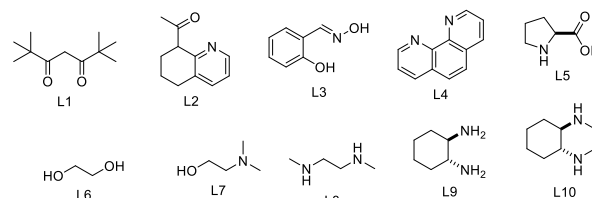


Figure 1. Copper catalyzed amidation of 3-iodotoluene in TPGS-750-M at



50 °C: Impact of various ligands in presence of NaAsc or D-Glucose. ^aReaction conditions: CuSO₄·5H₂O (10 mol%), ligands (20 mol%), NaOt-Bu (2 equiv.), 3-iodotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), TPGS-750-M (2 wt%), 50 °C, 20 h. ^bAverage yield of 2 runs. ^cYields were determined by HPLC/UV using benzophenone as an external standard.

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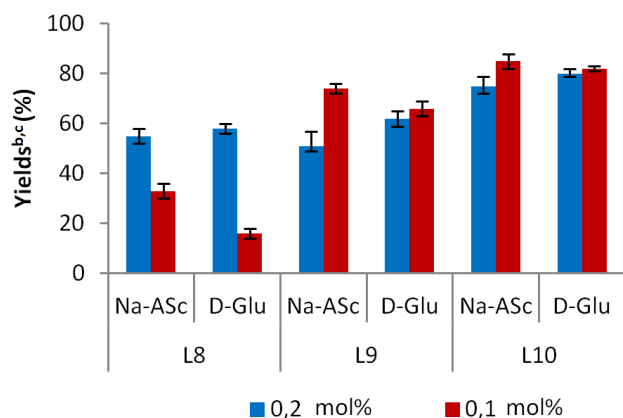
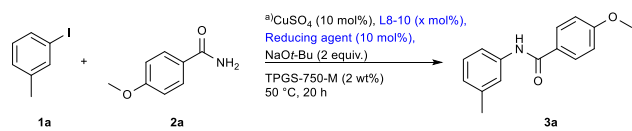


Figure 2. Copper catalyzed amidation of 3-iodotoluene in TPGS-750-M at 50 °C: Impact of ligands loading (L8, L9 and L10) in presence of NaAsc or D-glucose. ^aReaction conditions: CuSO₄ · 5H₂O (10 mol%), ligands (20 mol% or 10 mol%), NaOt-Bu (2 equiv.), 3-iodotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), TPGS-750-M (2 wt%), 50 °C, 20 h. ^bAverage yield of 2 runs. ^cYields were determined by HPLC/UV using benzophenone as an external standard.

and TPGS-750-M composed of vitamin E, iii) absence of organic solvents, and iv) broad substrate scope of both nucleophiles and aryl or heteroaryl iodides.

Results and Discussion

First, 3-iodotoluene **1** and 4-methoxybenzamide **2a** were used as the prototypical substrates to establish the most suitable conditions for our new catalytic system. CuSO₄ was selected as the Cu source as it was successfully used by Wang in combination with sodium ascorbate (NaAsc) in DMSO at 100 °C in a ligand-free N-arylation.^[18] However, the target product was not observed at 50 °C when the reaction was performed in water supplemented with TPGS-750-M (2 wt%) in combination with either NaAsc or D-glucose (Figure 1). Different reaction parameters were investigated to improve this coupling reaction in water (Figures 1–4). In particular, different commercially available ligands were tested using 10 mol% CuSO₄ as the Cu(II) catalyst, 10 mol% of NaAsc or D-glucose as the reducing agent, and 2 equiv of NaOt-Bu as the base in TPGS-750-M (2 wt%) at 50 °C. As reported previously, the linear β-keto ester (THMD) was inactive.^[11] Reactions promoted by different bidentate N, O (L2, L7) or O, O (L3, L5, and L6) chelators gave only traces of compound (Figure 1). Phenanthroline (L4) did not effectively help the Cu salts to improve the yield of **3a**. However, bidentate N, N-ligands such as dimethylethylenediamine (DMEDA, L8) or racemic (L9) showed a promising effect with

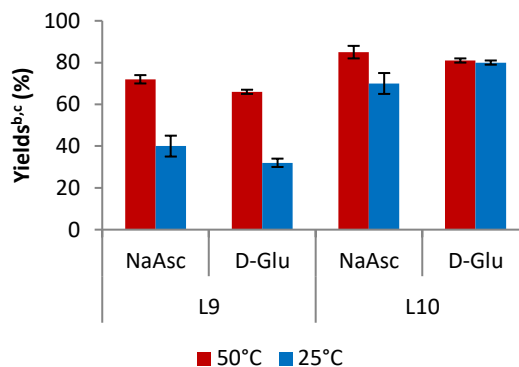
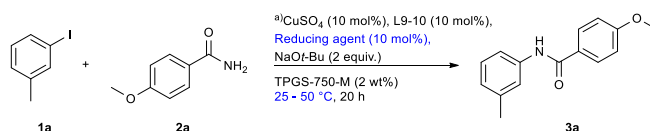


Figure 3. Copper catalyzed amidation of 3-iodotoluene in TPGS-750-M at 25 or 50 °C: Impact of ligands (L9, and L10) in presence of NaAsc or D-Glucose. ^aReaction conditions: CuSO₄ · 5H₂O (10 mol%), ligands (10 mol%), NaOt-Bu (2 equiv.), 3-iodotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), TPGS-750-M (2wt%), 25 or 50 °C, 20 h. ^bAverage yield of 2 runs. ^cYields were determined by HPLC/UV using benzophenone as an external standard.

50% and 57% yields, respectively. The replacement of NaAsc with D-glucose led to a slight increase in the yield. Further screening with racemic *trans*-di-methyl 1,2-cyclohexyldiamine (L10) resulted in a satisfactory yield (75% with NaAsc and 81% with D-glucose).

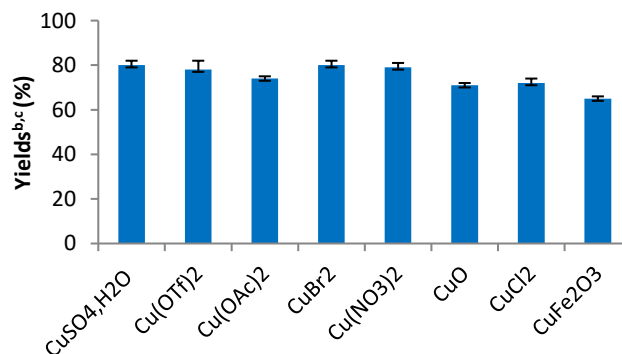
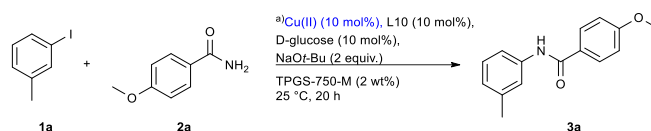


Figure 4. Impact of copper(II) salts: ^aReaction conditions: Copper(II) (10 mol%), L10 (10 mol%), NaOt-Bu (2 equiv.), 3-iodotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), TPGS-750-M (2wt%), 25 °C, 20 h. ^bAverage yield of 2 runs. ^cYields were determined by HPLC/UV using benzophenone as an external standard.

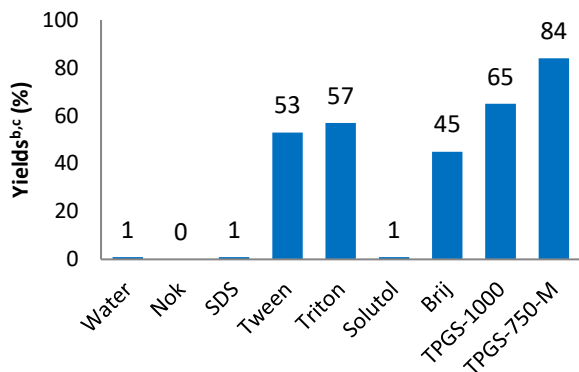
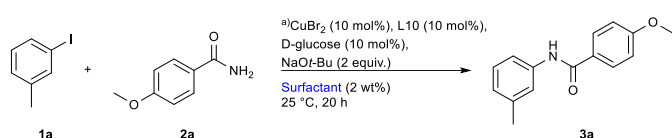


Figure 5. Impact of the surfactants ^aReaction conditions: CuBr₂ (10 mol%), L10 (10 mol%), NaOt-Bu (2 equiv.), 3-iodotoluene (1 equiv.), 4-methoxybenzamide (1.2 equiv.), TPGS-750-M (2 wt%), 25 °C, 20 h. ^bAverage yield of 2 runs. ^cYields were determined by HPLC/UV using benzophenone as an external standard.

Next, we evaluated the lower limit of ligand/catalyst ratio compatible with high yields. This ratio significantly affected the amidation cross-coupling reaction (Figure 2). In presence of NaAsc, reducing the catalyst/ligand ratio from 1:2 to 1:1 improved the formation of **3a** with either ligand L9 or L10. D-glucose was found to be independent of the ligand/metal ratio as comparable yields were obtained in both the cases. In contrast to L8, a significant decrease in the catalytic activity was observed in the presence of both the reducing agents. Finally, a decrease in the amount of CuSO₄ to 5% led to an incomplete consumption of 3-iodotoluene, or the reaction was inefficient (SI Figure S1).

Then, the effect of temperature was evaluated. Attempts to couple the iodohalides with amide **2a** at room temperature failed when L9 was used in combination with either NaAsc or D-glucose. However, when the reaction was conducted using L10 in the presence of D-glucose, this coupling was achieved even at room temperature. The use of NaAsc gave a lower yield under the same conditions.

The reaction was also carried out using different Cu sources as shown in Figure 3. Among them, CuSO₄, CuBr₂, CuNO₃, and Cu(OTf)₂ were found to have the same efficacy with a yield of 80%. Other Cu salts such as CuO, CuCl₂, and Cu(OAc)₂ provided slightly lower yields, while a significant drop of 20% conversion was observed with amorphous CuFe₂O₄. CuBr₂ was selected for this study because of its cost-effectiveness.

Further investigation revealed the nonefficacy of aryl bromide and triflate (SI Figure S2). Various surfactants were also tested under

the optimized conditions, but none of them showed a higher performance than TPGS-750-M 2% (Figure 5).

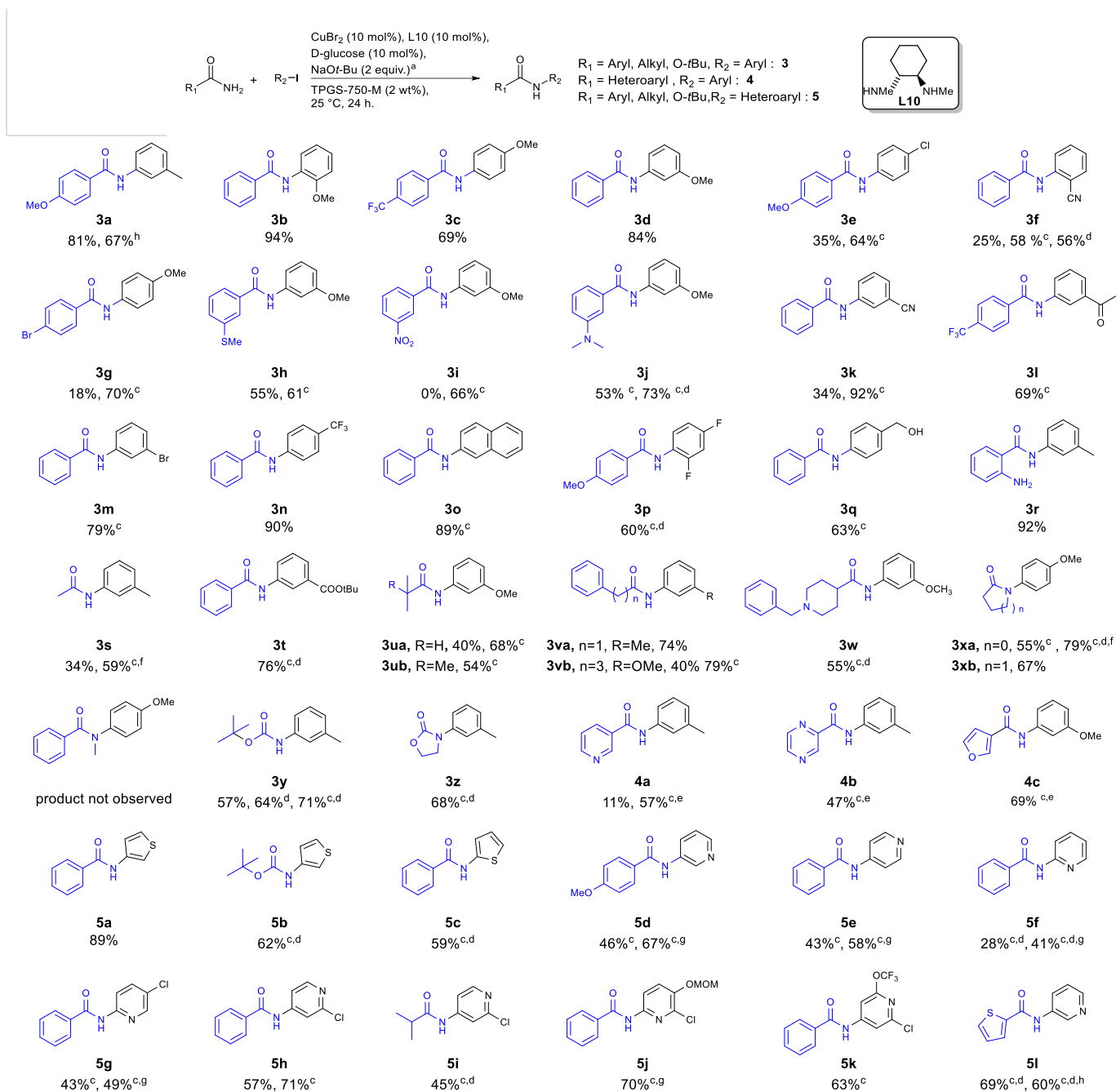
In the absence of surfactant, no reaction was observed. Only moderate yields were obtained when Brij 30 (45% yield), tween (53% yield), triton (57% yield), and TPGS 1000 (65% yield) were used. Surprisingly, the third-generation sterol-based surfactant Nok^[19] was inefficient under those conditions. This may be explained by the difference in the geometry of the micelles obtained using Nok (worm-like micelles) compared to those obtained using TPGS-750-M (spherical particles).

Lastly, it is important to notice that NaOt-Bu can be replaced by NaOH with only a slight decrease of yields (5-10%) for the N-arylation of **3a** and **3k** (see Table S1). However, in order to get the best yield, we choose to run the reaction in presence of NaOt-Bu.

Scope and limitations

Under the optimized set of conditions (10 mol% CuBr₂, 10 mol% racemic *trans*-dimethyl 1,2-cyclohexyldiamine (L10), 10 mol% D-glucose, 2 equiv. NaOt-Bu in TPGS-750-M (2 wt%, 1 M substrate concentration) at 25 °C), the scope and versatility of the reaction were investigated using variously substituted aryl iodides **1** and acetanilides **2** to prepare the corresponding benzanilides **3** at 25 or 50 °C depending on the solubility of the reactant. The results are shown in Table 1. Acetanilides substituted with electron-withdrawing as well as electron-donating groups such as MeO, SMe, Cl, Br, CF₃, NH₂, and NO₂ were well tolerated in the reaction, giving the corresponding benzanilides **3** in good yields. We were particularly pleased to find that **3l** could be efficiently prepared by this protocol as trifluoromethyl-substituted amides serve as important building blocks in the preparation of diverse agrochemicals and pharmaceuticals.^[20] Finally, the reaction of 2-aminobenzamide with 3-iodotoluene proceeded in an excellent yield and with complete selectivity for the reaction of the amide group (**3r**). This N-arylation was also amenable to diverse iodoaryl coupling partners including different electronic and steric substituents. The reaction tolerated diverse functional groups such as ester (**3t**), ketone (**3i**), trifluoromethyl (**3n**), and nitrile (**3f** and **3k**). Moreover, the use of an unprotected hydroxymethyl group enabled the arylation (**3q**, 63%). Particularly noteworthy is the reactivity difference exhibited by arylbromide versus aryliodide towards oxidative addition. The reaction of benzamide with 4-bromiodobenzene at 50 °C occurred on the iodine moiety with complete regioselectivity (**3m**, 79%). To further expand the scope of substrates, alkyl (**3s**, **3u**) and aralkyl (**3v**, **3w**) acetanilides were subjected to the standard reaction conditions; the target products were obtained in satisfactory yields (54–79%). Starting from the highly soluble acetamide, an excess of the amide was needed (5 equiv) to achieve a yield of 60% at 50 °C (**3s**). The reaction was also successfully extended to

Table 1 : Scope of amides and carbamates derivatives



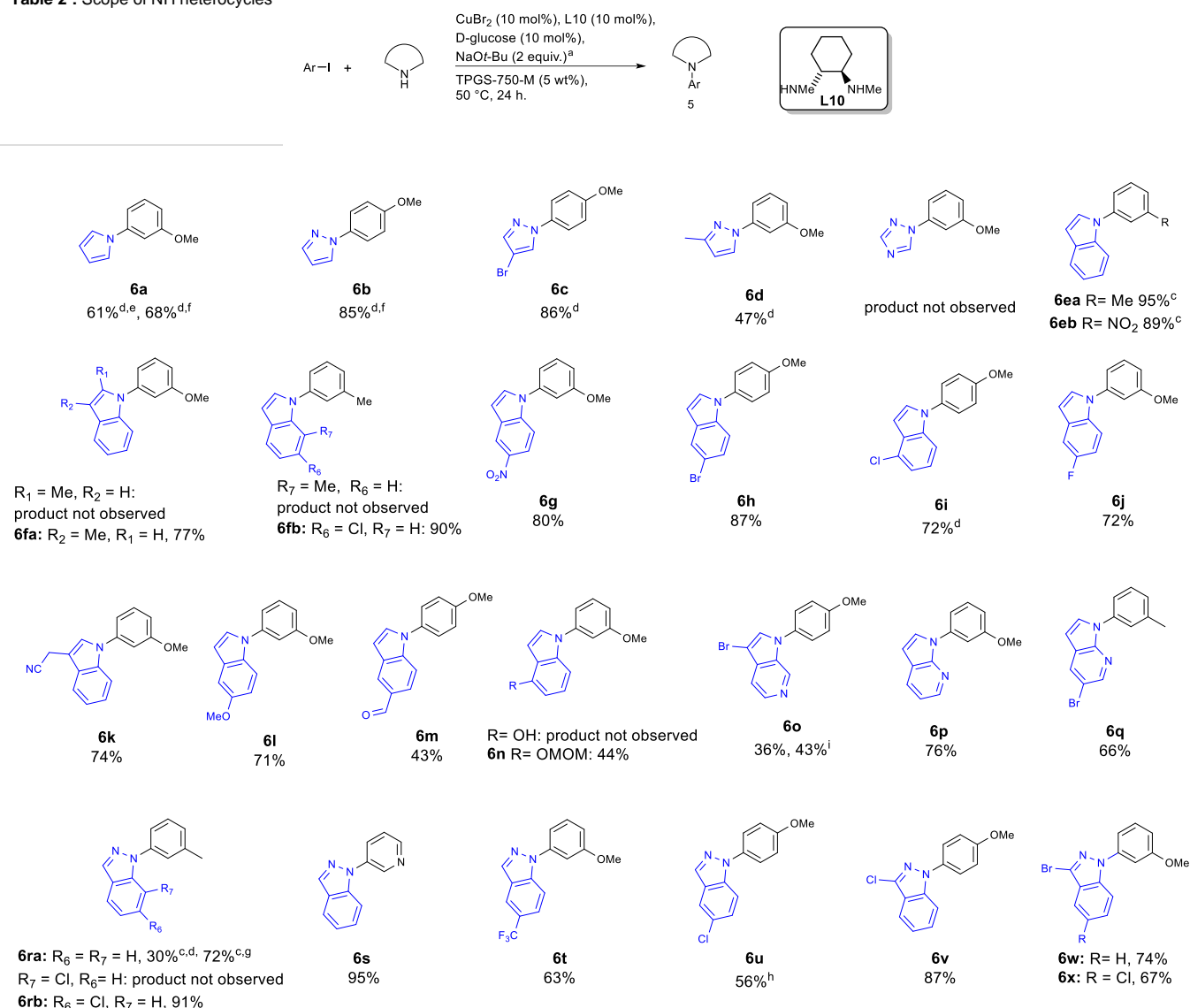
Reaction conditions : CuBr₂ (10 mol%), L10 (10 mol%), D-glucose (10 mol%), NaO*t*-Bu (2 equiv.), ArI (1 equiv.), RCONH₂ (1.2 equiv.), TPGS-750-M (2 wt%), 25 °C, 24 h. ^aYields refer to isolated, chromatographically, purified materials. ^bUnpublished products were fully characterized by NMR and HR-MS data. ^cReaction carried out at 50 °C. ^dUse of TPGS-750-M (5 wt%). ^eAmide (3 equiv.). ^fAmide (5 equiv.). ^gQuenched with NH₃. ^hProduct isolated by precipitation.

heteroaromatic amides. In the case of the reaction with nicotinamide, only 11% of the target product **4a** was observed under standard conditions. Interestingly, when the reaction was carried out with 3 equiv of the amide, the yield became 57%. Under the same conditions, *N*-aryl pyrazine- (**4b**) and furan- (**4c**)

carboxamide derivatives were obtained in 47% and 69% isolated yields, respectively.

To further evaluate our methodology, we attempted reactions with heteroaryl iodides. As shown in Table 1, generally the desired coupling products **5** were obtained in moderate-to-good yields depending on i) the position of the iodide and ii) the

Table 2 : Scope of NH heterocycles



Reaction conditions : CuBr₂ (10 mol%), L10 (10 mol%), D-glucose (10 mol%), NaOt-Bu (2 equiv.), ArI (1 equiv.), HetNH (1.2 equiv.), TPGS-750-M (5 wt%), 50 °C, 24 h. ^aYields refer to isolated, chromatographically, purified materials. ^bUnpublished products were fully characterized by NMR and HR-MS data. ^cReaction carried out at 25 °C. ^dUse of TPGS-750-M (2wt%). ^eNucleophile (3 equiv.). ^fNucleophile (5 equiv.). ^g18% on N₂. ^h12% on N₂. ⁱPreformulated.

reaction conditions. N-arylation of 3-iodothiophene was conducted at 25°C, and the target product **5a** was isolated in 89% yield. Similarly, the catalytic system was suitable for the amidation of 3(4)-iodopyridine derivatives, providing **5d** and **5e** in moderate yields (~40%). A significant improvement (+20% in yield) was achieved by quenching the reaction mixture with ammonia (67% for **5d** and 58 % for **5e**). The N-arylation of 2-iodopyridine or thiophene was tedious even at 50 °C (**5f**, 41%, **5c**, 59%). The presence of a second halogen in the pyridine moiety increased the efficiency of the coupling reaction as shown by **5h** (71%) and highly functionalized pyridine derivatives **5j** (70%)^[21a] and **5k**^[21b] (63%). Finally, the cross-coupling reaction was also effective when two heterocyclic partners were used. In particular, starting from 2-thienylamide and 3-iodotoluene, the N-arylated compound **5l** was isolated in 69% yield.

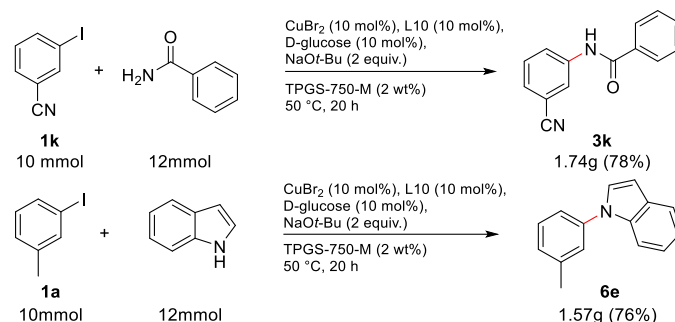
The reaction was affected by the steric hindrance of the nucleophile, because although cyclic aliphatic secondary amides such as pyrrolidine-2-one or its homolog (n = 0) afforded the coupling product **3x** in good yields, no reaction was observed starting from the acyclic *N*-methylbenzamide. Of particular interest was the reaction with *tert*-butylcarbamate, a protected ammonia equivalent. The reaction of 3-iodotoluene at room temperature afforded the target compound **3y** in 57% isolated yield. The use of 5 wt% TPGS-750-M at 25 °C or 50 °C improved the yield of **3y** to 64% and 71%, respectively. Similar results were obtained starting from 3-iodothiophene **5b**. Next, the N-arylation of oxazolidin-2-one with iodobenzene was performed. *N*-aryloxazolidin-2-ones have gained significant interest in the recent decade as illustrated by the FDA-approved drugs:

Toloxatone®^[22] and Rivaroxaban®^[23]. Under the micellar conditions, the five-membered ring cyclic carbamate (**3z**) was isolated in 68% yield.

To broaden the scope of our arylation protocol, the efficiency of our catalyst–ligand systems was evaluated for reactions involving weak nucleophilic nitrogen atoms such as azoles. The coupling of azoles is of great importance to the pharmaceutical industry. Pharmaceuticals incorporating this privileged motif display diverse biological activities such as anti-inflammatory, antiviral, antimicrobial, and anticancer activities.^[24] Therefore, the development of efficient methods to access highly functionalized azole derivatives with respect to sustainable chemistry is highly desirable.

As shown in Table 2, representative couplings involving pyrrole, pyrazole, indole, and indazole ring-containing substrates afforded the desired N-arylated coupling products **6** in moderate-to-good yields (43–95%) at 25 °C or 50 °C in TPGS-750-M 5 wt%. Attempts to N-arylate 1,2,4-triazole with 3-iodotoluene failed at 50 °C even with a higher loading of ligand (Cu:L = 1:2 and 1:4). The arylating agent was recovered after 20 h heating. The efficiency of the reaction was affected by the steric hindrance of an adjacent substituent as no reaction was observed starting from 2- or 7-substituted indoles and 7-substituted indazoles. However, displacement of the substituent from positions 2 to 3, or 7 to 6 restored the efficiency of the reaction, and **6fa**, **6fb** and **6rb** were obtained in respectively 77%, 90% and 91% isolated yields.

Azoles bearing both electron-donating and -withdrawing substituents coupled smoothly, affording the target products **6** in good yields and with a high tolerance of several functional groups (CF₃, CN, CHO, NO₂, F, Cl, Br, and OMOM). Unfortunately, as shown in Table 2, the methodology is not compatible with free phenol. However, when the phenol is protected (**6n**, OMOM), the desired product was obtained in a moderate yield of 44%. Notably, halogen substituents such as Cl and Br were well tolerated (**6c**, **6h–i**, **6q**, and **6u–x**), thus providing handles for postcoupling transformations.

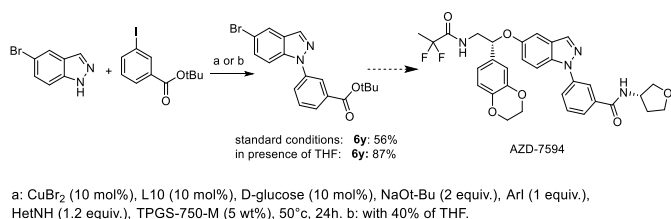


Scheme 2: Gram-scale experiments

Notably, our method provided a straightforward way to synthesize an advanced intermediate for the preparation of AZD-7594 actually under active development (Phase II) for chronic obstructive pulmonary diseases (COPD).^[25] Unfortunately, under our standard conditions, only 54% of the expected N1-Aryl indazole **6y** was isolated after the purification. Besides the remaining starting materials, we also observed the formation of a small amount of his regioisomer, the N2-Aryl indazole **6z** with a N¹/N²-selectivity of ~1:6. Addition of an organic solvent (THF) to the reaction mixture, as recently reported by Gallou and coworkers,^[26] was the key to success. The presence of a co-solvent channeled the reactive components of the system between water and the lipophilic micellar interior, playing both the roles of slightly increasing the solubility and rate of dissolution. To our pleasure, under these new conditions the target product **6y** was isolated in 87% yield (**6z**: 13%).

To demonstrate the usefulness of this novel N-amidation protocol, two gram-scale experiments were carried out under the standard conditions. Using 3-iodobenzonitrile (10 mmol) and benzamide, the corresponding N-(3-cyano-phenyl)benzamide **3k** was isolated in 78% yield. In addition, the reaction with indole and 3-iodotoluene also proceeded smoothly, affording product **6e** in 76% yield.

All the final compounds **3–6** were purified by flash chromatography using a step gradient algorithm to i) optimize the separation of the target compound and ii) use a minimal amount of solvent. However, to avoid the column chromatography step, we also developed a greener procedure to recover the final solid compounds. The strategy was based on a convenient purification procedure based on precipitation upon the addition of water. The micellar media was first extracted with isopropyl acetate and then passed through a cotton-wool filter to remove traces of Cu. The filtrate was concentrated under vacuum and then diluted with isopropanol. After the precipitation from cold water and filtration, this procedure allowed the isolation of **3a** and **5l** in 67% and 60% yields (Table 1), respectively, and the purity was higher than 98% (determined by HPLC). For these two examples, the reaction was run on a small



Scheme 1: Synthesis of an advanced intermediate for the preparation of AZD 7594.

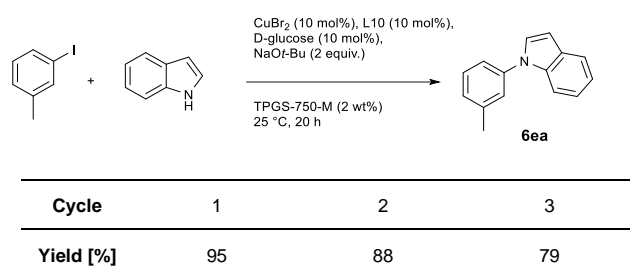


Figure 6. Recycling of the copper catalyst and the micellar phase

scale (see SI). Scale-up of the synthesis from laboratory scale to pilot scale will probably maximize the precipitation of the expected final compounds and in fact improve the product yields.

In order to investigate the greener and economical aspects of the developed catalytic system, a recyclability study was carried out for the *N*-arylation of indole with 3-iodotoluene. As illustrated in Figure 6 the yield drops from 95% to 88% for the second cycle and to 79% for the third cycle. These results validated the possibility to recycle CuBr_2 . After each cycle, the aqueous reaction mixture was extracted using diethyl ether to remove all traces of the product or reactants. The resulting aqueous solution containing the CuBr_2 catalyst was directly used for the next catalytic cycle.

Conclusions

We developed a facile, convenient and mild protocol for aqueous Ullmann cross-coupling catalysis. We successfully demonstrated that the catalytic system (CuBr_2 , D-glucose, L10, and NaOt-Bu) allowed the high-yielding arylation of diverse nitrogen nucleophiles at relatively low temperatures (25–50 °C). Diverse substituted aryl or heteroaryl iodides were readily coupled with several amides, carbamates, and azoles. With respect to azoles, the catalytic system was particularly efficient for condensations with substituted 3-, 4-, 5- and 6-indazole and indole derivatives. The method enables the selective conversion of polyhalogenated aromatics and provides access to differentially substituted pharmacologically relevant motifs. Mildness, low-cost, experimental simplicity, and ability to use water and D-glucose as the reducing agent are the features of the developed methodology that make it particularly well suited for industrial-scale syntheses.

Experimental Section

General procedure

Nucleophile (1.2 equiv.) and aryl or heteroaryl halide (1 equiv.) were added to an aqueous solution of TPGS-750-M (2 wt %, 1 mL/mmol). The mixture was degassed by bubbling Argon (5 min). NaOt-Bu (97% purity, 2 equiv.), CuBr_2 (10 mol%), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (10 mol%) and D-glucose (10 mol%) were added and the resulting mixture was stirred (at 1200 rpm) at 25 °C or 50 °C (20 h). The mixture was extracted twice

with 3 mL of isopropyl acetate. The combined organic layers were evaporated and the crude residue was purified by chromatographic column on silica gel using *n*-heptane and ethyl acetate as eluent.

4-Methoxy-*N*-(3-methylphenyl)benzamide 3a

Prepared following the general procedure, using CuBr_2 (11.2 mg, 0.050 mmol), *trans-N,N'*-dimethylcyclohexane-1,2-diamine (7.9 μL , 0.050 mmol), D-Glucose (9.0 mg, 0.050 mmol), 3-iodotoluene (64.2 μL , 0.500 mmol), 4-methoxybenzamide (90.7 mg, 0.600 mmol) and NaOt-Bu (99 mg, 1.000 mmol) in aqueous TPGS-750-M (2 wt %, 0.50 mL), followed by purification using column chromatography (SiO_2) and *n*-heptane/ethyl acetate (7:3), yielded **3a** as a white solid (98 mg, 0.405 mmol, 81%). mp = 117–119 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ ppm 2.34 (s, 3H), 3.87 (s, 3H), 6.95–6.97 (m, 3H), 7.25 (t, $J = 7.7$ Hz, 1H), 7.41 (d, $J = 7.7$ Hz, 1H), 7.51 (s, 1H), 7.80 (d, $J = 8.9$ Hz, 2H), 7.87 (br s, 1H); $^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ ppm 21.5, 55.4, 113.9, 117.2, 120.8, 125.1, 127.2, 128.8, 128.9, 138.0, 138.9, 162.4, 165.2.

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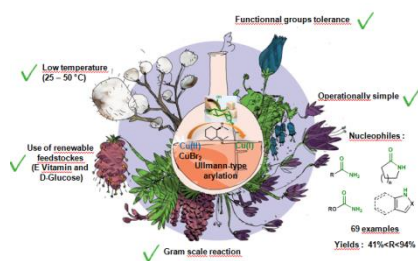
Keywords: amination • amides • NH heterocycle • copper • micelles

- [1] a) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337–2364; b) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; c) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400–5449; d) J. P. Corbert, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651–2710.
- [2] a) D. S. Surry, S. L. Buchwald, *Chem. Sci.* **2010**, *1*, 13–31; b) F. Monnier, M. Taillefer, *Angew. Chem. Int. Ed.* **2009**, *48*, 6954–6971; c) D. W. Ma, Q. Cai, *Acc. Chem. Res.* **2008**, *41*, 1450–1460; d) A. Casitas, X. Ribas, *Chem. Sci.* **2013**, *4*, 2301–2318.
- [3] a) K. Kunz, U. Scholz, D. Ganzler, *Synlett* **2003**, *15*, 2428–2439, b) E. J. Hennessy, S. L. Buchwald, *Org. Lett.* **2002**, *4*, 269–272, c) J. Lindley, *Tetrahedron* **1984**, *40*, 1433–1456, d) K. Moriwaki, K. Satoh, M. Takada, Y. Ishio, T. Ohno, *Tetrahedron Lett.* **2005**, *46*, 7559–7562.
- [4] A. Klapars, J. C. Antilla, X. H. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.
- [5] M. Taillefer, H. J. Cristau, P. Cellier, J. F. Spindler, WO Patent 053,885-A, 20 December **2002**.
- [6] a) A. Klapars, X. Huang, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428; b) D. Audisio, S. Messaoudi, J. B. Peyrat, J. D. Brion, M. Alami, *J. Org. Chem.* **2011**, *76*, 4995–5005; c) F. T. Zhou, J. J. Guo, J. G. Liu, K. Ding, S. Y. Yu, Q. Cai, *J. Am. Chem. Soc.* **2012**, *134*, 14326–14329.
- [7] a) G. Evano, N. Blanchard, M. Toumi, *Chem. Rev.* **2008**, *108*, 3054–3131; b) G. Evano, N. Blanchard, *Copper-Mediated Cross-Coupling Reactions*, John Wiley & Sons, New Jersey, **2014**.
- [8] a) C. Sambigiato, S. P. Marsden, A. J. Blacker and P. C. McGowan, *Chem. Soc. Rev.* **2014**, *43*, 3525–3550; b) F. Monnier, M. Taillefer, *Amination and Formation of sp² C–N Bonds*, (Eds. M. Taillefer and D. Ma), Springer Berlin Heidelberg, **2013**, pp. 173–204.

- [9] a) K. H. Shaughnessy, *Chem. Rev.* **2009**, *109*, 643-710; b) A. Chanda, V. V. Fokin, *Chem. Rev.* **2009**, *109*, 725-748; c) K. Bahrami, M. M. Khodaei, A. Nejati, *Green Chem.* **2010**, *12*, 1237-1241; d) X. Li, D. Yang., Y. Jiang, H. Fu, *Green Chem.* **2010**, *12*, 1097-1105; e) O. Saidi, A. J. Blaker, M. M. Farah, S. P. Marsden, J. M. Williams, *Chem. Commun.* **2010**, *46*, 1541-1543; f) G.-L. Li, K. K.-Y. Kung, L. Zou, H.-C. Chong, Y.-C. Leung, K. H. Wong, M.-K. Wong, *Chem. Commun.* **2012**, *48*, 3527-3529; g) J. Feng, G. Lu, M. Lv, C. Cai, *J. Org. Chem.* **2014**, *79*, 10561-10567; h) A. Kumar, A. K. Bishnoi, *RSC Adv.* **2015**, *5*, 20516-20520.
- [10] a) T. Dwars, E. Paetzold, G. Oehme, *Angew. Chem. Int. Ed.* **2005**, *44*, 7144-7199; b) K. Ahlford, J. Lind, L. Maler, H. Adolfsson, *Green Chem.* **2008**, *10*, 832-835; c) M. Srivastava, J. Singh, S. B. Singh, K. Tiwari, V. K. Pathak, J. Singh, *Green Chem.* **2012**, *14*, 901-905; d) R. D. Shukla, A. Kumar, *Green Chem.* **2015**, *17*, 848-851; e) G. L. Sorella, G. Strukul, A. Scarso, *Green Chem.* **2015**, *17*, 644-683; f) N. Singh, Y. Karpichev, R. Sharma, B. Gupta, A. K. Sahu, M. L. Satnam, K. K. Ghosh, *Org. Biomol. Chem.* **2015**, *13*, 2827-2848; g) B. H. Lipshutz, F. Gallou, S. Handa, *ACS Sustainable Chem. Eng.* **2016**, *4*, 5838-5849.
- [11] M. Bollenbach, P. Wagner, A. G. V. Aquino, J.-J. Bourguignon, F. Bihel, C. Salomé, M. Schmitt, *ChemSusChem* **2016**, *9*, 3244-3249.
- [12] a) C. Salomé, P. Wagner, M. Bollenbach, F. Bihel, J.-J. Bourguignon, M. Schmitt, *Tetrahedron* **2014**, *70*, 3413; (b) P. Wagner, M. Bollenbach, C. Doebelin, F. Bihel, J.-J. Bourguignon, C. Salomé, M. Schmitt, *Green Chem.* **2014**, *16*, 4170-4178.
- [13] P. P. Kung, B. W. Huang, G. Zhang, J. Z. Zhou, J. Wang, J. A. Digits, J. Skaptason, S. Yamazaki, D. Neul, M. Zientek, J. Elleraas, P. Mehta, M. J. Yin, M. J. Hickey, K. S. Gajiwala, C. Rodgers, J. F. Davies, M. R. Gehring, *J. Med. Chem.* **2010**, *53*, 499 - 503.
- [14] C. W. Lindsley, *Curr. Top. Med. Chem.* **2008**, *8*, 12.
- [15] V. R., Pattabiraman, J. W. Bode, *Nature* **2011**, *480*, 471e479
- [16] a) E. Armelin, L. Franco, A. Rodriguez-Galan, J. Puiggali, *Macromol. Chem. Phys.* **2002**, *203*, 48 - 58; b) M. A. Glomb, C. Pfahler, *J. Biol. Chem.* **2001**, *276*, 41638-41647; c) J. Zabicky, *The chemistry of Amides*, Wiley-Intersciences, New York, **1970**; d) A. Greenberg, C. M. Breneman, J. F. Liebman, *The amide linkage: Structural Significance in Chemistry, Biochemistry and Material Sciences*, John Wiley & sons: New York, NY **2000**; e) T. J. Deming, *Prog. Polym. Sci.* **2007**, *32*, 858-875; f) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* **2006**, *4*, 2337-2347.
- [17] a) G. W. Wang, T. T. Yuan, D. D. Li, *Angew. Chem.* **2011**, *123*, 1416 - 1419; *Angew. Chem. Int. Ed.* **2011**, *50*, 1380-1383; b) X. X. Zhang, W. T. Teo, P. W. H. Chan, *J. Organomet. Chem.* **2011**, *696*, 331-337.
- [18] Z. J. Quan, H. D. Xia, Z. Zhang, Y. X. Da, X. C. Wang, *Tetrahedron* **2013**, *69*, 8368-8374.
- [19] P. Klumphu, B. H. Lipshutz, *J. Org. Chem.* **2014**, *79*, 888-890.
- [20] a) F. Lerou, P. Jeschke, M. Schlosser, *Chem. Rev.* **2005**, *105*, 827-856; b) K. Mueller, C. Faeh, F. Dietrich, *Science* **2007**, *317*, 1881-1886; c) M. Shimizu, T. Hiyama, *Angew. Chem. Int. Ed.* **2005**, *44*, 214-231; d) P. Jeschke, *ChemBioChem* **2004**, *5*, 570-589.
- [21] Preparation of starting materials : a) C. Doebelin, P. Wagner, F. Bihel, N. Humbert, C. A. Kenfack, Y. Mely, J. -J. Bourguignon, M. Schmitt, *J. Org. Chem.* **2014**, *79*, 908-918; b) B. Manteau, P. Genix, L. Brelot, J. P. Vors, S. Pazenok, F. Giorno, C. Leuenberger, F. R. Leroux, *Eur. J. Org. Chem.* **2010**, *31*, 6043-6066.
- [22] a) F. Moureau, J. Wouters, D. P. Vercauteren, S. Collin, G. Evrad, F. Durant, F. Ducrey, J. J. Koenig, F. X. Jarreau, *Eur. J. Med. Chem.* **1994**, *29*, 269-277; b) D. S. Goldstein, Y. Jinsmaa, P. Sullivan, C. Holmes, I. J. Kopin, Y. Sharabi, *J. Pharmacol. Exp. Ther.* **2016**, *356*, 483-492.
- [23] a) H. Oberpichler-Schweng, *Med. Monatsschr. Pharm.* **2008**, *31*, 412-416; b) D. Kubitz, M. Becka, M. Zuehlsdorf, W. Mueck, *J. Clin. Pharmacol.* **2008**, *48*, 1366-1367.
- [24] a) I. P. Beletskaya, A. V. Cheprakov, *Coord. Chem. Rev.* **2004**, *248*, 2337-2364; b) E. M. Beccalli, G. Broggin, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318-5365; c) M. Newer, *Organic-Chemical Drugs and their Synonyms: An International Survey*, 7th ed., Akademic Verlag GmbH, Berlin, **1994**; d) H. Montgomery, *Agrochemicals Desk Reference: Environmental Data*, Lewis Publishers, Chelsea, MI, **1993**; e) J. P. Corbert, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651-2710; f) S. V. Ley, A. W. Thomas, *Angew. Chem. Int. Ed.* **2003**, *42*, 5400 -5449.
- [25] E. Carbo Tutusaus, D. Chan, *Drugs Fut.* **2016**, *41*, 267.
- [26] F. Gallou, P. Guo, M. Parmentier, J. Zhou, *Org. Process Res. Dev.* **2016**, *1388-1391*.

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