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Ruthenium-Catalyzed C-H Bond Heteroarylation of Triazoles Enabled by a Deconvolution Strategy

Rafael Gramage-Doria,^{*[a]} and Thierry Roisnel^[a]

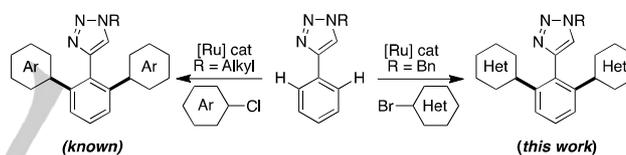
Abstract: Reaction optimization for C-H bond functionalization reactions with transition metal catalysts is traditionally based on long and tedious screening of multiple conditions. In this contribution we have applied a deconvolution strategy to identify reaction conditions suitable for the C-H bond heteroarylation of 1,2,3-triazoles with a ruthenium catalyst by performing only 18 experiments with mixtures of reagents instead of the theoretically 576 experiments that should have been considered individually. The activation and functionalization takes place at the *ortho* position of the phenyl ring attached to the 1,2,3-triazole directing group as confirmed by X-ray crystallographic studies. The bis- vs mono-heteroarylation was controlled by tuning the stoichiometry of the reagents. Such methodology was also applicable to aryl bromide coupling partners bearing *ortho*- and *meta*-substituents.

Introduction

1,2,3-Triazoles have become particularly relevant in the last decades due to the ease, versatile and modular synthesis that provides the copper(I)-catalyzed Huisgen 1,3-dipolar cycloaddition between terminal alkynes and azides.^[1] This unprecedented chemical space enabled 1,2,3-triazoles to find a large number of applications ranging from materials sciences to biology.^[2] However, the synthesis of the 1,2,3-triazole core containing bulky substituents at close proximity is rather challenging due to important steric restrictions and it has been met with success in limited cases with non-catalyzed synthetic sequences.^[3] On the other hand, bulky 1,2,3-triazoles appear as a promising class of compounds for medical applications^[4] as well as organocatalysts when transformed into its corresponding imidazolium salts.^[5]

In this context, the introduction of bulky substituents once the triazole is formed has been regarded as a useful approach. This can be targeted by C-H bond functionalization reactions employing transition metal catalysts with the triazole serving as a directing group. Several examples have shown their viability, although most of them are based on expensive and scarce rhodium and palladium catalysts.^[6] Interestingly, ruthenium complexes, which are significantly more available and less sensitive to air and moisture, were found to behave as efficient catalysts for the C-H bond functionalization of 1,2,3-triazoles.^[7,8] For instance, Ackermann and co-workers reported ruthenium catalysts able to perform arylation and alkenylation reactions on the C-H bond of the phenyl ring attached to the 1,2,3-triazole (Scheme 1, left).^[7] Similarly, Liu and co-workers employed ruthenium catalysts for the alkenylation of triazoles using alkynes and alkenes as coupling partners.^[8a] Recently, Chatani and co-workers have reported on ruthenium(0)-catalyzed *ortho*-

C-H bond carbonylations using 1,2,3-triazoles as directing groups.^[8b] Besides its obvious relevance, what all these studies have in common is the lack of examples enabling the introduction of heteroaromatic fragments at close proximity of the 1,2,3-triazole ring.^[6-8] This could be explained by the fact that the catalyst is not enough reactive and it can follow inhibition/deactivation by over-coordination to the heteroaromatic motifs. Furthermore, the identification of optimal reaction conditions for C-H bond functionalization reactions is mainly based on trial and error screening of all the individual possibilities.^[9] At this stage, we wondered whether it could be possible to apply deconvolution strategies for rapid identification of suitable reaction conditions for the ruthenium-catalyzed heteroarylation of 1,2,3-triazoles. Deconvolution strategies have been applied in the last years involving different transition metal-catalyzed reactions but not for the case of ruthenium catalysis so far.^[10] By performing reactions with mixture of reagents, deconvolution strategies enable a more efficient discovery of optimal reaction conditions with less experiments than traditional error and screening approach. Herein, we disclose the application of this strategy to ruthenium-catalyzed C-H bond heteroarylation reactions with 1,2,3-triazoles as directing groups (Scheme 1, right).



Scheme 1. Ruthenium-catalyzed C-H bond arylation (left) vs heteroarylation (right) of 1,2,3-triazoles.

Results and Discussion

First, we focused on the reaction of benchmark 1,2,3-triazole **1** with 4-bromopyridine as coupling partner (Figure 1). Then, we defined which parameters of the catalysis were fixed and which reagents could be used according to precedents from the literature.^[7-9] As solvents, we decided to screen water, toluene and *N*-methyl-2-pyrrolidone (NMP) at 150 °C during 48 hours; and as ruthenium pre-catalysts, RuCl₃·xH₂O (**Ru1**), [RuCl₂(*p*-cymene)]₂ (**Ru2**) and Ru₃(CO)₁₂ (**Ru3**) were chosen (Figure 1). As co-catalysts we considered up to eight carboxylate salts (**C1-C8**) and the same number of bases (**B1-B8**) (Figure 1). Initially, we performed three experiments in which all the reagents (ruthenium complexes **Ru1-Ru3**, carboxylate salts **C1-C8** and bases **B1-B8**) were mixed together with the three solvents respectively (step 1). Only the reaction conducted with NMP lead to some conversion (10 %) and consequently, it was selected as the solvent of choice for the next experiments. Then, three reactions were carried out in which each one contained a single ruthenium complex (step 2), indicating that [RuCl₂(*p*-cymene)]₂ (was the most efficient catalysts under these reaction

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conditions (12 % conversion). Next, we decided to divide in two groups the carboxylate salts (**C1-C4** and **C5-C8**) as well as the bases (**B1-B4** and **B5-B8**). Four reactions were carried out combining the two groups of carboxylate salts and the two groups of bases, respectively, with the already selected $[\text{RuCl}_2(p\text{-cymene})]_2$ complex and NMP as solvent (step 3). The best conversion (35 %) was observed from the reaction containing the mixture of **C1-C4** with **B1-B4**. We divided again the carboxylate salts in two groups (**C1-C2** and **C3-C4**) and the bases as well (**B1-B2** and **B3-B4**); and four reactions were done combining each of them (step 4). 55 % conversion was observed in the best scenario which after the last deconvolution step indicated that the most powerful catalytic systems consisted of $[\text{RuCl}_2(p\text{-cymene})]_2$ (5 mol%), KOAc (**C2**, 20 mol%), K_2CO_3 (**B2**, 3 equivalents) and NMP as solvent. In this manner, a conversion of 75 % was obtained with an isolated yield of **2a** of 65 % after purification by column chromatography. Consequently, efficient reaction conditions for such a challenging transformation were found with only 18 experiments in contrast with the 576 individual experiments that should have been conducted considering all the reagents employed individually. Additionally, we realized that the same reaction conditions applied to 4-iodopyridine as coupling partner were successful in a similar manner, however, when applied to 4-chloropyridine the conversion significantly decreased to <10 %.

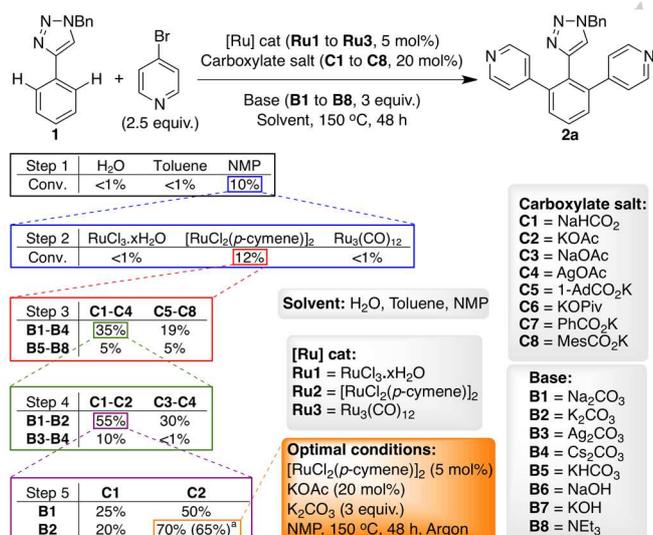
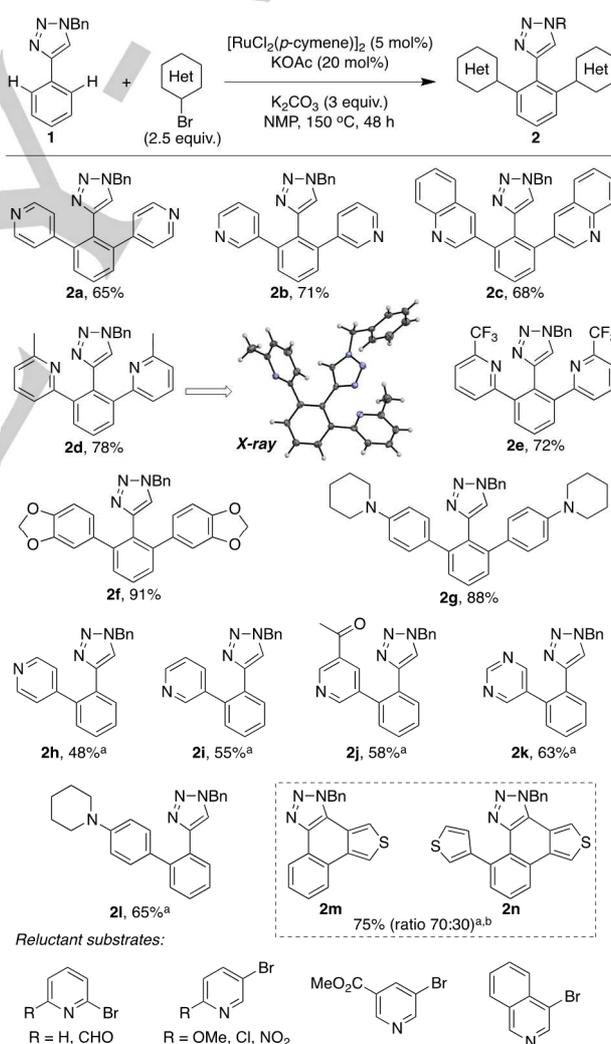


Figure 1. Deconvolution strategy for optimization of reaction conditions. [a] Isolated yield.

With the optimal reaction conditions in hand, we explored the scope of the reaction with different heteroaryl bromides (Scheme 2). In all the reactions an excess (2.5 equivalents) of heteroaryl bromide was used, leading to the bis-functionalized products as the major ones. For instance, 3-bromopyridine reacted with **1** in a similar manner as 4-bromopyridine leading to **2b** in 71 % yield. The bis-quinoline-containing triazole **2c** was obtained in 68 % yield, although its regioisomer 4-bromoisoquinoline did not react. Functionalized bromopyridines also reacted efficiently under the studied reaction conditions. For example, 2-bromo-6-

methylpyridine led to **2d** in 78 % yield. A single-crystal X-ray diffraction study unambiguously established the double heteroarylation at both *ortho* positions of the phenyl ring in **2d**.^[11] Trifluoro-containing pyridine **2e** was also obtained in a good yield (72 %). Dioxolane-containing **2f** and piperidine-containing **2g** were obtained in an excellent 91 and 88 % yield, respectively; indicating that other heterocycles are also compatible with the ruthenium-catalyzed C-H bond heteroarylation of triazoles. Decreasing by half the amounts of heteroaryl bromide and base (K_2CO_3) led to the mono-functionalized products as the major ones. For example, 4-pyridine- and 3-pyridine-containing triazoles **2h** and **2i** were obtained in 48 and 55 % yield, respectively. The reaction was also compatible with ketone functional groups enabling the synthesis of **2j** in 58 % yield. 5-Bromopyrimidine reacted efficiently leading to mono-functionalized **2k** in 63 % yield. Mono-piperidine-containing triazole **2l** was obtained in a similar yield (65 %). Trace amounts (<5%) of bis-functionalized products were observed for the synthesis of **2h**, **2i** and **2l**; where-

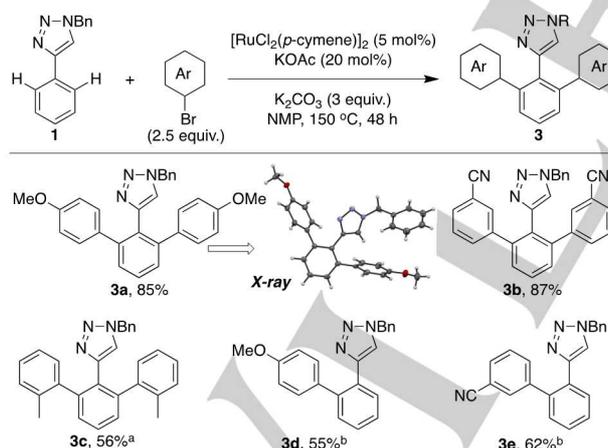


Scheme 2. Substrate scope and limitations. [a] Starting from 1.25 equivalents of heteroaryl bromide and 1.5 equivalents of K_2CO_3 . [b] Starting from 3-bromothiophene.

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-eas no bis-functionalization was detected during the formation of **2j** and **2k**. 3-Bromothiophene reacted with an unexpected outcome leading to a mixture of products **2m** and **2n** in 70:30 ratio (75% combined yield). **2m** seems to be formed by an additional double C-H bond functionalization between one C-H bond belonging to the thiophene ring and the one belonging to the triazole ring. A similar oxidative coupling between a 1,2,3-triazole ring and an intramolecular aryl ring using Pd(OAc)₂ as a catalyst was previously reported,^[7c] however the nature of the oxidant in the present case remains to be addressed. Unfortunately, we also noted that the reactions were not successful with 2-bromopyridine, aldehyde-, nitro-, chloro-, methoxy- and ester-containing bromopyridines (Scheme 2).^[12]

Lastly, we decided to study whether it was possible to perform also C-H bond arylation reactions of triazoles as it was done by Ackermann and co-workers with a different catalytic system also based on [RuCl₂(*p*-cymene)]₂ (30 mol% MesCO₂H and K₂CO₃ as base in toluene).^[7] We found that our above-described protocol provides comparable results, and in some cases slightly outperforms the previous findings (Scheme 3). For example, methoxy-containing **3a** was obtained in 85 % yield. A single-crystal X-ray diffraction study of **3a** unambiguously confirmed that the bis-functionalization takes place at both *ortho* positions of the phenyl ring attached to the triazole core.^[11] Nitrile groups (that were not studied before) at *meta* position were also tolerated with our protocol leading to bis-functionalized **3b** in 87 % yield. Even bulky substrates such as 2-bromotoluene were found to react giving rise to bis-functionalized **3c** in a decent yield (56 %). Reducing by half the amounts of coupling partner and base, we managed to obtain the mono-functionalized **3d** and **3e** as major products in 55 and 62 % yield, respectively.



Scheme 3. Ruthenium-catalyzed C-H bond arylation reactions of triazoles employing the optimal reaction conditions obtained by the deconvolution strategy. [a] Obtained as a mixture of atropisomers. [b] Starting from 1.25 equivalents of heteroaryl bromide and 1.5 equivalents of K₂CO₃.

Conclusions

In summary, we have introduced a deconvolution strategy in ruthenium catalysis to efficiently search for suitable reaction conditions enabling a difficult C-H bond heteroarylation reaction of 1,2,3-triazole fragments. In this way, a unique class of sterically crowded heterocycles, which are otherwise very difficult to synthesize by non-catalyzed sequences, has been obtained in good yields. The ruthenium-based catalytic system was found to be compatible with many relevant heteroaryl bromides such as pyridines, quinolines, dioxolanes, piperidines, pyrimidines and related substrates containing functional groups such as methyl, trifluoro, ketone or nitrile. It could be anticipated that by merging deconvolution strategies with transition metal-catalyzed C-H bond functionalization reactions, new protocols could be found in the near future.

Experimental Section

Deconvolution experiments for step 1: Substrate **1** (0.5 mmol, 0.118 g, 1 equiv.), 4-bromopyridine (1.25 mmol, 2.5 equiv.), all bases **B1-B8** (1.5 mmol, 3 equiv.), all carboxylate salts **C1-C8** (0.1 mmol, 0.20 equiv.), all ruthenium pre-catalysts **Ru1-Ru3** (0.025 mmol, 0.05 equiv.), and the corresponding solvent (water, toluene or NMP; 10 mL -to improve solubility-) were introduced in a dry Schlenk tube under argon atmosphere. Each reaction mixture was stirred at 150 °C for 48 h. Then, each reaction mixture was cooled down to room temperature and dissolved in dichloromethane (30 mL). After filtration over celite and evaporation of the solvents under vacuum, each reaction mixture was analysed by ¹H NMR spectroscopy.

Deconvolution experiments for step 2: Substrate **1** (0.5 mmol, 0.118 g, 1 equiv.), 4-bromopyridine (1.25 mmol, 2.5 equiv.), all bases **B1-B8** (1.5 mmol, 3 equiv.), all carboxylate salts **C1-C8** (0.1 mmol, 0.20 equiv.), the corresponding ruthenium pre-catalysts **Ru1-Ru3** (0.025 mmol, 0.05 equiv.), and NMP (10 mL -to improve solubility-) were introduced in a dry Schlenk tube under argon atmosphere. Each reaction mixture was stirred at 150 °C for 48 h. Then, each reaction mixture was cooled down to room temperature and dissolved in dichloromethane (30 mL). After filtration over celite and evaporation of the solvents under vacuum, each reaction mixture was analysed by ¹H NMR spectroscopy.

Deconvolution experiments for steps 3-5: Substrate **1** (0.5 mmol, 0.118 g, 1 equiv.), 4-bromopyridine (1.25 mmol, 2.5 equiv.), the corresponding bases **B1-B8** (1.5 mmol, 3 equiv.), the corresponding carboxylate salts **C1-C8** (0.1 mmol, 0.20 equiv.), [RuCl₂(*p*-cymene)]₂ (0.025 mmol, 0.015 g, 0.05 equiv.), and NMP (2 mL) were introduced in a dry Schlenk tube under argon atmosphere. Each reaction mixture was stirred at 150 °C for 48 h. Then, each reaction mixture was cooled down to room temperature and dissolved in dichloromethane (30 mL). After filtration over celite and evaporation of the solvents under vacuum, each reaction mixture was analysed by ¹H NMR spectroscopy.

General procedure for the Ru-catalyzed C-H bond double heteroarylation of triazoles: Substrate **1** (0.5 mmol, 0.118 g, 1 equiv.), the corresponding heteroaryl bromide (1.25 mmol, 2.5 equiv.), K₂CO₃ (1.5 mmol, 0.207 g, 3 equiv.), KOAc (0.1 mmol, 0.098 g, 0.20 equiv.), [RuCl₂(*p*-cymene)]₂ (0.025 mmol, 0.015 g, 0.05 equiv.), and NMP (2 mL) were introduced in a dry Schlenk tube under argon atmosphere. The reaction mixture was stirred at 150 °C for 48 h. Then, the reaction mixture was cooled down to room temperature and dissolved in dichloromethane (30 mL). After filtration over celite and evaporation of the solvents under vacuum, the desired product (**2**) was purified by silica gel column

chromatography with mixtures of heptane and ethyl acetate containing 1% of triethylamine.

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Keywords: C-H bonds • heterocycles • ruthenium • deconvolution screening • triazoles

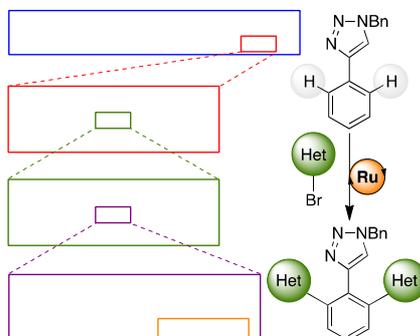
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- [12] For examples of absence of reactivity of aryl bromides containing aldehyde and nitro functional groups in ruthenium-catalyzed C-H bond functionalization, see: a) C. Bruneau, R. Gramage-Doria, *Adv. Synth. Catal.* **2016**, *358*, 3847-3856; b) R. Gramage-Doria, S. Achelle, C.

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The application of a deconvolution strategy to ruthenium catalyzed C-H bond functionalization provided appropriate reaction conditions to perform the unprecedented heteroarylation of triazole scaffolds in good yields. This was possible after screening 22 parameters (3 solvents, 3 ruthenium complexes as pre-catalysts, 8 carboxylate salts as co-catalysts and 8 bases) in only 18 designed experiments.

**Triazoles**

Rafael Gramage-Doria,* Thierry Roisnel

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**Ruthenium-Catalyzed C-H Bond
Heteroarylation of Triazoles Enabled
by a Deconvolution Strategy**