# Organic & Biomolecular Chemistry

## Accepted Manuscript

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DOI: 10.1039/C9OB00806C

COMMUNICATION

# Solvent-Free Ruthenium-Catalysed Triflate Coupling as a Convenient Method for Selective Azole-*o*-C–H Monoarylation

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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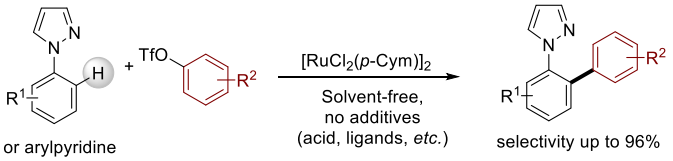
**Metal-catalysed *ortho*-directed C–H functionalization usually faces selectivity issues in the competition between mono- and disubstitution processes. We report herein the ruthenium-catalysed *N*-directed C–H monoarylation of arylpyrazoles with a selectivity up to 96% or that globally reaches values above 80%. This selectivity is an effect of solvent-free conditions that is associated with sulfonate reagents, in the absence of frequently used acidic additives.**

The development of general synthetic conditions that are compatible with sustainable chemistry and cost-efficiency is highly desirable. Selective C–H activation/functionalization reactions conducted under solvent-free conditions may result in the development of valuable strategies to form aromatic molecules in straightforward and atom-economic protocols.[1] The exploitation of coupling partners obtained from renewable resources like alcohols and phenols is also pertinent in such context. Accordingly, phenol derivatives are used in the synthesis of compounds with high added value.[2]

We recently reported carbon–carbon bond formation by reacting aryl trifluoromethyl sulfonates with arylpyrazoles in a C–H activation process using a ruthenium catalyst.[3] This approach based on phenol derivatives, where a triflate is used as electrophilic reagent, had remained up to date limited to only very few examples.[2,4] For instance, a 61:7 mixture of mono- and diarylated phenyl pyridine had been reported from a coupling employing $[RuCl_2(C_6H_6)]_2$ and $PPh_3$ in NMP.[4a] 5-Aryltetrazole had been monoarylated with $[RuCl_2(p\text{-Cymene})]_2$ and $MesCO_2H$ or the amino acid *N*-pivaloyl-*L*-valine (Piv-Val-OH) as co-catalyst in toluene in the presence of aryl bromides.[4b,c] Three examples of aryl triflate coupling had been reported with a selectivity control provided by the steric hindrance of a benzyl group on the directing-tetrazole.

In relation, by using aryl chlorides with a well-defined Ru(II) mesitylcarboxylate complex the monofunctionalization of two aryl pyridines and a phenyl pyrazole in toluene has been exemplified.[5a] For such selective monofunctionalization, another strategy has been the control exerted by additional external ligands such as: the sterically hindered diaminophosphine oxide for coupling tosylates,[5b] some bulky vinylphosphanes[5c] and (heterobiaryl)diarylphosphanes[5d] for coupling chlorides and bromides, or triphenylphosphine for coupling iodides.[5e] Another strategy to promote the monoarylation has been to slow down the global reaction rate by using water as the solvent.[6]

In this context, we disclosed conditions for the *ortho*-diarylation of arylheteroaryl substrates by using $[RuCl_2(p\text{-Cymene})]_2$ combined with pivalic acid (PivOH).[3] These conditions overcome the chemoselectivity issues related to the formation of mixtures of mono- and diarylated products by a highly efficient and quantitative C–H *ortho*-diarylation. We pursued investigation specifically devoted to promote selectivity in azoles monoarylation under atom-economic conditions. In the course of solvent optimization with solvents reputed eco-friendly,[7] we establish new conditions based on ruthenium-catalysed sulfonate couplings for the monoarylation of arylpyrazoles. This greener protocol with unmatched selectivity up to now was conducted under solvent-free conditions and in the absence of additional ligand and acidic assistance (Scheme 1). It opens thus a way to the synthesis in high yield of unequally *o*-diarylated polyaromatics.




**Scheme 1** Synthetic selective access to *o*-monoarylated azoles or pyridines under solvent- and additives-free conditions.

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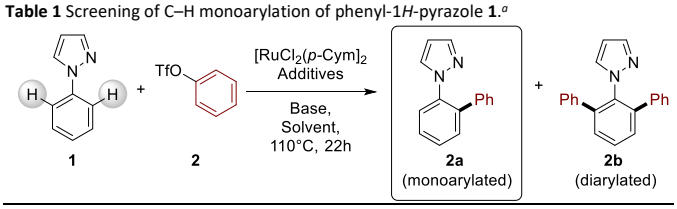
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

**Table 1** Screening of C–H monoarylation of phenyl-1*H*-pyrazole **1**.[a]

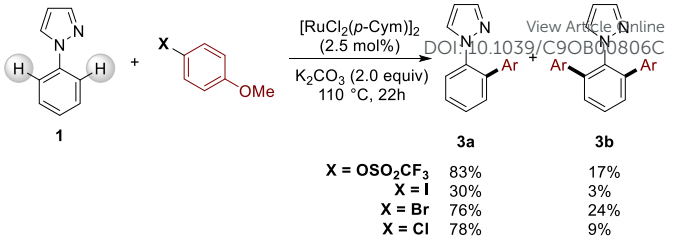



| Entry | Additive | Solvent | 1:2 (eq.) | Conv (%) | 2a (%) | 2b (%) |
|---|---|---|---|---|---|---|
| 1 | PivOH | $PhCF_3$ | 1:3 | 99 | / | 99 (93) |
| 2 | PivOH | $PhCF_3$ | 2:1 | 99 | 60 | 40 |
| 3 | PivOH | $PhCF_3$ | 3:1 | 99 | 80 | 20 |
| 4 | $MesCO_2H$ | $PhCF_3$ | 3:1 | 90 | 70 | 20 |
| 5 | Ac-Val-OH | $PhCF_3$ | 3:1 | 99 | 80 | 20 |
| 6 | $KNO_3$ | $PhCF_3$ | 3:1 | 70 | 64 | 6 |
| 7 | - | $PhCF_3$ | 3:1 | 99 | 80 | 20 |
| 8 | - | toluene | 3:1 | 85 | 62 | 23 |
| 9 | - | 1,4-dioxane | 3:1 | 76 | 54 | 22 |
| 10 | - | DMF | 3:1 | 42 | 26 | 16 |
| 11 | - | CPME | 3:1 | 52 | 42 | 10 |
| 12 | - | HOAc | 3:1 | <5 | <5 | 0 |
| 13 | - | $H_2O$ | 3:1 | 50 | 42 | 8 |
| 14 | - | - | 3:1 | 99 | 90 | 9 |

[a] Conditions: Phenyl-1*H*-pyrazole (1-3.0 equiv), phenyl triflate (1 equiv), $[RuCl_2(p\text{-Cym})]_2$ (2.5 mol%), additive (30 mol%), $K_2CO_3$ (2-4.0 equiv), in solvent (0.125 M) at 110°C, 22 h under argon. $^1H$ NMR yield, isolated under bracket. PivOH: pivalic acid. Ac-Val-OH: *N*-Acetyl-*L*-valine; $PhCF_3$: trifluoromethylbenzene; CPME: methoxycyclopentane.

Ruthenium-catalysed *o*-C–H activation/functionalization of pyrazole derivatives efficiently provides diarylated compounds from 3 equiv of triflates, by using $[RuCl_2(p\text{-Cym})]_2$ as precatalyst in trifluoromethylbenzene ($PhCF_3$) in the presence of substoichiometric quantities of pivalic acid (30 mol %, Table 1, entry 1).[3] Accordingly, our screening experiments devoted to promote monoarylation from aryl triflates started with the coupling of phenyl-*1H*-pyrazole **1** (2 equiv) with phenyl triflate (1 equiv) using thus this latter in default (Table 1, entry 2). Under these conditions, a mixture 60:40 of **2a:2b** mono- and diarylated compounds was respectively obtained. A significant amount of diarylated compound (20%) was still formed under a reduced ratio of triflate over pyrazole (1:3), whatever the acidic additive used (Table 1, entries 3-5).[5a] The use of $KNO_3$, tested as additive,[8] only negatively affected the reaction, leading to a much lower conversion despite a notable selectivity effect (entry 6). We then explored solvent effects at 0.125 M, using $PhCF_3$, toluene, 1,4-dioxane, DMF, methoxycyclopentane, acetic acid and water[6] (entries 7-13, respectively) to conclude that anhydrous $PhCF_3$ delivers the best conversion with however a selectivity limited to 80% of monoarylated product.

Since the development of more sustainable synthetic conditions includes the limitation of additional unnecessary solvent, we were pleased to observe that under solvent-free conditions (Table 1, entry 14)[9] a significant improvement in monoarylation selectivity occurs (90% of **2a**), with a total conversion based on phenyl triflate. This selectivity improvement was not only attributable to solvent-free conditions, but was also due to the use of a sulfonate reagent. Indeed, we achieved under comparable conditions the arylation of phenyl-1*H*-pyrazole using of 4-methoxyphenyl triflate or

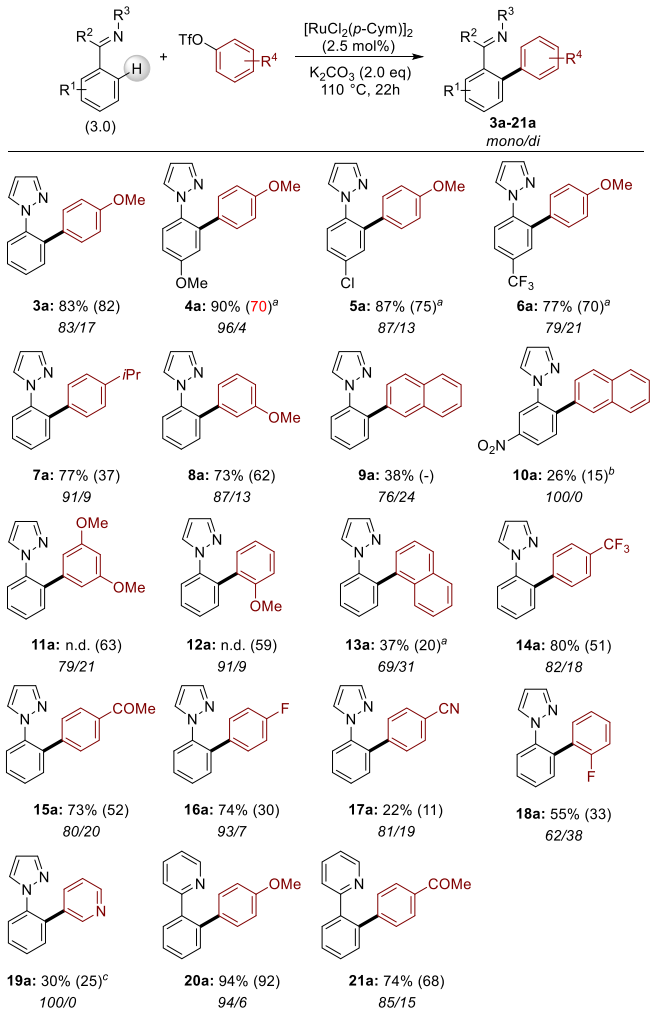





**Scheme 2** Solvent- and acidic additive-free conditions for arylation of phenyl-1*H*-pyrazole using 4-methoxyphenyl triflate and aryl halide as coupling partners.

aryl halide analogues as coupling partners (Scheme 2), which resulted in either the formation of diarylation products in bigger quantities (when X = Br) or a (much) lower general conversion (when X = Cl, I); the triflate being the best option for selective coupling. We were also pleased to achieve excellent conversion and selectivity at g scale, in the coupling of 4-methoxyphenyl triflate (5 mmol), with **3a** isolated pure in 77% yield (0.96 g). We thus used the solvent-free conditions determined to extend the scope of azoles selective monoarylation and various functionalized triflates were reacted with pyrazole or pyridine *N*-directing heterocycles (Scheme 3). While the addition of solvent is unnecessary when liquid reagents are used, in some cases, because of phase-transfer issues due to the solid state of starting triflate or azole, we added a minimum of $PhCF_3$ (according to Table 1, entry 7). The couplings of 4-methoxyphenyl triflate with phenyl-1*H*-pyrazole operate with high selectivity in the presence of electron-donating or electron-withdrawing groups in *para*-position of the pyrazole, thus the monoarylated compounds **4a**, **5a** and **6a** were isolated in 70-78% yield. It might be noted that some amount of the 4-chlorophenyl pyrazole reacted on itself that can be isolated from **5a** (See SI). Electron-rich triflates are also tolerated, but were found more difficult to couple: from 4-isopropylphenyl triflate and 3-methoxyphenyl triflate, monoarylated compounds **7a** and **8a** were isolated in 37 and 62% yield, respectively. In the case of 2-naphtyl triflate, the compound 9a could not be isolated from its diarylated counterpart –showing the importance of a selectivity achieved above 80%– but **10a** achieved from a nitroarylpyrazole and formed exclusively was isolated in modest 15% yield. Difunctionalized 3,5-dimethoxyphenyl triflate and 2- methoxyphenyl triflate were successfully coupled to isolate **11a** and **12a** in 63% and 59% yield respectively. While the coupling of 1-naphtyltriflate is achieved (**13a**), we observed that the steric congestion expected from polyaromatics does not specifically promote monoarylation since a fast second arylation occurs spoiling the global selectivity desired. A variety of electron-poor triflates, in which a useful functionality is present,[10] was successfully coupled to phenyl-1*H*-pyrazole: trifluoromethylated **14a** and fluoroaryl compounds **16a** and **18a** were isolated in 51, 30 and 33% yields, respectively. The ketone **15a** was isolated in 52% yield, while cyanoaryltriflate was found mostly unreactive (**17a**).

DOI: 10.1039/C9OB00806C

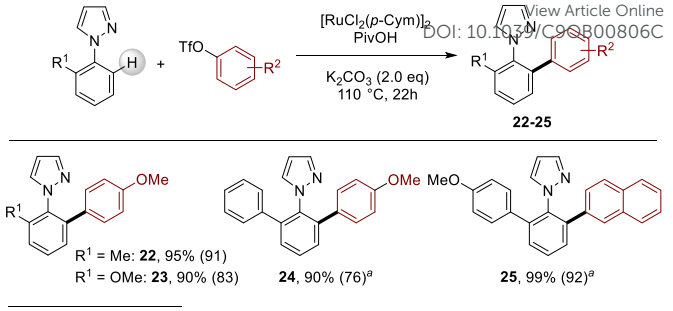



[a] $PhCF_3$ (0.25 M). [b] 2-naphthyl triflate (1.5 equiv), $[RuCl_2(p\text{-Cym})]_2$ (5 mol%), PivOH (60 mol%), $K_2CO_3$ (2.0 equiv.), $PhCF_3$ (0.25 M). [c] **1** (1.0 equiv), 3-pyridine triflate (3.0 equiv), $[RuCl_2(p\text{-Cym})]_2$ (2.5 mol%), PivOH (30 mol%), $K_2CO_3$ (4.0 equiv), $PhCF_3$ (0.25 M).

**Scheme 3** Selective monoarylation of *N*-directing heteroaryl derivatives from functional aryl triflates.

Interestingly, a pyridyltriflate was also tolerated giving monoarylation with a full selectivity albeit moderate 30% yield of **19a** (diarylation does not occur even under forcing conditions). Finally, the extension of the conditions to the monoarylation of arylpyridine was rewarding since compounds **20a** and **21a** were obtained with high to good selectivity (94 and 85% of monoarylation, respectively) and isolated in 92 and 68% yields.

As illustrated in Scheme 4, azole *o*-monoarylation achieved from triflates opens the way to the synthesis of unequally *o*-difunctionalized compounds in conditions that obviate the unnecessary addition of solvent. Compounds **22** and **23** formed in high yields above 90% (isolated in 91 and 83%, respectively) under solvent-free conditions. By using our conditions previously reported for the formation of diarylated pyrazoles,[3] we also achieved the synthesis of the new unequally substituted polyaromatics **24** and **25** in 76 and 92% isolated yield (Scheme 4).




[a] $[RuCl_2(p\text{-Cym})]_2$ (5 mol%), PivOH (60 mol%), $K_2CO_3$ (2.0 equiv.), $PhCF_3$ (0.25 M).

**Scheme 4** Synthesis of unequally *o*-difunctionalized azoles.

## Conclusions

We reported a new protocol for selective *ortho*-C–H monoarylation of arylpyrazole substrates by using *N*-directed ruthenium-catalysed triflates coupling in solvent-free conditions. The additive-free conditions that are associated with aryl triflate coupling allows good reactivity and chemoselectivity in *ortho* C–H monofunctionalization. Conversely, halide counterparts provide under these conditions lower selectivity or/and unsatisfactory conversion. This protocol tolerates electron-donating and electron-withdrawing substituents in *para*-, *meta*- and *ortho*-position of aryl triflates, and the use of functionalized arylpyrazoles and pyridines is also illustrated. This convenient method for selective azole-*o*-C–H monoarylation opens the way to a two-step of unequally *o*-difunctionnalized polyaromatics in excellent yield.

## Conflicts of interest

"There are no conflicts to declare".

## Acknowledgements

This work was supported by the ANR-PRC 2016 program (ALCATRAS, ANR-16-CE07-0001-01), the CNRS, Université Bourgogne Franche-Comté, Conseil Régional de Bourgogne through the plan d'actions regional pour l'innovation (PARI, program CDEA, 3MIM) and the fonds européen de développement regional (FEDER). This research program is affiliated to the European COST action CHAOS (C–H Activation in Organic Synthesis).

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