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Phenol Derivatives in Ruthenium-Catalyzed C–H Arylation: a General Synthetic Access to Azole-Based Congested Polyaromatics

Julien Roger*^[a] and Jean-Cyrille Hierso*^[a,b]

Dedication ((optional))

Abstract: Aryl triflates and related phenolates are suitable electrophile coupling partners for the ruthenium-catalyzed direct arylation of heteroaromatic substrates using azole *N*-directed sp²-C–H activation. We report herein convenient conditions in the efficient *ortho*-C–H functionalization of aryl- pyrazoles, thiazoles and pyridines where [RuCl₂(*p*-Cym)]₂ precatalyst is employed with pivalic acid (PivOH) as co-catalyst. Different phenolate derivatives were successfully coupled which tolerate a large scope of electron-rich substituents in *para*-, *meta*- and highly hindered *ortho*-position. Electron-withdrawing aryl triflates were found less reactive, making the general reactivity of these electrophiles complementary to those of aryl chlorides and deactivated bromides. This cost-effective ruthenium C–H activation/arylation synthesis of poly(hetero)aromatics was concurrently examined using triflates, mesylates, sulfonates and carbonates, and was also successfully extended to the use of diethyl carbonate as an eco-friendly solvent.

Introduction

Selective C–H activation/arylation reactions have resulted in the development of valuable strategies to form aromatic molecules in straightforward and atom-economic protocols.^[1] Further development of general synthetic conditions which are compatible with cost-efficiency and sustainable chemistry is highly desirable. For instance, the use of more eco-friendly solvents at lower temperatures is pertinent.^[2] This approach may be advantageously combined with the exploitation of coupling partners obtained from renewable resources. In this context, investigation on the use of electrophile alternatives to haloarenes, obtained for instance from alcohols is highly appropriate. Many alcohols are directly available from bio-resources, and the preparation of reactive alcohol derivatives is generally easy to achieve. Accordingly, because of their wide availability, rather low cost and practical protection abilities, phenols are frequently used in total synthesis. The phenolic group can be used to direct and introduce the desired functionality into aromatic rings, and then

can achieve carbon–carbon bond formation via the corresponding sulfonate. In this regard, palladium-catalyzed C–H functionalization has successfully exploited sulfonates which are prepared from phenolic materials, providing thus coupling reagents that are crystalline and fairly stable towards hydrolysis.^[3] The use of aryl trifluoromethyl sulfonates in ruthenium-based catalysis is limited to date to very few examples. The relatively low-cost of ruthenium as transition metal is yet very attractive for cost-efficient industrial applications.^[4] Phenyl triflate as electrophilic reagent was reported by Oi *et al.* in the presence of [RuCl₂(C₆H₆)]₂ and PPh₃ in NMP and led to a mixture 61:7 of mono/diarylated phenyl pyridine.^[4a] 5-Aryltetrazole was monoarylated with [RuCl₂(*p*-Cym)]₂ and MesCO₂H or the amino acid *N*-pivaloyl-*L*-valine (Piv-Val-OH) as co-catalyst in toluene in the presence of aryl bromides. Three examples of aryl triflates were reported under such conditions.^[4b,c] Weix and coworkers reported the coupling of 2-methylbenzoic acid with phenyl triflate using [RuCl₂(*p*-Cym)]₂ and 4,4'-di-*tert*-butyl-2,2'-dipyridyl (dtbbpy) as ligand in NMP with a moderate 58% yield.^[4d] Similar yields for the same substrates were obtained in the presence of the cationic [Ru(*t*BuCN)₆](BF₄)₂, with KOC(CF₃)₃, in *t*BuCN at 140°C.^[4e] Clearly, general protocols for efficient *N*-ligand directed *ortho*-arylation of aromatics using sulfonates is still lacking. Based on our recent works in using azole ligands^[5] for palladium-catalyzed aromatic halogenation reactions^[6] we devised conditions for the exploitation of aryl trifluoromethylsulfonates as valuable electrophile coupling partners for aromatic azoles by using ruthenium-catalyzed *N*-ligands directing C–H activation/arylation. The catalytic system combining [RuCl₂(*p*-Cym)]₂ and pivalic acid promotes C–H functionalization of a wide range of highly functionalized phenolate derivatives using pyrazoles, benzothiazoles and pyridines as directing groups. We introduced additionally an eco-friendly protocol employing diethyl carbonate as solvent in ruthenium catalytic arylation with triflates.

Results and Discussion

Aryl triflates as coupling partners for phenyl-1*H*-pyrazole

Poly(hetero)aromatic and biphenyl motifs are valuable synthetic scaffolds in contemporary chemistry with regards to their wide application as pharmaceuticals, agrochemicals, and in material sciences.^[7] Biphenyls bind to a wide range of proteins with high levels of specificity with antihypertensive, antithrombotic antirheumatic, anti-inflammatory and analgesic properties.^[8] In the convergent construction of these scaffolds the research focus has shifted to direct C–H metal-catalyzed functionalization of arenes. The development of methods using cost-effective ruthenium-catalyzed C–H arylation has provided attractive routes to classical organometallic cross-coupling approaches.^[1c,d] Accordingly, our screening experiments started with the coupling

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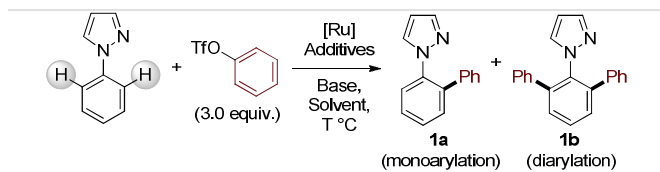
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of phenyl-1*H*-pyrazole and phenyl triflate, both commercially available (Table 1). We achieved coupling by using [RuCl₂(*p*-Cymene)]₂ in toluene in the presence of KOAc. In the absence of ruthenium phenyl-1*H*-pyrazole was found to be unreactive in refluxing toluene (Table 1, entry 1). Conversely, in the presence of 2.5 mol% of [RuCl₂(*p*-Cym)]₂ (*i.e.* 5 mol% of [Ru]), a good conversion of pyrazole starting material (87%) yielded an unsatisfactory mixture of 24% of the biphenyl **1a** and 63% of diarylated **1b** (entry 2).

Table 1. Ruthenium catalysed coupling of phenyl-1*H*-pyrazole with phenyl triflate (Scheme 1).^[a]



entry	additive (mol%)	solvent	T °C	base (equiv.)	Conv. (%)	1a (%)	1b (%)
1 ^[b]	–	toluene	110	KOAc (4)	0	0	0
2	–	toluene	110	KOAc (4)	87	24	63
3	–	PhCF ₃	110	KOAc (4)	96	29	67
4	–	dioxane	110	KOAc (4)	90	26	64
5 ^[c]	–	PhCF ₃	110	KOAc (4)	90	42	48
6	–	PhCF ₃	110	K ₂ CO ₃ (4)	75	33	42
7	Ac-Val-OH (30)	PhCF ₃	110	K ₂ CO ₃ (4)	94	20	74
8	PivOH (30)	PhCF ₃	110	K ₂ CO ₃ (4)	99	0	99 (94) ^[d]
9 ^[e]	PivOH (30)	PhCF ₃	110	K ₂ CO ₃ (4)	64	37	27
10	PivOH (30)	PhCF ₃	80	K ₂ CO ₃ (4)	77	29	48

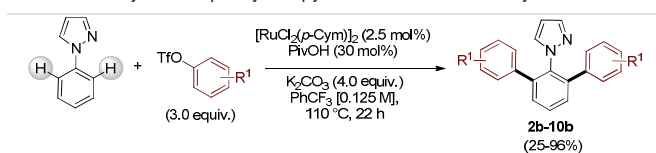
^[a] Conditions: phenyl-1*H*-pyrazole (1 equiv.), phenyl triflate (3 equiv.), base (4 equiv.), [RuCl₂(*p*-Cym)]₂ (2.5 mol%), additive (30 mol%), solvent [0.125 M based on phenyl-1*H*-pyrazole], 22 h, argon. Conversion and yields are determined by ¹H NMR based on phenyl-1*H*-pyrazole. PhCF₃: trifluoromethylbenzene; Ac-Val-OH: *N*-Acetyl-*L*-valine; PivOH: pivalic acid. ^[b] No ruthenium catalyst. ^[c] Pre-catalyst [Ru(OPiv)₂(*p*-Cym)] (2.5 mol%). ^[d] Isolated yield. ^[e] Pre-catalyst [RuCl₂(*p*-Cym)]₂: 1.25 mol%.

Trifluoromethylbenzene, used as solvent, was found more effective with a 96% conversion of pyrazole giving however only 67% of **1b** (entry 3). Using 1,4-dioxane did not improve the conversion or the selectivity (entry 4). [Ru(OPiv)₂(*p*-Cym)] previously used for *ortho*-arylation of functionalized arenes with aryl chlorides^[9] essentially provided a much lower selectivity with a 42:48 mixture of **1a** and **1b** (entry 5). Changing the base for K₂CO₃ did not improve this selectivity (42% of **1a**, entry 6). In the presence of *N*-acetyl-*L*-valine (Ac-Val-OH) amino acid a notable improvement was achieved with a 74% yield obtained for **1b**

(entry 7). Finally, high conversion and selectivity in diarylated **1b** was achieved by using 30 mol% of PivOH as additive (entry 8). A lower catalyst loading of 1.25 mol% of [RuCl₂(*p*-Cym)]₂ (2.5 mol% of [Ru]), or a lower temperature (80 °C) clearly limited the efficiency of the catalyst in the *ortho*-directed diarylation (entries 9 and 10, respectively). Interestingly, monoarylation was preferentially achieved by tuning of the heteroaryl/triflate ratio (2/1) thus yielding 70% of **1a** (See SI).

With the optimized conditions in hands, we investigated the scope of functional aryl triflates tolerated in this coupling with phenyl-1*H*-pyrazole (Table 2).

Table 2. Diarylation of phenyl-1*H*-pyrazole from functional aryl triflates.^[a]



entry	Major product	Conv. (%) ^[b]	Selectivity (%) ^[b]	Yield (%) ^[c]
1	2b (Me)	100	96	89
2	3b (iPr)	100	79	72
3	4b (MeOC)	100	99	96
4	5a	30	100	25
5	6b	100	94	90
6	7b (OMe)	100	99 ^[d]	95
7	8b (Me)	100	90 ^[d]	83
8	9b (MeO)	100	48 ^[d]	38

9		100	99 ^[d]	85
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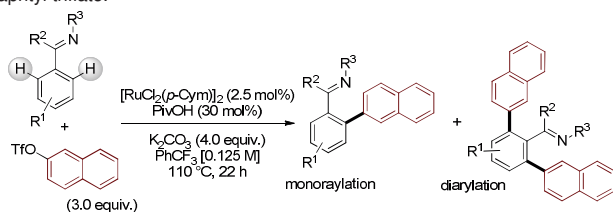
^[a] Conditions: phenyl-1*H*-pyrazole (1.0 equiv.), aryl triflate (3.0 equiv.), [RuCl₂(*p*-Cym)]₂ (2.5 mol%), PivOH (30 mol%), K₂CO₃ (4.0 equiv.), PhCF₃ (0.125 M), 110 °C, under argon, 22 h. ^[b] Determined by ¹H NMR based on the phenyl-1*H*-pyrazole. ^[c] Isolated yield. ^[d] Pre-catalyst [RuCl₂(*p*-Cym)]₂ (5 mol%), PivOH additive (60 mol%).

Electron-donating alkyl substituents placed in *para*-position of the aryl triflate, such as methyl and isopropyl groups, gave polyaromatic **2b** (89%) and **3b** (72%) in very good isolated yields (Table 2, entries 1-2). 4-Acetylphenyl triflate was also easily coupled and **4b** was obtained with a high isolated yield of 96% (Table 2, entry 3). Electron-poor aryl triflates were found significantly less reactive and 5 mol% of [RuCl₂(*p*-Cym)]₂ with 60 mol% of pivalic acid were necessary to isolate the monoarylated **5a** from 2-pyridyl triflate in 25% yield (Table 2, entry 4). 4-In the same conditions, nitrophenyl triflate did not react with phenyl-1*H*-pyrazole and was recovered unchanged after 22 h. On the other hand, congested *meta*-substituted aryl triflates were efficiently coupled and 2-naphthyl triflate reacted with phenyl-1*H*-pyrazole to give **6b** in 90% isolated yield (entry 5). 3,6-Dimethoxyphenyl triflate was found more demanding and by doubling the catalyst loading of [Ru]/PivOH catalyst diarylated **7b** was isolated in excellent 95% yield (entry 6). *Ortho*-substituted aryl triflates were also used for the formation of highly congested (hetero)polyaromatic **8b-10b** (Table 2, entries 7-9). By using 5 mol% of the [RuCl₂(*p*-Cym)]₂ and 60 mol% of pivalic acid, the *ortho*-methylated **8b** was isolated in excellent 90% yield (entry 7). The formation of *ortho*-methoxylated **9b** was more difficult (formed in 48% together with the monoarylated **9a** in 52%) and isolated yields of **9b** and **9a** were moderate (38% and 42%, respectively, entry 8). High conversion to the pentaphenyl 1-(2,6-di(naphthalene-1-yl)phenyl)-1*H*-pyrazole **10b** was achieved with a high 85% isolated yield (entry 9).

N-directing heteroaryl derivatives as coupling partners for aryl triflates

We further applied these general coupling conditions to other heteroaryl substrates which incorporate functions at the aromatic or heteroaromatic moieties. By using the bulky 2-naphthyl triflate coupling partner we investigated the direct arylation of variously substituted arylpyrazoles, pyridines and thiazoles (Table 3). Using 2.5 mol% of [RuCl₂(*p*-Cym)]₂ with 30 mol% of PivOH, and K₂CO₃ in trifluoromethylbenzene at 110 °C, the 1-(4-trifluoromethylphenyl)-1*H*-pyrazole gave diarylated **11b** in 79% isolated yield with a 87% selectivity (Table 3, entry 1).

Table 3. Ruthenium-catalyzed *N*-directing heteroaryl derivatives coupling to 2-naphthyl triflate.^[a]



entry	substrate	Major product	Conv.	Selectivity	Yield
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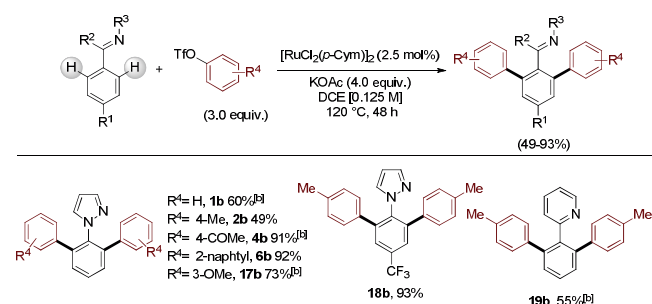
		(%) ^[b]	(%) ^[b]	(%) ^[c]
1		100	13/87	79
2		nd ^[d]	nd	43
3 ^[e]		26	100/0	15
4		nd ^[d]	nd	55
5		100	13/87	81
6 ^[f]		63	17/83	40

^[a] Conditions: heteroaryl (1.0 equiv.), 2-naphthyl triflate (3.0 equiv.), [RuCl₂(*p*-Cym)]₂ (2.5 mol%), PivOH (30 mol%), K₂CO₃ (4.0 equiv.), PhCF₃ (0.125 M based on phenyl-1*H*-pyrazole), 110 °C, under argon, 22 h. ¹H NMR yield based on the heteroaryl. ^[b] NMR yield. ^[c] Isolated yield. ^[d] Not determined since several side-products co-exist. ^[e] 2-naphthyl triflate (1.5 equiv.), [RuCl₂(*p*-Cym)]₂ (5 mol%), PivOH (60 mol%), K₂CO₃ (2.0 equiv.). ^[f] [RuCl₂(*p*-Cym)]₂ (5 mol%), PivOH (60 mol%).

The coupling of 4-chlorophenyl pyrazole was found to be more challenging, giving a moderate 43% isolated yield of **12b** (entry 2). The lack of selectivity is possibly due to competitive oxidative addition of chloride to ruthenium. From 3-nitrophenyl pyrazole arylation occurs selectively in the *para*-position from nitro substituent, giving a modest 15% yield of monoarylated **13a** (entry 3, see also Table S1 in SI). Conversely, 2-(4-chloro-1*H*-pyrazol-1-yl)-phenyl coupled with 2-naphthyl triflate to give **14b** in 55% isolated yield (entry 4). Thus, a functional group on the *N*-directing pyrazole unit was tolerated in ruthenium catalysis, while we have recently shown that similar palladium *ortho*-C–H functionalization from substituted pyrazole directing groups is a very challenging issue.^[9a] These coupling were successfully extended to C–H *ortho*-functionalization of 2-phenylpyridine with 2-naphthyl triflate, which furnished **15b** in 85% isolated yield (entry 5), and to 2-phenylbenzothiazole that gave **16b** in very good 83% yield (40% after workup, entry 6).

Coupling in dichloroethane (DCE) solvent of aryl triflates and heteroaryles

Ruthenium-catalyzed arylation using *N*-directing ligands have been mostly performed in solvents such as NMP or 1,4-dioxane, which are considered as poor eco-friendly solvents regarding waste issues (incineration, recycling, bio-treatments and VOC emissions) and toxicity (reprotoxicity, mutagenicity).^[2b] Toluene and its derivatives, such as xylene and trifluoromethylbenzene are up to now considered less harmful and might be recommended as valuable media alternatives. Progress in ruthenium-catalyzed C–H arylation has been achieved by using aryl chloride electrophile coupling partners in water,^[10] and by the employment of tosylates first in NMP, then in water and solvent-free conditions.^[11] We envisioned that sustainable conditions could be also reached by the employment of aryl triflate derivatives in diethylcarbonate (DCE) as solvent.^[12] We tested our present catalytic protocol in this purpose. By using DCE further optimization appeared to be necessary, and we satisfactorily coupled aryl triflates with *N*-directing arylpyrazole and arylpyridine after careful conditions screening (Table S2 in SI).



Scheme 1. Ruthenium-catalyzed triflate coupling in diethyl carbonate.^[a]

In the presence of [RuCl₂(*p*-Cym)]₂ and KOAc in DCE at 120 °C, we obtained **1b** in 60% after 48 h (Scheme 1). The coupling of aryl triflates with phenyl-1*H*-pyrazole was extended to yield the polyaromatic methylated **2b**, acetylated **4b**, naphthylated **6b** and methoxylated **17b** with fairly good to excellent yield (49%, 91%, 92% and 73% respectively). The catalytic system also successfully achieved 4-tolyl triflate coupling with 1-(4-trifluoromethylphenyl)-1*H*-pyrazole to give **18b** in 93% yield, and the coupling with 2-phenylpyridine gave **19b** in 55% yield.

General reactivity of phenolate coupling partners

The general reactivity and comparative adequacy of various phenolates in C–C coupling is a question generally poorly addressed while it may be decisive in the efficiency of catalytic processes. Herein, we comparatively tested different leaving groups derived from 2-naphthol under our general conditions. Phenol derivatization is easy to handle and we synthesized at gram scale (up to 2 g) five sulfonate, carbonate and acetate reagents. The introduction of trifluoromethane sulfonate group was performed under anhydrous conditions using trifluoromethane sulfonic anhydride to give **20a** in 91% isolated yield (Table 4, entry 1). Similarly, we achieved the synthesis of tosylate **20b**, mesylate **20c**, carbonate **20d** and acetate **20e** in 85% to 99% yield (Table 4, entries 2-5). Naphthalen-2-yl 4-methylbenzenesulfonate **20b** reacted with phenyl-1*H*-pyrazole to

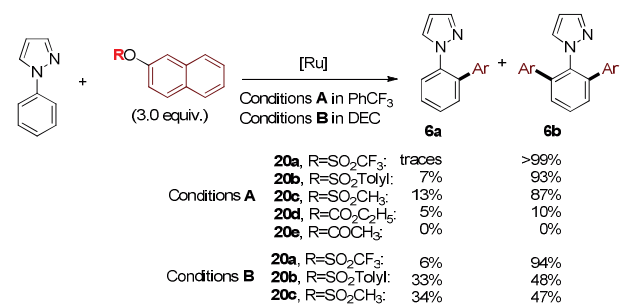
give diarylated **6b** in high 93% yield (Scheme 2, conditions **A**). Interestingly our protocol in PhCF₃ was found very efficient since related studies using tosylates have been limited to single arylation reactions.^[11a,11b] The mesylate derivative was found slightly less reactive but achieved a very good 87% yield (Scheme 2, conditions **A**). A limitation of our protocol was reached with the coupling of carbonates since ethyl naphthalen-2-yl carbonate **20d** achieved only a limited conversion to a mixture of **6a** and **6b** (5% and 10%, respectively). Finally, naphthalen-2-yl acetate **20e** did not react under these conditions.

Table 4. Sulfonates and carbonates from 2-naphthol (**20**).

entry	Reagent (equiv.)	Leaving group	Isolated Yield (%)
1 ^[a]	Tf ₂ O (1.2)	-OSO ₂ CF ₃	20a , 91
2 ^[b]	ClSO ₂ Tolyl (3.0)	-OSO ₂ Tolyl	20b , 90
3 ^[c]	ClSO ₂ CH ₃ (3.0)	-OSO ₂ CH ₃	20c , 85
4 ^[d]	ClCO ₂ C ₂ H ₅ (3.0)	-OSO ₂ C ₂ H ₅	20d , 91
5 ^[e]	ClCOCH ₃ (3.0)	-OCOCH ₃	20e , 99

Conditions: ^[a] 2-naphthol (**20**, 1 equiv.), NEt₃ (1.5 equiv.), trifluoromethane sulfonic anhydride (1.2 equiv.) in dry CH₂Cl₂ at 0 °C; ^[b] 2-naphthol (**20**, 1 equiv.), NEt₃ (3.0 equiv.), *p*-toluenesulfonyl chloride (3.0 equiv.) in CH₃CN at RT; ^[c] 2-naphthol (**20**, 1 equiv.), NEt₃ (3.0 equiv.), methanesulfonyl chloride (3.0 equiv.) in CH₃CN at RT; ^[d] 2-naphthol (**20**, 1 equiv.), NEt₃ (3.0 equiv.), ethyl chloroformate (3.0 equiv.) in CH₂Cl₂ at RT; ^[e] 2-naphthol (**20**, 1 equiv.), NEt₃ (3.0 equiv.), acetyl chloride (3.0 equiv.) in CH₂Cl₂ at RT.

In DEC solvent slower reactions were achieved for naphthalen-2-yl sulfonate **20b** and **20c** (Scheme 2, conditions **B**), to give after 48 h a mixture of unreacted phenyl-1*H*-pyrazole reagent, monoarylated **6a** and diarylated **6b** in 19/33/48 ratio.



Conditions **A**: phenyl-1*H*-pyrazole (1.0 equiv.), phenolate derivatives (3.0 equiv.), [RuCl₂(*p*-Cym)]₂ (2.5 mol%), PivOH (30 mol%), K₂CO₃ (4.0 equiv.), PhCF₃ (0.125 M), 110 °C, under argon, 22 h.

Conditions **B**: phenyl-1*H*-pyrazole (1.0 equiv.), phenolate derivatives (3.0 equiv.), [RuCl₂(*p*-Cym)]₂ (2.5 mol%), KOAc (4.0 equiv.), diethyl carbonate (0.125 M), 120 °C, under argon, 48 h. ¹H NMR yield based on phenyl-1*H*-pyrazole.

Scheme 2. Phenolate derivatives in Ru-catalyzed *ortho*-sp²-C–H arylation of arylpyrazole.

Conclusions

We reported general conditions for selective *ortho*-diarylation of various arylheteroaryl substrates by using *N*-ligand directed ruthenium-catalyzed coupling of highly functionalized aryl phenolate derivatives. The complex [RuCl₂(*p*-Cym)]₂ combined

with pivalic acid (PivOH), allows very efficient coupling in *ortho* C–H functionalization of aryl triflates, which overcome the chemoselectivity issues related to mixtures of mono and diarylation products. Our general protocol tolerated electron-donating substituents in *para*-, *meta*- and *ortho*-position of aryl triflates, including significantly congested substituents. Functionalized arylpyrazoles, pyridines and thiazoles were also tolerated, while this is known to be rather difficult in related palladium C–H functionalization. Additionally, these valuable alternative electrophile coupling partners could be used in eco-friendly solvent diethyl carbonate. Finally, these efficient coupling conditions were successfully extended to sulfonates such as tosylates and mesitylates. Further studies would address metal-catalyzed reactions promoting the more reluctant phenolate derivatives we identified herein such as carbonates and acetates.

Experimental Section

General procedure for ruthenium-catalysed *N*-directed *ortho*-C–H arylation. (i) In trifluoromethylbenzene: as a typical experiment, in an oven-dried 20 ml Schlenk tube equipped with a magnetic stirring bar was charged phenyl-1*H*-pyrazole (66 μ l, 0.5 mmol), phenyl triflate (320 μ l, 1.5 mmol), K₂CO₃ (276 mg, 2 mmol), [RuCl₂(*p*-Cym)]₂ (7.8 mg, 2.5 mol%) and PivOH (15 mg, 30 mol%) in trifluoromethylbenzene (4 ml). The mixture was stirring at 110 °C under argon during 22 h. After extraction (CH₂Cl₂/H₂O), the organic layer was removed *in vacuum*. The crude product was purified by column chromatography on silica or recrystallization (heptane/ethyl acetate) and affords the corresponding product. (ii) In diethyl carbonate (DEC): as a typical experiment, in an oven-dried 20 ml Schlenk tube equipped with a magnetic stirring bar was charged phenyl triflate (320 μ l, 1.5 mmol), KOAc (196 mg, 2 mmol) and [RuCl₂(*p*-Cym)]₂ (7.8 mg, 2.5 mol%) and placed under vacuum for 20 minutes. Under argon, phenyl-1*H*-pyrazole (66 μ l, 0.5 mmol) was added with diethyl carbonate (4 ml). The mixture was stirring at 110 °C under argon during 22 h. After extraction (CH₂Cl₂/H₂O), the organic layer was removed *in vacuum*. The crude product was purified by column chromatography on silica or recrystallization (heptane/ethyl acetate) and affords the corresponding product.

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Keywords: biphenyl • C–H activation • dichloroethane • sulfonates • triflates

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