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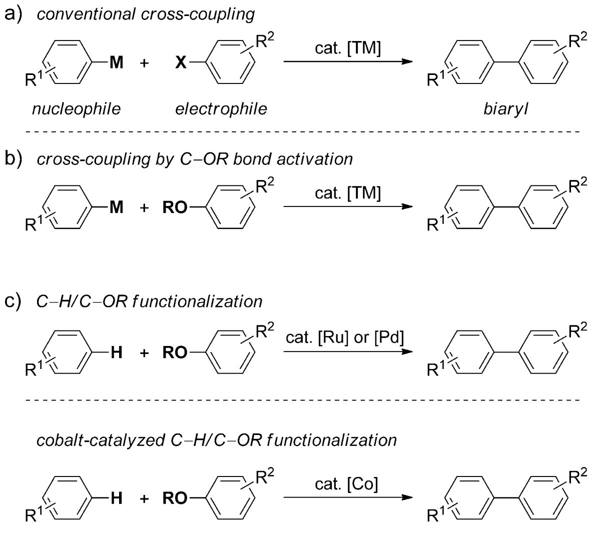
Biaryl Synthesis

Cobalt-Catalyzed Direct Arylation and Benzylation by C–H/C–O Cleavage with Sulfamates, Carbamates, and Phosphates**

*Weifeng Song and Lutz Ackermann**

Dedicated to Professor Lutz F. Tietze on the occasion of his 70th birthday

Efficient methods for the selective preparation of biaryls are of key importance, as these structural motifs are crucial building blocks for natural products, liquid crystals, and functional materials. Particularly, palladium-catalyzed cross-coupling reactions between nucleophilic metalated arenes and electrophilic aryl halides have matured into indispensable tools for the synthesis of substituted biaryls (Scheme 1 a).[1] However, recent focus has shifted towards catalytic arylations with phenol derivatives as organic electrophiles, because these arylating reagents are inexpensive, readily accessible, and can easily be implemented as directing groups in versatile arene functionalization strategies.[2] Unfortunately, the high C–O bond strength in phenols calls for the activation of these precursors, which has been predominantly achieved with expensive fluorine-containing reagents.[3] However, notable recent progress in cross-coupling chemistry has been accomplished with challenging C–C bond formations using fluorine-free, yet difficult to activate, aryl tosylates, phosphates, sulfamates, or carbamates (Scheme 1 b).[4,5] Although these methods have proven to be highly versatile, they are inherently limited, as they rely on prefunctionalized organometallic starting materials. Thus, a significantly more sustainable strategy is represented by the direct transformation of ubiquitous C–H bonds as latent functional groups.[6] Thus far, C–H bond arylations with fluorine-free phenol-based electrophiles were accomplished on heteroarenes with the aid of palladium complexes,[7] whereas nickel catalysts were elegantly utilized by Itami for the most recent direct arylations of C–H acidic azoles.[8] On the contrary, the direct arylation of arenes with aryl tosylates or mesylates is, to date, unfortunately restricted to relatively expensive complexes of the rare transition metals ruthenium[9,10] and palladium (Scheme 1 c).[11]



Scheme 1. Strategies to achieve a versatile and economically attractive biaryl synthesis. [TM] = transition metal complex.

Recent seminal contributions by the research groups of Nakamura and Yoshikai highlighted the power of inexpensive cobalt[12] catalysts for direct C–H bond alkylations.[13,14] In considering the most recent success in cobalt-catalyzed direct arylations through radical intermediates,[6,15–17] as well as the non-radical direct arylations with Grignard reagents reported by Wang and Shi,[18] we became fascinated by developing step-economical cobalt-catalyzed biaryl syntheses through challenging C–H/C–O bond cleavages, which we herein report.

We initiated our studies by exploring the reaction conditions for the direct arylation with electronically deactivated sulfamate **2a** (Table 1). Although mono- or bidentate phosphine ligands unfortunately provided unsatisfactory results (entries 1–3), N-heterocyclic carbene (NHC)[19,20] precursors were more effective for catalytic C–H bond transformations, with *N,N*-bis(mesityl)imidazolium chloride (IMesHCl) delivering optimal yields (entries 4–8). Notably, the bases lithium hexamethyldisilazide (LiHMDS) and KO*t*Bu failed to affect the desired direct arylation with aryl sulfamates **2**, and CyMgCl[21] was instead found to be the additive of choice (Cy = cyclohexyl; entries 8–12). Among the solvents tested, polar aprotic 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU) proved beneficial for direct alkylations (entries 8 and 13–15), as was recently noted by Nakamura.[13b,d] Also, comparable catalytic efficacies were observed for both cobalt(II) and cobalt(III) complexes (entries 8 and 17).

We next explored the scope of the cobalt-catalyzed C–H bond arylation with aryl sulfamates **2** using the optimized catalytic system (Scheme 2). Notably, electron-rich, and thus

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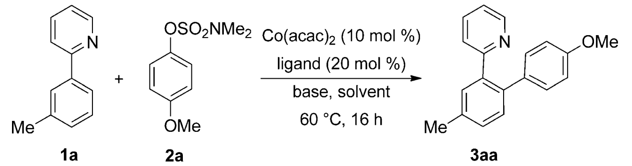
Table 1: Optimization of the direct arylation reaction with sulfamate **2a**.[a]

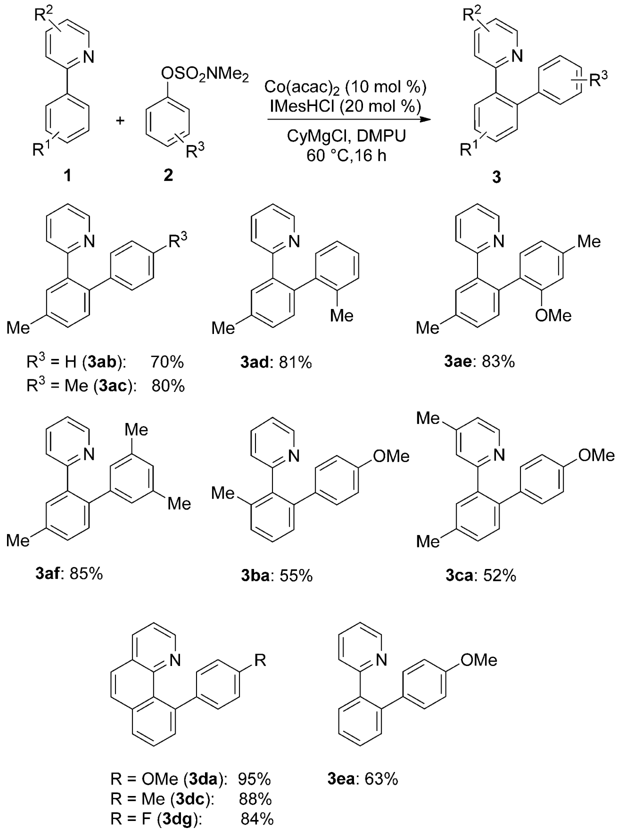


Entry	Ligand	Base	Solvent	Yield [%][b]
1	–	CyMgCl	DMPU	15
2[c]	dppe	CyMgCl	DMPU	–
3	PCy_3	CyMgCl	DMPU	21
4	phenanthroline	CyMgCl	DMPU	11
5	sIPrHCl	CyMgCl	DMPU	42
6	sIMesHCl	CyMgCl	DMPU	40
7	IPrHCl	CyMgCl	DMPU	47
8	**IMesHCl**	**CyMgCl**	**DMPU**	**82**
9	IMesHCl	KO*t*Bu	DMPU	–
10	IMesHCl	LiHMDS	DMPU	–
11	IMesHCl	MeMgCl	DMPU	59
12	IMesHCl	*t*BuMgCl	DMPU	40
13	IMesHCl	CyMgCl	NMP	–
14	IMesHCl	CyMgCl	toluene	–
15[d]	IMesHCl	CyMgCl	DMPU	38
16[e]	IMesHCl	CyMgCl	DMPU	–
17[f]	**IMesHCl**	**CyMgCl**	**DMPU**	**80**

[a] Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), $Co(acac)_2$ (10 mol%), ligand (20 mol%), base (2.0 equiv), solvent (1.0 mL), 60°C, 16 h. [b] Yield of isolated product. [c] 10 mol% of ligand was used. [d] Reaction run at 23°C. [e] Reaction run without $Co(acac)_2$. [f] $Co(acac)_3$ (10 mol%). acac = acetyl acetonate, dppe = 1,2-bis(diphenylphosphino)ethane, Cy = cyclohexyl, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone, IPrH = *N*,*N*-bis(2,6-diisopropylphenyl)imidazolium, IMesH = *N*,*N*-bis(mesityl)imidazolium, LiHMDS = lithium hexamethyldisilazide, NMP = *N*-methyl-2-pyrrolidone, sIPrH = *N*,*N*-bis(2,6-diisopropylphenyl)imidazolinium, sIMesH = *N*,*N*-bis(mesityl)imidazolinium.

deactivated for an oxidative addition, aryl sulfamates **2** were effectively converted, even when bearing sterically hindered *ortho* substituents. Moreover, various pyridyl-substituted arenes chemoselectively provided the desired mono-arylated products **3**.

The cobalt catalyst was not restricted to the use of sulfamates **2** as electrophiles, but also allowed for the first C–H bond arylations of arenes with widely accessible aryl carbamates **4** (Scheme 3). Both electron-rich carbamates and functionalized, electron-deficient aryl carbamates were converted with remarkably high catalytic efficacy, even at ambient temperature (**3aa**). Furthermore, both arenes with electron-donating substituents and arenes with electron-withdrawing substituents delivered the desired products **3** in high yield. A variety of different pyridyl-directing groups could be employed to ensure site-selectivity, as could a less electron-donating 2-pyrimidyl-substituent (**3ha**). As to the reaction mechanism, an intramolecular competition experiment[13a] with *meta*-fluoro-substituted arene **1i** site-selectively furnished biaryl **3ia** through functionalization of the kinetically more acidic C–H bond. Moreover, aryl carbamates **4h** and **4i**, which are functionalized with sterically hindered substituents in the *ortho* position, delivered the desired products **3ah** and **3ai**, thereby illustrating the power of aryl carbamates for strategies that merge directed *ortho* metalation (DoM) and C–H bond functionalization.



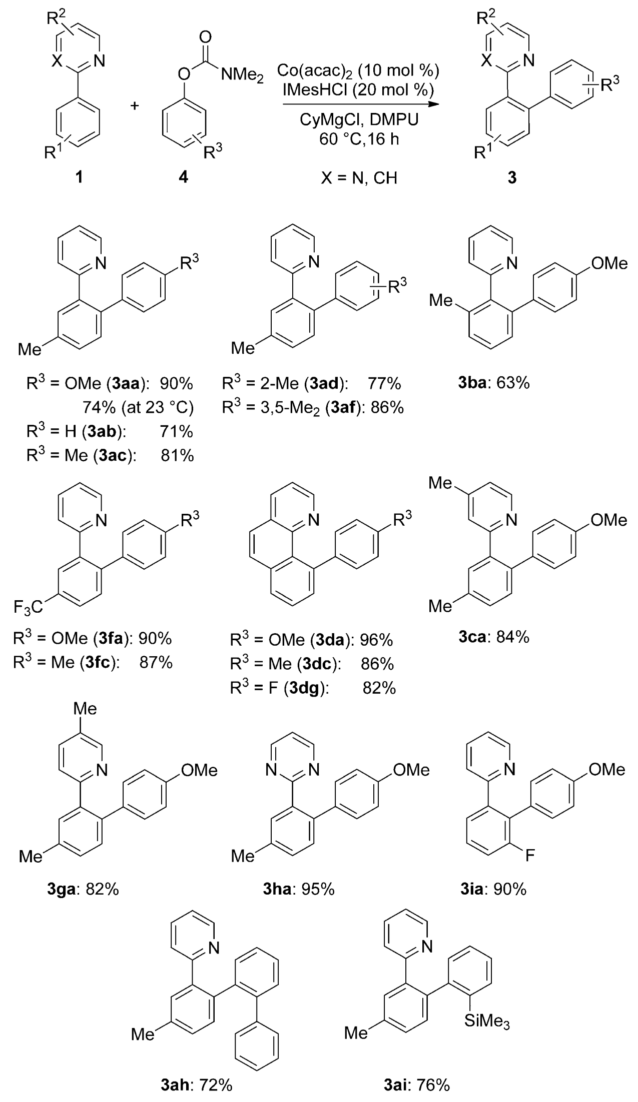
Scheme 2. Cobalt-catalyzed direct arylations with aryl sulfamates **2**.

Likewise, heteroarenes **5** served as valuable substrates for the cobalt-catalyzed direct arylation with aryl sulfamate **2g** and carbamates **4** (Scheme 4). Indeed, mono-*N*-substituted indoles **5** were selectively arylated at the C2 position, which allowed for the synthesis of, among other products, sterically encumbered heterobiaryl **6bd**, a feature that should prove instrumental for future applications to asymmetric C–H bond arylations.

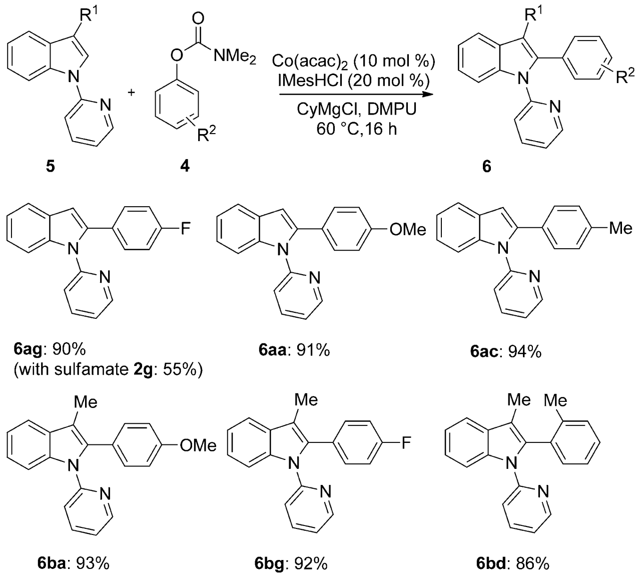
Remarkably, the inexpensive cobalt catalyst also enabled direct benzylation[22–24] reactions on indoles **5** (Scheme 5). Indeed, the C_{sp^2}–C_{sp^3} bond formation was realized with benzyl phosphate **7** under remarkably mild reaction conditions,[25] that is, at ambient temperature.

Considering the unique reactivity of the cobalt catalyst, we became interested in probing its mode of action. To this end, intermolecular competition experiments between aryl sulfamates **2** and carbamates **4** revealed the latter to display a significantly higher inherent reactivity (Scheme 6a,b) and electron-deficient carbamates were preferentially converted (Scheme 6c).

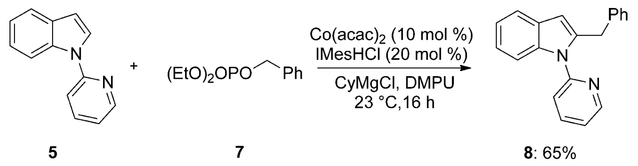
A direct arylation with aryl sulfamate **2a** in the presence of one equivalent of 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) led to the formation of desired product **3aa** in a yield of 68%. This result is comparable to the that obtained in the absence of the radical scavenger (Table 1, entry 8). This finding suggests that a radical reaction mechanism in the direct C–H/C–O arylation is unlikely, as was previously noted



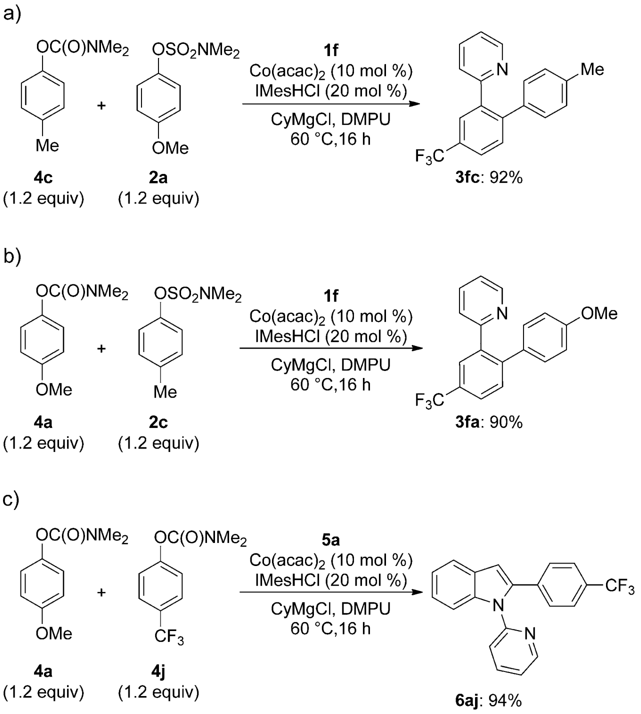
Scheme 3. Cobalt-catalyzed C–H/C–O arylations with carbamates **4**.



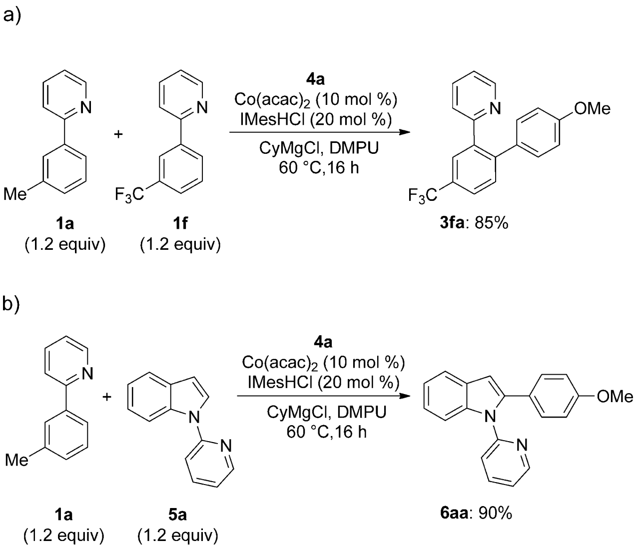
Scheme 4. Cobalt-catalyzed direct arylation of heteroarenes **5** with aryl carbamates **4** and sulfamates **2**.



Scheme 5. Cobalt-catalyzed direct benzylation with phosphate **7**.



Scheme 6. Competition experiments with electrophiles **2** and **4**.



Scheme 7. Competition experiments with different (hetero)arenes.

by Wang and Shi for C–H bond functionalizations with Grignard reagents.[18] Moreover, intermolecular competition experiments with differently substituted arenes and heteroarenes provided strong support for a non-S_EAr-type reaction manifold (Scheme 7a).[26] Instead, the reactivity of the arene is likely governed by the kinetic C–H bond acidity, as is indicated by the selective conversion of indole **5a**, as compared to arene **1a** (Scheme 7b).

In summary, we have reported the first use of inexpensive cobalt catalysts for direct C–H bond arylation and benzylation with phenol-derived organic electrophiles through challenging C–H/C–O bond cleavage. The high catalytic efficacy of the versatile cobalt catalyst set the stage for unprecedented metal-catalyzed direct arylation and benzylation of arenes[27] with easily accessible fluorine-free aryl sulfamates, carbamates, and phosphates. Importantly, mechanistic studies provided strong evidence for a non-radical reaction manifold, and the C–H/C–O bond arylation proved viable even at ambient temperature.

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Keywords: biaryls · carbamates · cobalt · phosphates · sulfamates

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[23] Attempted direct benzylations with carbamates **4** or sulfamates **2** as electrophiles, or utilizing substrate **1a**, have thus far not provided the desired products. However, the direct arylation of arene **1a** with an aryl phosphate delivered product **3aa** in 32% yield of isolated product.

[24] The direct arylation of substrate **1a** with an aryl triflate only provided an unsatisfactorily low yield of the desired product, whereas aryl chlorides gave more promising results.

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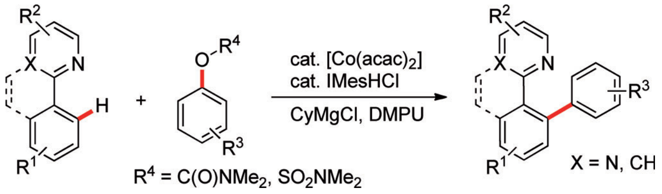
[27] Reactions with arenes bearing amides or aldimines as directing groups have thus far provided only unsatisfactory results.

Communications

Biaryl Synthesis

W. Song, L. Ackermann* ____ ■■■■–■■■■

Cobalt-Catalyzed Direct Arylation and Benzylation by C–H/C–O Cleavage with Sulfamates, Carbamates, and Phosphates



Inexpensive cobalt catalysts enable the first direct arylation and benzylation of (hetero)arenes with aryl carbamates, sulfamates, and phosphates with ample scope. The non-radical C–H/C–O arylation reaction even proved viable at ambient temperature.

Biarylsynthese

W. Song, L. Ackermann* ____ ■■■■–■■■■

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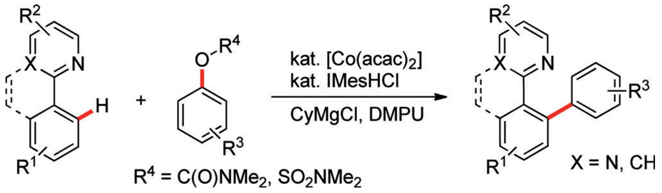

Preiswerte Cobalt-Katalysatoren ermöglichen die erste direkte Arylierung und Benzylierung von (Hetero)arenen mit einer Vielzahl von Arylcarbamaten, -sulfamaten und -phosphaten. Die nicht-radikalische C-H/C-O-Arylierung gelang sogar bei Umgebungstemperatur.

Communications

Biaryl Synthesis

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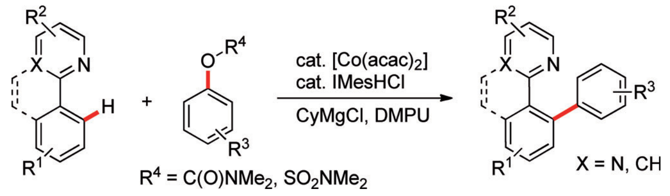

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