ChemPubSoc Europe

DOI: 10.1002/chem.201500552

CHEMISTRY
A European Journal
Communication

C–H Activation

Cobalt-Catalyzed C–H Arylations with Weakly-Coordinating Amides and Tetrazoles: Expedient Route to Angiotensin-II-Receptor Blockers

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Abstract: Cobalt-catalyzed C–H arylations enabled the synthesis of biaryl tetrazoles, which are key structural motifs in antihypertensive angiotensin-II-receptor blockers. Thus, weakly-coordinating benzamides were employed for step-economical C–H arylations with ample scope. Further, a low-valent NHC complex enabled first cobalt-catalyzed C–H functionalization by tetrazole assistance.

Hypertension is among the most prevalent diseases in developed countries, and nonpeptidic angiotensin-II-receptor blockers (ARBs), such as Valsartan, Losartan or Candesartan (Figure 1), have been identified as particularly effective antihypertensives.[1,2] As a direct consequence, ARBs are produced in more than 1000 t annual scale for clinical treatment. The unifying structural motif of numerous nonpeptidic ARBs is represented by the 5-biaryl tetrazole scaffold. Thus far, these biaryl moieties were mostly accessed through palladium-catalyzed cross-coupling reactions using nucleophilic organometallic coupling reagents.[3] The required prefunctionalized nucleophiles are not readily available and their syntheses involve numerous synthetic operations, which generate undesired waste. A significantly more step-economical alternative is represented by the direct arylation of otherwise unreactive C–H bonds.[4] Despite the practical importance of biaryl tetrazoles, C–H arylations of aryl tetrazoles were thus far only accomplished with ruthenium(II) catalysts.[1,5]

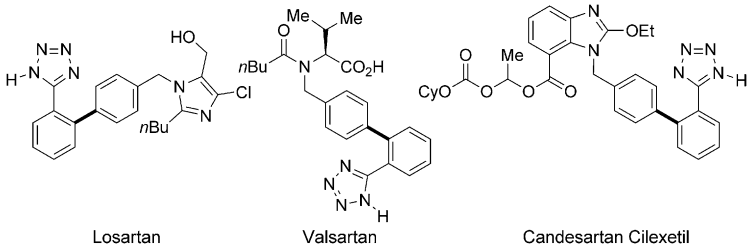

Figure 1. ARBs featuring biaryl tetrazoles.

The relatively high costs of 4d or 5d late transition metal C–H activation catalysts have resulted in a strong demand for a novel catalyst design, exploiting naturally abundant first row transition metals.[6] In recent years, inexpensive cobalt complexes have emerged as powerful catalysts for C–H functionalizations with organic electrophiles.[7–9] However, in spite of considerable progress,[7,10–12] cobalt-catalyzed C–H arylations continue to face major limitations in that strongly coordinating directing groups, namely pyridines, imines or pyrimidines, are a prerequisite for all direct arylations (Scheme 1 a), which renders further modifications of the obtained products often particularly challenging. Hence, cobalt-catalyzed C–H functionalizations with weakly coordinating[13,14] amides or tetrazoles have unfortunately thus far proven elusive. Within our program on the use of inexpensive metals for sustainable C–H activation,[15,16] and inspired by elegant studies from Nakamura and Ilies on catalyzed alkylations,[17] we have established two novel protocols, providing expedient access to biaryl tetrazoles of type **4** (Scheme 1 b). Thus, we devised cobalt-catalyzed C–H arylations with weakly-coordinating benzamides **1**, as well as direct arylations of synthetically useful aryl tetrazoles **3**. Notable features of our strategy include i) the use of an inexpensive cobalt catalyst, ii) an unusually broad substrate scope that involves weakly-coordinating X-type amides and L-type[18] tetrazoles, as well as iii) a high catalytic efficacy reflected by short reaction times of 30 min and/or low catalyst loadings.

In consideration of the facile transformation of amides **5** to tetrazoles **4**,[19] we initially set out to probe different reaction conditions for the C–H arylation of weakly-coordinating benzamide **1** with inexpensive aryl chlorides **2** (Table 1 and Table S1 in the Supporting Information). Thus far, all reported cobalt-catalyzed direct arylations with organic (pseudo)halides were accomplished with either of the two N-heterocyclic carbene (NHC)[20,21] preligands IMesHCl (**6a**) or IPrHCl (**6b**).[10–12] However, preligands **6a** and **6b** delivered the desired product **5aa** only in unsatisfactory low yields, even at a relatively high catalyst loading of 10 mol % (entries 1 and 2). A similar observation was made when employing the saturated analogues sIMesHCl (**6c**), and sIPrHCl (**6d**) (entries 3 and 4), or the tertiary phosphine PPh_3 (entry 5). Cobalt catalysts derived from isopropyl-

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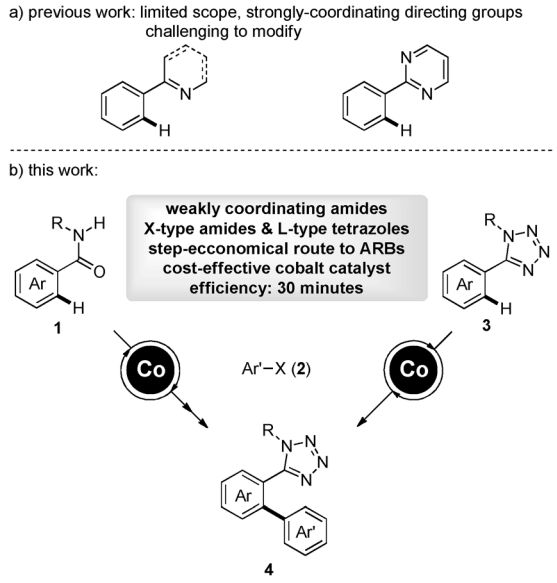
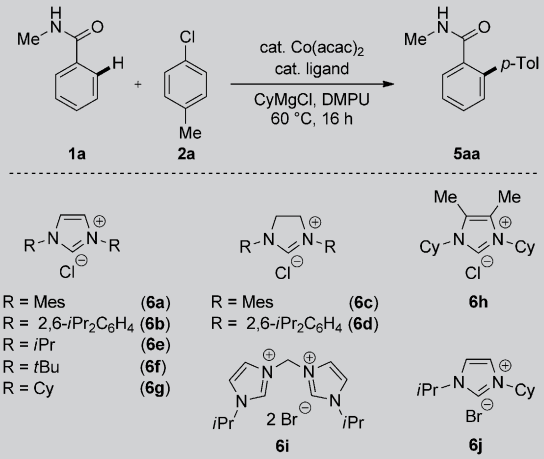
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201500552.



Scheme 1. Cobalt-catalyzed C–H arylation to access key ARB intermediates **4**.

Table 1. Optimization of cobalt-catalyzed C–H arylation.[a]

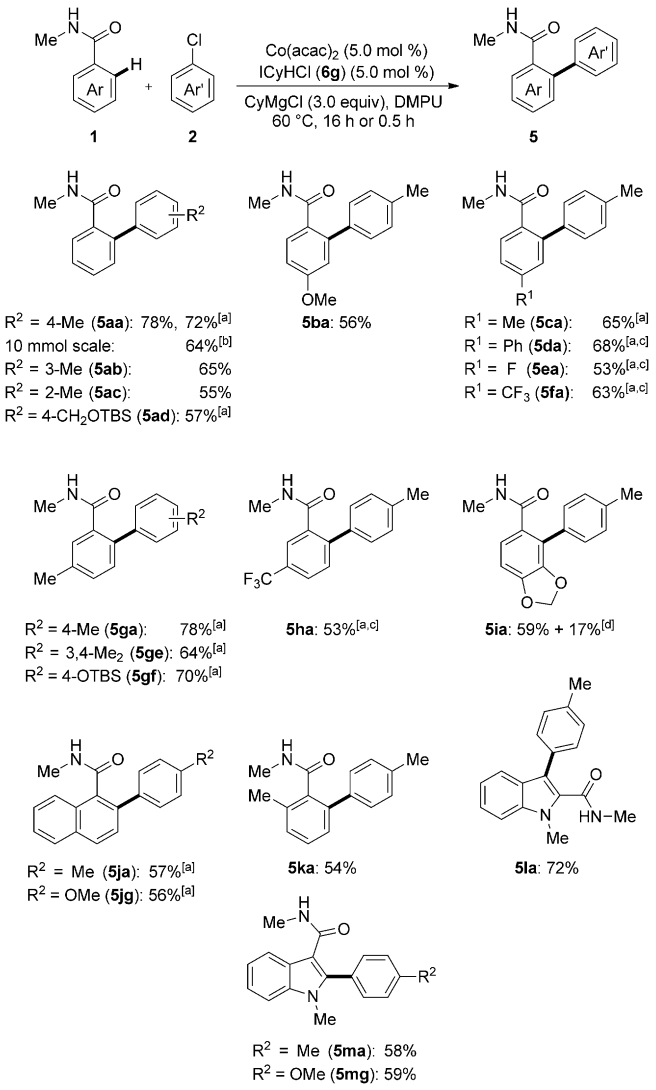


Entry	$Co(acac)_2$ [mol%]	Ligand	Yield[b] [%]
1	10.0	IMesHCl (**6a**)	23[c]
2	10.0	IPrHCl (**6b**)	<5[c]
3	10.0	sIMesHCl (**6c**)	16[c]
4	10.0	sIPrHCl (**6d**)	–[c]
5	10.0	PPh_3	13[c]
6	10.0	**6e**	29[c]
7	10.0	**6f**	<5[c]
8	10.0	**6g**	47[c]
9	***5.0***	***6g***	***78***
10	–	**6g**	–
11	5.0	**6h**	32
12	5.0	**6i**	<5
13	5.0	**6j**	26

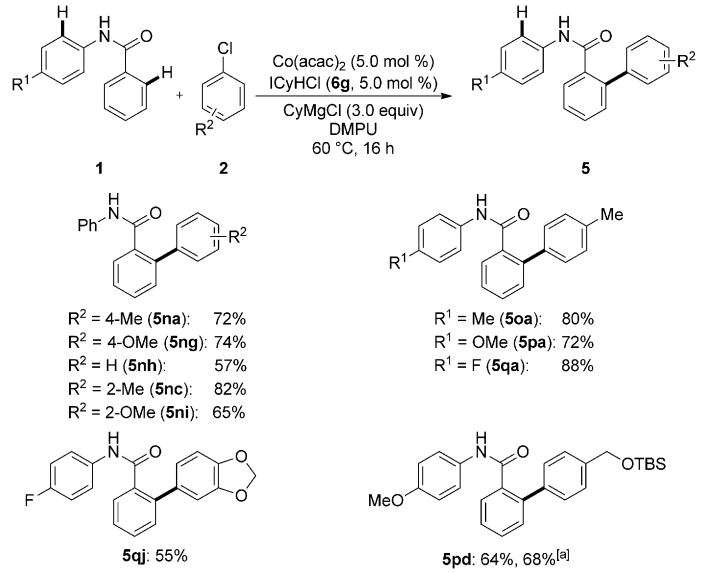
[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), cat. $Co(acac)_2$, ligand (5 mol%), CyMgCl (3.0 equiv), DMPU (1.0 mL), 60 °C, 16 h. [b] Yield of isolated product. [c] **2a** (0.75 mmol), ligand (20 mol%).

substituted NHC **6e** were previously shown to be effective for direct alkylations,[22] but proved unsuitable for the C–H arylation with benzamides **1a** (entries 6 and 7), highlighting the challenge associated with the use of weakly-coordinating amides. In contrast, among various NHC precursors, ICyHCl (**6g**) proved to be optimal with an ideal ligand to cobalt ratio of 1:1 (entries 8 and 9). Under these reaction conditions the catalyst loading could also be significantly reduced (entry 9). The more electron-rich pre-NHC **6h**, the bidentate derivative **6i** and the unsymmetrically substituted pre-NHC **6j** failed to improve the catalytic efficacy (entries 10–13).

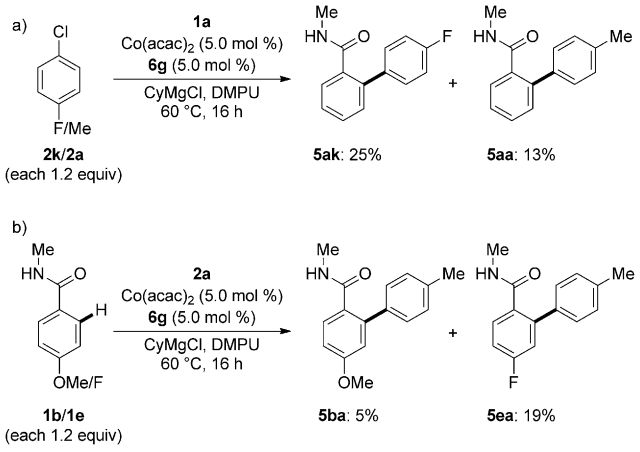
With the optimized cobalt catalyst in hand, we tested its versatility in the C–H arylation with weakly coordinating benzamides **1** (Scheme 2). Various aryl chlorides **2** as well as un- or *para*-substituted benzamides **1** were identified as viable substrates for direct arylations under remarkably mild reaction conditions.[23] Intramolecular competitions with *meta*-substituted arenes **1g** and **1h** were largely governed by steric interactions, unless a secondary directing group effect was exerted by an additional Lewis-basic entity (**5ia**). More sterically hindered



Scheme 2. Scope of cobalt-catalyzed C–H arylation.[a] 30 min.[b] $Co(acac)_2$ (2.0 mol%), **6g** (2.0 mol%).[c] $Co(acac)_2$ (10 mol%), **6g** (10 mol%).[d] Major regioisomer shown, isolated yield of the minor C-6 regioisomer.



Scheme 3. Cobalt-catalyzed C–H arylation of *N*-aryl amides **1**.[a] 30 min.



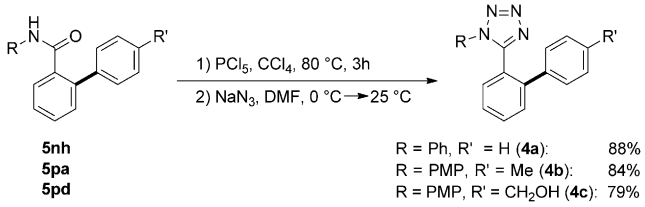
Scheme 4. Competition experiments between a) aryl chlorides **2** and b) benzamides **1**.

ortho-substituted benzamides **1j** and **1k** were successfully employed as well, which should prove instrumental for potential applications of this technology to asymmetric synthesis.[24,25] The widely applicable cobalt catalyst was not limited to aromatic benzamides. Indeed, heteroaromatic indole derivatives **1l** and **1m** also led to site-selective C–H arylations. The outstanding catalytic efficacy and robustness of the user-friendly cobalt catalyst was among others reflected by C–H functionalizations i) with low catalyst loading of only 2.0 mol%, ii) on 1.4 g scale and/or iii) with remarkably short reaction times of only 30 min. Generally, the mass balance was accounted for by recovered unreacted starting material as well as small amounts of diarylated products.

Intramolecular competition experiments with various *N*-aryl benzamides **1n–p** bearing two aromatic moieties led to the chemo-selective C–H arylation on the benzamide, while the anilide motif remained untouched (Scheme 3).

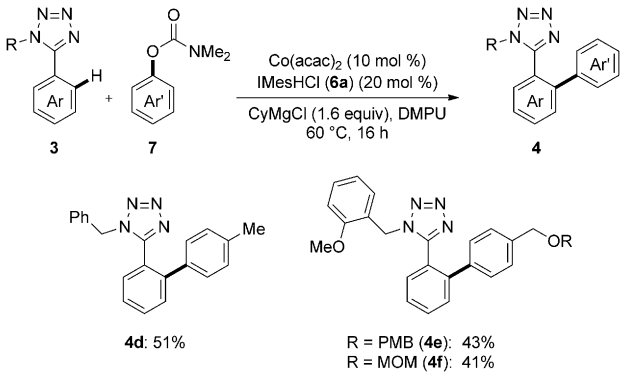
Given the efficacy of the versatile cobalt-catalyzed C–H arylation by weak coordination, we performed studies to delineate its working mode. Independent experiments with isotopically labeled substrates indicated the C–H cobaltation not to be kinetically relevant (KIE ≈ 1.0), and provided evidence for a reversible D/H exchange reaction (Scheme S1 and S2 in the Supporting Information). A set of intermolecular competition experiments revealed electron-deficient benzamides **1** and electron-poor aryl chlorides **2** to be more reactive than their electron-rich counterparts (Scheme 4). These observations can be rationalized in terms of a catalytic cycle involving an initial reversible C–H cobaltation.[8]

The unique synthetic utility of the cobalt-catalyzed C–H arylation by weak amide assistance was illustrated by the facile transformation[19] of the *ortho*-arylated benzamides **5** to the desired biaryl tetrazoles **4** (Scheme 5).



Scheme 5. Facile preparation of biaryl tetrazoles **4**.

Finally, we explored the possibility of devising an even more step-economical approach to biaryl tetrazoles **4** through unprecedented cobalt-catalyzed C–H activation by tetrazole assistance. Intriguingly, a low-valent cobalt catalyst derived from preligand **6a** proved effective here, thereby chemo-selectively delivering the desired products **4**.[26] It is noteworthy that the tetrazole-assisted C–H arylation proceeded by C–H/C–O cleavages[27] with challenging aryl carbamates **7** as the electrophiles (Scheme 6). While the reactions proceeded with rather modest yields, they represent—to the best of our knowledge - the first example of C–H functionalization of aryl tetrazoles using inexpensive first row transition metals.



Scheme 6. Tetrazole-assisted C–H arylation with carbamates **7**.

In summary, we have established novel strategies for cobalt-catalyzed syntheses of biaryl tetrazoles through C–H activation. Thus, low-valent cobalt catalysts derived from NHCs enabled first direct arylations by weak coordination. The arylated benzamides were formed with high site- and chemo-selectivities as well as ample scope, and provided expedient access to biaryl tetrazoles—key scaffolds of ARB blockbuster drugs. Mechanistic studies were suggestive of a reversible C–H cobaltation and a rate-determining reductive elimination. The power of the user-friendly cobalt catalysis was further illustrated by unprecedented tetrazole-assisted C–H activations with 3d transition metal complexes.

Acknowledgements

Generous support by the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement no. 307535, and the Chinese Scholarship Program (fellowship to J.L.) is gratefully acknowledged.

Keywords: amides · arylation · C–H activation · cobalt · tetrazoles

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Received: February 10, 2015
Published online on ■■ ■■, 0000

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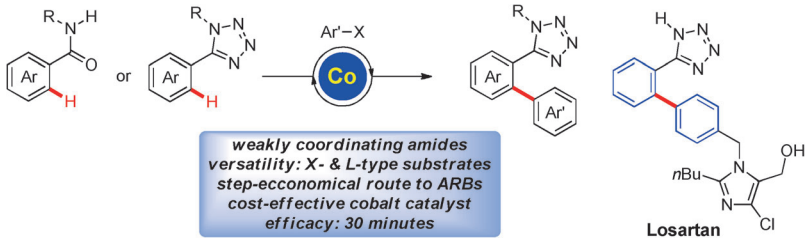
Cobalt-Catalyzed C–H Arylations with Weakly-Coordinating Amides and Tetrazoles: Expedient Route to Angiotensin-II-Receptor Blockers



Broadly applicable cobalt-catalyzed C–H arylations with weakly-coordinating amides or tetrazoles provided step-economical access to biaryl tetrazoles as key structural motifs of angiotensin-II-receptor blockers (ARBs), such as the blockbuster drug Losartan (see scheme).