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Ruthenium(II)-Catalyzed C−H Arylation of Azoarenes by Carboxylate Assistance

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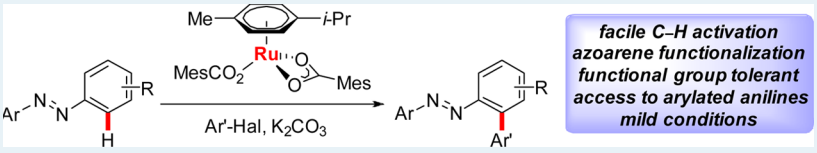
Supporting Information



ABSTRACT: Ruthenium(II)carboxylate complexes enabled the unprecedented direct C−H arylation of azoarenes with aryl halides through chelation assistance. The mild reaction conditions of the optimized C−H functionalization process resulted in a remarkable functional group tolerance. The proximity-induced C−H arylation proceeded with high positional selectivity and could be performed in a one-pot protocol along with a azoarene reduction, providing expedient access to ortho-arylated anilines.

KEYWORDS: *anilines, arylation, azoarenes, C−H activation, ruthenium*

Transition metal-catalyzed cross-coupling reactions[1,2] are indispensable tools for the synthesis of unsymmetrically substituted biaryls, valuable building blocks in, among others, natural products, liquid crystals, drugs, or crop protection agents.[2] Because these methods strongly rely on the synthesis and use of prefunctionalized starting materials, direct C−H arylations[3] have received significant recent attention as environmentally benign and economically superior alternatives.[4] Hence, the step-economy of biaryl synthesis has been significantly improved with the aid of versatile transition metal complexes for C−H functionalizations.[3,5] Particularly, ruthenium(II) complexes have been identified as powerful catalysts for chelation-assisted[6,7] C−H arylations using organic halides as electrophilic arylating reagents,[8] with carboxylate assistance as an enabling technology.[9] Despite these recent advances, ruthenium-catalyzed direct arylations of aniline derivatives, including azoarenes,[10,11] with organic (pseudo)-halides[12] have unfortunately thus far proven elusive, whereas rhodium- or palladium-catalyzed functionalizations of azoarenes were largely achieved in an oxidative fashion.[11] Given the practical importance of ortho-arylated anilines as key structural motifs in fungicides (Figure 1) as well as of azoarenes in material sciences[10,11] and as molecular switches,[13] we became attracted by establishing reaction conditions for C−H arylations of substituted azoarenes with user-friendly organic electrophiles, on which we report herein. Notably, the optimized catalytic system showed a high efficacy through carboxylate assistance[14−16] with broad functional group tolerance and set the stage for a one-pot synthesis of ortho-arylated anilines.

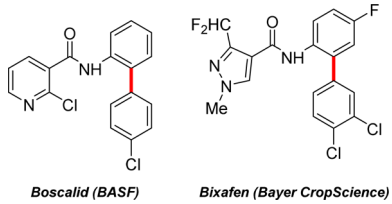


Figure 1. Representative ortho-arylated anilides with fungicidal activity.

We initiated our studies by evaluating reaction conditions for the C−H arylation of azoarene **1a** with aryl bromide **2a** (Table 1 and Tables S-1−S-3 in the Supporting Information). Preliminary experiments indentified ruthenium(II) complex $[RuCl_2(p\text{-cymene})]_2$ as the most powerful catalyst. Among a variety of bases (Na_2CO_3, K_3PO_4, KOAc, NaOAc, or CsOPiv), K_2CO_3 furnished optimal results. A set of representative additives was probed and revealed $MesCO_2H$ as being superior, thereby delivering the arylated product **3aa** with high chemo and positional selectivity (Table 1, entries 1−6). It is noteworthy that KOAc and the phosphoric acid diester $(PhO)_2P(O)OH$[17] also furnished the arylated product **3aa**. The C−H arylation did not occur in the absence of the ruthenium catalyst (entry 7), and the loading of the preligand $MesCO_2H$ could be reduced without a significant loss of catalytic activity (entries 8 and 9). As to the solvent, 1,4-dioxane was found to be most suitable, and the use of THF, DCE, *t*-AmOH, toluene, or *o*-xylene led to somewhat lower yields under otherwise identical reaction conditions (entries 10−14). In contrast, solvents, such as DMSO, AcOH, or MeOH, failed to provide the desired product **3aa**.[18]

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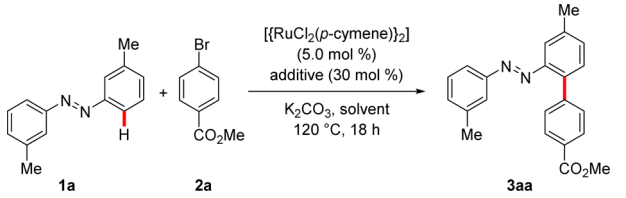
Table 1. Optimization of Ruthenium-Catalyzed C−H Arylation of Azoarene 1a[a]



1a 2a 3aa

entry	additive	solvent	yield (%)
1	PPh_3	1,4-dioxane	44
2	$(PhO)_2P(O)OH$	1,4-dioxane	74
3	KPF_6	1,4-dioxane	75
4	KOAc	1,4-dioxane	79
5	*t*-$BuCO_2H$	1,4-dioxane	76
6	$MesCO_2H$	1,4-dioxane	87
7	$MesCO_2H$	1,4-dioxane	[b]
8	$MesCO_2H$	1,4-dioxane	83[c]
9	$MesCO_2H$	1,4-dioxane	54[d]
10	$MesCO_2H$	THF	42
11	$MesCO_2H$	DCE	43
12	$MesCO_2H$	*t*-AmOH	75
13	$MesCO_2H$	PhMe	83
14	$MesCO_2H$	*o*-xylene	84

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (0.5 mmol), base (2.0 equiv), $[RuCl_2(p\text{-cymene})]_2$ (5.0 mol %), additive (30 mol %), solvent (2.0 mL), 120 °C, 18 h, isolated yields. [b]In the absence of $[RuCl_2(p\text{-cymene})]_2$. [c]$MesCO_2H$ (15 mol %). [d]$[RuCl_2(p\text{-cymene})]_2$ (2.5 mol %).

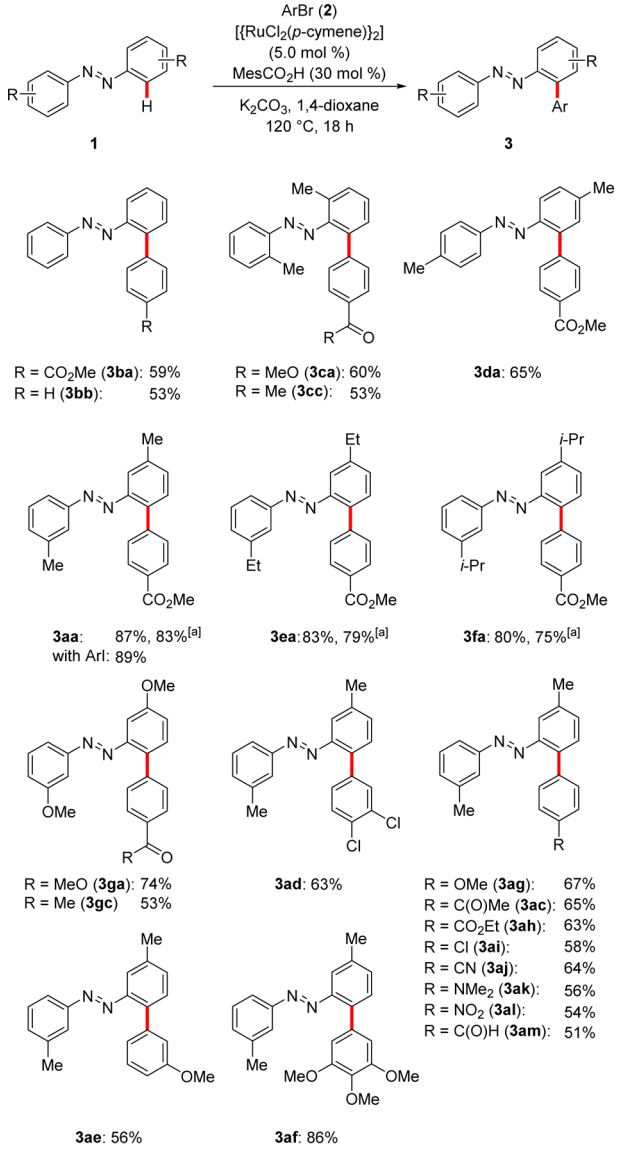
With the optimized reaction conditions in hand, we explored the substrate scope of the ruthenium(II)-catalyzed C−H arylation employing substituted azoarenes **1** and bromoarenes **2** (Scheme 1). The most user-friendly ruthenium(II) catalyst was found to be widely applicable and allowed for the direct C−H functionalization of the parent azobenzene **1b** as well as of azoarenes **1c** and **1d** bearing ortho or para substituents, respectively. Here, only minor amounts of the 2,2′-diarylated products **3′** were formed, even when using an excess of the aryl bromide **2a** (**3ca′**: 10% isolated yield).[18] Intramolecular competition experiments with meta-substituted substrates **1a**, and **1e−1g** generally occurred with excellent positional selectivities at the less hindered C(6)−H bonds. The optimized ruthenium(II) catalyst displayed a useful chemoselectivity in that valuable electrophilic functional groups, such as chloride, enolizable ketone, ester, amine, nitro, or aldehyde substituents, were fully tolerated. The electronic nature of the aryl bromide did not significantly affect the catalysts' performance, and both electron-deficient as well as more challenging electron-rich electrophiles were efficiently converted.

The ruthenium(II) catalyst was not limited to aryl bromides **2** as the electrophilic arylating reagents. Indeed, heteroaromatic electrophiles **2k−2m** proved to be viable substrates, as well, thereby delivering the thiophene and indole derivatives **3ak−3am** (Scheme 2).

Furthermore, direct arylations of the unsymmetrically substituted azoarene **1h** occurred with excellent regiocontrol, thereby delivering azoarene **3ha** as the sole product (Scheme 3).

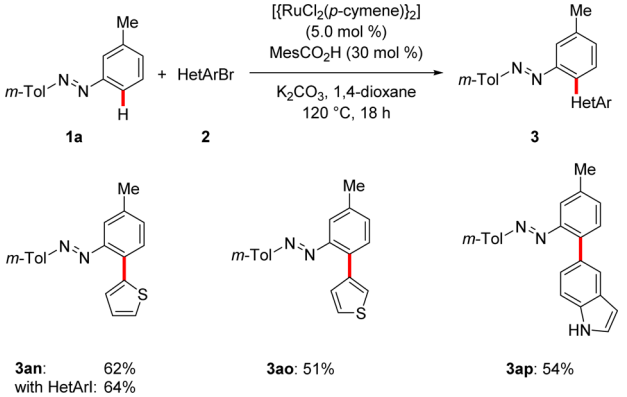
The well-defined ruthenium(II) biscarboxylate complex **4**[19,20] was found to be a competent C−H arylation catalyst, as well, which at the same time allowed for a significant reduction of the catalyst loading (Scheme 4; Table 1, entry 9).

Scheme 1. Scope of C−H Arylation



[a] KOAc as the additive.

Scheme 2. Ruthenium(II)-Catalyzed C−H Functionalization with Heteroaryl Bromides 2



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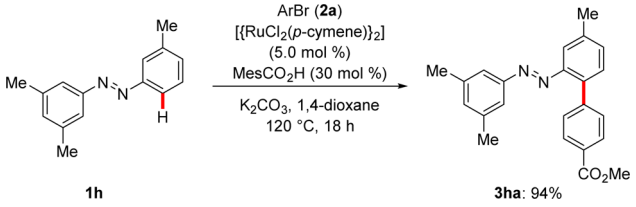
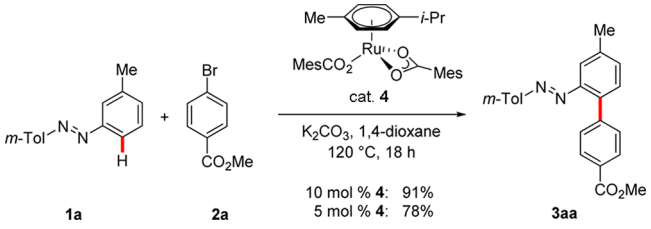
Scheme 3. C−H Arylation of Unsymmetrical Azoarene 1h

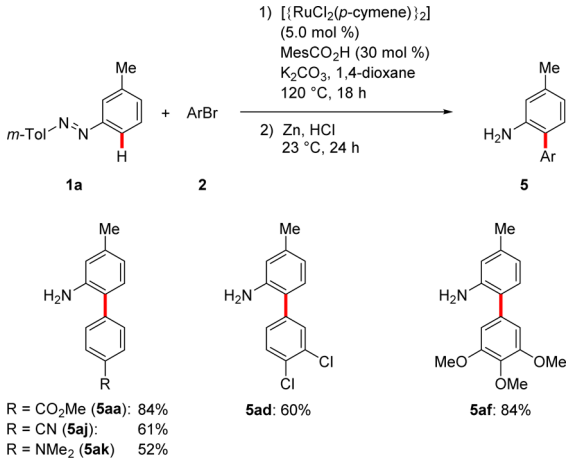


Scheme 4. Well-Defined Ruthenium(II) Biscarboxylate Catalyst 4 for C−H Arylation



We were pleased to find that the ruthenium(II)-catalyzed C−H arylation strategy could be conducted in a one-pot protocol, along with an in situ reduction of the arylated azoarenes **3**. Thus, we identified a practical method that furnishes ortho-arylated anilines **5** in a highly economical manner (Scheme 5).

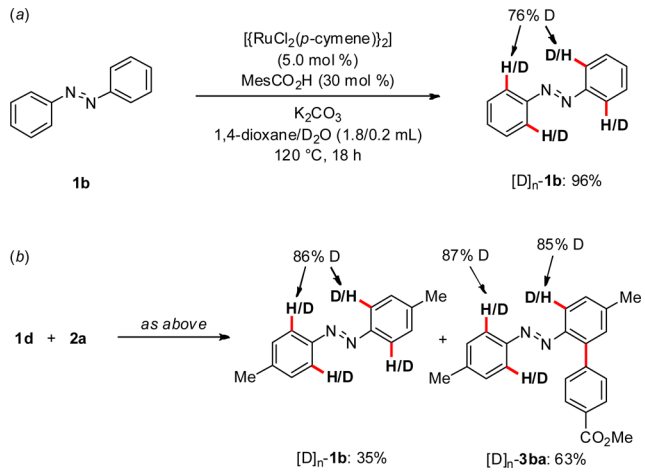
Scheme 5. One-pot Synthesis of ortho-Arylated Anilines 5

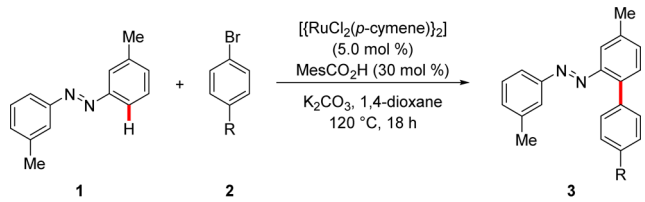


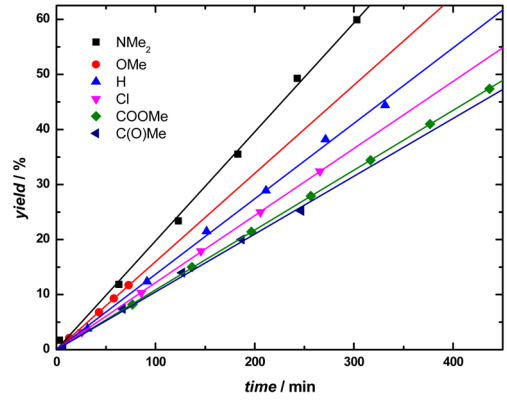
In consideration of the unique selectivity of the ruthenium-(II)-catalyzed C−H functionalizations of azoarenes, we performed experimental studies to probe the working mode of the ruthenium(II) biscarboxylate-mediated C−H activation. To this end, the use of the deuterated cosolvent D_2O clearly revealed a significant H/D scrambling, solely occurring in the ortho position. This observation highlights the reversible[19,21] nature of the C−H ruthenation step (Scheme 6).

Because the C−H metalation was identified as being reversible, we subsequently determined the initial rates for reactions with differently para-substituted aryl bromides **2** (Figure 2). A Hammett plot was constructed from the correlation between the initial rates and the σ_p values. The plot resulted in a linear fit with a negative slope of −0.21, indicating that electron-donating groups facilitate the C−H arylation. In contrast to our previous findings,[19] this observation renders a rate-limiting C−Br oxidative addition

Scheme 6. H/D-Exchange Experiments in the Presence of D_2O







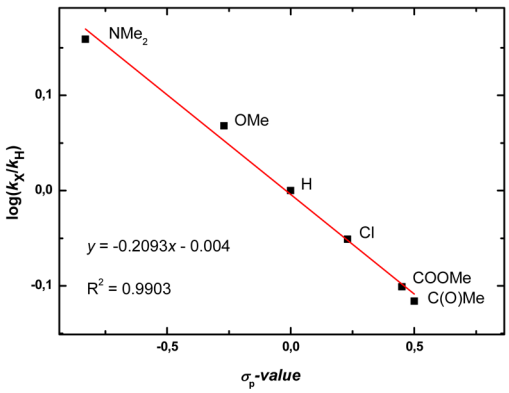


Figure 2. Hammett plot correlation using aryl bromides **2**.

less likely. Instead, our results can be rationalized in terms of a rate-determining reductive elimination.

On the basis of our observations and our previous mechanistic findings on ruthenium-catalyzed direct arylations,[18]

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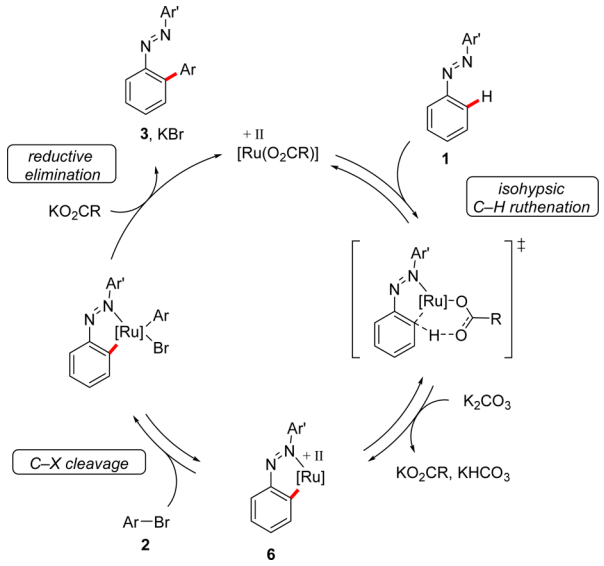
we propose the catalytic cycle to initiate by a reversible, isohypsic cyclometalation with a ruthenium(II) complex, delivering the five-membered ruthena(II)cycle **6** (Scheme 7).

Scheme 7. Proposed Catalytic Cycle



Thereafter, the activation of the organic electrophile occurs, likely involving SET-type elementary steps. Finally, a reductive elimination liberates the desired product **3** and regenerates the catalytically active ruthenium(II) species.

In summary, we have reported on the direct arylation of azoarenes[22] with organic electrophiles. Hence, versatile ruthenium(II)biscarboxylate catalysts enabled efficient direct arylations of diversely decorated azoarenes with high levels of chemo-, regio-, and positional selectivity. Notably, the catalytic system proved tolerant of valuable electrophilic functional groups. The C–H arylation process could be carried out along with a reduction of the arylated azoarenes, providing (step-)economical access to ortho-arylated anilines, important structural motifs in numerous bioactive compounds.

REPRESENTATIVE PROCEDURE: RUTHENIUM(II)-CATALYZED C–H ARYLATION OF AZOARENES 1

In a 20 mL predried, screw-capped, sealed tube, a suspension of (*E*)-1,2-di-*m*-tolyldiazene (**1a**) (210 mg, 1.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol %), $MesCO_2H$ (24.6 mg, 30 mol %), K_2CO_3 (138 mg, 1.0 mmol), and methyl 4-bromobenzoate (**2a**) (108 mg, 0.5 mmol) in 1,4-dioxane (2.0 mL) was stirred at 120 °C for 18 h under a N_2 atmosphere. At ambient temperature, the reaction mixture was diluted with CH_2Cl_2 (75 mL) and filtered through a pad of Celite and silica gel, and the solvents were removed in vacuo. The crude product was purified by column chromatography on silica gel (*n*-hexane/CH_2Cl_2: 7/3) to yield **3aa** (150 mg, 87%) as an orange solid (mp = 136–137 °C).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00939.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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