

Regioselective Ruthenium-Catalyzed
Direct Benzylations of Arenes through
C–H Bond Cleavages

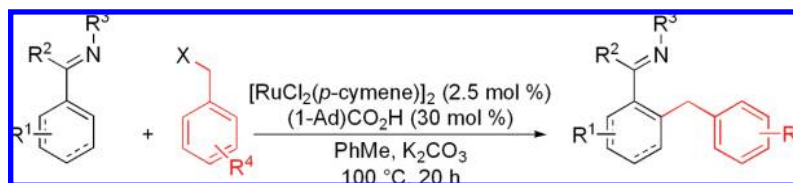
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ABSTRACT



Highly regioselective ruthenium-catalyzed direct benzylations through C–H bond cleavages were accomplished under remarkably mild, nonacidic reaction conditions, for which experimental studies suggested a S_EAr -type mechanism not to be operative.

The diarylmethane moiety is an indispensable structural motif in various compounds with biological activities.¹ A useful approach for its preparation is represented by acid-catalyzed benzylations of arenes through electrophilic aromatic substitution (S_EAr) reactions.^{2–4} Unfortunately, these valuable processes are often associated with significant limitations, such as (i) their restriction to electron-rich arenes, (ii) their low chemo- and/or regioselectivities, and (iii) their low tolerance of acid-labile functional groups. A popular alternative for the selective synthesis of diarylmethane derivatives

relies on nucleophilic additions of organometallic reagents to benzaldehydes, along with subsequent reductions of the thus obtained alcohols.^{1,5} Further, a more redox-economical⁶ strategy involves transition-metal-catalyzed cross-coupling reactions between organometallic reagents and benzyl ha-

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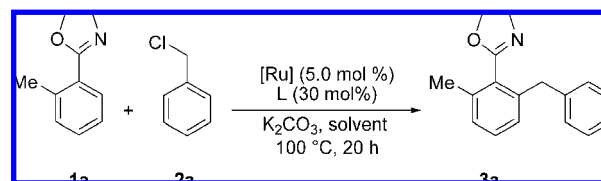
lides.^{7–9} However, these two methodologies require the use of stoichiometric amounts of organometallic reagents, which are predominantly prepared through deprotonations with strong bases.

During recent years, metal-catalyzed C–H bond functionalizations have matured to being increasingly viable alternatives to traditional cross-coupling reactions, which avoid the use of organometallic reagents in stoichiometric quantities. Thus, various protocols for efficient catalytic direct arylations for versatile biaryl syntheses were established.¹⁰ Contrarily, methods for intermolecular¹¹ direct alkylations with aliphatic halides are scarce.¹² In this context, significant progress was very recently accomplished by Hoarau¹³ and Fagnou,¹⁴ as well as by Yu,¹⁵ by devising reaction conditions for palladium-catalyzed direct alkylations of heteroarenes or benzoic acids, respectively. We, on the contrary, developed ruthenium catalysts for direct alkylations^{16,17} of arenes

employing unactivated alkyl halides.¹⁸ Given the practical importance of efficient diarylmethane syntheses, we consequently became interested in exploring unprecedented ruthenium-catalyzed direct benzylation reactions under non-acidic⁴ reaction conditions. Herein, we wish to report on the development of such a protocol, as well as experimental mechanistic studies providing evidence for a non-S_EAr-type mechanism.

At the outset, we explored various (pre)ligands and ruthenium precursors for the direct functionalization of arene **1a** with benzyl chloride **2a** (Table 1). Representative

Table 1. Optimization of Direct Benzylation of Arene **1a**^a



entry	[Ru]	L	solvent	yield
1	[RuCl ₂ (<i>p</i> -cymene)] ₂	---	PhMe	10% ^b
2	[RuCl ₂ (<i>p</i> -cymene)] ₂	PPh ₃	PhMe	<5% ^b
3	[RuCl ₂ (<i>p</i> -cymene)] ₂	HIMesCl	PhMe	<5% ^b
4	[RuCl ₂ (<i>p</i> -cymene)] ₂	HIPrCl	PhMe	<5% ^b
5	[RuCl ₂ (<i>p</i> -cymene)] ₂	SHIPrCl	PhMe	<5% ^b
6	[RuCl ₂ (<i>p</i> -cymene)] ₂	KOAc	PhMe	<10% ^b
7	[RuCl ₂ (<i>p</i> -cymene)] ₂	PhCO ₂ H	PhMe	26% ^b
8	[RuCl ₂ (<i>p</i> -cymene)] ₂	MesCO ₂ H	PhMe	81%
9	[RuCl ₂ (<i>p</i> -cymene)] ₂	<i>i</i> -PrCO ₂ H	PhMe	60%
10	[RuCl ₂ (<i>p</i> -cymene)] ₂	<i>t</i> -BuCO ₂ H	PhMe	76%
11	[RuCl ₂ (<i>p</i> -cymene)] ₂	(1-Ad)CO ₂ H	PhMe	81%
12	[RuCl ₂ (<i>p</i> -cymene)] ₂	(1-Ad)CO ₂ H	NMP	<5% ^b
13	[RuCl ₂ (<i>p</i> -cymene)] ₂	(1-Ad)CO ₂ H	1,4-dioxane	46% ^b
14	[RuCl ₂ (PPh ₃) ₃]	(1-Ad)CO ₂ H	PhMe	32% ^b
15	[RuCl ₂ (cod)] _n	(1-Ad)CO ₂ H	PhMe	<10% ^b

^a Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), [Ru] (5.0 mol %), L (30 mol %), K₂CO₃ (1.00 mmol), PhMe (2.0 mL), 100 °C, 20 h.

^b GC-conversion; HIMes = *N,N'*-bis-(2,4,6-trimethylphenyl)imidazolium, (S)HIPr = *N,N'*-bis-(2,6-di-*iso*-propylphenyl)imidazol(in)ium.

phosphines or N-heterocyclic carbene precursors¹⁹ did not enable the desired transformation (entries 1–5). However, when employing carboxylic acids²⁰ as additives, more satisfactory results were obtained (entries 6–11), with sterically demanding derivatives providing the highest yields (entries 8 and 11).

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(22) Preliminary experiments indicated that the formation of *N*-benzyl pyridinium salts was not of relevance for ruthenium-catalyzed direct benzylations of pyridine derivatives.

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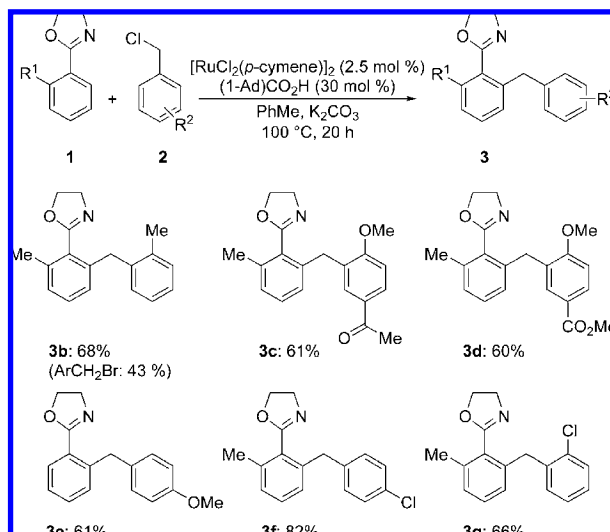
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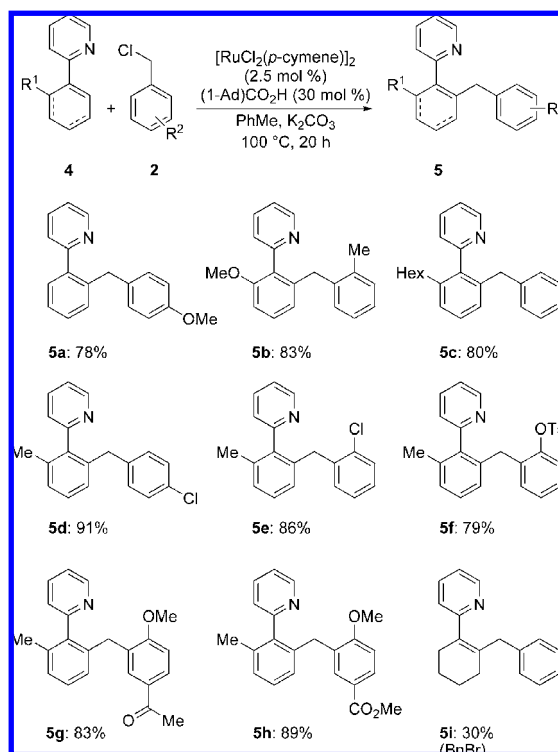
With an optimized catalytic system in hand, we explored its scope in the direct benzylation of arenes **1** under nonacidic reaction conditions (Scheme 1). Interestingly,

Scheme 1. Direct Benzylations of Oxazoline Derivatives **1**



benzyl chlorides **2** gave rise to more efficient catalysis than did the corresponding bromides, as illustrated with

Scheme 2. Direct Benzylations of Pyridine Derivatives **4**

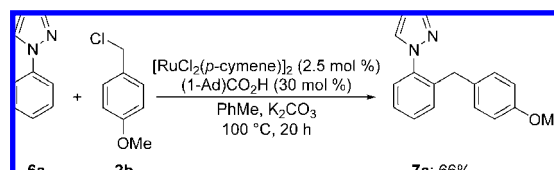


the synthesis of diarylmethane **3b**. Due to the mild reaction conditions, important functional groups, such as esters or enolizable ketones on the aromatic moieties of chlorides **2**, were well tolerated by the catalytic system. Furthermore, electrophiles displaying both benzyl and aryl chlorides were coupled chemoselectively at the former functionality, a valuable asset for further catalytic functionalization chemistry.

Direct benzylations through C–H bond cleavages were not restricted to oxazoline-substituted arenes **1**. Indeed, pyridine-substituted arenes or alkenes **4** were functionalized regioselectively, delivering diarylmethanes **5a–5h** and alkene **5i**, again with a useful functional group tolerance (Scheme 2).^{21,22}

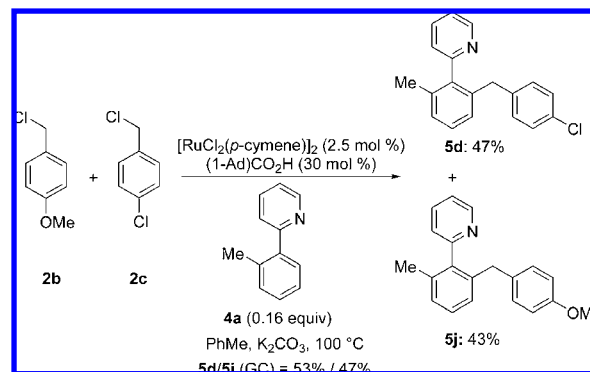
Likewise, the ruthenium complex derived from carboxylic acid $(1\text{-Ad})\text{CO}_2\text{H}$ allowed for a highly regioselective direct benzylation of pyrazolyl-substituted arene **6a** (Scheme 3).

Scheme 3. Direct Benzylation of Pyrazol Derivative **6a**



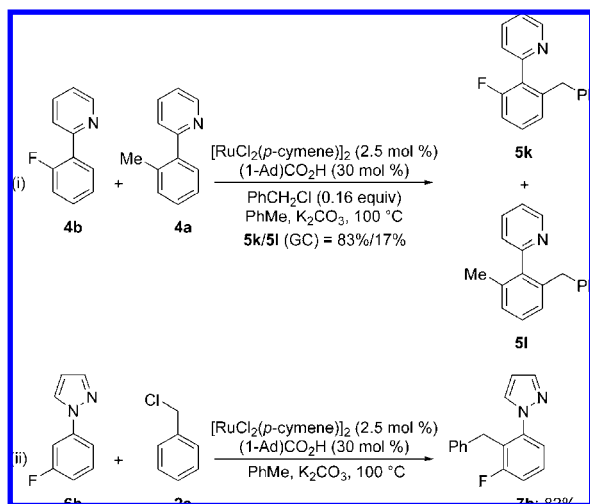
Despite the recent significant impact of ruthenium-catalyzed direct C–H bond functionalizations with aryl^{16b–i,20} or alkyl¹⁸ halides, experimental studies on their mechanism are very rare. To gain insight into the working mode of the present catalytic system, we conducted intermolecular competition experiments, which indicated a slight preference for more electron-deficient benzyl chloride **2c** (Scheme 4).

Scheme 4. Intermolecular Competition Experiment between Chlorides **2b** and **2c**



Moreover, inter- and intramolecular competition experiments between differently substituted arenes highlighted that (i) less nucleophilic pyridine derivative **4b** was benzylated preferentially²³ and that (ii) *meta*-fluoro-substituted arene **6b**

Scheme 5. Inter- and Intramolecular Competition Experiments between Substituted Arenes



was functionalized regioselectively at its more C–H acidic *ortho*-position (Scheme 5). On the basis of these experimental observations, a simple $\text{S}_{\text{E}}\text{Ar}$ -type mechanism seems less likely to be operative. On the contrary, the acidities of the C–H bonds to be functionalized appear to be of relevance, which is in good agreement with a concerted cyclometalation/deprotonation mechanism.

In conclusion, we have developed a broadly applicable ruthenium catalyst for highly regioselective direct benzylations of various arenes under remarkably mild, nonacid reaction conditions. Further, experimental mechanistic studies provided evidence for a non- $\text{S}_{\text{E}}\text{Ar}$ -type catalytic manifold.

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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