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

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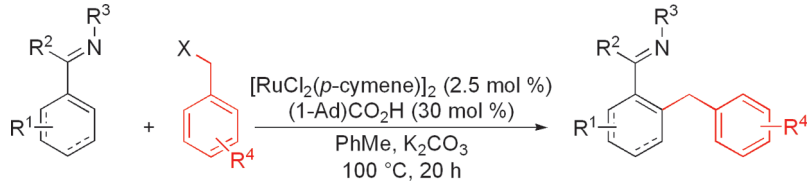
ABSTRACT



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-economical[6] strategy involves transition-metal-catalyzed cross-coupling reactions between organometallic reagents and benzyl ha-

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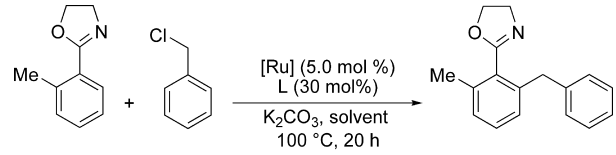
lides.[7−9] However, these two methodologies require the use of stoichiometric amounts of organometallic reagents, which are predominantly prepared through deprotonations with strong bases.

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 intermolecular[11] direct alkylations with aliphatic halides are scarce.[12] In this context, significant progress was very recently accomplished by Hoarau[13] 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 dirarylmethane syntheses, we consequently became interested in exploring unprecedented ruthenium-catalyzed direct benzylation reactions under nonacidic[4] 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	$[RuCl_2(p\text{-cymene})]_2$	---	PhMe	10%[b]
2	$[RuCl_2(p\text{-cymene})]_2$	PPh_3	PhMe	<5%[b]
3	$[RuCl_2(p\text{-cymene})]_2$	HIMesCl	PhMe	<5%[b]
4	$[RuCl_2(p\text{-cymene})]_2$	HIPrCl	PhMe	<5%[b]
5	$[RuCl_2(p\text{-cymene})]_2$	SHIPrCl	PhMe	<5%[b]
6	$[RuCl_2(p\text{-cymene})]_2$	KOAc	PhMe	<10%[b]
7	$[RuCl_2(p\text{-cymene})]_2$	$PhCO_2H$	PhMe	26%[b]
8	$[RuCl_2(p\text{-cymene})]_2$	$MesCO_2H$	PhMe	81%
9	$[RuCl_2(p\text{-cymene})]_2$	$i\text{-PrCO}_2H$	PhMe	60%
10	$[RuCl_2(p\text{-cymene})]_2$	$t\text{-BuCO}_2H$	PhMe	76%
11	$[RuCl_2(p\text{-cymene})]_2$	$(1\text{-Ad})CO_2H$	PhMe	81%
12	$[RuCl_2(p\text{-cymene})]_2$	$(1\text{-Ad})CO_2H$	NMP	<5%[b]
13	$[RuCl_2(p\text{-cymene})]_2$	$(1\text{-Ad})CO_2H$	1,4-dioxane	46%[b]
14	$[RuCl_2(PPh_3)_3]$	$(1\text{-Ad})CO_2H$	PhMe	32%[b]
15	$[RuCl_2(cod)]_n$	$(1\text{-Ad})CO_2H$	PhMe	<10%[b]

[a] Reaction conditions: **1a** (0.50 mmol), **2a** (0.75 mmol), [Ru] (5.0 mol %), L (30 mol %), K_2CO_3 (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 precursors[19] did not enable the desired transformation (entries 1−5). However, when employing carboxylic acids[20] 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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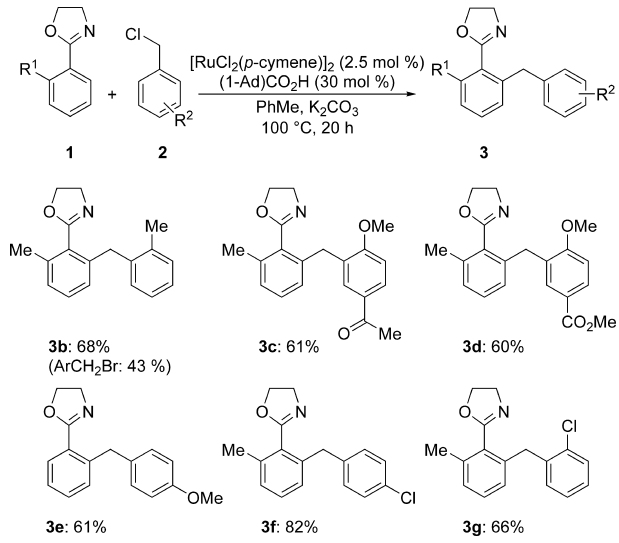
(21) Catalytic or (over-)stoichiometric amounts of typical Lewis acids, such as $FeCl_3$ or $AlCl_3$, did not provide benzylated products under otherwise identical reaction conditions.

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

(23) This product ratio could also be the result of a steric effect exerted by the *ortho*-methyl substituent in substrate **4a**.

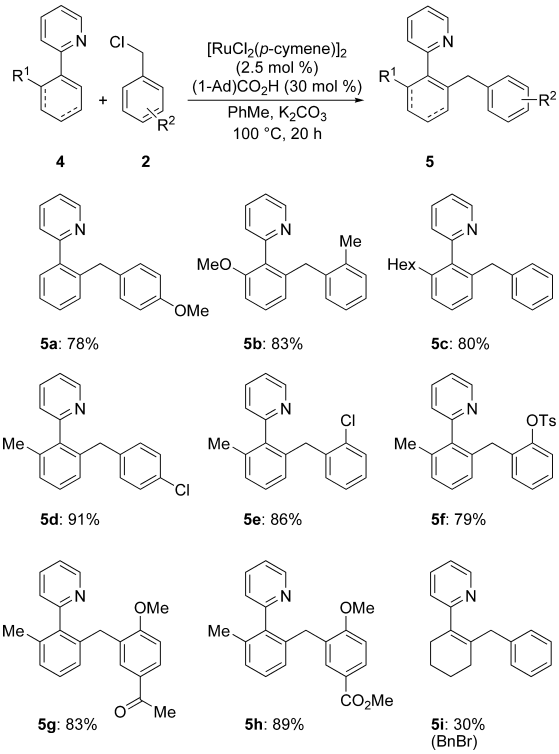
With an optimized catalytic system in hand, we explored its scope in the direct benzylation of arenes **1** under nonacidic reaction conditions (Scheme 1). Interestingly,

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**

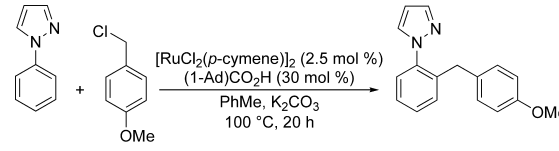


the synthesis of diarylmethane **3b**. Due to the mild reaction conditions, important functional groups, such as esters or enolizable ketones on the aromatic moieties of chlorides **2**, were well tolerated by the catalytic system. Furthermore, electrophiles displaying both benzyl and aryl chlorides 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 functionlized regioselectively, delivering diarylmethanes **5a**−**5h** and alkene **5i**, again with a useful functional group tolerance (Scheme 2).[21,22]

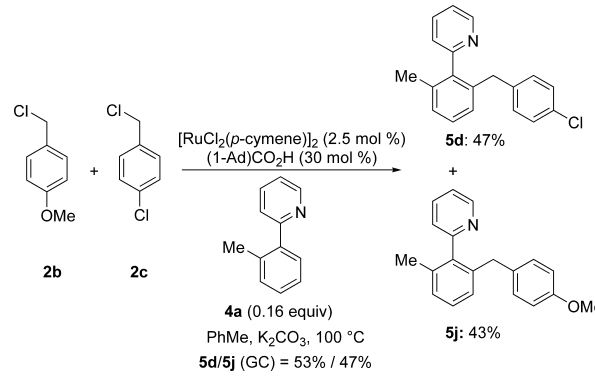
Likewise, the ruthenium complex derived from carboxylic acid (1-Ad)CO_2H allowed for a highly regioselective direct benzylation of pyrazolyl-substituted arene **6a** (Scheme 3).

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



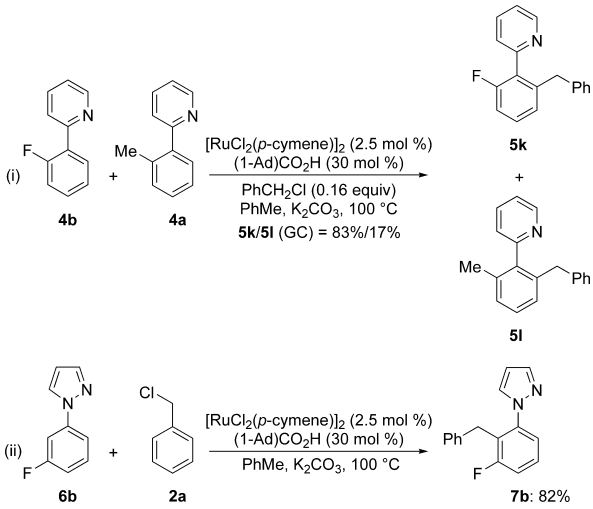
Despite the recent significant impact of ruthenium-catalyzed direct C−H bond functionalizations with aryl[16b−i,20] or alkyl[18] halides, experimental studies on their mechanism are very rare. To gain insight into the working mode of the present catalytic system, we conducted intermolecular competition 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 preferentially[23] 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 S_EAr-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-S_EAr-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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