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Carboxylate Assistance for Catalyzed Hydroarylations of Methylenecyclopropanes

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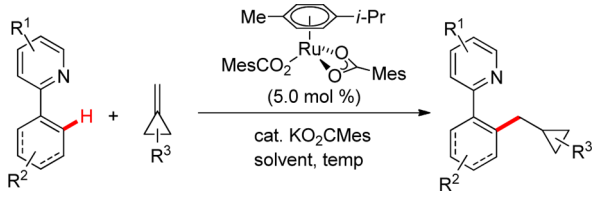
ABSTRACT



Carboxylate assistance enabled efficient and chemoselective ruthenium(II)-catalyzed hydroarylations and hydroalkenylations of highly strained methylenecyclopropanes via C−H bond activation occurring with ring conservation of the cyclopropane moieties.

The catalyzed functionalization of otherwise unreactive C−H bonds represents an environmentally benign tool for the formation of C−C bonds in a step-economical fashion.[1] Metal-catalyzed additions of arenes onto C−C multiple bonds—hydroarylation reactions[2]—are particularly attractive due to their perfect atom economy,[3] with notable progress being accomplished with versatile ruthenium[4] catalysts.[5] In this context, we recently reported on the significant rate acceleration caused by carboxylates[1a,6] in ruthenium-catalyzed hydroarylations with

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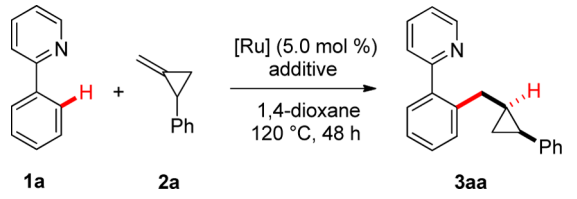
10.1021/ol402037f

Table 1. Optimization of Ruthenium-Catalyzed Hydroarylation[a]



1a 2a 3aa

entry	[Ru]	additive (amt (mol %))	yield (%)
1	–	X-Phos (10)	0
2	$[RuCl_2(cod)]_n$	X-Phos (10)	53
3	$[RuCl_2(cod)]_n$	KOAc (100)	55
4	$[RuCl_3(H_2O)_n]$	CsOAc (100)	60
5	$[RuCl_3(H_2O)_n]$	NaOAc (300)	62
6	**$[RuCl_3(H_2O)_n]$**	**KOAc (100)**	**76**
7	$[RuCl_3(H_2O)_n]$	KOAc (30)	57
8	$[RuCl_3(H_2O)_n]$	KO_2CMes (30)	66
9	$[RuCl_2(p\text{-cymene})]_2$	KO_2CMes (30)	66
10	$[Ru(MesCO_2)_2(p\text{-cymene})]$ (**4**)	–	79
11	$[Ru(MesCO_2)_2(p\text{-cymene})]$ (**4**)	KO_2CMes (10)	82
12	**$[Ru(MesCO_2)_2(p\text{-cymene})]$ (4)**	**KO_2CMes (20)**	**97**

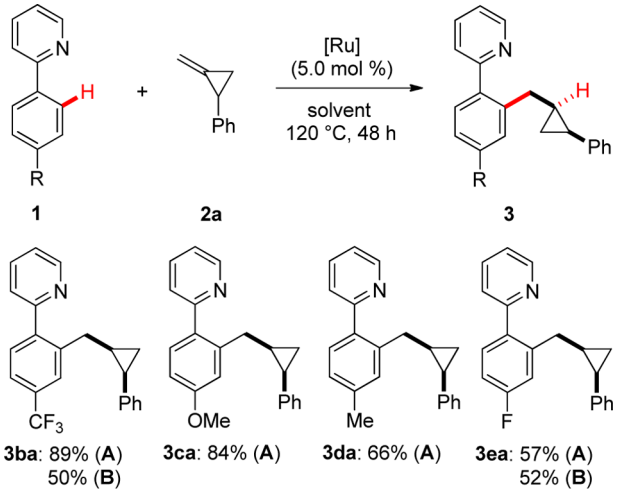
[a] Reaction conditions: **1a** (1.0 mmol), **2a** (3.0 mmol), [Ru] (5 mol %), 1,4-dioxane (3.0 mL), 120 °C, isolated yields. X-Phos = [dicyclohexyl(2′,4′,6′-triisopropylbiphenyl-2-yl)phosphine].

simple nonactivated alkenes.[7] In continuation of these studies, we observed that the efficacy and chemoselectivity of hydroarylations with highly strained methylenecyclopropanes (MCPs)[8−10] can be significantly improved through carboxylate-assisted ruthenium(II) catalysis, the results of which we present herein.

At the outset of our studies, we explored representative ruthenium precursors and additives in the hydroarylation of 2-phenylmethylenecyclopropane (**2a**) with 2-phenylpyridine (**1a**) in 1,4-dioxane at 120 °C (Table 1).

While no reaction occurred in the absence of a ruthenium catalyst (entry 1), the use of inexpensive KOAc in combination with $[RuCl_3(H_2O)_n]$ proved highly effective (entries 3−8) and outperformed the previously used $[RuCl_2(cod)]_n$/X-Phos catalytic system[9] (entry 2). However, the well-defined ruthenium complex $[Ru(MesCO_2)_2(p\text{-cymene})]$ (**4**)[11] was found to be optimal (entries 9 and 10), particularly in the presence of cocatalytic amounts of KO_2CMes (entries 11 and 12).

Scheme 1. Hydroarylations with Disubstituted Arenes **1**[a]

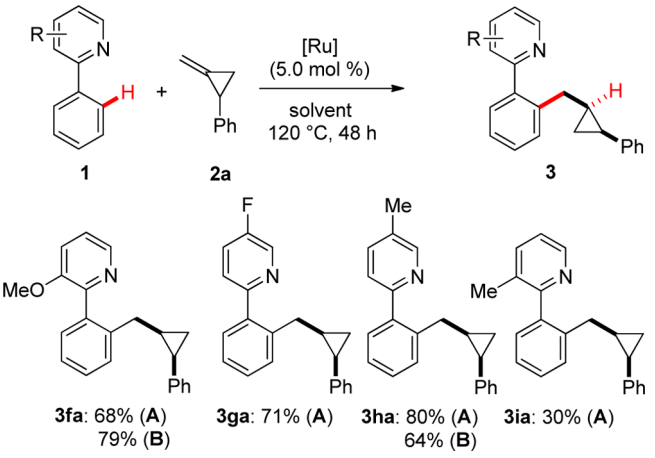


1 2a 3

3ba: 89% (**A**) 50% (**B**) **3ca**: 84% (**A**) **3da**: 66% (**A**) **3ea**: 57% (**A**) 52% (**B**)

[a] Reaction conditions: **1** (1.0−2.0 mmol), **2a** (3.0 equiv); (**A**) $[Ru(MesCO_2)_2(p\text{-cymene})]$ (**4**; 5.0 mol %)/KO_2CMes (20 mol %); (**B**) $[RuCl_3(H_2O)_n]$ (5.0 mol %)/KOAc (1 equiv); 1,4-dioxane or PhMe (3.0 mL), 120 °C, 48 h.

Scheme 2. Carboxylate-Assisted Hydroarylations with Disubstituted Pyridines[a]



1 2a 3

3fa: 68% (**A**) 79% (**B**) **3ga**: 71% (**A**) **3ha**: 80% (**A**) 64% (**B**) **3ia**: 30% (**A**)

[a] Reaction conditions: **1** (1.0−2.0 mmol), **2a** (3 equiv); (**A**) $[Ru(MesCO_2)_2(p\text{-cymene})]$ (**4**; 5.0 mol %)/KO_2CMes (20 mol %), (**B**) $[RuCl_3(H_2O)_n]$ (5.0 mol %)/KOAc (1 equiv); 1,4-dioxane or PhMe (3.0 mL), 120 °C, 48 h.

With two highly selective catalytic systems in hand, we studied their application to the hydroarylation of methylenecyclopropane **2a** through C−H bond activation using 2-phenylpyridine derivatives **1** substituted on the aryl moiety (Scheme 1). Notably, both catalytic systems delivered the ortho-alkylated arenes **3** in high yields and with excellent chemoselectivity.

Furthermore, 2-arylpyridines substituted at the heteroaromatic moiety were found to be viable substrates as

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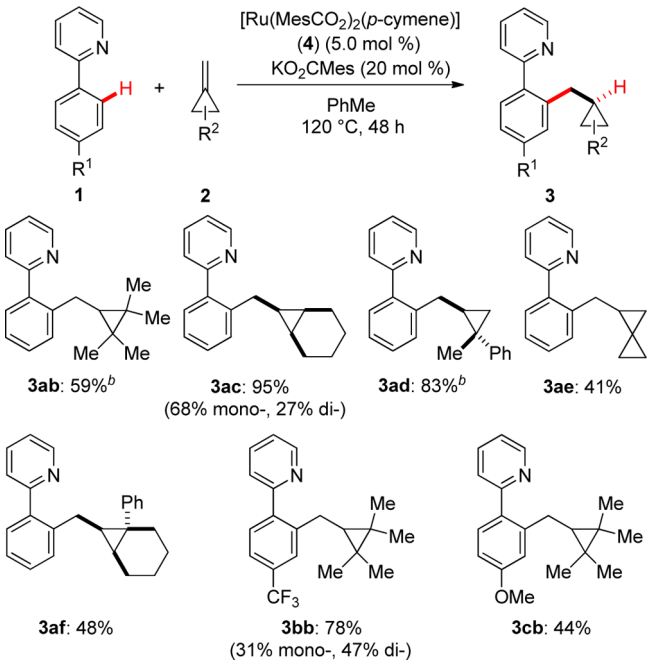
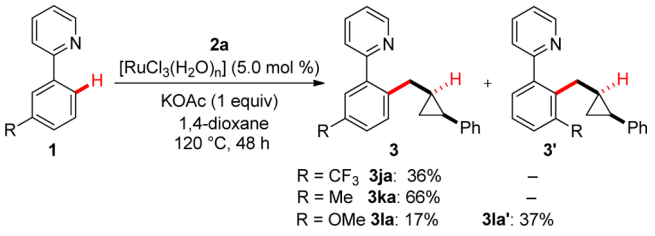
Scheme 3. Hydroarylations of Substituted Methylenecyclopropanes **2**[a]



[a] Reaction conditions: **1** (1.0–2.0 mmol), **2** (3.0 equiv), [Ru(MesCO$_2$)$_2$(*p*-cymene)] (**4**) (5.0 mol %)/KO$_2$CMes (20 mol %), PhMe (3.0 mL), 120 °C, 48 h; isolated yields. [b] Reaction in 1,4-dioxane.

Scheme 4. Hydroarylations with Meta-Substituted Arenes **1**



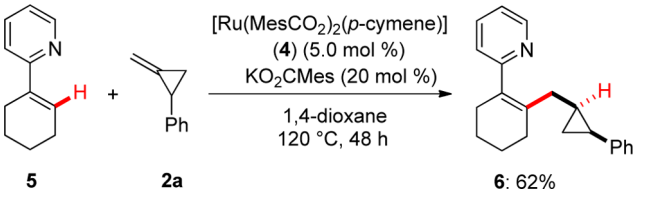
well, thereby delivering the desired products **3fa**–**3ha** (Scheme 2). The synthesis of product **3ia** proceeded less efficiently, likely due to the increased steric interactions exerted by the 3-methyl substituent.

The ruthenium catalyst [Ru(MesCO$_2$)$_2$(*p*-cymene)] (**4**) was not limited to substrates displaying the substituents on the phenylpyridines **1** (Schemes 1–3)[12] but was also found to be applicable to alkyl-substituted methylenecyclopropanes **2** as well as methylenespiropentane (**2e**) (Scheme 3). In these transformations, the anti-Markovnikov trans hydroarylation with retention of the cyclopropane moieties was significantly improved in comparison with the catalyst derived from [RuCl$_2$(cod)]$_n$/X-Phos, for which undesired ring-opening reactions were unfortunately observed.[9a]

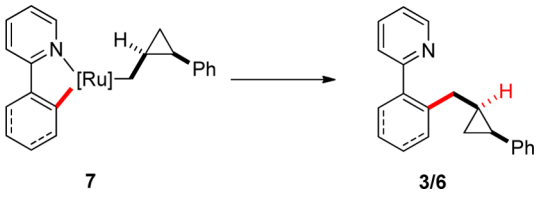
(12) Arenes bearing pyrazoles or imines as the directing groups gave less satisfactory results.

(13) For a recent notable C–H bond functionalization with MCPs partially occurring through ring opening, see: Cui, S.; Zhang, Y.; Wu, Q. *Chem. Sci.* **2013**, *4*, 3421–3426 and references cited therein.

Scheme 5. Hydroalkenylation with Alkene **5**



Scheme 6. Proposed Key Intermediate **7**



Experiments with meta-substituted arenes **1** generally led to preferential alkylation at the less hindered 6-position (Scheme 4). However, the C–H bond functionalization at substrate **1l** with a *m*-methoxy substituent furnished a mixture of the minor 6-substituted (**3la**) and the major 2-substituted (**3la′**) products. The predominant formation of the latter can be rationalized in terms of a secondary chelating effect exerted by the methoxy substituents.

The highly active catalyst **4** also enabled the difficult functionalization of the nonaromatic C(sp^2)–H bond in alkene **5** to yield the desired hydroalkenylation product **6** (Scheme 5).

As to the catalyst working mode, we propose that the carboxylate ligand improves the chemoselectivity of the ruthenium catalysts, thereby favoring the formation of desired products **3**/**6** from the key intermediate **7** (Scheme 6).

In summary, we have developed a novel protocol for challenging ruthenium-catalyzed hydroarylations and hydroalkenylations of highly strained methylenecyclopropanes **2** via C–H activation employing ruthenium carboxylates as the catalysts. Carboxylate assistance thus allowed for not only significantly more efficient transformations but also more selective anti-Markovnikov trans hydroarylations of substituted methylenecyclopropanes with retention of the cyclopropane moieties.[13]

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

The authors declare no competing financial interest.