

Carboxylate Assistance for Catalyzed Hydroarylations of Methylenecyclopropanes

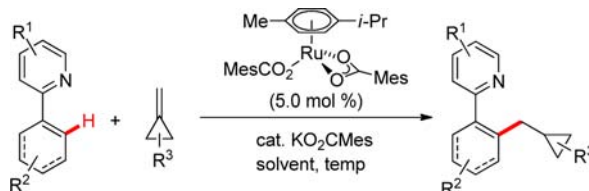
Marvin Schinkel,[†] Jan Wallbaum,[†] Sergei I. Kozhushkov,[†] Ilan Marek,[‡] and Lutz Ackermann^{*,†}

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität, Tammannstraße 2, 37077 Göttingen, Germany, and Schulich Faculty of Chemistry, Technion-Israel Institute of Technology, 32000 Haifa, Israel

Lutz.Ackermann@chemie.uni-goettingen.de

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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 reactions²—are particularly attractive due to their perfect atom economy,³ with notable progress being accomplished with versatile ruthenium⁴ catalysts.⁵ In this context, we recently reported on the significant rate acceleration caused by carboxylates^{1a,6} in ruthenium-catalyzed hydroarylations with

[†] Georg-August-Universität.

[‡] Technion-Israel Institute of Technology.

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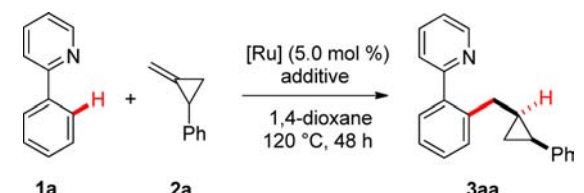
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Table 1. Optimization of Ruthenium-Catalyzed Hydroarylation^a



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 ₂ O)] _n	CsOAc (100)	60
5	[RuCl ₃ (H ₂ O)] _n	NaOAc (300)	62
6	[RuCl₃(H₂O)]_n	KOAc (100)	76
7	[RuCl ₃ (H ₂ O)] _n	KOAc (30)	57
8	[RuCl ₃ (H ₂ O)] _n	KO ₂ CMes (30)	66
9	[RuCl ₂ (<i>p</i> -cymene)] ₂	KO ₂ CMes (30)	66
10	[Ru(MesCO ₂) ₂ (<i>p</i> -cymene)] (4)	—	79
11	[Ru(MesCO ₂) ₂ (<i>p</i> -cymene)] (4)	KO ₂ CMes (10)	82
12	[Ru(MesCO₂)₂(<i>p</i>-cymene)] (4)	KO₂CMes (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).

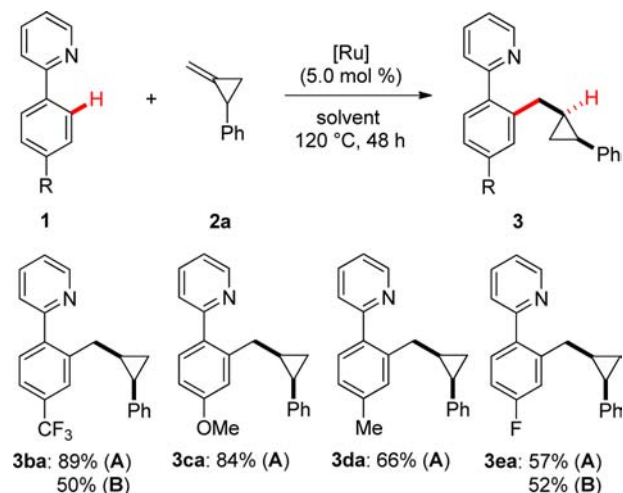
While no reaction occurred in the absence of a ruthenium catalyst (entry 1), the use of inexpensive KOAc in combination with [RuCl₃(H₂O)]_n proved highly effective (entries 3–8) and outperformed the previously used [RuCl₂(cod)]_n/X-Phos catalytic system⁹ (entry 2). However, the well-defined ruthenium complex [Ru(MesCO₂)₂(*p*-cymene)] (**4**)¹¹ was

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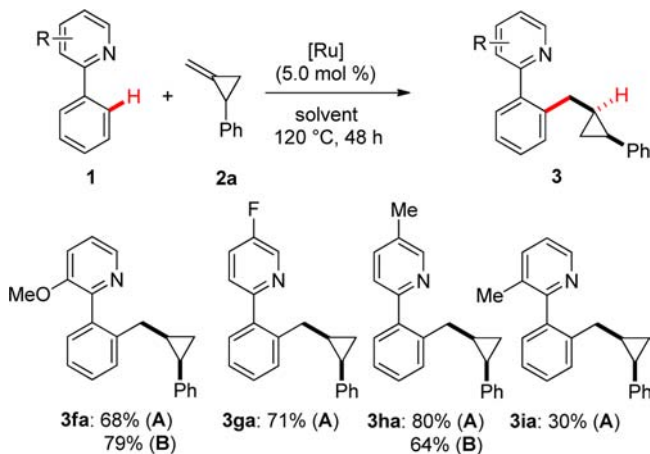
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Scheme 1. Hydroarylations with Disubstituted Arenes **1^a**



^a Reaction conditions: **1** (1.0–2.0 mmol), **2a** (3.0 equiv); (A) [Ru(MesCO₂)₂(*p*-cymene)] (**4**; 5.0 mol %)/KO₂CMes (20 mol %); (B) [RuCl₃(H₂O)]_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



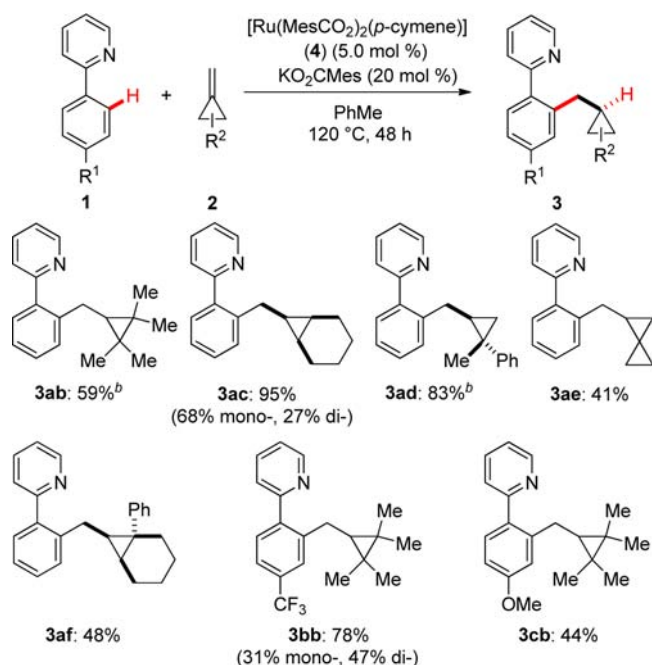
^a Reaction conditions: **1** (1.0–2.0 mmol), **2a** (3 equiv); (A) [Ru(MesCO₂)₂(*p*-cymene)] (**4**; 5.0 mol %)/KO₂CMes (20 mol %); (B) [RuCl₃(H₂O)]_n (5.0 mol %)/KOAc (1 equiv); 1,4-dioxane or PhMe (3.0 mL), 120 °C, 48 h.

found to be optimal (entries 9 and 10), particularly in the presence of cocatalytic amounts of KO₂CMes (entries 11 and 12).

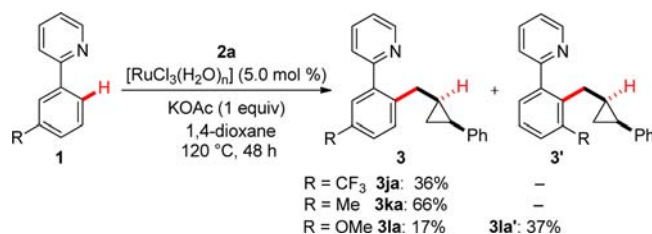
With two highly selective catalytic systems in hand, we studied their application to the hydroarylation of methylenecyclopropane **2a** through C–H bond activation using 2-phenylpyridine derivatives **1** substituted on the aryl moiety (Scheme 1). Notably, both catalytic systems delivered the ortho-alkylated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

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

Scheme 3. Hydroarylations of Substituted Methylenecyclopropanes **2**^a



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



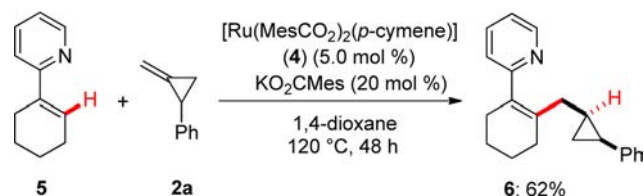
well, thereby delivering the desired products **3fa–3ha** (Scheme 2). The synthesis of product **3ia** proceeded less efficiently, likely due to the increased steric interactions exerted by the 3-methyl substituent.

The ruthenium catalyst [Ru(MesCO₂)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 [RuCl₂(cod)]_n/X-Phos, for which undesired ring-opening reactions were unfortunately observed.^{9a}

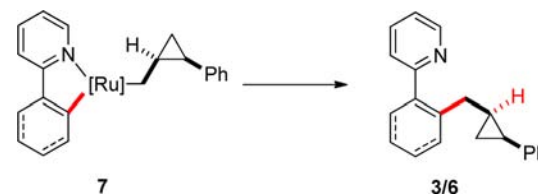
(12) Arenes bearing pyrazoles or imines as the directing groups gave less satisfactory results.

(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 **11** 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(sp²)–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 ¹H and ¹³C 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.