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Grignard-Type Arylation of Aldehydes *via* a Rhodium-Catalyzed C–H Activation under Mild Conditions

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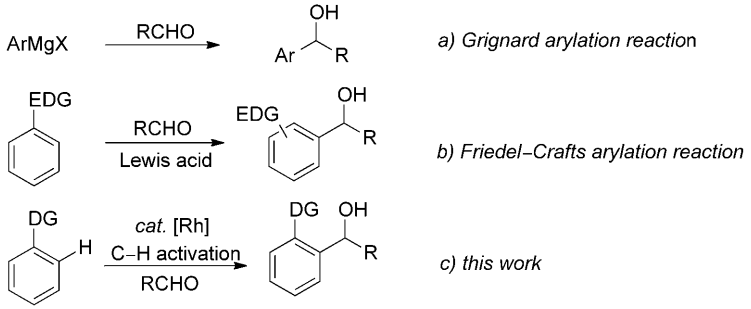
Abstract: An efficient Grignard-type arylation of aldehydes *via* aryl C–H activation was achieved under mild conditions catalyzed by rhodium. The reaction provides an easy access to a wide variety of benzyl alcohols and can tolerate various functional groups as well as air and water.

Keywords: aldehydes; arylation; C–H activation; Grignard-type reaction; rhodium catalysis

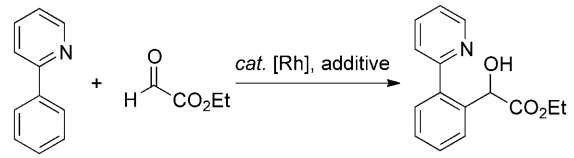
The Grignard-type nucleophilic addition of organometallic reagents to aldehydes (and ketones) represents one of the most important developments in the history of organic chemistry.[1] For Grignard-type arylations, it generally requires the pre-generation of an organometallic reagent such as arylmagnesium halide from stoichiometric aryl halides and magnesium (Scheme 1, route a). In addition, the use of anhydrous solvents, inert atmosphere, and protection of acidic functionalities such as hydroxy groups are essential.[2] To overcome the latter limitations, Grignard-type nucleophilic additions of arylmetal reagents to aldehydes in aqueous media[3] have been developed recently; however pre-formation of the organometallic reagents is still required.[4] Alternatively, arylation of aldehydes can be realized by the well known Friedel–Crafts reaction,[5] which is limited to highly electron-rich arenes and usually produces a mixture of regioisomers (Scheme 1, route b). The development of overall catalytic isomerization reactions is among the greatest challenges in future synthetic chemistry.[6] With the recent great advances in catalytic arene C–H activations,[7] we envisioned an alternative Grignard-type arylation of aldehdyes *via* the addition of an organometallic species, generated *in situ* from simple arenes *via* C–H activation (Scheme 1, route c). Herein we report an unprecedented Grignard-type arylation of aldehydes *via* a rhodium-catalyzed aryl C–H activation and subsequent nucleophilic addition under very mild reaction conditions. More importantly, the reaction can proceed efficiently in the presence of water, in air, and can tolerate acidic functional groups such as hydroxy groups without using protecting groups.

To begin our study, we first examined the reaction of 2-phenylpyridine (**1a**) and ethyl glyoxylate (**2a**) using rhodium catalysts based on our early work on related arylations with arylmetal reagents in air and water.[8] To our delight, the desired nucleophilic addition product **3a** was obtained in the presence of a catalytic amount of $(COD)_2RhBF_4$, albeit the yield was



Scheme 1. Various arylation reactions of aldehydes.

Table 1. Optimization of the reaction conditions.[a]



1a 2 3a

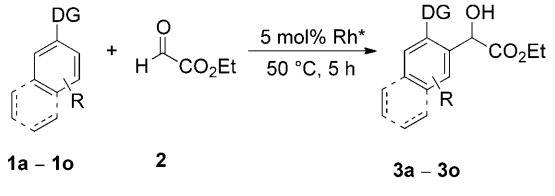
Entry	Rh (mol%)	Additive (mol%)	Solvent	Yield[b] [%]
1	$(COD)_2Rh(BF_4)$ (5)	–	CH_2Cl_2	5
2	$[Cp^*RhCl_2]_2$ (2.5)	–	CH_2Cl_2	0
3	$[Cp^*RhCl_2]_2$ (2.5)	AgOTf	CH_2Cl_2	84
4	$[Cp^*RhCl_2]_2$ (2.5)	$AgBF_4$	CH_2Cl_2	76
5	$[Cp^*RhCl_2]_2$ (2.5)	$AgPF_6$	CH_2Cl_2	94
6	$[Cp^*RhCl_2]_2$ (2.5)	$AgSbF_6$	CH_2Cl_2	95
7	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	CH_2Cl_2	98[c]
8	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	$CHCl_3$	96
9	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	DCE	94
10	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	THF	84
11	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	*t*-BuOH	66
12	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	toluene	33
13	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	CH_3CN	17
14	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	CH_2Cl_2	96[d]
15	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	–	CH_2Cl_2	96[e]
16	$(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5)	H_2O (20 μL)	CH_2Cl_2	95[f]

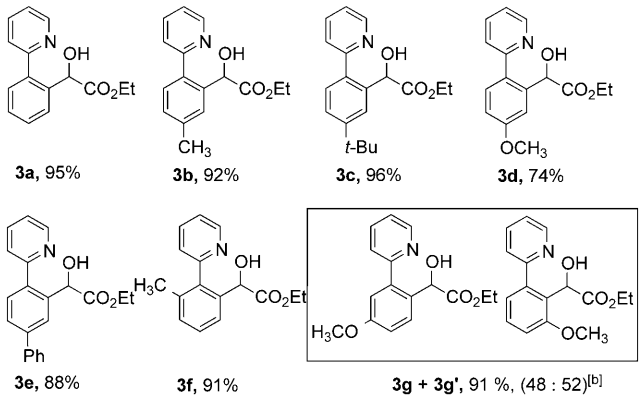
[a] *Conditions:* **1a** (0.1 mmol), **2** (0.15 mmol), [Rh], additive (10 mol%), solvent (1 mL), reacted at 50 °C for 12 h under argon, unless otherwise noted.
[b] Determined by ^1H NMR analysis of the crude reaction mixture using an internal standard.
[c] Reaction completed in 1 h.
[d] 40 °C, 5 h.
[e] Room temperature, 24 h.
[f] 50 °C, 24 h under air.

rather low (Table 1, entry 1). During our study, Bergman[9] and Shi[10] independently reported the rhodium-catalyzed nucleophilic addition of phenylpyridine to Boc- and Ts-aldimine derivatives, respectively. Similar to these studies, the use of $[Cp^*RhCl_2]_2$ as a catalyst did not generate any aldehyde-addition product (entry 2), which can be attributed to the reduced Lewis acidity caused by the strong σ bonding between rhodium and chlorine in $[Cp^*RhCl_2]_2$. To increase its Lewis acidity, different silver salts were tested as the chloride abstractor (entries 3–6). The yield increased dramatically from 5% to 84% on addition of AgOTf. While $AgBF_4$ and $AgPF_6$ were also effective, $AgSbF_6$ was found to be the best one and the NMR yield of the nucleophilic addition product **3a** increased to 95%. These positive results further prompted us to use the pre-purified $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (Rh*; Cp* = pentamethylcyclopentadienyl) as the catalyst directly, leading to near quantitative formation of product **3a** (entry 7). This C–H activation and nucleophilic addition process can be performed not only in lower polarity solvent such as CH_2Cl_2, $CHCl_3$ and DCE, but also in much more polar THF and *tert*-butyl alcohol (entries 8–13). The yield dropped on using toluene as the solvent due to the low solubility of the Rh-catalyst in toluene. Acetonitrile was not a good solvent for the reaction, possibly due to coordination of the nitrile group to the rhodium catalyst, lowering its Lewis acidity. It is worth noting that this reaction can also be performed at 40 °C or even at room temperature with comparable yields after a longer reaction time (entries 14 and 15). Furthermore, this reaction was not sensitive to either water or O_2, and a similar yield was obtained when the reaction was performed in the presence of water and under air atmosphere (entry 16).

Under the optimized conditions, the substrate scope of this novel Grignard-type arylation of ethyl glyoxylate (**2**) *via* C–H activation was explored. As shown by the results in Table 2, all the 2-phenylpyridine analogues tested (**1a**–**1i**) reacted with ethyl glyoxylate (**2**) smoothly to produce the corresponding alcohols efficiently, regardless whether the phenyl group was substituted by electron-withdrawing or electron-donating groups. The influence of substituents at different positions of the phenyl ring was also examined. The *ortho*-methyl substrate **1f** reacted with ethyl glyoxylate in high yield and the *meta*-methoxy sub-

Table 2. The reaction of 2-phenylpyridine analogues with ethyl glyoxylate.[a]





[a] *Conditions:* **1a** (0.2 mmol), **2** (0.3 mmol), $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5 mol%, 0.01 mmol), CH_2Cl_2 (2 mL), reacted at 50 °C for 5 h under argon, unless otherwise noted. The yield of isolated product is reported.

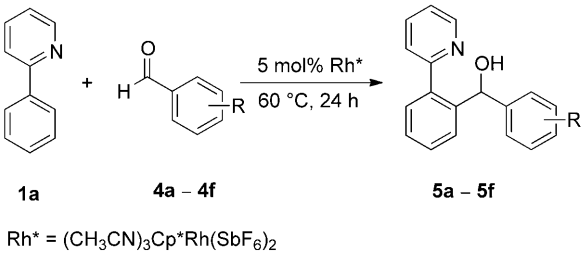
[b] Determined by ^1H NMR analysis of the crude reaction mixture.

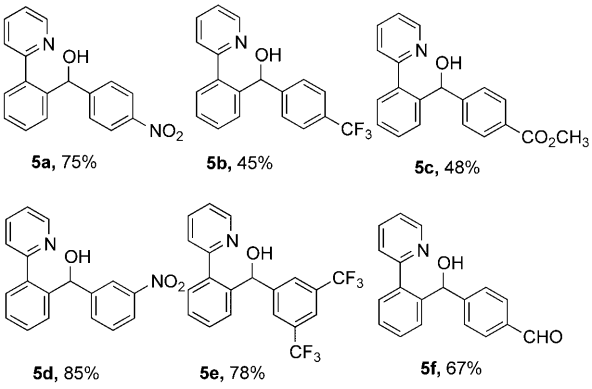
[c] Reacted at 50 °C for 48 h.

strate **1g** gave two regioisomers with a ratio of 48:52 in 91% total yield. 2-β-Naphthylpyridine **1j** was also applicable to this reaction and only one nucleophilic addition product was obtained. Pyridinyl directing group with a methyl substituent at C-6 **1k** also showed good reactivity, resulting in a 93% yield of **3k**. Other nitrogen-containing heterocyclic substituents such as quinolinyl, pyrimidinyl, pyrazolyl and oxazolyl can also act as the directing group, and the corresponding arylation products **3l–3o** were obtained in moderate to high yields.

Encouraged by the high yields between the reaction of 2-phenylpyridine analogues and ethyl glyoxylate, the application of this novel reaction to other aldehydes was investigated. However, under the optimized reaction condtions (5 mol% Rh*, 50 °C, 5 h in CH_2Cl_2), 2-phenylpyridine (**1a**) was not reactive towards the unsubstituted benzaldehyde. Compared to ethyl glyoxylate, benzaldehyde is much less nucleophilic, therefore aromatic aldehydes with electron-withdrawing groups were tested next (Table 3). To our delight, the reaction of 4-nitrobenzaldehyde (**4a**) and 2-phenylpyridine produced **5a** in 75% yield. 4-Trifluoromethylbenzaldehyde (**4b**) and 4-methoxycarbonylbenzaldehyde (**4c**) were also applicable, albeit resulting in lower yields. Other electron-deficient aromatic aldehydes such as 3-nitrobenzaldehyde (**4d**) and 3,5-bis(trifluoromethyl)benzaldehyde (**4e**) reacted with 2-phenylpyridine (**1a**) smoothly and good yields were obtained in both cases. Interestingly, when terephthalaldehyde (**4f**) was used, only one aldehyde functional group took part in this reaction and the other remained intact, which renders the product for further functionalizations readily.

Table 3. The reaction of 2-phenylpyridine and aromatic aldehydes.[a]

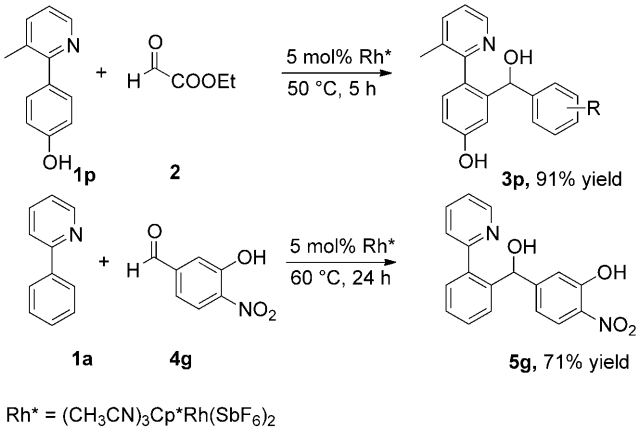




[a] *Conditions:* **1a** (0.2 mmol), **4** (0.4 mmol), $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (5 mol%, 0.01 mmol), CH_2Cl_2 (0.4 mL), reacted at 60 °C for 24 h under argon, unless otherwise noted. The yield of isolated product is reported.

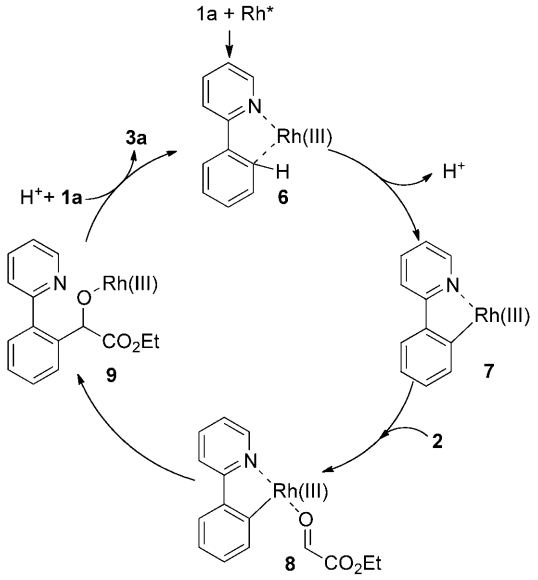
To further demonstrate the potential applications of this reaction, more challenging substrates containing unprotected hydroxy groups were examined (Scheme 2). The 2-phenylpyridine analogue **1p** bearing a free hydroxy group reacted with ethyl glyoxylate (**2**) to afford **3p** in 91% yield. Likewise, 2-phenylpyridine (**1a**) reacted with 3-hydroxy-4-nitrobenzaldehyde to produce **5g** in 71% yield.

A tentative mechanism to rationalize this novel rhodium-catalyzed Grignard-type aldehyde-arylation reaction *via* C–H activation is illustrated in Scheme 3. First, the coordination of rhodium catalyst (Rh*) to 2-phenylpyridine and subsequent electrophilic substitution generates the arylrhodium complex **7**, releasing one equivalent of proton at the same time. Then, the carbonyl group of the aldehyde coordinates to the arylrhodium complex **7** to produce arylrhodium complex **8**, which is followed by the nucleophilic addition of the aryl species to the activated carbonyl group to yield the rhodium alkoxide **9**. Protonation of **9** releases the nucleophilic addition product and regenerates of the rhodium catalyst (Rh*).



Rh* = $(CH_3CN)_3Cp^*Rh(SbF_6)_2$

Scheme 2. The arylation of aldehydes bearing unprotected hydroxy groups.



Scheme 3. Tentative mechanism for the Grignard-type aldehyde arylation *via* rhodium-catalyzed C–H activation.

In summary, we have developed an efficient Grignard-type arylation of aldehyde *via* a rhodium-catalyzed aryl C–H activation and subsequent nucleophilic addition under mild conditions. Unlike the classical Grignard-type reaction, the current reaction does not require the pre-generation of a stoichiometric quantity of organometallic reagents and can tolerate a wide range of functional groups such as esters, halide, nitro, and an additional aldehyde. Compounds bearing free hydroxy groups can be used directly in high yields without any protecting groups. Furthermore, the reaction can occur efficiently in the presence of water and under an air atmosphere. The scope, mechanism, and application of this novel reaction are under investigation.

Experimental Section

General Experimental Procedure

An oven-dried reaction vessel was charged with $(CH_3CN)_3Cp^*Rh(SbF_6)_2$ (Rh*, 8.4 mg, 5 mol%, 0.01 mmol), CH_2Cl_2 (2 mL), 2-phenylpyridine (**1a**, 31 mg, 0.2 mmol) and ethyl glyoxylate (**2**, 60 μL, 0.3 mmol, 50% solution in toluene) under argon. The vessel was sealed and heated at 50 °C (oil bath temperature) for 5 h. The resulting mixture was cooled to room temperature, filtered through a short silica gel pad and transferred to silica gel column directly and eluted with hexanes and ethyl acetate (1:1) to give product **3a**; yield: 49 mg (95%).

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References

[1] a) V. Grignard, *C. R. Acad. Sci.* **1900**, *130*, 1322–1324; b) M. S. Kharasch, O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*; Prentice-Hall: New York, **1954**.

[2] B. J. Wakefield, *Organomagnesium Methods*, in: *Organic Synthesis Best Synthetic Methods Series*, (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Academic Press, San Diego, **1995**.

[3] a) T.-H. Chan, L. Li, Y. Yang, W. Lu, *Clean Solvents, Alternative Media for Chemical Reactions and Processing*, (Eds.: M. A. Abraham, L. Moens), ACS Symposi-

um Series 819, Washington, **2002**, p 166; b) C.-J. Li, T.-H. Chan, *Comprehensive Organic Reactions in Aqueous Media*, Wiley & Sons, New York, **2007**; c) C.-J. Li, *Chen. Rev.* **2005**, *105*, 3095–3165.

[4] a) L. Leseurre, J.-P. Genêt, V. Michelet, in: *Green Solvents, Handbook of Green Chemistry*, (Eds.: P. T. Anastas, C.-J. Li), Wiley-VCH, Weinheim, **2010**; b) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169–196; c) T.-H. Chan, C.-J. Li, Z.-Y. Wei, *J. Chem. Soc. Chem. Commun.* **1990**, 505–506.

[5] a) R. C. Fuson, H. H. Weinstock, G. E. Ullyot, *J. Am. Chem. Soc.* **1935**, *57*, 1803–1804; b) T. B. Poulsen, K. A. Jorgensen, *Chem. Rev.* **2008**, *108*, 2903–2915; c) R. M. Roberts, A. A. Khalaf, *Friedel–Crafts Alkylation Chemistry. A Century of Discovery*, Marcel Dekker, New York, **1984**.

[6] B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[7] For representative reviews, see: a) F. Pogan, P. H. Dixneuf, *Adv. Synth. Catal.* **2009**, *351*, 1737–1743; b) T. Naota, H. Takaya, S. I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599–2660; c) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; d) C. Jia, T. Kitamura, Y. Fujiwara, *Acc. Chem. Res.* **2001**, *34*, 633–639; e) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1770; f) R. H. Crabtree, *J. Organomet. Chem.* **2004**, *689*, 4083–4091; g) K. Godula, D. Sames, *Science* **2006**, *312*, 67–72; h) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147–1169; i) E. M. Beccalli, G. Broggini, M. Martinelli, S. Sottocornola, *Chem. Rev.* **2007**, *107*, 5318–5365; j) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; k) J. C. Lewis, R. G. Bergman, J. A. Ellman, *Acc. Chem. Res.* **2008**, *41*, 1013–1025; l) B.-J. Li, S. Yang, Z.-J. Shi. *Synlett* **2008**, 949–957; m) M. M. Diaz-Requejo, P. J. Pérez, *Chem. Rev.* **2008**, *108*, 3379–3394; n) X. Chen, K. M. Engle, D. H. Wang, J. Q. Yu, *Angew. Chem.* **2009**, *121*, 5196–5217; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; o) C. Copéret, *Chem. Rev.* **2010**, *110*, 656–680; p) I. Mkhalid, J. Barnard, T. Marder, J. Murphy, J. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931; q) A. E. Shilov, G. B. Shul′pin, *Chem. Rev.* **1997**, *97*, 2879–2932; r) F. Kakiuchi, S. Murai, *Acc. Chem. Res.* **2002**, *35*, 826–834; s) *Activation and Functionalization of C–H Bonds*, (Eds.: K. I. Goldberg, A. S. Goldman), ACS Symposium Series 885, Washington, DC, **2004**.

[8] a) C.-J. Li, *Acc. Chem. Res.* **2002**, *35*, 533–538; b) C.-J. Li, Y. Meng, *J. Am. Chem. Soc.* **2000**, *122*, 9538–9539.

[9] A. S. Tsai, M. E. Tauchert, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2011**, *133*, 1248–1250.

[10] Y. Li, W.-H. Wang, W.-P. Huang, X.-S. Zhang, K. Chen, Z.-J. Shi, *Angew. Chem.* **2011**, *123*, 2163–2167; *Angew. Chem. Int. Ed.* **2011**, *50*, 2115–2119.

[11] For an excellent review on rhodium-catalyzd C–H activation, see: J. Bouffard, K. Itami, *Top. Curr. Chem.* **2010**, *292*, 231–280.

