



A RhCl(PPh₃)₃/BF₃·OEt₂ co-promoted direct C–C cross-coupling of alcohols at β-position with aldehydes

Shu-Yu Zhang, Yong-Qiang Tu*, Chun-An Fan, Ming Yang, Fu-Min Zhang*

State Key Laboratory of Applied Organic Chemistry and Department of Chemistry, Lanzhou University, Lanzhou 730000, PR China

ARTICLE INFO

Article history:

Received 24 March 2009

Revised 28 April 2009

Accepted 5 May 2009

Available online 8 May 2009

Keywords:

C–C coupling

C–H functionalization

Rhodium(I) catalyst

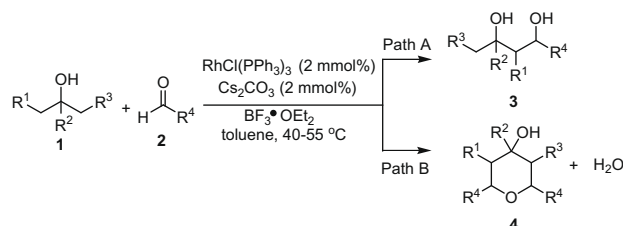
α,β-Unsaturated carbonyl compound

ABSTRACT

A novel RhCl(PPh₃)₃/BF₃·OEt₂ co-promoted direct C–C cross-coupling of primary and secondary alcohols at β-position with aldehyde was developed. This reaction could provide an efficient synthesis of a series of α,β-unsaturated aldehydes and diarylidene ketones, just from simple and easily available alcohols and aldehydes.

© 2009 Elsevier Ltd. All rights reserved.

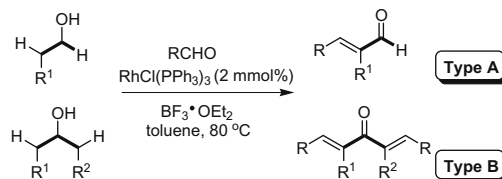
C–C bond formation via C–H bond functionalization is important and fundamental to all of organic chemistry, in which the direct C–C cross-coupling of alcohols with unsaturated substrates (olefins, aldehydes, or ketones)¹ has recently become one of the most attractive methodologies since it not only constructs new C–C bond and introduces a oxygenating functional, but also displays atom economy and environmentally benign characters.² In connection with our research interest in this subject,³ our previous effort had led to a discovery that the combination of transition metal catalyst/Lewis acid system could accomplish the direct C–C cross-coupling of C=C of olefins with primary alcohols at α-position via sp³ C–H activation, and most recently we reported that a novel C–C cross-coupling of tertiary alcohols at β-position with the C=O of aldehydes could be realized through the co-promotion of RhCl(PPh₃)₃/BF₃·OEt₂ system (Scheme 1).⁴ It was noteworthy



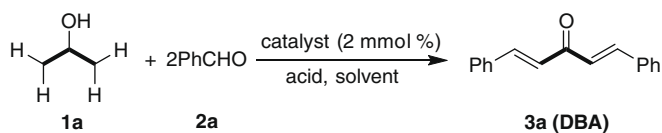
Scheme 1. Cross-coupling of tertiary alcohols with aldehydes.

* Corresponding authors. Tel.: +86 931 8912293; fax: +86 931 8915557 (Y.-Q. Tu).
E-mail addresses: tuyq@lzu.edu.cn (Y.-Q. Tu), zhangfm@lzu.edu.cn (F.-M. Zhang).

that this reaction could be selectively achieved, by tuning the substrate structure of alcohols, and afforded either the structurally diverse 1,3-diols or polysubstituted tetrahydropyranes (THPs). This achievement encouraged us to make a more extensive study toward the primary and secondary alcohols. Gratifyingly, under the co-promotion of RhCl(PPh₃)₃/BF₃·OEt₂ without additive, a novel C–C cross-coupling of primary and secondary alcohols at β-position with the C=O of aldehyde could be realized (Scheme 2). Depending on the property starting alcohols, this reaction could selectively provide a series of structurally diverse α,β-unsaturated aldehydes (Type A) and diarylidene ketones (Type B). This transformation paves a way to develop a new synthetic method for the cinnamaldehyde-type compounds, commencing with simple, cheap, and easily available material. These products (e.g., cinnamaldehyde and its derivatives, DBA) are important starting materials and/or key intermediates for chemical, perfume, agrochemical, liquid crystal as well as for pharmaceutical industries. To the best of our knowledge, this kind of Rh-catalyzed/Lewis acid-mediated C–C cross-coupling reaction between primary and secondary



Scheme 2. Cross-coupling of 1° and 2° alcohols with aldehydes.

Table 1
Optimization of reaction conditions^a

Entry	Complex	Solvent	Lewis acid	Yield ^b (%)
1	RhCl(PPh ₃) ₃	THF	BF ₃ ·OEt ₂	—
2	RhCl(PPh ₃) ₃	(CH ₂ Cl) ₂	BF ₃ ·OEt ₂	52
3	RhCl(PPh ₃) ₃	Toluene	BF ₃ ·OEt ₂	88
4	RhCl(PPh ₃) ₃	CH ₃ CN	BF ₃ ·OEt ₂	—
5	Rh(CO)(PPh ₃) ₂	Toluene	BF ₃ ·OEt ₂	72
6	IrCl ₃	Toluene	BF ₃ ·OEt ₂	—
7	RuCl ₃	Toluene	BF ₃ ·OEt ₂	—
8	RuCl ₂ (PPh ₃) ₂	Toluene	BF ₃ ·OEt ₂	62
9	AuCl ₃	Toluene	BF ₃ ·OEt ₂	—
10	PtCl ₂	Toluene	BF ₃ ·OEt ₂	—
11	Pd(OAc) ₂	Toluene	BF ₃ ·OEt ₂	45
12	RhCl(PPh ₃) ₃	Toluene	HgCl ₂	—

^a Reaction condition: Aldehyde (1 mmol) was reacted with alcohol (2.5 mmol) in the presence of metal catalyst (0.02 mmol) and Lewis acid (1.2 mmol) at 60–80 °C for 8–12 h.

^b Isolated yield based on aldehyde used.

alcohols with aldehydes has not been reported before. Herein, we present our preliminary experiment results.

Our initial investigation focused on a wide search for the coupling conditions (Table 1). Thus *i*-PrOH was subjected to the model reaction with PhCHO using the combination of transition metal catalyst and Lewis acid in appropriate solvent. Among the conditions tested, gratifyingly, the combination of RhCl(PPh₃)₃ (2 mmol %) and BF₃·OEt₂ in toluene (entry 3) proved to be the best result for this coupling reaction, which provided the desired product **3a** in 88% yield.


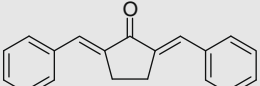

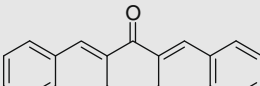

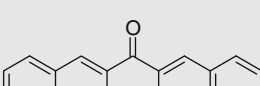

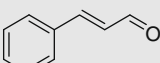

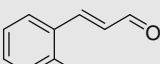

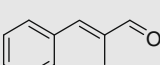
Following the above optimized condition, a series of primary and secondary alcohols and aldehydes were further investigated. As shown in Table 2, the C–C coupling of various alcohols at β-position with aldehydes proceeded smoothly, and a range of structurally diverse and important α,β-unsaturated carbonyl compounds, such as cinnamaldehyde **3k**, dibenzylideneacetone **3a** (DBA), could be straightforward and rapidly prepared. In particular for secondary alcohols (entries 1–9), reactions (Type B) gave the dibenzylideneacetone and its analogues **3b–j** via a double cross-coupling assembly in good yields. Notably, if the reaction was intermitted after 8 h, a much higher yield could be obtained. For example, in entry 1, a 98% brsm yield with 63% conversion could be received. For primary alcohols (entries 10–12), the products **3k–m** were exclusively

Table 2
Cross-coupling of 1° and 2° alcohols with aldehydes^a

Entry	Substrates	Products	Yield ^b (%)
1	1a + 2b	3b	76
2	1b + 2a	3c	82
3	1b + 2c	3d	83
4	1b + 2d	3e	78
5	1b + 2e	3f	91
6	1b + 2f	3g	87

(continued on next page)

Table 2 (continued)

Entry	Substrates	Products	Yield ^b (%)
7	 1c	 3h	74
8	 1d	 3i	81
9	 1e	 3j	65
10	 1f	 3k	38 (78) ^c
11	 1f	 3l	34 (82) ^c
12	 1g	 3m	36 (90) ^c

^a All products were characterized by NMR and mass spectrometry.

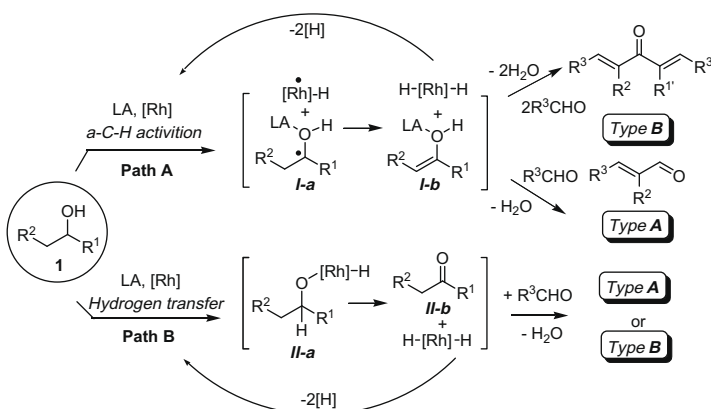
^b Isolated yield based on the aldehyde 2 used.

^c Yield based on recovered starting material.

obtained after 18 h in 78–90% yield based on the smooth recovery of starting aldehydes.⁹

The reaction mechanism could be explained on the basis of our previous reports (**Path A**)³ or the reported 'Hydrogen Autotransfer Process' under base (**Path B**)^{1c,5,6} in the following two sequences

(Scheme 3). In path A, Lewis acid-mediated/Rh-catalyzed α -C-H bond activation of alcohol may be firstly involved in this coupling, yielding the radical species **I-a**. Compared with our previous report,³ the presence of aldehyde instead of olefin in current system allowed the generation of enol **I-b** and rhodium dihydride complex



Scheme 3. Possible pathways for cross-coupling of alcohols at β -position with aldehydes.

H–[Rh]–H followed by β -H elimination in **I-a**,⁷ since aldehyde is much less reactive toward the radical addition of **I-a** than olefin. Then aldol condensation gave the product of Type A ($R^1 = H$), or double aldol processes of **I-b** accomplished Type B reaction ($R^1 = \text{alkyl}$). In path B, the [Rh] oxidation of the alcohols gave the corresponding aldehyde **II-b** and metal dihydride intermediate,⁸ and followed by an aldol condensation to give the α,β -unsaturated aldehydes, or a double aldol condensation to yield the diarylidene ketone compounds. No reduction products could be received in our experimental. Further synthetic application of these reactions is currently continued in our group.

Acknowledgments

We thank the financial support of NSFC (Nos. 20621091, 20672048 and 20732002) and the '111' Program of Chinese Education Ministry.

References and notes

- For recent reviews, see: (a) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731–1770; (b) Jun, C. H.; Moon, C. W.; Lee, D. Y. *Chem. Eur. J.* **2002**, *8*, 2422–2428; (c) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358–2364; (d) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222–234; (e) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34–46.
- (a) Trost, B. M. *Science* **1991**, *254*, 1471–1477; (b) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246; (c) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705.
- (a) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A.; Zhao, Y.-M.; Xia, W.-J. *J. Am. Chem. Soc.* **2005**, *127*, 10836–10837; (b) Jiang, Y.-J.; Tu, Y.-Q.; Zhang, E.; Zhang, S.-Y.; Cao, K.; Shi, L. *Adv. Synth. Catal.* **2008**, *350*, 552–556; (c) Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Shi, L.; Cao, K.; Zhang, E. *Chem. Eur. J.* **2008**, *14*, 10201–10205.
- Zhang, S.-Y.; Tu, Y.-Q.; Fan, C.-A.; Jiang, Y.-J.; Shi, L.; Cao, K. *Adv. Synth. Catal.* **2008**, *350*, 2189–2193.
- For recent selected examples of transition metal-catalyzed C–C cross-coupling between ketones and alcohols under base conditions, see: (a) Cho, C. S.; Kim, B. T.; Lee, M. J.; Kim, T.-J.; Shim, S. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 958–960; (b) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66*, 9020–9022; (c) Nishibayashi, Y.; Wakiji, I.; Ishii, Y.; Uemura, S.; Hidai, M. *J. Am. Chem. Soc.* **2001**, *123*, 3393–3394; (d) Edwards, M. G.; Williams, J. M. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4740–4743; (e) Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126*, 72–73; (f) Edwards, M. G.; Jazzar, R. F. R.; Panie, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, D. D. *Chem. Commun.* **2004**, 90–91; (g) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedra, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913–6915; (h) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3819–3822; (i) Yamada, Y. M. A.; Uozumi, Y. *Org. Lett.* **2006**, *8*, 1375–1378; (j) Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2006**, 4367–4378; (k) Yamada, Y. M. A.; Uozumi, Y. *Tetrahedron* **2007**, *63*, 8492–8498; (l) Mierde, H. V.; Voort, P. V. D.; Vos, D. D.; Verpoort, F. *Eur. J. Org. Chem.* **2008**, *9*, 1625–1631.
- A LiClO₄-amine mediated direct aldol process between ketones and alcohols by contemporary aldol-Tishchenko methodologies, see: Markert, M.; Mahrwald, R. *Synthesis* **2004**, 1429–1433.
- Branchaud, B. P.; Choi, Y. L. *Tetrahedron Lett.* **1988**, *29*, 6037–6038.
- Santosh Laxmi, Y. R.; Bäckvall, J.-E. *Chem. Commun.* **2000**, 611–612.
- General procedure:** To a flame-dried 25 mL flask were sequentially added toluene (4 mL), alcohol (2.5 mmol), and RhCl(PPh₃)₃ (20 mg, 0.02 mmol) under argon atmosphere. The reaction system was stirred at 30 °C for 20 min. The aldehyde (1 mmol) was added and stirred at 30 °C for 20 min, and then the freshly distilled BF₃·OEt₂ (0.15 mL, 1.2 mmol) was added. The reaction was heated using oil bath to 80 °C, and stirred at 80 °C for further 8–18 h until TLC analysis showed the reaction was completed. Then the reaction was cooled to rt, and diluted with ethyl acetate (3 mL) followed by addition of saturated aqueous NaHCO₃ (3 mL). The organic layer was separated, and the aqueous phase was re-extracted with ethyl acetate (3×3 mL). The combined organic extracts were washed with brine (10 mL), dried over dried Na₂SO₄, and purified by the flash chromatography to afford the desired products. **Spectral data for selected products:** Compound **3c**: ¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.77–1.80 (m, 2H), 2.91–2.95 (m, 4H), 7.32–7.48 (m, 10H), 7.82 (s, 2H); ¹³C NMR (CDCl₃, 100 MHz, ppm) 22.9, 28.4, 128.3, 128.5, 130.3, 135.9, 135.1, 136.9, 190.3; MS *m/z* (%) 274 (M⁺, 68), 273 (100), 247 (5), 217 (24), 169 (10), 141 (11), 128 (16), 115 (31). Compound **3l**: ¹H NMR (CDCl₃, 400 MHz, ppm): δ 1.94 (d, *J* = 0.8 Hz, 3H), 7.25 (m, 1H), 7.37–7.45 (m, 3H), 7.66 (d, *J* = 8.0 Hz, 1H), 9.68 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz, ppm) 10.8, 124.5, 127.2, 130.4, 130.5, 133.1, 148.0, 195.3; MS *m/z* (%) 226 (M⁺ (⁸¹Br), 1), 224 (M⁺ (⁷⁹Br), 1), 145 (100), 116 (20), 115 (50), 91 (8).