ORGANIC
LETTERS

2009
Vol. 11, No. 10
2213−2215

Zn/InCl$_3$-Mediated Pinacol Cross-Coupling Reactions of Aldehydes with α,*β*-Unsaturated Ketones in Aqueous Media

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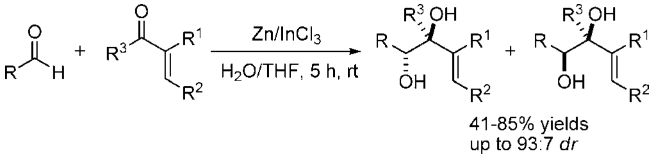
Received March 25, 2009

ABSTRACT



A zinc/indium chloride−mediated pinacol cross-coupling reaction between aldehyde and α,*β*-unsaturated ketone in aqueous media was developed. The 1,2-diols were obtained in moderate to good yields with up to 93:7 diastereoselectivity.

Pinacol coupling of carbonyl compounds is an important reaction for the formation of 1,2-diols and has received considerable attention from organic chemists.[1] However, most of the reported pinacol coupling reactions were focused on the homocoupling of the carbonyl compounds, accompanied by reductive products.[1f−l] The relevant pinacol cross-coupling reaction of two different carbonyl compounds is more challenging and remains relatively unexplored.[2] In 2001, Takai and co-workers reported the first pinacol cross-coupling reactions of aliphatic aldehydes with α,*β*-unsaturated ketones using air-sensitive CrCl$_2$ and R$_3$SiCl as coupling reagents to afford various 1,2-diols in good to excellent yields.[3] However, the method using toxic and expensive CrCl$_2$ is mainly limited to aliphatic aldehydes, and the reactions have to be carried out under strictly anhydrous conditions. If the reaction can be developed to proceed in water with the elimination of the above limitations, its applicability will be greatly enhanced. In continuation of our efforts to develop organic transformations in aqueous media with many inherent advantages over reactions in conventional organic solvents,[4,5] herein we report an efficient pinacol cross-coupling reaction of aldehyde and α,*β*-unsaturated ketone using Zn/InCl$_3$ in aqueous media. The 1,2-diols can

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(1) For reviews, see: (a) Dushin, R. G. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Eds.; Pergamon: Oxford, 1995; Vol. 12, pp 1071−1095. (b) Robertson, M. In *Comprehensive Organic Synthesis I*; Trost, B. M., Eds.; Pergamon: New York, 1991; Vol. 3, pp 563−611. (c) Furstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed.* **1996**, *35*, 2443–2469. (d) McMurry, J. E. *Chem. Rev.* **1989**, *89*, 1513–1524. (e) McMurry, J. E. *Acc. Chem. Res.* **1983**, *16*, 405–411. For selected examples, see: (f) Hinakubo, Y.; Matsukawa, S. *Org. Lett.* **2003**, *5*, 1221–1223. (g) Li, T. H.; Chan, T. H. *Org. Lett.* **2000**, *2*, 1129–1132. (h) Bhar, S.; Panja, C. *Green Chem.* **1999**, *1*, 253–255. (i) Mečarová, M.; Toma, Š. *Green Chem.* **1999**, *1*, 257–259. (j) Tsukinoki, T.; Kawaji, T.; Hashimoto, I.; Mataka, S.; Tashiro, M. *Chem. Lett.* **1997**, *26*, 235–236. (k) Tanaka, K.; Kishigami, S.; Toda, F. *J. Org. Chem.* **1990**, *55*, 2981–2983. (l) Wang, C. Y.; Pan, Y. J.; Wu, A. X. *Tetrahedron* **2007**, *63*, 429–434. (m) Buchammagari, H.; Toda, Y.; Hirano, M.; Hosono, H.; Takeuchi, D.; Osakada, K. *Org. Lett.* **2007**, *9*, 4287–4289. (n) Barden, M. C.; Schwartz, J. *J. Am. Chem. Soc.* **1996**, *118*, 5484–5485. (o) Takenaka, N.; Xia, G. Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 13198–13199. (p) Hirao, T.; Xu, X. L. *J. Org. Chem.* **2005**, *70*, 8594–8596. (q) Yang, H. W.; Wang, H. S.; Zhu, C. J. *J. Org. Chem.* **2007**, *72*, 10029–10034. (r) Ueda, T.; Kanomata, N.; Machida, H. *Org. Lett.* **2005**, *7*, 2365–2368. (s) Aspinall, H. C.; Greeves, N.; Valla, C. *Org. Lett.* **2005**, *7*, 1919–1922. (t) Handy, S. T.; Omune, D. *Org. Lett.* **2005**, *7*, 1553–1555. (u) Groth, U.; Jeske, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 574–576.

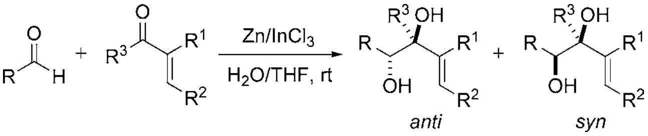
(2) (a) Konradi, A. W.; Kemp, S. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1994**, *116*, 1316–1323. (b) Kraynack, E. A.; Pedersen, S. F. *J. Org. Chem.* **1993**, *58*, 6114–6117. (c) Groth, U.; Jung, M.; Vogel, T. *Chem.−Eur. J.* **2005**, *11*, 3127–3135.

(3) (a) Takai, K.; Morita, R.; Toratsu, C. *Angew. Chem., Int. Ed.* **2001**, *40*, 1116–1119. (b) Takai, K.; Morita, R.; Matsushita, H.; Toratsu, C. *Chirality* **2003**, *15*, 17–23.

10.1021/ol900619d CCC: $40.75

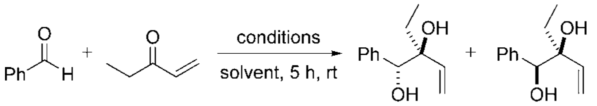
be obtained in moderate to good yields with up to 93:7 diastereoselectivity (Scheme 1).

Scheme 1. Pinacol Cross-Coupling Reaction of Aldehyde with α,β-Unsaturated Ketone in Aqueous Media



Initially, we examined the effect of different metallic coreductants and solvents on the pinacol cross-coupling of benzaldehyde **1** and ethyl vinyl ketone **2** at room temperature. The results are summarized in Table 1.

Table 1. Optimization of Reaction Conditions Using Benzaldehyde **1** and Ethyl Vinyl Ketone **2**[a]



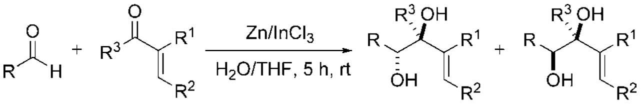
1 **2** **3**

entry	conditions	solvent	yield[b] (%) anti:syn[c]
1	In/$InCl_3$	H_2O/THF	<10[d]
2	Al/$InCl_3$	H_2O/THF	trace
3	Mg/$InCl_3$	H_2O/THF	0
4	Fe/$InCl_3$	H_2O/THF	0
5	Sn/$InCl_3$	H_2O/THF	0
6	**Zn/$InCl_3$**	**H_2O/THF**	**80 (49:51)**
7	Zn/$ZnCl_2$	H_2O/THF	72 (48:52)
8	Zn/$In(OTf)_3$	H_2O/THF	37 (46:54)
9	Zn/$AuCl(PPh_3)$	H_2O/THF	42 (46:54)
10	Zn	H_2O/THF	21 (50:50)
11	$InCl_3$	H_2O/THF	0
12	Zn/$InCl_3$	H_2O	55 (49:51)
13	Zn/$InCl_3$	THF	18 (49:51)
14	Zn/$InCl_3$	CH_3CN	trace
15	Zn/$InCl_3$	hexane	trace

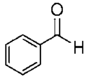
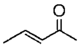
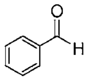
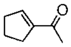
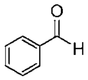
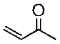
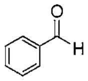
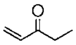
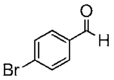
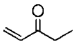
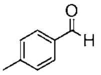
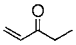
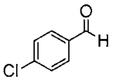
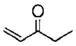
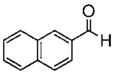
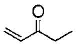
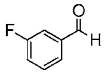
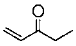
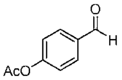
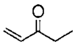
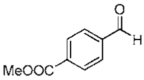
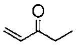
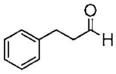
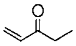
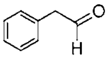
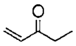
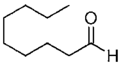
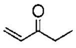
[a] The reaction was carried out at rt for 5 h using Zn (1 mmol), $InCl_3$ (0.05 mmol), **1** (0.5 mmol), **2** (1 mmol), H_2O (5 mL), and THF (5 mL). [b] Isolated yield. [c] Diastereoselectivity was determined by isolation and/or ^1H NMR analysis. [d] β,γ-Unsaturated ketone was obtained as the major product as reported previously.[6]

As shown in Table 1, among the different metals investigated, Zn/$InCl_3$ was observed to be an effective system for the pinacol coupling reaction of **1** and **2** in aqueous media. The reaction proceeded efficiently to furnish the corresponding 2-ethyl-1-phenylbut-3-ene-1,2-diol **3** in 80% yield (Table 1, entry 6). When other metals such as In, Al, Mg, Fe, and Sn were used, poor yields or no cross-coupled 1,2-diol product was observed (Table 1, entries 1−5). It is important to note that the use of metal (i.e., zinc) is indispensable for the pinacol coupling reaction; without it, no desired product was obtained (Table 1, entry 11). It is noteworthy that without the use of $InCl_3$, the reaction using Zn proceeded sluggishly to give the desired product in lower yield (Table 1, entry 10). It was also found that a better yield could be obtained when H_2O/THF (1:1) was used as cosolvent compared to pure H_2O, THF, or other organic solvents (Table 1, entries 12−15).

Table 2. Pinacol Cross-Coupling Reaction Using Various Aldehydes and α,β-Unsaturated Ketones[a]



1a-k **2a-d** **3a-n**

entry	aldehyde **1**	ketone **2**	product **3**	yield (%)[b]	anti: syn[c]
1	 **1a**	 **2a**	**3a**	55	61:39
2	 **1a**	 **2b**	**3b**	62	44:56
3	 **1a**	 **2c**	**3c**	76	42:58
4	 **1a**	 **2d**	**3d**	80	49:51
5	 **1b**	 **2d**	**3e**	70	36:64
6	 **1c**	 **2d**	**3f**	76	47:53
7	 **1d**	 **2d**	**3g**	82	30:70
8	 **1e**	 **2d**	**3h**	59	16:84
9	 **1f**	 **2d**	**3i**	75	39:61
10	 **1g**	 **2d**	**3j**	85	40:60
11	 **1h**	 **2d**	**3k**	63	20:80
12	 **1i**	 **2d**	**3l**	51 (56)[d]	90:10[e]
13	 **1j**	 **2d**	**3m**	48 (52)[d]	83:17
14	 **1k**	 **2d**	**3n**	31 (41)[d]	93:7

[a] The reaction was carried out at rt for 5 h using Zn (1 mmol), $InCl_3$ (0.05 mmol), aldehyde (0.5 mmol), α,β-unsaturated ketone (1 mmol), H_2O (5 mL), and THF (5 mL). [b] Isolated yield. [c] Diastereoselectivity was determined by isolation and/or ^1H NMR analysis. [d] Using $InBr_3$ instead of $InCl_3$ with the similar diastereoselectivity. [e] The *anti*:*syn* ratio is 65:35 when the temperature is 75 °C.

We next examined the generality of the reaction by using a wide variety of α,β-unsaturated ketones and aldehydes. As shown in Table 2, Zn/$InCl_3$ efficiently mediated the pinacol cross-coupling reactions of various aldehydes and α,β-unsaturated ketones in H_2O/THF at room temperature to afford the corresponding 1,2-diols in moderate to good yields. It is gratifying to find that when aliphatic aldehyde **1i** was used as substrate, the reaction also proceeded efficiently with **2d** to furnish the desired product **3l** in moderate yield with high diastereoselectivity (Table 2, entry 12). It was also found that the yields for the aliphatic aldehydes could be enhanced by using $InBr_3$ instead of $InCl_3$ (Table 2, entries 12−14). Similar to Takai's report, the *syn*:*anti* selectivity changed with the reaction temperature (Table 2, entry 12).

The structure of one of the products, **3d** was further confirmed by a single-crystal X-ray diffraction analysis (Figure 1).[7]

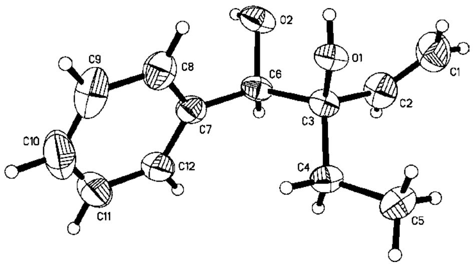
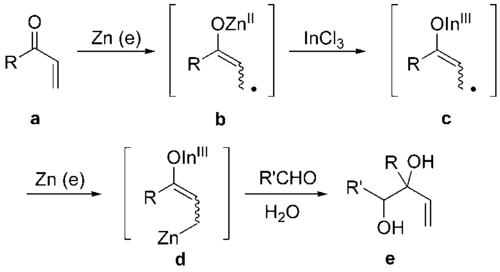


Figure 1. ORTEP diagram of the single-crystal X-ray structure of compound **3d** (*syn* structure).

A possible mechanism is proposed as shown in Scheme 2.[3b] The reaction is initiated by a single-electron transfer from zinc to the α,β-unsaturated ketone to form a radical enolate anion **b**. Fast trapping of the oxygen−metal bond in the radical enolate anion **b** by $InCl_3$ gives the γ-In(III)-substituted allylic radical **c**. The radical **c** is further reduced by zinc to furnish the corresponding allylic zinc species **d**. Finally, coupling of the γ-In(III)-substituted allylic zinc species **d** with an aldehyde followed by quenching of the resulting 1,2-diolate with water generates the desired product **e**.

Scheme 2. Proposed Reaction Mechanism



In summary, we have reported an efficient pinacol cross-coupling reaction of aldehydes with α,β-unsaturated ketones promoted by Zn/$InCl_3$ in aqueous media. It provides an atom-economical and straightforward access to a wide variety of 1,2-diols. Synthetic applications of the reaction to an intramolecular-type pinacol cross-coupling reaction, as well as insight into its detailed mechanism, are currently in progress.

Acknowledgment. We gratefully acknowledge the Nanyang Technological University and Singapore Ministry of Education Academic Research Fund Tier 2 (No. T206B1221 and T207B1220RS) for funding of this research.

Supporting Information Available: Additional experimental procedures and spectral data for all the compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Crystallographic data (including structure factors) for compound **3d** (CCDC 716671) reported in this paper have been deposited with the Cambridge Crystallographic Data Centre. See the Supporting Information for details.