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In/InCl$_3$-Mediated Cross-Coupling Reactions of Methyl Vinyl Ketone with Benzaldehyde in Aqueous Media

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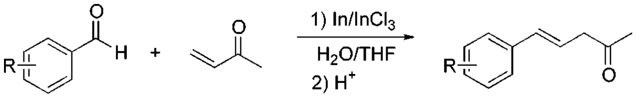
ABSTRACT

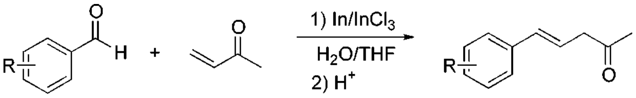


Various β,γ-unsaturated ketones were successfully prepared by cross-coupling reactions of methyl vinyl ketone (MVK) with benzaldehydes mediated by In/InCl$_3$ in aqueous media.

Among versatile metal-mediated organic transformations, syntheses involving indium are of current interest because of their distinctive mediatory ability for many organic reactions in aqueous media.[1] The low first ionization potential of indium metal compared with that of Mg, Sn, or Zn, as well as its exceptional stability in water, makes the metal applicable to many organic reactions.[2] We previously employed its unique reducing property in aqueous media to pinacol coupling of benzaldehyde[3] and dehalogenation of 3-iodomethylcephems.[4]

In view of the recent interest in the use of indium in some powerful organic reactions, we have focused our research on the mediatory effect of indium in the Michael reaction, which is one of the most efficient methods for carbon−carbon bond formation and which has broad applications in organic synthesis.[5] Herein we report that indium-mediated reaction of benzaldehydes and methyl vinyl ketone proceeded smoothly in the presence of InCl$_3$ in aqueous media to form β,γ-unsaturated ketones. Thus, benzaldehydes were reacted with methyl vinyl ketone (MVK, 300 mol %) in the presence of indium powder (200 mol %) and InCl$_3$ (50 mol %) in a solvent mixture of THF and H$_2$O (1:2, v/v) at ambient temperature for 6−8 h. Addition of 1 N HCl to the reaction mixture afforded the desired β,γ-unsaturated ketones in good to moderate yields (Scheme 1). MVK was used in excess due to its susceptibility to dimerization.

Scheme 1. Indium-Mediated Cross-Coupling Reaction of MVK with Benzaldehyde



This reaction provides a markedly effective access to β,γ-unsaturated ketones that are known to be useful intermediates in the synthesis of fine chemicals.[6] To date, this is the first report that indium can facilitate the coupling reaction of

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(2) (a) Cintas, P. *Synlett* **1995**, 1087. (b) Hashmi, A. S. K. *J. Prakt. Chem.* **1998**, *340*, 84.

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(4) Chae, H.; Cho, S.; Keum, G.; Kang, S. B.; Pae, A. N.; Kim, Y. *Tetrahedron Lett.* **2000**, *41*, 3899.

(5) (a) Wang, L.; Sun, X.; Zhang, Y. *Synth. Comm.* **1998**, *28*, 3263. (b) Bergman, E. D.; Ginsburg, D.; Rappo, R. *Org. React.* **1959**, *10*, 179.

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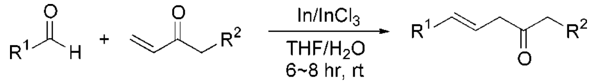
benzaldehydes and methyl vinyl ketone to give β,γ-unsaturated ketones. The results of In/$InCl_3$-mediated cross-coupling reactions of various benzaldehydes with MVK are summarized in Table 1.[7]

Table 1. Reaction of Various Aldehydes with MVK[a]



entry	R^1	R^2	conditions:[b] solvent	isolated yield (%)
1	4-FPh	H	THF	67[c]
2	4-FPh	H	H_2O	59[c]
3	4-FPh	H	THF:H_2O (1:1)	79[c]
4	4-FPh	H	THF:H_2O (1:2)	79
5[d]	4-FPh	H	THF:H_2O (1:1)	
6[e]	4-FPh	H	THF:H_2O (1:1)	
7	Ph	H	THF:H_2O (1:1)	69
8	2-FPh	H	THF:H_2O (1:1)	74
9	4-*t*-BuPh	H	THF:H_2O (1:1)	68
10	4-MeO_2CPh	H	THF:H_2O (1:1)	59
11	4-MeOPh	H	THF:H_2O (1:2)	71
12	4-NCPh	H	THF:H_2O (1:1)	72
13	4-HOPh	H	THF:H_2O (1:1)	40
14	2-furyl	H	THF:H_2O (1:1)	44
15	PhCH=CH	H	THF:H_2O (1:1)	58
16[f]	4-FPh	H	THF:H_2O (1:1)	78
17	4-FPh	Me	THF:H_2O (1:1)	62

[a] All reactions were carried out on a 0.5 mmol scale. [b] Aldehyde:MVK: In:$InCl_3$ = 1:3:2:0.5. [c] GC yield. [d] Without In, 2.5 equiv of $InCl_3$ was used. [e] Without $InCl_3$, 2.5 equiv of In was used. [f] Instead of In and $InCl_3$, 2.5 equiv of InCl was used.

Generally, the yields of the products are not affected by the nature of substituents on the phenyl ring (entries 1−4, 7−13, 16, and 17). The reaction also proceeded with heteroaromatic aldehyde (entry 14). With the absence of In or $InCl_3$, the reaction did not occur (entries 5 and 6). The yield decreased when THF or H_2O was used as the only solvent (entries 1 and 2). Employing other solvents besides THF or H_2O also led to disappointing results. With cinnamaldehyde, not only the cross-coupled product but also a small amount of the pinacol coupling product was detected (entry 15).[8] When other Lewis acids, such as $SnCl_4$, $FeCl_3$, and $CuCl_2$, instead of $InCl_3$ were used, low yields (21−38%) resulted. It should be noted that the reaction using InCl alone without In also proceeded well to give the β,γ-unsaturated ketone in 78% yield (entry 16). When an aldehyde reacted with ethyl vinyl ketone instead of MVK as a Michael acceptor, a coupling product was produced in 62% yield (entry 17). These reaction conditions were extended to other Michael acceptors such as acrolein, acrylonitrile, ethyl acrylate, and acrylic acid, but the reaction did not proceed.

The reaction mechanism is not clear, but we now report that the reaction is likely to proceed by a radical mechanism involving the radical-anion intermediate of MVK[9] formed from indium (Figure 1). Then the reaction intermediate undergos radical cyclopropanation and addition to benzaldehyde. Upon addition of BHT (butylated hydroxytoluene) to the reaction, a rate retardation effect was detected.[10] When the reaction was followed by ^1H NMR in a 1:1 mixture of THF-d_8 and D_2O, the cyclopropanyl proton signals[11] were observed at δ 1.2−0.5 as multiplet.[12] Quenching the reaction mixture with DCl[13] in D_2O after an appropriate reaction time and examination of the $CDCl_3$-extracted products by ^1H NMR showed the signal of the 5-phenyl-4-penten-2-one[14] together with peaks of some MVK decomposed compounds.

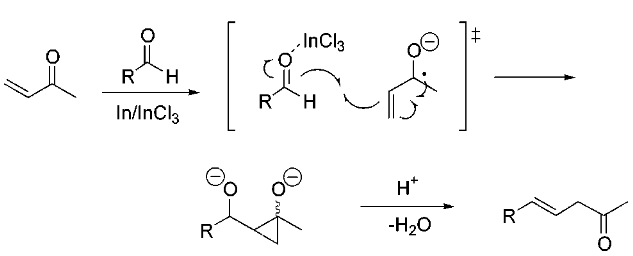


Figure 1. Plausible mechanism.

In conclusion, we have extended the scope of indium metal to a cross-coupling reaction of an α,β-unsaturated ketone

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(6) (a) Valle, L. D.; Stille, J. K.; Hegedus, L. S. *J. Org. Chem.* **1990**, *55*, 3019. (b) Chang, S.; Yoon, J.; Brookhart, M. *J. Am. Chem. Soc.* **1994**, *116*, 1869. (c) Yoshida, H.; Oomori, K.; Miyata, H.; Onzuka, K.; Fuse, K. JP 08081406, 1996; *Chem. Abstr.* **1996**, *125*, 57554.

(7) **Typical experimental procedure** (Table 1, entry 4): A mixture of 4-fluorobenzaldehyde (53.6 μL, 0.5 mmol), In (−100 mesh, 114.8 mg, 1 mmol), $InCl_3$ (55.3 mg, 0.25 mmol), and MVK (124.9 μL, 1.5 mmol) in a mixture of THF and H_2O (1:2, 3 mL) was stirred at ambient temperature for 6 h. After the addition of 1 N HCl (1.5 mL), the reaction mixture was stirred for 30 min and extracted with ethyl acetate (15 mL × 3). The combined organic phase was washed with brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel with a mixture of hexane and ethyl acetate (10:1) to give 5-(4-fluorophenyl)-4-penten-2-one (70.6 mg, 79% yield).

(8) In the absence of MVK, the pinacol product of cinnamaldehyde was isolated in 79% yield as a mixture of *dl* and *meso* isomers (84:16).

(9) Two types of radical-anion (1,2- and 1,4-) of methyl vinyl ketone were possible. See: Pons, J.-M.; Zahra, J.-P.; Santelli, M. *Tetrahedron Lett.* **1981**, *22*, 3965.

(10) The retardation was analyzed by GC yield of the product formed. In the absence of BHT, the β,γ-unsaturated ketone was formed in 35% and 81% yield after 1 h and 4 h, respectively. In the presence of 0.1 equiv of BHT, however, the corresponding yields were 28% and 53% and under 0.5 equiv of BHT, the results were 5% and 15% yields, respectively.

(11) ^1H NMR of the cyclopropanol intermediate (entry 7, THF-d_8/D_2O) δ 7.4 (m, 5H), 4.9−4.2 (m, 1H), 2.5−2.0 (4s, 3H), 1.2−0.5 (m, 3H).

(12) Some examples of the synthesis of cyclopropanol by cyclopropanation of β,γ-unsaturated ketone were reported. (a) With $CrCl_2$: Toratsu, C.; Fujii, T.; Suzuki, T.; Takai, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2725. (b) With $CrCl_2$ and a catalytic amount of $NiCl_2$: Montgomery, D.; Reynolds, K.; Stevenson, P. *J. Chem. Soc., Chem. Commun.* **1993**, 363.; (c) with Me_3SnLi and $TiCl_4$ (cat.): Sato, T.; Watanabe, M.; Watanabe, T.; Onoda, Y.;, Murayama, E. *J. Org. Chem.* **1988**, *53*, 1894. (d) With Zn/HCl: Elphimoff-Felkin, I.; Sadra, P. *Tetrahedron* **1975**, *31*, 2781.

(13) Examples of the ring-opening reactions of cyclopropanols: (a) Corey, E. J.; Ulrich, P. *Tetrahedron Lett.* **1975**, 3685. (b) Gibson, D. H.; DePuy, C. H. *Chem. Rev.* **1974**, *74*, 605. and see ref 12a.

(14) ^1H NMR (300 MHz, $CDCl_3$) δ 7.38−7.19 (m, 5H), 6.46 (d, J = 16.0 Hz, 1H), 6.30 (dt, J = 15.9, 6.9 Hz, 2H), 3.32 (d, J = 6.9 Hz, 2H), 2.19 (s, 3H).

with benzaldehydes and provided a very effective access to the β,γ-unsaturated ketones in satisfactory yields. Further study on the exact reaction mechanism and application of this protocol to organic synthesis are currently underway in our laboratory.

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