Indium(I) Catalysis

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Catalytic Activation of Pinacolyl Allylboronate with Indium(I): Development of a General Catalytic Allylboration of Ketones**

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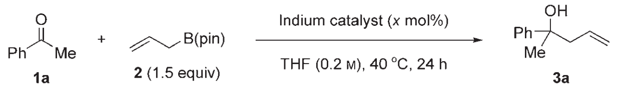
The discovery and development of new catalytic methods for efficient C–C bond formations is one of the most important tasks in synthetic organic chemistry.[1] In this context, the allylation of ketones[2] is among the most useful and challenging transformations in organic synthesis, as the resulting tertiary homoallylic alcohols have proved to be highly versatile intermediates and synthetic building blocks.[3] Typical protocols for the allylation of ketones involve the use of allylindium reagents generated in situ under Barbier-type conditions from allyl halides and a stoichiometric amount of indium(0)[4] or indium(I).[5] Catalytic methods that have been reported include various catalytic enantioselective allylstannations of ketones employing chiral indium(III) Lewis acids[6] and others.[7] However, the substrate scope for ketones is generally not satisfactory and furthermore these methods require the use of more than one equivalent of toxic stannanes, which is undesirable with respect to safety and environmental considerations. In recent years, significant advances in ketone allylation have been achieved through the development of catalytic (asymmetric) allylsilylations by using (chiral) copper(I)[8] or silver(I)[9] Lewis acids.[10] Most recently, very elegant, catalytic asymmetric allylborations catalyzed by chiral Lewis[11] or Brønsted[12] acids have also been reported.[13] However, with only a handful of exceptions, the substrate generality is limited and therefore a truly general catalytic allylation method for ketones remains to be developed.

The chemistry of indium in its low oxidation state (I)[14] is an underexplored area, and only sporadic examples of its use as stoichiometric reagents have been reported.[15] To the best of our knowledge, a catalytic synthetic method involving the use of a "catalytic" amount of indium(I) is to date unknown. Nevertheless, it has been shown that, depending on the nature of the ligand by which it is coordinated, indium(I) can act as a Lewis acid[16] or Lewis base[17] owing to the presence of both free p orbitals and a lone pair of electrons.[18] Indeed, a recent report revealed that indium(I) as a σ donor is able to form donor–acceptor complexes with electron acceptors such as boron derivatives.[17] On the basis of this concept involving two Group 13 elements, we hypothesized that indium(I) as a Lewis base catalyst might activate a Lewis acidic allylboronate through formation of a metal–metal bond, and that the bimetallic allylborate so generated might enhance nucleophilicity towards electrophiles such as ketones. Herein we report the unprecedented catalytic activation of pinacolyl allylboronate with indium(I) and its application to the general catalytic allylboration of ketones.

Our initial experiments were conducted with the reaction of acetophenone (**1a**) with pinacolyl allylboronate (**2**; 1.5 equiv) as model substrates in dry THF at 40 °C (Table 1). As the indium source, we employed a stoichiometric amount of commercially available indium(I) iodide,[19] which was selected for its higher stability compared with other indium(I) halides.

Table 1: Examination of various indium catalysts in the allylation of acetophenone (**1a**) with pinacolyl allylboronate (**2**).



Entry	Indium cat. (x [mol %])	Yield [%][a]
1	–	trace
2	InI (100)	quant.
3	InI (50)	quant.
4	InI (20)	99
5	InI (10)	85
6	InI (5)	88
7	InI (1)	70 (99)[b]
8	In^0 (20) + InI_3 (10)	quant.
9	In^0 (20)	4
10	InI_3 (10)	3
11	InCl (20)	65
12	InBr (20)	87
13	InOTf (20)	39
14	$In(OTf)_3$ (20)	16

[a] Yields after preparative thin-layer or flash chromatography (silica gel). B(pin): pinacolyl boronate; OTf: trifluoromethanesulfonate. [b] Concentration of 1 M in THF under otherwise identical conditions.

As shown, the noncatalyzed reaction essentially did not proceed, with only a trace amount of product being formed even after 24 h (Table 1, entry 1). Gratifyingly, however, the indium(I)-mediated transformation cleanly afforded the desired tertiary homoallylic alcohol **3a** in quantitative yield (Table 1, entry 2). Next, we reduced the amount of catalyst to 50 mol % and then to 20 mol %, which provided, to our delight, the desired product in quantitative and 99 % yields,

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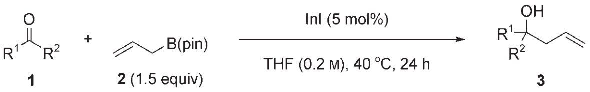
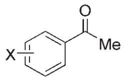
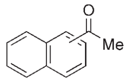
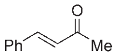
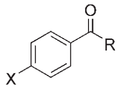
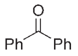
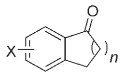
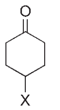
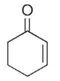
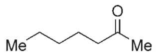
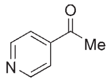
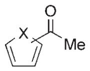
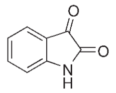
respectively (Table 1, entries 3 and 4).[20] These excellent "catalytic" results are remarkable because, in general, stoichiometric amounts of indium(I) reagents are required for indium-mediated Barbier-type[5] and Reformatsky-type reactions,[21] palladium-to-indium transmetallations,[22] or radical-generating reactions.[23] Further examination of catalyst loadings (Table 1, entries 5–7) revealed that use of as little as 1 mol % of indium(I) gave the desired addition product in up to 70 % isolated yield after 24 h (use of more concentrated conditions gave 99 % yield; entry 7).[24,25] Various other solvents such as dichloromethane, *N*,*N*-dimethylformamide, acetonitrile, ethanol, and water were examined but proved to be significantly less effective than tetrahydrofuran. Next, several control experiments were carried out (Table 1, entries 8–10). Indium(I) is known to be rather prone to redox disproportionation thereby generating indium(0) and indium(III) in a molar ratio of 2:1. If this is the case in the current system, indium metal might activate **1a** and/or **2** through single electron transfer, whereas indium(III) as a Lewis acid might activate **1a** and/or **2**. The combined use of indium(0) and indium(III) iodide in a molar ratio of 2:1 provided product **3a** in quantitative yield (Table 1, entry 8). On the other hand, use of either indium catalyst independently proved to be ineffective (Table 1, entries 9 and 10). These experiments strongly support the idea that indium(I) is the active catalyst species here and suggest redox synproportionation (in situ formation of indium(I) from indium(0) and indium(III)) as the cause of the excellent result in entry 8 (Table 1). The best catalyst among the indium(I) halides was shown to be indium(I) iodide, a trend which can be ascribed to its higher thermodynamic stability compared with indium(I) chloride and bromide (Table 1, entry 4 vs entries 11 and 12). As indium(I) iodide has a very low solubility in THF, the more soluble indium(I) triflate[26] was used as a catalyst; however, in this case, product **3a** was obtained in moderate yield (39 %; Table 1, entry 13). Interestingly, this result was still superior to that observed with indium(III) triflate (16 %; Table 1, entry 14), which is generally accepted to be a better Lewis acid.

Next, we investigated the substrate generality for the allylation of ketones **1** with allylboronate **2** using 5 mol % of indium(I) iodide (Table 2). Gratifyingly, it was found that the reaction displayed good generality and various substituted aryl methyl ketones including an α,β-unsaturated substrate were transformed into the corresponding tertiary homoallylic alcohols in excellent yields (Table 2, entries 1–8). Moreover, aryl ethyl, aryl propyl, and diaryl ketones proved to be very good substrates (Table 2, entries 9–12). In addition, various cyclic aromatic and aliphatic as well as acyclic aliphatic ketones were shown to undergo smooth allylation (Table 2, entries 13–19). Note that both α,β-unsaturated substrates tested underwent exclusive 1,2-addition (Table 2, entries 8 and 18). Finally, a range of heterocyclic ketones were converted into the corresponding tertiary homoallylic alcohols with high yields (Table 2, entries 20–24). Importantly, several functionalities such as hydroxy, methoxy, amino, amide, chloro, bromo, and nitro groups were compatible with the mild conditions of this operationally simple indium(I)-catalyzed C–C bond formation.

Table 2: Substrate generality for the indium(I) iodide catalyzed allylation of ketones **1** with allylboronate **2**.

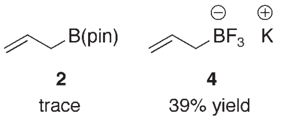


Entry	Ketone **1**		Yield [%][a]
1		**1a**: X = H	88
2		**1b**: X = 3,5-di-OH	quant.
3		**1c**: X = 2-Br	97
4		**1d**: X = 4-NH_2	99
5		**1e**: X = 4-NO_2	91
6		**1f**: 1-naphthyl	quant.
7		**1g**: 2-naphthyl	98
8		**1h**	quant.
9		**1i**: R = Et, X = OH	98
10		**1j**: R = Et, X = Cl	99
11		**1k**: R = *n*Pr, X = Cl	90
12		**1l**	99
13		**1m**: *n* = 1, X = 5-OMe	81
14		**1n**: *n* = 1, X = 6-Me	85
15		**1o**: *n* = 2, X = 6-OMe	70
16		**1p**: X = H	90
17		**1q**: X = Ph	72[b]
18		**1r**	70
19		**1s**	81
20		**1t**	55
21		**1u**: X = O, 2-furyl	92
22		**1v**: X = S, 2-thienyl	98
23		**1w**: X = S, 3-thienyl	quant.
24		**1x**	80

[a] Yields after preparative thin-layer or flash chromatography (silicagel). [b] Mixture of two diastereoisomers (ratio 85:15).

Our attention then turned to the mechanism of this reaction. As mentioned in our working hypothesis above, one possible pathway involves catalytic activation of allylboronate **2** with indium(I) as a Lewis base, thereby generating bimetallic allylborate **A** with enhanced nucleophilicity (Figure 1). Alternatively, the iodide-induced formation of an allylborate of type **B** might be imagined. In this context, note that allyltrifluoroborate **4** was found to be significantly more reactive in the noncatalyzed allylation of ketone **1a** than allylboronate **2** (39 % yield vs trace amount, Figure 1; cf. Table 1, entry 1).[27]

To examine the possibility of Lewis base activation of **2**, we used tetrabutylammonium difluorotriphenylsilicate (TBAT; 20 mol %) or tetrabutylammonium fluoride (TBAF; 100 mol %) as fluoride anion sources in the allylation of **1a**



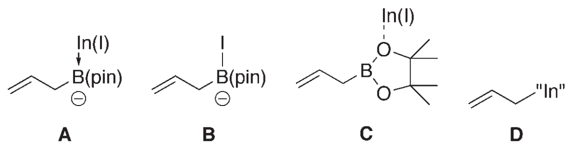


Figure 1. Possible intermediates **A**–**D** in the indium(I) iodide catalyzed allylation of ketones **1** with **2**.

with **2**. However, these metal-free Lewis base reagents proved to be only moderately effective (10% and 59% yields, respectively).[28] These results indicate that simple Lewis base activation of **2** might not be sufficient, and that indium(I) might additionally act as a Lewis acid activator of **1a** (dual-activation mechanism). On the other hand, simple activation of **1a** and/or **2**[29] with indium(I) as a Lewis acid (to form intermediate **C**) seems unlikely considering our results with more Lewis acidic indium(III) reagents (much lower yields; cf. Table 1, entries 10 and 14). Finally, another mechanism might involve catalytic activation of allylboronate **2** through boron-to-indium transmetallation to generate allylindium species of type **D**.[30] To establish whether in situ generated allylindium was responsible for the observed reactivity, we examined allylindium reagents prepared independently under Barbier-type conditions from allyl bromide or allyl iodide using a stoichiometric amount of indium metal or indium(I) iodide. However, under our typical reaction conditions (use of **1a**, THF, 40 °C), the desired product **3a** was formed only in moderate to good yields (60–85%). Whilst it must be acknowledged that these results cannot completely rule out a boron-to-indium transmetallation pathway, they indicate that in situ generated allylindium reagents are unlikely to play an important role in the indium–boron system, which is the subject of the current presentation. Preliminary ^{1}H and ^{11}B NMR experiments in [D$_8$]THF at 40 °C with allylboronate **2** and indium(I) iodide in the absence of ketone **1a** revealed slow formation of allylindium(I) and allylindium(III) diiodide, whereas no evidence for an allylborate species of type **A** or **B** was observed. Furthermore, monitoring of indium(I) iodide catalyzed allylation of **1a** with **2** by NMR spectroscopy showed that the initially formed product is the allylborated ketone (O–B bond), which was transformed into homoallylic alcohol **3a** upon hydrolysis.

In conclusion, we have discovered an unprecedented catalytic activation of pinacolyl allylboronate with indium(I)[31] and have applied this novel method successfully to a general catalytic allylboration of ketones. To the best of our knowledge, this report represents not only the first example of a catalytic synthetic method involving the use of a "catalytic" amount of indium(I) but also the first catalytic activation of a Group 13 element (boron) with another member of Group 13 in its low oxidation state (indium). Further mechanistic studies on the catalytic activation of allylboronates with indium(I) and the application of this concept to other (asymmetric) C–C bond formations are ongoing in our laboratories.

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Keywords: allylation · boron · C–C coupling · indium · ketones

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[1] a) *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis* (Ed.: J. Tsuji), Wiley, Chichester, **2000**; b) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, Weinheim, **2000**.

[2] In contrast to ketones, many allylation methods have been reported for aldehydes. For recent reviews on the allylation of aldehydes, see: a) A. Yanagisawa in *Comprehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, pp. 965–979; b) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2794.

[3] For selected examples of the use of tertiary homoallylic alcohols, see: a) J. Barluenga, A. Diéguez, F. Rodríguez, F. J. Fañanás, *Angew. Chem.* **2005**, *117*, 128–130; *Angew. Chem. Int. Ed.* **2005**, *44*, 126–128; b) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2005**, *7*, 3577–3579; c) Y. Takada, S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *Org. Lett.* **2006**, *8*, 2515–2517; d) S. Hayashi, K. Hirano, H. Yorimitsu, K. Oshima, *J. Am. Chem. Soc.* **2006**, *128*, 2210–2211; e) P. Zhao, C. D. Incarvito, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 9642–9643; f) T. Ohmura, H. Furukawa, M. Suginome, *J. Am. Chem. Soc.* **2006**, *128*, 13366–13367.

[4] For selected examples, see: a) V. Nair, C. N. Jayan, S. Ros, *Tetrahedron* **2001**, *57*, 9453–9459; b) J. G. Lee, K. I. Choi, A. N. Pae, H. Y. Koh, Y. Kang, Y. S. Cho, *J. Chem. Soc. Perkin Trans. 1* **2002**, 1314–1317; c) H. Y. Kim, K. I. Choi, A. N. Pae, H. Y. Koh, J. H. Choi, Y. S. Cho, *Synth. Commun.* **2003**, *33*, 1899–1904; d) V. Nair, S. Ros, C. N. Jayan, S. Viji, *Synthesis* **2003**, 2542–2546.

[5] S. Araki, H. Ito, N. Katsumura, Y. Butsugan, *J. Organomet. Chem.* **1989**, *369*, 291–296.

[6] For selected examples, see: a) Y.-C. Teo, J.-D. Goh, T.-P. Loh, *Org. Lett.* **2005**, *7*, 2743–2745; b) J. Lu, M.-L. Hong, S.-J. Ji, Y.-C. Teo, T.-P. Loh, *Chem. Commun.* **2005**, 4217–4218; c) J. Lu, S.-J. Ji, Y.-C. Teo, T.-P. Loh, *Tetrahedron Lett.* **2005**, *46*, 7435–7437; d) J. Li, S.-J. Ji, *Chin. J. Chem.* **2006**, *24*, 1439–1442.

[7] For selected examples, see: a) H. Hanawa, S. Kii, K. Maruoka, *Adv. Synth. Catal.* **2001**, *343*, 57–60; b) A. Cunningham, S. Woodward, *Synthesis* **2002**, 43–44; c) K. M. Waltz, J. Gavenonis, P. J. Walsh, *Angew. Chem.* **2002**, *114*, 3849–3851; *Angew. Chem. Int. Ed.* **2002**, *41*, 3697–3699; d) S. Kii, K. Maruoka, *Chirality* **2003**, *15*, 68–70; e) A. Cunningham, V. Mokal-Parekh, C. Wilson, S. Woodward, *Org. Biomol. Chem.* **2004**, *2*, 741–748; f) A. J. Wooten, J. G. Kim, P. J. Walsh, *Org. Lett.* **2007**, *9*, 381–384.

[8] Use of a CuCl/TBAT catalyst and allylsilane (racemic version): S. Yamasaki, K. Fujii, R. Wada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2002**, *124*, 6536–6537.

[9] Use of a AgF/chiral diphosphine catalyst and allylsilane: M. Wadamoto, H. Yamamoto, *J. Am. Chem. Soc.* **2005**, *127*, 14556–14557.

[10] For a stoichiometric method for enantioselective ketone allylation using a chiral strained allylsilane, see: N. Z. Burns, B. M. Hackman, P. Y. Ng, I. A. Powelson, J. L. Leighton, *Angew. Chem.* **2006**, *118*, 3895–3897; *Angew. Chem. Int. Ed.* **2006**, *45*, 3811–3813.

[11] Use of a CuF$_2$/chiral diphosphine catalyst and allylboronate: R. Wada, K. Oisaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911.

[12] Use of a chiral diol catalyst and allylboronate: S. Lou, P. N. Moquist, S. E. Schaus, *J. Am. Chem. Soc.* **2006**, *128*, 12660–12661.

[13] For stoichiometric methods for enantioselective ketone allylation using a chiral allylboronate or allylborane, see: a) T. R. Wu, L. Shen, J. M. Chong, *Org. Lett.* **2004**, *6*, 2701–2704; b) E. Canales, K. G. Prasad, J. A. Soderquist, *J. Am. Chem. Soc.* **2005**, *127*, 11572–11573.

[14] For recent reviews on the lower oxidation states of indium, see: a) D. G. Tuck, *Chem. Soc. Rev.* **1993**, *22*, 269–276; b) J. A. J. Pardoe, A. J. Downs, *Chem. Rev.* **2007**, *107*, 2–45.

[15] In contrast, indium(III) derivatives are commonly used in catalytic quantities as Lewis acid catalysts (see Ref. [6]).

[16] C. G. Andrews, C. L. B. Macdonald, *Angew. Chem.* **2005**, *117*, 7619–7622; *Angew. Chem. Int. Ed.* **2005**, *44*, 7453–7456.

[17] R. J. Wright, A. D. Phillips, N. J. Hardman, P. P. Power, *J. Am. Chem. Soc.* **2002**, *124*, 8538–8539.

[18] For a recent highlight on this topic, see: S. Aldridge, *Angew. Chem.* **2006**, *118*, 8275–8277; *Angew. Chem. Int. Ed.* **2006**, *45*, 8097–8099.

[19] Indium(I) iodide is commercialized as 10-mesh beads, but the powdered form gave identical results.

[20] The use of other allylboronates under the employed conditions proved to be less efficient than the use of pinacolyl allylboronate (**2**).

[21] S. A. Babu, M. Yasuda, I. Shibata, A. Baba, *Org. Lett.* **2004**, *6*, 4475–4478.

[22] a) S. Araki, T. Kamei, T. Hirashita, H. Yamamura, M. Kawai, *Org. Lett.* **2000**, *2*, 847–849; b) I. R. Cooper, R. Grigg, W. S. MacLachlan, V. Sridharan, M. Thornton-Pett, *Tetrahedron Lett.* **2003**, *44*, 403–405; c) H. Miyabe, Y. Yamaoka, T. Naito, Y. Takemoto, *J. Org. Chem.* **2003**, *68*, 6745–6751; d) H. Miyabe, Y. Yamaoka, T. Naito, Y. Takemoto, *J. Org. Chem.* **2004**, *69*, 1415–1418; e) G. Fontana, A. Lubineau, M.-C. Scherrmann, *Org. Biomol. Chem.* **2005**, *3*, 1375–1380.

[23] B. C. Ranu, T. Mandal, *Tetrahedron Lett.* **2006**, *47*, 2859–2861.

[24] The use of a smaller amount of allylboronate **2** (1.1 equiv, 20 mol% InI, 0.2 M in THF; or 1.0 equiv, 5 mol% InI, 0.5 M in THF) proved to be equally effective (90% and 84% yields, respectively) compared with conditions of entry 6 (Table 1; 1.5 equiv, 5 mol% InI, 0.2 M in THF, 88% yield).

[25] It is notable that in all indium(I) iodide catalyzed experiments (Table 1, entries 2–7) no undesired compounds such as pinacol coupling type or reduction products were detectable in the crude reaction mixtures.

[26] Indium(I) triflate was prepared from commercially available indium(I) chloride and triflic acid in toluene at room temperature according to a known procedure: C. L. B. Macdonald, A. M. Corrente, C. G. Andrews, A. Taylor, B. D. Ellis, *Chem. Commun.* **2004**, 250–251.

[27] On the other hand, use of 20 mol% indium(I) iodide in combination with trifluoroborate **4** (1.5 equiv) in the allylation of ketone **1a** provided product **3a** in only 41% yield.

[28] Additionally, TBAI (tetrabutylammonium iodide; 100 mol%) was used as a catalyst in an NMR experiment under our typical conditions (use of **2**, [D$_8$]THF, 40°C); however, conversion of ketone **1a** into product **3a** was not observed.

[29] Lewis acid activation of allylboronates of type **2** through coordination of a boronate alkoxy ligand to the corresponding Lewis acid has been reported. However, this catalytic method has been applied only to the use of aldehydes as electrophiles: a) J. W. J. Kennedy, D. G. Hall, *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587; b) for a recent minireview on the activation of boron reagents, see: J. W. J. Kennedy, D. G. Hall, *Angew. Chem.* **2003**, *115*, 4880–4887; *Angew. Chem. Int. Ed.* **2003**, *42*, 4732–4739; c) M. Gravel, H. Lachance, X. Lu, D. G. Hall, *Synthesis* **2004**, 1290–1302; d) V. Rauniyar, D. G. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 4518–4519.

[30] For electrochemical in situ formation and regeneration of allylindium(I), see: G. Hilt, K. I. Smolko, *Angew. Chem.* **2001**, *113*, 3514–3516; *Angew. Chem. Int. Ed.* **2001**, *40*, 3399–3402.

[31] Indium is known as a “rare metal”, thus catalytic use of indium is highly important: *The Elements* (Ed.: J. Emsley), 3rd ed., Oxford Press, Oxford, **1998**.