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Catalytic Use of a Soluble Organoindium(III) Species for Allylation and Crotylation of Ketones with Boronates

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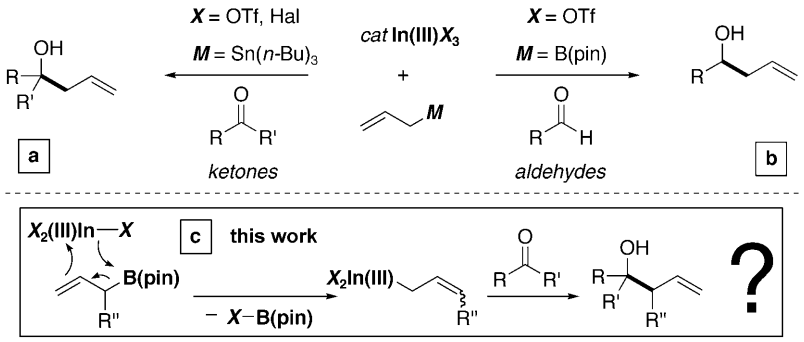
Abstract: The unprecedented use of a soluble organoindium species, indium(III) hexamethyldisilazide [In(III)(hmds)$_3$], for catalytic carbon–carbon bond formations between ketones and boronates, is reported. Various functionalized tertiary homoallyl alcohols were generated easily in high yields. Remarkably, free hydroxy and primary amine functionalities proved to be tolerated. A rate acceleration and markedly improved diastereoselectivities were observed in the presence of methanol. Based on preliminary NMR experiments and the α-selectivity with an α-substituted boronate, we assume the *in situ* generation of reactive allylindium(III) species through catalytic boron-to-indium transmetalation.

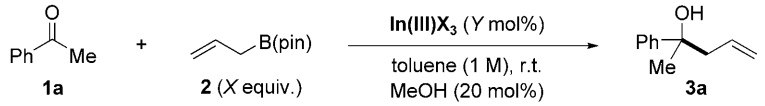
Keywords: boron; C–C bond formation; indium; silazides; transmetalation

Ketone allylation is among the most challenging[1] and useful transformations in organic synthesis. The resulting tertiary homoallyl alcohols have proved to be versatile intermediates and building blocks.[2] Typical protocols for ketone allylation involve the use of Barbier-type allylindium (In) species, generated *in situ* from allyl halides, with a *stoichiometric* amount of In(0) or In(I).[3] *Catalytic* methods include allyl stannations employing In^{III}[4] or other[5] Lewis acids. With the aim of avoiding toxic stannanes, important advances have been achieved through allyl silylations using transition metal catalysts.[6] More recently, allyl borations employing transition metal catalysts[7] or metal-free conditions[8] have been reported. As part of our research program concerns the use of *non-toxic reagents and catalysts*, we have become interested in the main group metal *indium*, as it has a low toxicity, is inexpensive, safe, and selective, and is tolerant toward functional groups.[9] While *conventional inorganic* In(III) Lewis acids [for example, In(III)Cl$_3$ and In(III)(OTf)$_3$] are commonly used as catalysts for various C–C bond formations,[9] In(III)-catalyzed *ketone* allylation typically requires the use of *toxic stannanes* (Scheme 1 a).[4] In the postulated mechanisms, the In(III) catalyst may: (i) act as a Lewis acid to activate the ketone for addition of the nucleophilic allylstan-



Scheme 1. (**a**) and (**b**) Precedents for In(III)-catalyzed carbonyl allylation, and (**c**) working hypothesis for the present study. Key: pin = pinacolyl.

Table 1. In(III)-catalyzed allylation of **1a** with **2**.



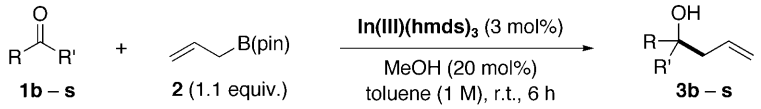
Entry	**2** (*X* equiv.)	**In(III)X$_3$** (*Y* mol%)	MeOH	Time [h]	Yield [%][a]
1	1.5	–	–	12	ND
2	1.5	In(III)Cl_3 (5)	–	12	19
3	1.5	In(III)$(OTf)_3$ (5)	–	12	ND[b]
4	1.5	In(III)F_3 (5)	–	12	6
5	1.5	In(III)$(OH)_3$ (5)	–	12	7
6	1.5	In(III)$(hmds)_3$ (5)	–	12	71
7	1.1	In(III)$(hmds)_3$ (5)	+	6	93
8	1.1	In(III)$(hmds)_3$ (3)	+	6	86
9	1.1	In(III)$(hmds)_3$ (2)	+	6	95[c]
10	1.1	In(III)$(hmds)_3$ (1)	+	24	76[c]

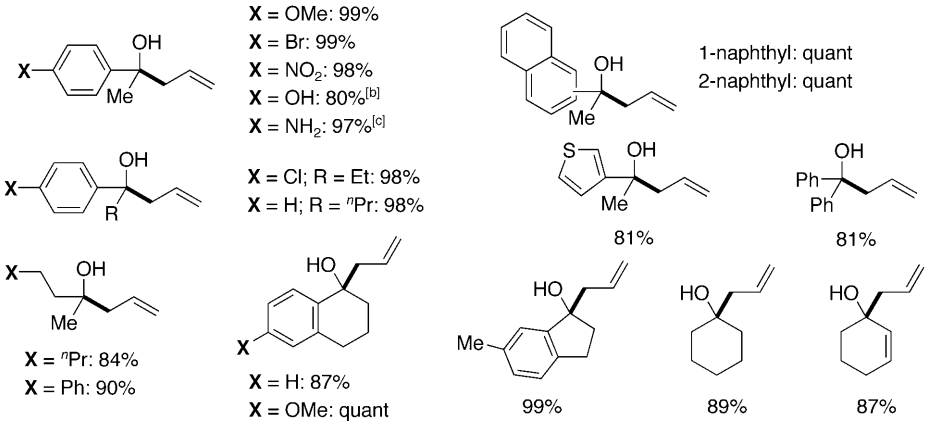
[a] Isolated yields of **3a** after purification on silica gel (PTLC). ND = not detected.
[b] Although full consumption of **1a** was observed, the reaction mixture proved to be messy with the formation of several undesired products, among which was the diallylated by-product of **1a**.
[c] Concentration of **1a** in toluene: 2 M.

nane,[4b–e] or (ii) trigger Sn-to-In transmetalation with the resulting allylindium species being the real nucleophile.[4a] *Non-toxic boronates* are significantly less reactive, and require Lewis acid or base activation.[10] The use of classic In(III) catalysts for the allyl boration of carbonyl compounds has only been reported with *aldehydes* (Scheme 1 b).[11] Indeed, in our earlier studies on In(I) and In(0),[12] compounds such as In(III)$(OTf)_3$ and In(III)I_3 proved to be ineffective in ketone allyl borations. These conventional, inorganic indium(III) salts seem either not to promote B-to-In transmetalation,[11] or do so only sluggishly.[12] Intrigued by these observations, and being aware that In(III) is more stable than In(I),[12] we sought a novel In(III) catalyst that was capable of catalyzing ketone allylations using non-toxic boronates (Scheme 1 c). The ideal catalyst would activate *electrophilic* allyl boronates: (i) as a σ-Lewis base (coordinated to the Lewis acidic boron atom = hard-hard interaction), and (ii) as a π-Lewis acid (coordinated to the C=C double bond = soft-soft interaction), to generate *in situ nucleophilic* allylindium(III) species (B-to-In transmetalation). Here, we report an unprecedented use of a soluble organoindium species, indium(III) hexamethyldisilazide [In(III)$(hmds)_3$], for catalytic activation of boronates for allylation and diastereoselective crotylation of ketones.

Initial experiments were conducted using the reaction between acetophenone (**1a**) and allyl boronate **2** as model (Table 1). Various In(III) catalysts (5 mol%) were screened in dry toluene at room temperature for 12 h. As expected, the uncatalyzed reaction did not proceed under the conditions employed (entry 1), whereas In(III)Cl_3 as the most widely used indium source, provided **3a** in only 19% yield (entry 2). The latter result may be ascribed either to the poor B-to-In transmetalation ability of this indium catalyst, or to the low reactivity of the corresponding transient allylindium reagent. In addition, with the stronger Lewis acid In(III)$(OTf)_3$, only undesired compounds were formed, among which was the undesired diallylated by-product of **1a** (entry 3). Therefore, we hypothesized that the ideal In(III) catalyst should have: (i) a more Lewis basic ligand or counteranion *X* with a higher boron affinity to promote efficient B-to-In transmetalation (= hard-hard interaction, *cf.* Scheme 1 c), and (ii) an attenuated Lewis acidity to suppress overreactions. Thus, we examined In(III)F_3 and In(III)$(OH)_3$ (entries 4 and 5); the disappointing results may be explained by the low solubility of these inorganic metal salts. Therefore, we employed indium(III) hexamethyldisilazide [In(III)$(hmds)_3$],[13] an indium amide source with a substantially higher solubility in organic solvents. Gratifyingly, the catalytic use of this compound provided **3a** in a promising yield (71%, entry 6). To the best of our knowledge, this result represents the *first example of In(III)$(hmds)_3$ being used as a catalyst for organic synthesis.*[14] Further improvement was achieved by using dry methanol (20 mol%) as an additive (entries 7–10), resulting in a shorter reaction time (6 h), even with a catalyst loading of only 2 mol% (entry 9). It should be noted that the catalyst loading could be reduced to as little as 1 mol% under more concentrated conditions with an extended reaction time (entry 10).

Table 2. Scope of the In(III)-catalyzed allylation with **2**.[a]



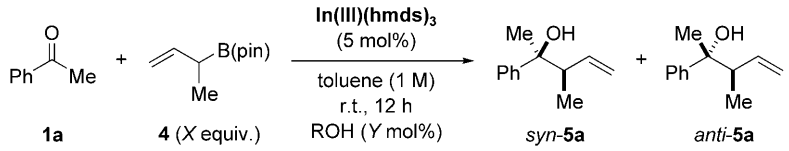


[a] Isolated yields of **3b–s** after purification on silica gel (PTLC).
[b] *Reaction conditions:* In(III)(hmds)$_3$ (10 mol%), THF, 24 h.
[c] *Reaction conditions:* In(III)(hmds)$_3$ (10 mol%), 24 h.

Next, we investigated the scope for ketones (Table 2). The present catalytic carbon–carbon bond formation proceeded smoothly with various acyclic or cyclic aromatic, heteroaromatic, and aliphatic ketones. Furthermore, we consider the compatibility of the In(III) amide catalyst with unprotected O–H and N–H bonds to be remarkable. These results highlight the usefulness of our developed methodology.

We then examined In(III)-catalyzed crotylation of acetophenone using α-methylallyl boronate **4** (Table 3). In the absence of methanol, this catalytic C–C bond formation proceeded slowly to give the desired α-adduct **5a** exclusively in 49% yield, albeit with a poor diastereomeric ratio (*syn*:*anti* = 1.3:1; entry 1). It is noteworthy that γ-addition of **4** was *not* detected. Both the reactivity and the selectivity were improved in the presence of a catalytic amount of methanol as an additive (entry 2), which confirmed the trend observed in the allylation study (*cf.* Table 1). Ethanol and *tert*-butyl alcohol proved to be less effective (en-

Table 3. In(III)-catalyzed crotylation of **1a** with **4**.



Entry	**2** (*X* equiv.)	ROH (*Y* mol%)	Yield [%][a]	*syn*-**5a**:*anti*-**5a**[b]
1	1.1	–	49	1.3:1
2	1.1	MeOH (20)	99	3.2:1
3	1.1	EtOH (20)	56	1.9:1
4	1.1	*t*-BuOH (20)	57	1.1:1
5	1.1	MeOH (100)	63	4.0:1
6	1.1	MeOH (300)	57	10.1:1
7	1.1	MeOH (500)	72	13.3:1
8[c]	1.5	MeOH (300)	87	11.5:1

[a] Isolated yields of **3a** after purification on silica gel (PTLC).
[b] The diastereomeric ratios were determined by ^{1}H NMR spectroscopic analysis of the corresponding isolated product **5a**.
[c] Concentration of **1a** in toluene: 2 M.

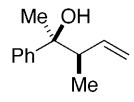
tries 3 and 4). The diastereomeric ratio of **5a** was improved markedly by increasing the amount of methanol progressively to 500 mol% (*syn*:*anti* = 13.3:1; entry 7). Finally, slightly modified conditions provided **5a** in 87% yield with a *syn*:*anti* ratio of 11.5:1 (entry 8).

The practical potential of this new In(III) amide catalyst was demonstrated through the highly selective crotylation of several ketones (Table 4). It is noted that in all cases (i) γ-adducts were *not* observed, and (ii) the desired α-products **5** were isolated in high yields with high *syn*-diastereoselectivity.

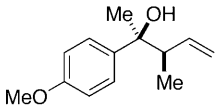
From a mechanistic point of view, the rare, exclusive α-selectivity observed with allyl boronate **4** strongly suggests a B-to-In transmetalation.[15] In this context, it should be noted that the corresponding (*E*)- and (*Z*)-crotyl boronates were shown to react only very sluggishly with **1a**, which is most likely due to steric hindrance (methyl group) at the γ-position during the transmetalation step. ^{1}H and ^{11}B NMR spectroscopic analysis of **2** or **4** in the presence of In(III)$(hmds)_3$ (without **1a** or MeOH) revealed a particularly slow B-to-In transmetalation. Therefore, the initially intended transmetalation process (*cf.* Scheme 1c) seems to be unlikely. At present, we believe that, in the *absence of methanol*, ketone **1a** (as a Lewis base) may activate **4**, resulting in the formation of the corresponding crotylindium amide species, and *boron-activated* **1a**. The crotylindium intermediate may add to the activated electrophile in an *acyclic* transition state to provide **5a** with a low diastereoselectivity (*cf.* Table 3, entry 1). In contrast, in the *presence of an excess of methanol*, this potential Lewis base may trigger B-to-In transmetalation to generate the corresponding crotylindium reagent, which may then react with *uncoordinated* **1a** in a *cyclic* Zimmerman–Traxler-type transition state to give **5a** with high *syn*:*anti* ratios (*cf.* Table 3, entries 6–8). Alternatively, In(III)$(hmds)_3$ may undergo ligand exchange *via* alcoholysis with methanol.[16] In addition, methanol may play a key role in the catalyst turnover step.[17]

The chemistry detailed in this report represents the first catalytic use of a main group 13 metal amide, In(III)$(hmds)_3$, in organic synthesis.[14] The catalytic carbon–carbon bond formations between ketones and boronates proceeded under very mild conditions in high yields with exclusive regioselectivity (α) and high configurational selectivities (*syn*). The most characteristic features of this novel organoindium(III) species are: (i) its remarkable solubility in organic solvents, (ii) its excellent π-Lewis acidity for B-to-In transmetalation, and (iii) the high reactivity of the corresponding *in situ* generated allylindium species. Significantly, in the context of ketone allylation, the new In(III) amide catalyst allows one to *replace toxic stannanes by non-toxic boronates.* Current efforts are being directed toward further mechanistic studies, an asymmetric version, and novel transformations catalyzed by this unique indium(III) Lewis acid.

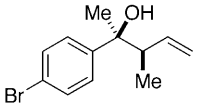
Table 4. Preliminary scope for crotylation with **4**.[a]



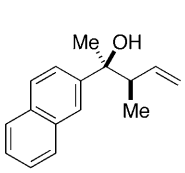
5a:
87% yield
syn:*anti* = 11.5:1



5b:
89% yield
syn:*anti* = 11.5:1



5c:
93% yield
syn:*anti* = 9.0:1



5h:
93% yield
syn:*anti* = 9.0:1

[a] Isolated yields of α-adducts **5a–c** and **5h** after purification on silica gel (PTLC).

[b] *Reaction conditions:* **4** (1.5 equiv.), In(III)$(hmds)_3$ (5 mol%), MeOH (300 mol%), toluene (1–2 M), room temperature, 12 h.

Experimental Section

General Procedure

Indium(III) hexamethyldisilazide[13] (0.1–10 mol%), dry toluene (0.5–2 M), dry methanol (20–300 mol%), the corresponding ketone **1a–1s** (0.4 mmol), and the corresponding boronates **2** or **4** (1.1–1.5 equiv.) were added successively to a flame-dried, 5-mL screw vial with a magnetic stirring bar under argon. The reaction mixture was stirred at room temperature until complete consumption of the corresponding ketone **1** occurred (monitored by ^{1}H NMR analysis of aliquots of the reaction mixtures). The crude reaction mixture was quenched with saturated aqueous Na_2CO_3 solution and extracted with dichloromethane. The organic phases were dried (Na_2SO_4), filtered, and concentrated under vacuum, before purification using preparative thin-layer or flash column chromatography (eluent = hexane → hexane/ethyl acetate = 2:1) to afford the corresponding tertiary homoallyl alcohols **3a–3s**, or **5a–5c**, and **5h**.

Acknowledgements

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[15] Isomerization of allyl boronate **4** and/or product **5a** *via* $In(III)(hmds)_3$ catalysis, under the present conditions, was not observed.

[16] Indeed, $[In(III)(O\text{-}t\text{-}Bu)_3]_2$ is accessible from $In(III)(hmds)_3$ through alcoholysis with *tert*-butyl alcohol (3 equiv.) in toluene at reflux for 24 h (see ref.[13b]). It should be noted that the same alcoholysis reaction using $In(III)Cl_3$ does not proceed with complete conversion, resulting in mixed In(III) compounds (see ref.[13b]).

[17] A reviewer suggested that an acyclic transition state may be possible to give a *syn*-product. We cannot deny this possibility at this moment.

