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Catalytic Use of Indium(0) for Carbon–Carbon Bond Transformations in Water: General Catalytic Allylations of Ketones with Allylboronates

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Innovative catalysis for effective C–C bond transformations in water is an exciting challenge in organic synthesis.¹ During our studies toward environmentally benign catalyst systems in water, we have recently become interested in In(0), a nontoxic, inexpensive, and water-compatible main group metal.² While organoindium reagents are known to tolerate various functional groups,² more than a stoichiometric amount of In metal³ is typically required in synthesis.^{2,4–6} To the best of our knowledge, the catalytic use of In(0) for C–C bond formation is unknown.^{7,8}

Recently, remarkable advances in catalytic allylations of ketones⁹ have been achieved using stannanes,¹⁰ silanes,¹¹ boron reagents,¹² and *in situ* prepared manganese compounds¹³ in combination with various catalysts. Unfortunately, these reactions rely on strictly anhydrous conditions and/or on the use of more than 1 equiv of corrosive and/or toxic allylation agents. Moreover, with only a single exception,^{12a} the substrate scope is limited. Clearly, with respect to safety and environmental concerns, development of general catalytic allylations of ketones in water is of central importance. In earlier reports,¹⁴ we have disclosed indium(I) iodide catalyzed allylations of ketones and acylhydrazones with allylboronates. However, this low oxidation state catalyst readily decomposes in water (redox-disproportionation; see Supporting Information (SI)).¹⁵ We report here the unprecedented catalytic use of In(0) for general catalytic C–C bond transformations in water.

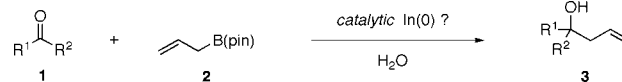
The model study was carried out using acetophenone (**1a**; R¹ = Ph, R² = Me) and allylboronate **2** (pin = pinacolyl) in water (Scheme 1); the noncatalyzed reaction essentially did not proceed, while in the presence of 100 mol% of In(0) powder the desired product **3a** (R¹ = Ph, R² = Me) was cleanly obtained in 83% yield (SI).¹⁶ To our surprise, we were able to quantitatively recover the In metal after the reaction (Figure 1).^{17,18} Importantly, based on this crucial observation, we succeeded in reducing the catalytic loading to as little as 0.1 mol% under rigorously optimized conditions (90% yield; SI).^{16,19} It is truly remarkable that this C–C bond formation selectively proceeds with a catalytic amount of In(0), since generally 1 to 2 equiv of In metal are required for metal-to-In transmetalations.^{4a,c} We then screened organic solvents to confirm the required presence of water (SI). Under neat conditions only a trace amount of product **3a** was formed; therefore, we were able to rule out that this reaction proceeds in concentrated organic phase droplets. Moreover, the use of various organic solvents²⁰ proved to be ineffective; thus, water likely plays a key role in the present reaction. This dramatic solvent effect stands in sharp contrast to our earlier report on In(I) catalysis, in which anhydrous THF was the most efficient solvent.^{14a}

Next, we carried out additional experiments to gain mechanistic insights. The independent use of In(I) and (III) compounds (3 mol%) for the allylation of **1a** with **2** in water revealed that In(I) was significantly more active than In(III) (SI).^{21,22} A possible B-to-In transmetalation was examined by using an allylindium species, independently generated *in situ* from allyl bromide with In(0) (100 mol%) in water; the isolated yield was moderate (40%). Preliminary ¹H and ¹¹B NMR spectroscopic experiments in D₂O with allylboronate **2** in the presence of In(0) (100 mol%) indicated substantial decomposition of **2** in the absence of **1a**; another allyl species could not be identified. NMR spectroscopic monitoring of the In(0)-catalyzed



Figure 1. Recovery of metal ingot after In(0)-catalyzed allylation.^{17,18}

Scheme 1. In(0)-Catalyzed Allylation of Ketones **1** with **2** in Water



allylation of **1a** with **2** in D₂O revealed the direct formation of product **3a**; the allylborated ketone (O–B bond) was not detected.

At the current stage, we believe that simple Lewis base or acid activation of **2** with In(0) does not play the key role in our catalytic system (species **A** or **B**; SI). It is proposed that In shows a new type of catalytic activation of both allylboronate and ketone; the key may be the use of water as a small polar protic solvent with a high dielectric constant, being able to activate In(0) as a Lewis base (species **C**; SI).^{23,24} Thus, In(0) may serve as a surface-activated dual catalyst capable of activating **2** as a Lewis base and **1a** as a Lewis acid. Alternatively, In(0) may transfer one electron to the B atom of **2** (SET),²⁵ thereby triggering the formation of a reactive allylindium(I) reagent at the metal surface *via* catalytic transmetalation (species **D**; SI). We surmise that the reaction proceeds at the In metal surface.

Next, we investigated the scope of ketones **1** for this In(0)-catalyzed allylation with **2** under optimized conditions (Scheme 1, Table 1).¹⁹ High yields were obtained for various aromatic, heteroaromatic, and aliphatic ketones. Remarkably, both acyclic and cyclic substrates containing various functional groups such as fluoro, bromo, hydroxy, methoxy, and amino groups were tolerated.

Moreover, we examined the use of α -methylallylboronate **4** to demonstrate the potential of this In(0)-catalyzed C–C bond formation in water (Table 2). We observed highly unusual formal α -addition²⁶ of **4** to all tested ketones **1**; γ -adducts were not detected. Interestingly, this constitutional selectivity contrasts with the exclusive γ -addition of **4** to carbonyl compounds under Lewis or Brønsted acid catalysis²⁷ and is consistent with catalytic transmetalation at the In metal surface (species **D**; SI).²⁸ Gratifyingly, the corresponding products **5** were obtained with exceptionally high *syn*-diastereoselectivity²⁹ in high yields. We consider these results remarkable since geometrically pure crotyl reagents^{10b,11–13} are generally required to selectively form these adducts, but with the exception of sporadic reports,^{10b,11c,12b} diastereoselectivities proved to be modest.^{11a,b,12a,13}

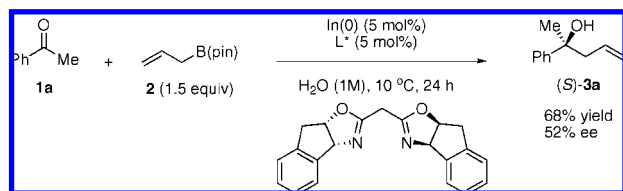
Finally, we investigated the catalytic asymmetric allylation of **1a** with **2** in water by using In(0)²² combined with a chiral bis(oxazoline) ligand in a molar ratio of 1:1 (Scheme 2). The desired

Table 1. Scope of Ketones **1** for In(0)-Catalyzed Allylation with **2** in Water¹⁹

entry	ketone 1	yield (%)	entry	ketone 1	yield (%)
1	1a : R ¹ = Ph, R ² = Me	92	12	1l : R ^{1,2} = -(CH ₂) ₅ -	88
2	1b : R ¹ = 2-F-C ₆ H ₄ , R ² = Me	91	13	1m : R ^{1,2} = -(CH ₂) ₄ -	90
3	1c : R ¹ = 2-Br-C ₆ H ₄ , R ² = Me	98	14	1n : R ^{1,2} = -CH=CH-(CH ₂) ₃ -	82
4	1d : R ¹ = 2-HO-C ₆ H ₄ , R ² = Me	90	15	1o : R ¹ = <i>n</i> -pent, R ² = Me	86
5	1e : R ¹ = 2-MeO-C ₆ H ₄ , R ² = Me	96	16	1p : α-tetralone	90
6	1f : R ¹ = 4-Me-C ₆ H ₄ , R ² = Me	89	17	1q : β-tetralone	99
7	1g : R ¹ = 1-naphthyl, R ² = Me	87	18	1r : R ¹ = 2-thienyl, R ² = Me	95
8	1h : R ¹ = Ph, R ² = Et	95	19	1s : R ^{1,2} = -(CH ₂) ₂ NBn(CH ₂) ₂ -	88
9	1i : R ¹ = Ph, R ² = <i>n</i> -Pr	92	20	1t : R ¹ = 4-pyridyl, R ² = Me	81
10	1j : R ¹ = Ph(CH ₂) ₂ , R ² = Me	97	21	1u : R ¹ = 3-pyridyl, R ² = Me	87
11	1k : R ¹ = 4-MeO-C ₆ H ₄ (CH ₂) ₂ , R ² = Me	95	22	1v : R ¹ = 2-furyl, R ² = Me	82

Table 2. In(0)-Catalyzed Formal α-Addition of **4** to Ketones **1** in Water

entry	ketone 1	yield (%)	α/γ	syn-5/anti-5
1	1a : R ¹ = Ph, R ² = Me	99	>99:1	58:1
2	1b : R ¹ = 2-F-C ₆ H ₄ , R ² = Me	93	>99:1	32:1
3	1e : R ¹ = 2-MeO-C ₆ H ₄ , R ² = Me	90	>99:1	1:65
4	1g : R ¹ = 1-naphthyl, R ² = Me	75	>99:1	84:1
5	1p : α-tetralone	72	>99:1	32:1
6	1u : R ¹ = 3-pyridyl, R ² = Me	91	>99:1	40:1

Scheme 2. Preliminary Study of Asymmetric In(0) Catalysis in Water

homoallylic alcohol **3a** was isolated with 52% ee in 68% yield, which is to the best of our knowledge the best result so far obtained for catalytic asymmetric allylation of **1a** in water. Other more effective methods require strictly anhydrous conditions.^{10a,c,11–13}

In conclusion, we have discovered an unprecedented catalytic use of In(0) for C–C bond transformations. Remarkably, water is required for these general allylations to proceed. Importantly, the In metal catalyst can be recovered and reused without loss of activity. Moreover, the potential of this concept has been demonstrated through highly regio- and diastereoselective reactions and its applicability to asymmetric catalysis in water. Further mechanistic studies on the catalytic activation of B reagents with In(0) in water and the extension of this strategy to other catalytic bond transformations will be reported in due course.

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Supporting Information Available: Full experimental details and NMR spectral reproductions for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (16) No undesired compounds such as pinacol coupling type or reduction products were detectable in the crude reaction mixtures.
- (17) Proof of In(0) by SEM, EDS, ICP, and XFA analyses (SI).
- (18) Figure 1 shows the reaction system with 10 mol% of In powder before reaction (left) and recovered In ingot after reaction (right). The recovered ingot could be reused without loss of activity (SI).
- (19) Optimized conditions: **1** (0.5 mmol), **2** (1.5 equiv), In(0) (3 mol%), H₂O (1 M), 30 °C, 24 h. Ga(0) as a catalyst proved to be much less effective (low yield); the use of allylsilanes did not give any reaction.
- (20) *n*-Hexane, toluene, THF, DCM, MeCN, DMF, MeNO₂, DMSO, *t*-BuOH, *n*-BuOH, *i*-PrOH, EtOH.
- (21) In(I) readily decomposed upon contact with water to form In(0), which is surmised to be the real catalyst;²² In(III) is stable in water.
- (22) Kinetics and selectivity control experiments were also carried out (SI).
- (23) Partial electron transfer from the oxygen lone pair of H₂O to the In metal surface may occur (Lewis base activation).
- (24) Alternatively, water may be necessary for the stabilization of key intermediates or the hydrolysis of the assumed O–B bond in the initially formed allylborated ketone. The size, the H-bonding ability, and the proton acidity of the solvent might be critical as well.
- (25) Single electron transfer (SET) might be facilitated by the low first ionization enthalpy of In (558.3 kJ/mol): <http://www.webelements.com>.
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- (28) Crotylboronates proved to be unreactive in the present reaction system.
- (29) The *anti*-diastereoselectivity for substrate **1e** (Table 2, entry 3) might be explained with bidentate coordination of **1e** to the crotylindium species (SI).

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