ACCOUNTS
of chemical research

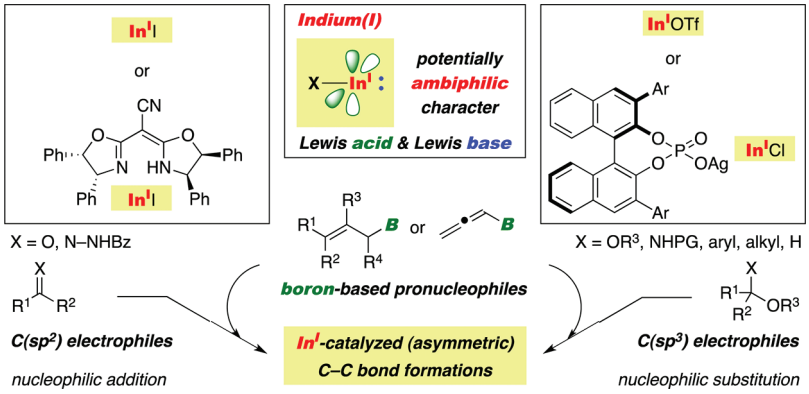
Low-Oxidation State Indium-Catalyzed C–C Bond Formation

UWE SCHNEIDER‡ AND SHŪ KOBAYASHI*

The University of Tokyo, Department of Chemistry, School of Science and Graduate School of Pharmaceutical Sciences, Hongo, 7-3-1 Bunkyo-ku, Tokyo 113-0033, Japan

RECEIVED ON JANUARY 14, 2012

CONSPECTUS



The development of innovative metal catalysis for selective bond formation is an important task in organic chemistry. The group 13 metal indium is appealing for catalysis because indium-based reagents are minimally toxic, selective, and tolerant toward various functional groups. Among elements in this group, the most stable oxidation state is typically +3, but in molecules with larger group 13 atoms, the chemistry of the +1 oxidation state is also important. The use of indium(III) compounds in organic synthesis has been well-established as Lewis acid catalysts including asymmetric versions thereof. In contrast, only sporadic examples of the use of indium(I) as a stoichiometric reagent have been reported: to the best of our knowledge, our investigations represent the first synthetic method that uses a catalytic amount of indium(I).

Depending on the nature of the ligand or the counteranion to which it is coordinated, indium(I) can act as both a Lewis acid and a Lewis base because it has both vacant p orbitals and a lone pair of electrons. This potential ambiphilicity may offer unique reactivity and unusual selectivity in synthesis and may have significant implications for catalysis, particularly for dual catalytic processes. We envisioned that indium(I) could be employed as a metallic Lewis base catalyst to activate Lewis acidic boron-based pronucleophiles for selective bond formation with suitable electrophiles. Alternatively, indium(I) could serve as an ambiphilic catalyst that activates both reagents at a single center.

In this Account, we describe the development of low-oxidation state indium catalysts for carbon–carbon bond formation between boron-based pronucleophiles and various electrophiles. We discovered that indium(I) iodide was an excellent catalyst for α-selective allylations of C(sp^2) electrophiles such as ketones and hydrazones. Using a combination of this low-oxidation state indium compound and a chiral semicorrin ligand, we developed catalytic highly enantioselective allylation, crotylation, and α-chloroallylation reactions of hydrazones. These transformations proceeded with rare constitutional selectivities and remarkable diastereoselectivities. Furthermore, indium(I) triflate served as the most effective catalyst for allylations and propargylations of C(sp^3) electrophiles such as *O,O*-acetals, *N,O*-aminals, and ethers, and we applied this methodology to carbohydrate chemistry. In addition, a catalyst system composed of indium(I) chloride and a chiral silver BINOL-phosphate facilitated the highly enantioselective allylation and allenylation of *N,O*-aminals. Overall, these discoveries demonstrate the versatility, efficiency, and sensitivity of low-oxidation state indium catalysts in organic synthesis.

1. Introduction

Development of innovative metal catalysis for selective bond formation is an important task in organic chemistry.[1] Group 13 occupies a distinguished position in the periodic table, being adjacent to group 14 with carbon as the element of central importance in organic chemistry. In

Published on the Web 05/24/2012 www.pubs.acs.org/accounts
10.1021/ar300008t

FIGURE 1. Indium(III) versus indium(I).

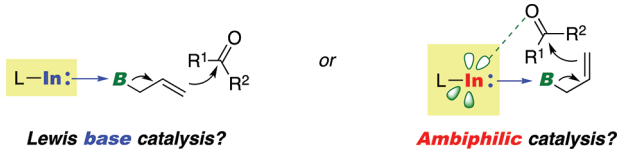


FIGURE 2. Unprecedented indium(I) catalysis?

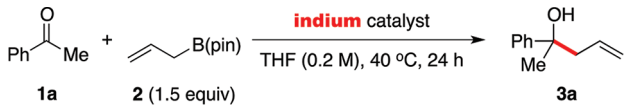
general, the oxidation state +III is the most stable among group 13 elements; however, going down the group, the low-oxidation state +I becomes increasingly relevant.[2] The group 13 metal indium is appealing for catalysis because indium-based compounds have low toxicity, are selective, and are tolerant toward various functional groups.[3] Indeed, *indium(III)* reagents are well-established Lewis *acids* in synthesis, including asymmetric catalysis.[4] In contrast, the chemistry of indium in its *low-oxidation state +I* is underexplored; only sporadic examples of its use as a stoichiometric reagent have been reported.[5] To the best of our knowledge, at the outset of our investigations a synthetic method involving the use of a catalytic amount of indium(I) was unknown. Nevertheless, it has been shown that *indium(I)* may act as an *acid* and as a *base* because of the presence of both vacant p orbitals and an electron lone pair.[6] This potential *ambiphilicity* may offer unique reactivity and unusual selectivity in synthesis, and may have significant implications for catalysis, especially for dual catalytic processes.

2. Initial Concept for Unprecedented Indium(I) Catalysis

2.1. Conventional Indium(III) versus Unexploited Indium(I). Group 13 elements, e.g., indium, in their most stable oxidation state of +III are typically strong Lewis acids because these species possess a vacant low-energy p orbital (Figure 1). Indeed, *indium(III)* is among the most commonly employed Lewis *acids* in synthesis, including asymmetric catalysis.[4] In sharp contrast, indium(I) has both vacant p orbitals and an electron lone pair (Figure 1).[6] Thus, *indium(I)* may be considered as both an *acid* and a *base*.[6] Compared with indium(III), indium(I) is more electron-rich and is therefore a weaker Lewis acid. However, the dual acid–base character of indium(I), which may be called *ambiphilicity*, may offer unique opportunities in synthesis. This intriguing feature of indium(I) may have significant implications for the development of dual catalysis.

2.2. Indium(I) as a Metallic Lewis Base or an Ambiphilic Catalyst? Recently, Power and co-workers have demonstrated that an electron-rich indium(I) species can act as a metallic σ-donor to form a stoichiometric donor–acceptor complex with a boron electron-pair acceptor.[7] On the basis of this seminal report, we envisioned the development of *innovative catalytic* processes, provided (i) a boron-based compound with a transferable organic moiety is used and (ii) the indium(I)–boron(III) interaction is relatively weak. We anticipated that allylic boron compounds could be suitable targets. Conceptually, indium(I) may thus be employed as a *metallic Lewis base* catalyst to activate Lewis acidic allyl boron pronucleophiles for bond formation with electrophiles such as ketones (Figure 2). Alternatively, because it should still display Lewis acidity, indium(I) may be envisaged as an *ambiphilic* catalyst that may activate both reagents (Figure 2). This scenario would correspond to dual catalytic activation of two substrates at a single metal center. Importantly, asymmetric catalysis may be accessible if a chiral ligand is attached to indium(I).

TABLE 1. Examination of Various Indium Catalysts for Ketone Allylation[8]



entry	indium catalyst (mol %)	yield[a] (%)
1		trace
2	$In^{I}I$ (100)	quant
3	$In^{I}I$ (20)	99
4	In^{0} (20)	4
5	$In^{III}I_3$(10)	3
6	$In^{I}Cl$ (20)	65
7	$In^{I}Br$ (20)	87
8	$In^{I}OTf$ (20)	39
9	$In^{III}(OTf)_3$ (20)	16
10	$In^{I}I$ (1)	99[b]

[a]Isolated yield of **3a** after purification on silica gel (preparative thin-layer chromatography (PTLC)). [b]1 M in THF under otherwise identical conditions.

3. Catalytic Use of Indium(I) for C–C Bond Formation with C(sp^2) Electrophiles

3.1. Allylation and Crotylation of Ketones with Allyl Boronates: Rare α-Selectivity. Initially, we investigated catalytic activation of allylic boronates for C–C bond formation with ketones. We first examined the reaction between

SCHEME 1. Scope for Ketone Allylation[8]

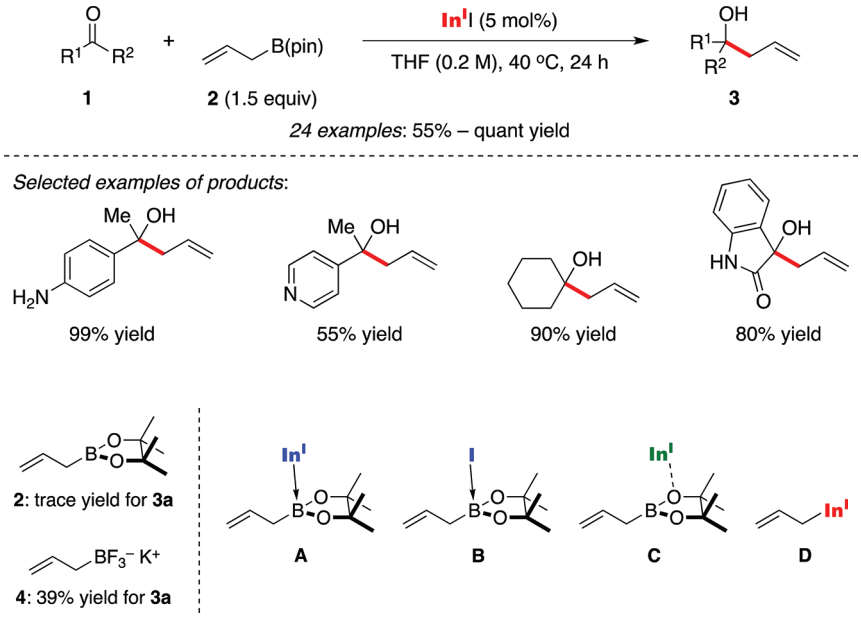
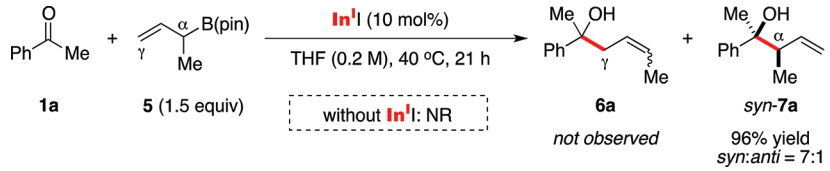


FIGURE 3. Mechanistic scenarios for indium(I) catalysis.[8]

SCHEME 2. Mechanistic Control Experiment[9]



acetophenone (**1a**) and allyl boronate **2** in tetrahydrofuran (THF) (Table 1).[8] We employed commercially available indium(I) iodide as the indium source, which—in the absence of appropriate ligands—has a relatively low solubility in organic solvents.

In contrast to the uncatalyzed reaction, the indium(I)-mediated transformation cleanly afforded the desired homoallylic alcohol **3a** (Table 1, entry 1 versus entry 2); a similar result was observed at 20 mol % catalyst loading (entry 3). Indium(I) may redox-disproportionate to form indium(0) and indium(III) in a molar ratio of 2:1.[2] In the present study, however, the use of these potential indium catalysts proved to be ineffective (entries 4 and 5), which supports the idea that indium(I) is the real catalyst. The best counteranion among the indium(I) compounds tested was shown to be iodide (entry 3 versus entries 6–8). Interestingly, indium(I) triflate was a better catalyst than indium(III) triflate (entry 8 versus entry 9), although indium(III) is a stronger Lewis acid than indium(I). Finally, the catalyst loading could be decreased to 1 mol % (entry 10).

The scope proved to be excellent, including various acyclic or cyclic aromatic and aliphatic ketones as well as a range of heterocyclic ketones (Scheme 1).[8] Importantly, several functionalities, such as hydroxy, methoxy, amino, amido, chloro, bromo, and nitro groups, were tolerated.

Next, we investigated the mechanism of this unprecedented indium(I) catalysis.[8] Allyl trifluoroborate **4** was found to be significantly more reactive in the uncatalyzed ketone allylation than was **2** (Figure 3). As mentioned in our working hypothesis, one catalysis pathway may involve activation of **2** with indium(I) as a metallic Lewis base, thereby generating allyl borate **A** with enhanced nucleophilicity (Figure 3). Alternatively, the iodide-induced formation of allyl borate **B** may be imagined (Figure 3). Therefore, we used fluoride anion sources in the allylation of **1a** with **2**. However, these metal-free Lewis bases proved to be only moderately effective, which may indicate that sole Lewis base activation of **2** is insufficient for effective C–C bond formation; thus, indium(I) may simultaneously act as a Lewis acid activator of **1a** (dual activation). On the other hand, sole Lewis acid activation of **2**

with indium(I), to form intermediate **C** (Figure 3), seems unlikely considering our poor results with more Lewis acidic indium(III). Finally, another mechanism may involve activation of **2** through transmetalation to generate allyl indium(I) (**D**, Figure 3). Therefore, we examined allyl indium reagents prepared independently under Barbier-type conditions from allyl halides; however, product **3a** was formed only in moderate yields in these cases. NMR experiments with **2** and indium(I) iodide, in the absence of **1a**, proved to be inconclusive regarding the identity of the catalytically active species.

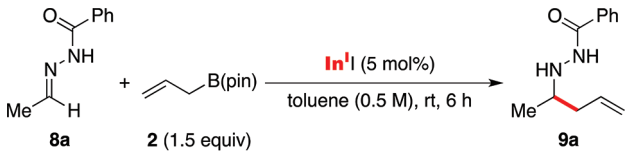
Thus, we carried out an experiment with α-methylallyl boronate **5**, for which α- and γ-addition products may be obtained (Scheme 2).[9] In contrast to the uncatalyzed reaction, indium(I) catalysis furnished exclusively the rare α-adduct **7a**; the conventional γ-adduct **6a** was not detected. These results suggest transmetalation as the most likely pathway.

At this stage, we had discovered an unprecedented catalytic activation of allylic boronates with indium(I) and had applied this method successfully to a general catalytic ketone allylation and crotylation.[8,9] Next, we aimed to investigate imines as substrates. Clearly, our goal was to develop *catalytic asymmetric imine allylation and crotylation*, the latter of which required complete α-addition.

3.2. Allylation and Crotylation of Hydrazones: An Intriguing Effect of Alcohols on Reactivity and Diastereoselectivity. We selected *N*-benzoylhydrazones as imine surrogates because they are bench-stable and their C–C bond-formed products (hydrazides) are cleavable to release the corresponding free amines.[10] The model reaction dealt with the use of hydrazone **8a** and boronate **2** in toluene (Table 2).[11] The use of methanol proved to be crucial in obtaining the homoallylic hydrazide **9a** (Table 2, entry 1 versus entry 2). This phenomenon may be ascribed to methanol being (i) a better solvent for **8a** than is toluene, (ii) an additional Lewis base for **2**, or (iii) the required Brønsted acid for the catalyst turnover. The use of 5 equiv of methanol in the presence of catalytic indium(I) proved to be optimal (entry 3); in the absence of indium(I), the yield dropped substantially (entry 4).

These conditions proved to be applicable to various hydrazones **8** (Scheme 3).[11] The scope includes both aliphatic and aromatic aldimines and ketimines; a variety of

TABLE 2. Hydrazone Allylation: Effect of Methanol on Reactivity[11]



entry	In^{I}I (5 mol %)	MeOH	yield[a] (%)
1	+	–	trace
2	+	+ (1 equiv)	40
3	+	+ (5 equiv)	99
4	–	+ (5 equiv)	25

[a]Isolated yield of **9a** after purification on silica gel (PTLC).

SCHEME 3. Scope for Hydrazone Allylation; Ketone Allylation Revisited[11]

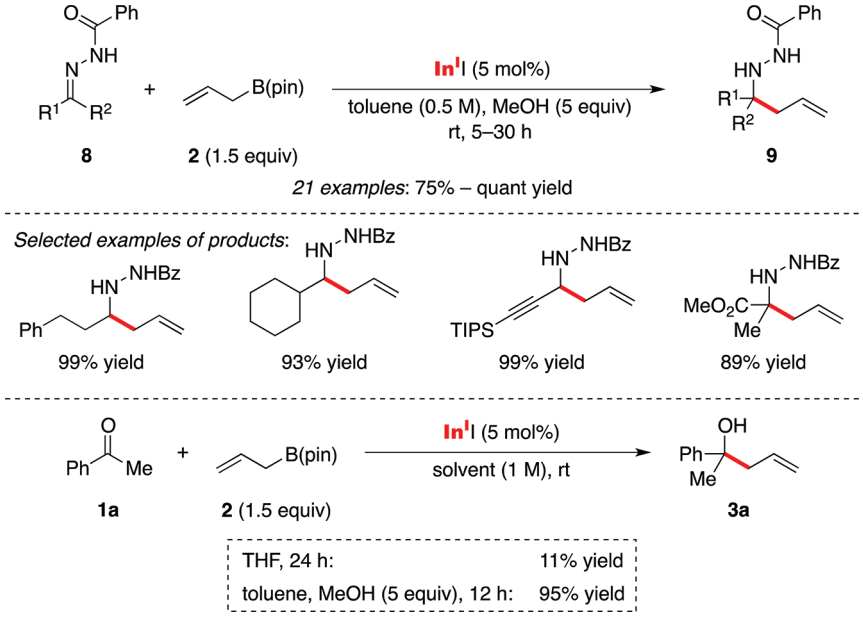
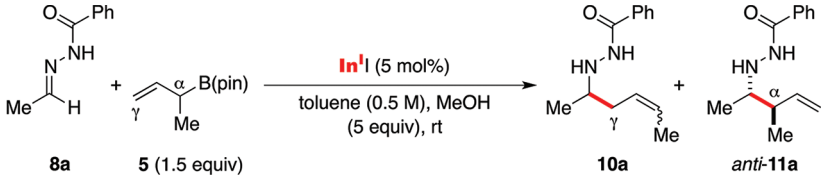


TABLE 3. Hydrazone Crotylation: Effect of Indium(I) on Reactivity and Regioselectivity[12]

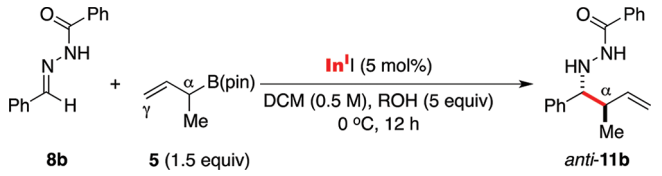


8a **5** (1.5 equiv) **10a** *anti*-**11a**

entry	**In^{I}**I (5 mol %)	time (h)	yield[a](%)	α/γ	*anti*-**11a**/*syn*-**11a**
1	−	36	36	1:6.7	5.3:1
2	+	6	87	11.5:1	5.3:1

[a]Isolated yield of a mixture of **10a** and **11a** after purification on silica gel (PTLC).

TABLE 4. Hydrazone Crotylation: Effect of Alcohols on Reactivity and Diastereoselectivity[12]



8b **5** (1.5 equiv) *anti*-**11b**

entry	ROH (5 equiv)	yield[a] (%)	α/γ	*anti*-**11b**/*syn*-**11b**
1		9	>99:1	13.3:1
2	MeOH	57	>99:1	6.7:1
3	EtOH	86	>99:1	7.3:1
4	^{i}prOH	29	>99:1	32.3:1
5	^{t}BuOH	8	>99:1	>99:1
6	PhOH	20	>99:1	5.7:1
7	$HOCH_2CH_2OH$	25	>99:1	2:1
8	HFIP	17	>99:1	4.6:1

[a]Isolated yield of **11b** after purification on silica gel (PTLC).

functional groups are tolerated as well. Moreover, ketone allylation could be significantly improved with this new solvent system (Scheme 3).[11]

Next, we examined hydrazone crotylation (Table 3).[12] The initial set of experiments employing hydrazone **8a** and boronate **5** revealed a dramatic effect of indium(I) on reactivity and regioselectivity. Indeed, the uncatalyzed reaction proceeded only sluggishly, resulting in the predominant formation of the conventional γ-adduct **10a** (Table 3, entry 1). However, catalytic use of indium(I) resulted not only in rate acceleration but also in the preferred generation of the rare α-adduct **11a** (entry 2). These experiments clearly demonstrated the impact of indium(I) on the reaction outcome.

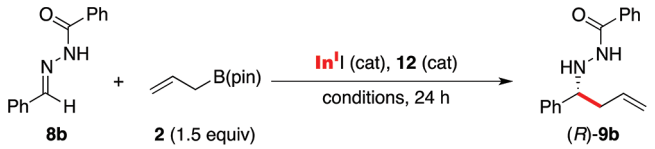
In view of a synthetically useful asymmetric crotylation, we optimized regio- and diastereoselectivities (Table 4).[12] A quick solvent screening revealed dichloromethane (DCM) to be a better solvent than toluene. Indeed, the reaction between **8b** and **5** at 0 °C proceeded with complete α-selectivity and afforded an improved diastereoselectivity, despite a very low yield for **11b** (Table 4, entry 1). In analogy to the allylation series,[11] we screened various alcohols (entries 2−8). Regardless of the employed protic additive, the reaction proceeded α-selectively. Although ethanol was found to be the best solvent for reactivity (entry 3), the use of *tert*-butanol provided complete diastereoselectivity (entry 5).

For the scope of this diastereoselective crotylation, we selected isopropanol as a protic cosolvent.[12] Accessible substrates include aliphatic, aromatic, alkenyl, alkynyl, and α-ester hydrazones providing both high to complete α-regioselectivity and *anti*-diastereoselectivity. These new conditions proved to be applicable as well to diastereoselective ketone crotylation.[12]

At this stage, we had uncovered various indium(I)-catalyzed *racemic* C−C bond formations with allylic boronates.[8,9,11,12] NMR-spectroscopic analyses suggested the in situ generation of reactive allylic indium(I) species via transmetalation.[11] Next, we turned our attention to the development of *asymmetric catalysis*.

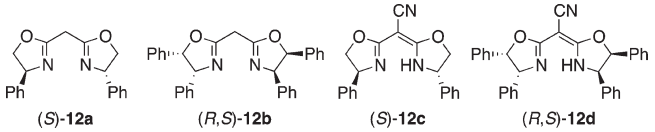
3.3. First Asymmetric Low-Oxidation State Indium Catalysis: Use of a Chiral Ligand. The crucial importance of indium(I) ligation for both structural and physical properties[7,13] and chemical reactivity[14] has been demonstrated. However, a *chiral* indium(I) complex and its use for *asymmetric* C−C bond formation were unknown when we started our investigations into asymmetric catalysis. Initial experiments dealt with a ligand screening for the reaction employing hydrazone **8b** and boronate **2** in the presence of a catalytic amount of indium(I) (Table 5).[15] Chiral bis(oxazoline) ligands (*S*)-**12a** and (*R*,*S*)-**12b** were found to give the desired product **9b** with promising asymmetric induction; in DCM at room temperature (rt), (*R*,*S*)-**12b** proved to be more efficient than (*S*)-**12a** (Table 5, entries 1 and 2). Although the

TABLE 5. Optimization and Control Experiments for Asymmetric Indium(I) Catalysis[15]



entry	In^{I}I (mol %)	**12** (mol %)	conditions	yield[a] (%)	*er*
1	10	(*S*)-**12a** (10)	DCM, rt	40	81:19[b]
2	10	(*R*,*S*)-**12b** (10)	DCM, rt	65	86:14
3	10	(*R*,*S*)-**12b** (10)	toluene, rt	36	62:38
4	10	(*R*,*S*)-**12b** (10)	toluene–MeOH (16:1), rt	89	96:4
5	5	(*R*,*S*)-**12b** (10)	toluene–MeOH (16:1), 0 °C	quant	98:2
6[c]	5	(*S*)-**12c** (5)	toluene–MeOH (16:1), 0 °C	90	97:3[b]
7[c]	5	(*R*,*S*)-**12d** (5)	toluene–MeOH (16:1), 0 °C	99	98:2
8	5	(*R*,*S*)-**12d** (5)	toluene–EtOH (16:1), 0 °C	21	98:2
9[d]	5	(*R*,*S*)-**12d** (5)	toluene–^{i}PrOH (16:1), 0 °C	quant	95:5
10[c]		(*R*,*S*)-**12d** (5)	toluene–MeOH (16:1), 0 °C	trace	ND
11[d]	5[e]	(*R*,*S*)-**12d** (5)	toluene–MeOH (16:1), 0 °C	25	89:11

[a]Isolated yield of **9b** after purification on silica gel (PTLC). [b]Use of (*S*)-**12a** or (*S*)-**12c**/(*S*)-**9b** was obtained as the major enantiomer. [c]Reaction time: 12 h. [d]Reaction time: 48 h. [e]Use of In^{III}I$_3$ instead of In^{I}I; ND = not determined.



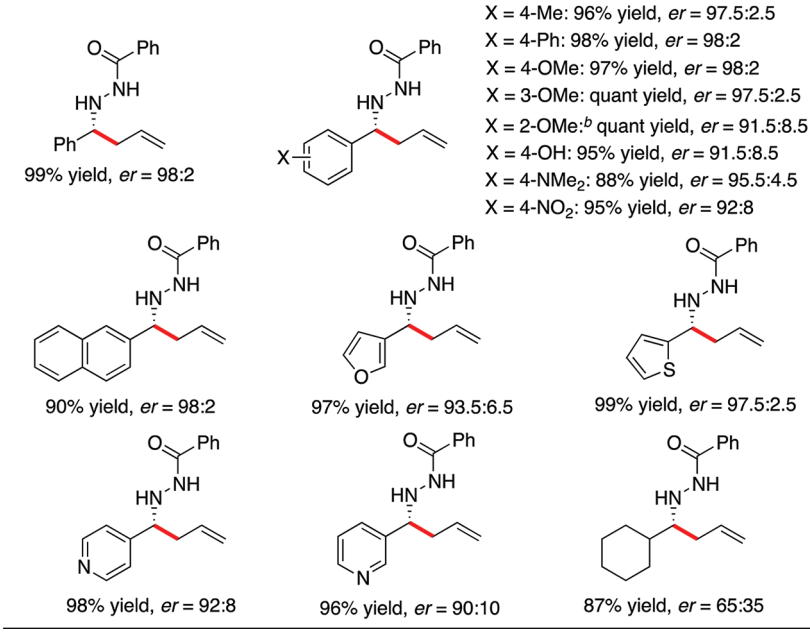
enantioselectivity dropped in toluene, high asymmetric induction was restored in toluene–MeOH (16:1; entries 3 and 4). Further experiments at 0 °C revealed that the use of chiral semicorrin ligands (*S*)-**12c** and (*R*,*S*)-**12d** showed a significant rate enhancement, while maintaining the exceptional level of asymmetric induction (entries 5–7). Other alcohols did not lead to further improvement (entries 8 and 9). The allylation essentially did not proceed in the absence of indium(I), and indium(III) proved to be substantially less effective (entries 10 and 11).

We consider this unprecedented asymmetric indium(I) catalysis remarkable from several points of view. (i) Contrary to reported reactions of indium(I) halides with Lewis bases (ligands),[2,14] we did not observe redox-disproportionation of indium(I). (ii) We did not detect oxidative insertion of indium(I) into the reactive C–Cl bond of DCM, as reported for indium(I)–crown ether complexes.[14] (iii) To the best of our knowledge, the excellent enantioselectivity obtained for product **9b** is to date the best result for metal-catalyzed asymmetric allylation of aromatic imine derivatives.[16] (iv) These findings reveal the crucial role of chiral ligands **12a**–**d** in stabilizing the intrinsically labile indium(I) center and in creating an excellent asymmetric environment.

Next, we investigated the scope for hydrazones **8** (Table 6).[15] Various aromatic or heteroaromatic substrates bearing important functionalities, such as free hydroxy, methoxy, tertiary amino, and nitro groups, were allylated in high yields with excellent enantioselectivity. Aliphatic hydrazones proved to be less efficient in terms of asymmetric induction.

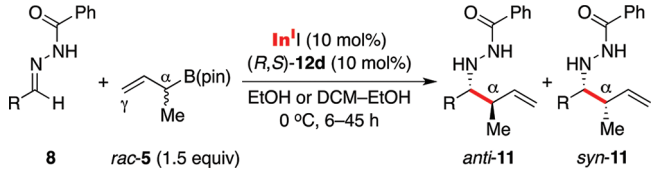
We then examined catalytic asymmetric crotylation (Table 7).[15] Initial trials with **8a** and *rac*-**5** under our reported racemic conditions,[12] in the presence of various chiral ligands, provided the desired product **11a** only with disappointing selectivities. After extensive experimentation, however, excellent selectivities for α-adducts **11** could be obtained using various aromatic or heteroaromatic substrates **8** in the presence of a catalyst system composed of indium(I) iodide and ligand (*R*,*S*)-**12d**. Characteristic features of this asymmetric indium(I) catalysis are as follows. (i) The unusual α-*selectivity* observed with *rac*-**5** contrasts with its exclusive γ-*selectivity* in the absence of a catalyst[17] and under acid catalysis;[18] this rare α-selectivity suggests transmetalation *prior* to C–C bond formation. (ii) Geometrically pure crotyl reagents are not required, and the use of boronate *rac*-**5** provided enantiomerically enriched *anti*-**11**, which is remarkable as the preparation of **5** in *enantiomerically enriched* form is not trivial.[18] (iii) Our *catalytic indium(I)* procedure provides substantially higher constitutional and configurational selectivities for product **11a** compared with a recently reported *stoichiometric indium(0)* method.[19]

TABLE 6. Scope for Enantioselective Hydrazone Allylation[15]



[a]Isolated yield of **9** after purification on silica gel (PTLC). [b]Reaction temperature: −20 °C.

TABLE 7. Scope for Enantioselective Hydrazone Crotylation[15]

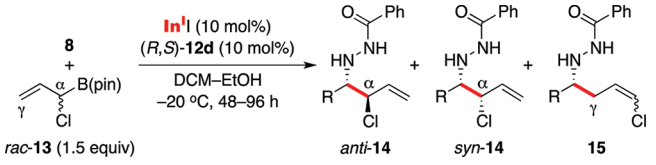


entry	R	α/γ	yield[a] (%)	*anti*-**11**/*syn*-**11**	*er* (*anti*-**11**)
1	Ph	>99:1	85	19:1	97:3
2[b]	4-Me−C_6H_4	>99:1	quant	8:1	96:4
3	4-MeO−C_6H_4	>99:1	86	19:1	96.5:3.5
4	3-MeO−C_6H_4	>99:1	90	7:1	94.5:5.5
5[c]	4-HO−C_6H_4	>99:1	98	11:1	94:6
6	6-Cl−C_6H_4	>99:1	83	17:1	92:8
7[b]	3-furyl	>99:1	98	11:1	96.5:3.5
8	2-thienyl	>99:1	quant	15:1	94:6

[a]Isolated yield of α-adduct **11** after purification on silica gel (PTLC). [b]Reaction temperature: −20 °C. [c]Use of (*S*)-**12c**: the opposite enantiomer was obtained as the major enantiomer.

Next, we employed α-chloroallyl boronate *rac*-**13** (Table 8),[15] a rarely used yet versatile nucleophile that adds in the absence of a catalyst with γ-selectivity to electrophiles.[20] Remarkably, under the present asymmetric

TABLE 8. Enantioselective Hydrazone α-Chloroallylation[15]



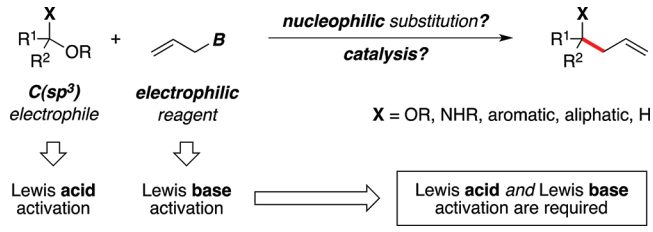
entry	R	α/γ	yield[a] (%)	*anti*-**14**/*syn*-**14**	*er* (*anti*-**14**)
1	Ph	49:1	84	99:1	92:8
2	2-naphthyl	99:1	71	33:1	90.5:9.5
3	2-thienyl	>99:1	89	99:1	93:7

[a]Isolated yield of α-adduct **14** after purification on silica gel (PTLC).

indium(I) catalysis, *rac*-**13** displays almost exclusive α-selectivity. Highly functionalized α-adducts **14** were formed in good yields with exceptionally high *anti*-diastereoselectivities and high enantioselectivities.

Our attention then turned to the mechanism of this catalytic asymmetric C–C bond formation.[15] Indium(I) iodide and the semicorrin ligand (*R*,*S*)-**12d** (ratio = 1:1) were stirred in toluene–MeOH (16:1) at rt for 1 h. MALDI–TOF

SCHEME 4. Catalytic Nucleophilic Substitution with an Electrophilic Allylic Boron Reagent?



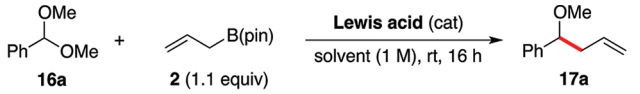
analyses of this mixture revealed the in situ generation of a metal–ligand complex in a ratio of 1:1. NMR-spectroscopic analyses of this complex, in order to monitor a plausible transmetalation, proved to be inconclusive. Nevertheless, we propose the in situ formation of chiral allylic indium–ate complexes (from **2**, *rac*-**5**, and *rac*-**13**), which may undergo C–C bond formation with **8** via a *cyclic transition state* to provide **9**, *anti*-**11**, and *anti*-**14**, respectively. This chemistry[15] represents the *first example of asymmetric indium(I) catalysis*, which is of fundamental importance.

4. Catalytic Use of Indium(I) for C–C Bond Formation with C(sp^3) Electrophiles

4.1. Allylation and Propargylation of *O,O*-Acetals and *N,O*-Aminals: A Borono Variant of Hosomi–Sakurai Reactions. Allylic boronates have been employed for *uncatalyzed* additions to C(sp^2) electrophiles, such as aldehydes, to form homoallylic alcohols.[17,20] This unique reactivity is ascribed to internal Lewis base activation (C=O → B) in a cyclic transition state. After a seminal report on *metal-catalyzed* addition of allylic boronates to aldehydes,[21] *catalytic* additions to ketones and imines have been developed.[8,9,11,12,15,22] Acetals, aminals, ethers, and carbohydrates are abundant in nature and play a key role in synthesis. Allylation of these C(sp^3) electrophiles provides the corresponding unsaturated products. Typically, this challenging C–C coupling proceeds via Lewis acid activation to form a stabilized carbenium ion that can react with a *nucleophilic* allylic silane in an acyclic transition state (Hosomi–Sakurai reaction).[23] *Electrophilic* allylic boronates have not been employed in this context, although they may offer significant advantages, such as unique reactivity and selectivity. In the quest for new electrophiles compatible with our indium(I) catalysis,[8,9,11,12,15] we envisioned C(sp^3) electrophiles in *nucleophilic substitutions* with boronates, and sought a *dual catalyst capable of activating both reagents* (Scheme 4).

Initial experiments employing acetal **16a** and boronate **2** with or without indium(I) halides in toluene proved to be

TABLE 9. Screening of Lewis Acids for Acetal Allylation[24]



entry	**Lewis acid** (mol %)	solvent	conversion[a] (%)
1		toluene	NR
2	**In^{I}**I(20)	toluene	trace
3	**In^{I}**Br (20) or **In^{I}**Cl (20)	toluene	NR
4	**In^{I}**OTf (20)	toluene	>99 (95)[a]
5	**In^{III}**(OTf)$_3$ (20)	toluene	ND (12)[b]
6	**Ga^{III}**(OTf)$_3$ or **Al^{III}**(OTf)$_3$ or **Cu^{I}**OTf (20)	toluene	trace
7	**Sc^{III}**(OTf)$_3$ (20)	toluene	2
8	**Cu^{II}**(OTf)$_2$ (20)	toluene	5
9	**Ag^{I}**OTf or **Zn^{II}**(OTf)$_2$ (20)	toluene	NR
10	**In^{I}**OTf (5)	toluene	>99
11	**In^{I}**OTf (5)	hexane	>99
12	**In^{I}**OTf (5)	DCM	>95
13	**In^{I}**OTf (5)	THF	20
14	**In^{I}**OTf (1)	toluene	>99 (91)[b]

[a]Conversion of **16a** to **17a** determined by ^{1}H NMR spectroscopic analysis of aliquots of the reaction mixtures. [b]Isolated yield of homoallyl ether **17a** after purification on silica gel (PTLC); NR = no reaction; ND = not determined (due to the formation of byproduct).

disappointing (Table 9, entries 1–3).[24] These poor results, likely due to the low solubility of indium(I) halides, prompted us to examine the more soluble indium(I) triflate;[25] to our delight the reaction proceeded smoothly to provide **17a** in excellent yield (entry 4). Next, we examined other metal triflates, and to our surprise these stronger Lewis acids were found to be ineffective (entries 5–9); note that indium(I) proved to be substantially better than indium(III) (entry 4 versus entry 5). These results indicated that—in contrast to classic allylic silanes—a strong Lewis acid, for the activation of **16a**, is not sufficient to promote C–C bond formation with **2**. *Rather, the ability to activate both reagents seems to be crucial.* A solvent screening revealed toluene and hexane to be the best of those examined (entries 10–13). The catalyst loading could be reduced to 1 mol % (entry 14).

Next, we investigated the scope (Scheme 5).[24] This transformation proceeded smoothly with acyclic or cyclic aromatic, heteroaromatic, and aliphatic acetals **16** and displays remarkable compatibility with free hydroxy, ether, aromatic bromo, ester, trifluoromethyl, and carbamoyl groups, as well as aliphatic bromo and chloro functionalities. Moreover, this protocol proved to be applicable to the allylation of aminal **18a** to furnish homoallylic amide **19a** (Scheme 5).[26]

Next, we turned our attention to the reaction mechanism by employing various substituted allylic reagents, to see whether γ- or α-adducts **20a** or **21a** are observed (Table 10).[24] As expected, the use of *silane* **22** provided the conventional γ-*adduct* **20a**. In sharp contrast, the use of

SCHEME 5. Scope for Acetal Allylation;[24] Application to Aminals[26]

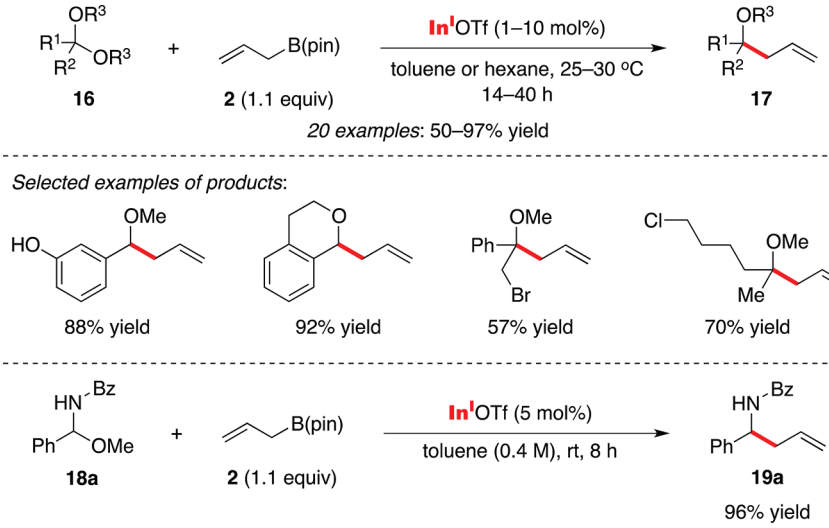
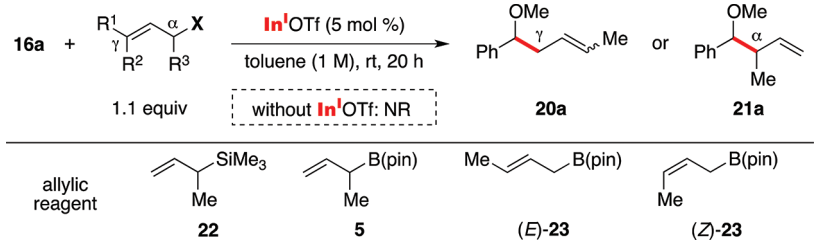


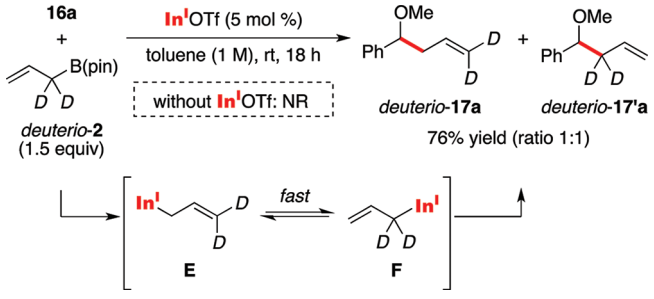
TABLE 10. Mechanistic Control Experiments[24]



product	**20a** (γ)	**21a** (α)	**21a** (α)	**21a** (α)
yield[a] (%)	87	83	11 (61)[b]	43 (77)[c]
ratio	*E*/*Z* = 1.2:1	*anti*/*syn* = 1.2:1	*anti*/*syn* = 1.2:1	*anti*/*syn* = 1.2:1

[a]Isolated yield of homoallylic ethers **20a** or **21a** after purification on silica gel (PTLC). [b]Conditions: (*E*)-**23** (1.5 equiv), 40 °C, 50 h. [c]Conditions: (*Z*)-**23** (1.5 equiv), rt, 50 h. **X** = *B* or *Si*; R^1, R^2, R^3 = H or Me.

SCHEME 6. Deuterium Labeling Experiments[24]



boronate **5** resulted in the formation of the rare α-*adduct* **21a**. Both crotyl boronates **23** gave almost an identical result with respect to regio- and diastereoselectivity compared with **5**, suggesting the same reactive intermediate for all three boron reagents. The α-selectivity with **5** may indicate transmetalation, whereas the lower reactivity of **23** may be explained by slower transmetalation because of the steric demand at the γ-position.

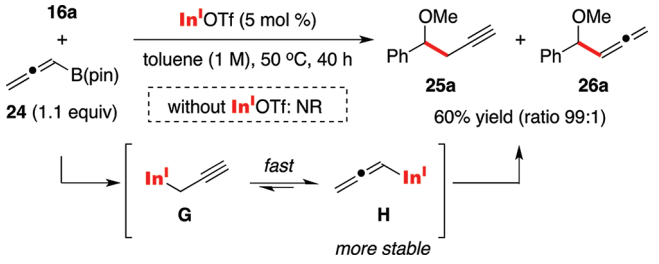
To test the transmetalation hypothesis, boronate *deuterio*-**2** was used (Scheme 6).[24] We observed the formation of an equimolar mixture of regioisomers *deuterio*-**17a** and *deuterio*-**17′a**. This result may be ascribed to the transmetalative generation of the *nucleophilic* allylic indium(I) species **E** and **F** (fast equilibrium), thereby scrambling the deuterium label. **E** and **F** display similar stability and equal reactivity.

On the basis of the observed reactivity and selectivity profile, we propose a transmetalative S_N1 mechanism, in which indium(I) acts as a *dual* catalyst. (i) As an *acid* it activates the acetal to generate in situ an oxocarbenium triflate and indium(I) methoxide. (ii) The latter delivers the

required *base* to the allylic boronate to generate in situ an allylic indium(I) species (transmetalation), which may react with the oxonium intermediate in an acyclic transition state (C–C bond formation).

Importantly, this methodology proved to be applicable to propargylation (Scheme 7).[24] Indeed, **16a** was converted regiospecifically with **24** into homopropargyl ether **25a**. This C–C coupling may also be explained with transmetalation to generate propargyl and allenyl indium(I) species **G** and **H** (fast equilibrium). The more stable allenyl intermediate **H** may act as the real nucleophile. This study represents the first main group metal-catalyzed activation of allylic boronates for C–C bond formation with C(sp^3) electrophiles.

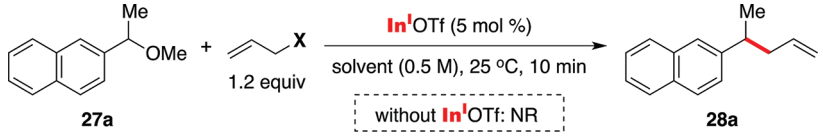
SCHEME 7. Regiospecific Acetal Propargylation[24]

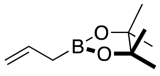
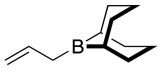


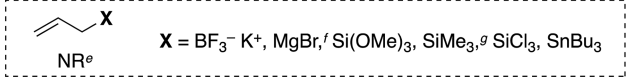
4.2. Alkyl–Allyl Cross-Coupling with Ethers and Carbohydrates: A Borane as a Key Reagent. Aliphatic ethers are appealing substrates in catalytic cross-couplings because they are readily available compounds. However, catalytic activation of ethers under mild conditions is challenging because of the relatively strong C–OR bond and the poor leaving ability of $^-$OR. On the basis of our earlier studies with acetals,[24] we aimed to examine aliphatic ethers.

In initial experiments, under our earlier indium(I) conditions,[24] we employed ether **27a** and *boronate* **2** (Table 11, entry 1).[27] However, the desired product **28a** was hardly observed, which may be ascribed to the stable C–OMe bond of **27a**. Therefore, we used stronger Lewis acid cocatalysts in addition to indium(I) triflate; however, all attempts failed. Thus, we anticipated that a more Lewis acidic boron compound may result in a facilitated C–B bond activation. To our delight, when 9-BBN-derived *borane* **29** was employed in apolar solvents, the desired reaction with **27a** proceeded smoothly to provide **28a** in full conversion (entries 2–6). A reaction did not occur in Lewis basic or polar solvents such as THF or MeCN (entries 7 and 8). Strikingly, the use of other allyl reagents did not provide any desired product or afforded very low yields after extended reaction

TABLE 11. Cross-Coupling with an Ether: Screening of Allyl Reagents[27]

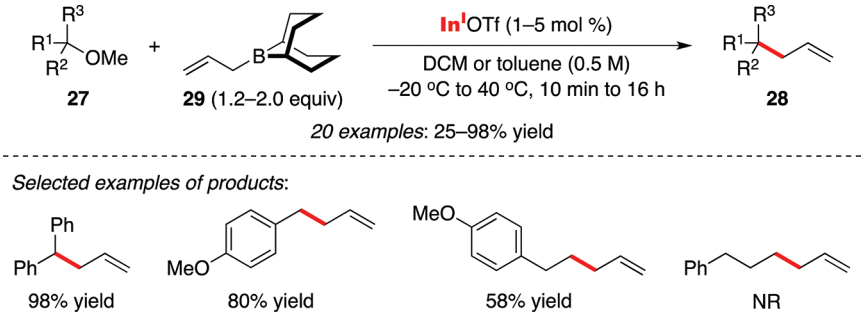


entry	allyl reagent	solvent	conversion[a] (%)
1	 **2**	DCM	trace[b]
2		DCM	>99
3		$CDCl_3$	>99
4		toluene	>99
5	 **29**	benzene	>99
6		hexane	>95
7		THF	NR
8		MeCN	NR
9		DCM	>99[c] (86)[d]

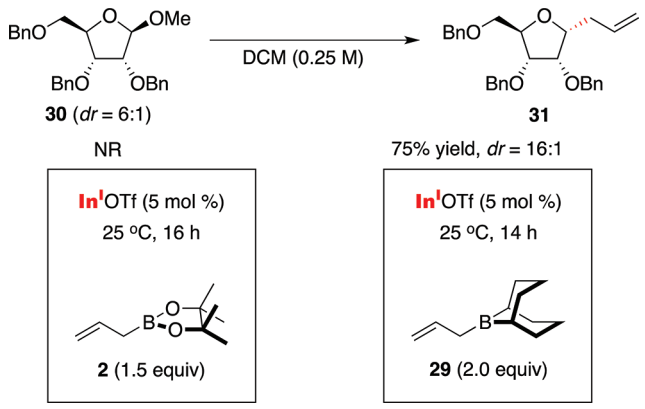


[a]Conversion of **27a** to **28a** was determined by ^{1}H NMR-spectroscopic analysis of aliquots of the reaction mixtures. [b]Conversion: 14% after 24 h. [c]Conditions: In^{I}OTf (1 mol %), DCM (0.5 M), rt, 90 min. [d]Isolated yield of **28a** after purification on silica gel (PTLC). [e]NR = no reaction; no trace of **28a** even after 14 h. [f]A solution of the Grignard reagent (1 M in ether) was employed. [g]Conversion: <5% after 18 h.

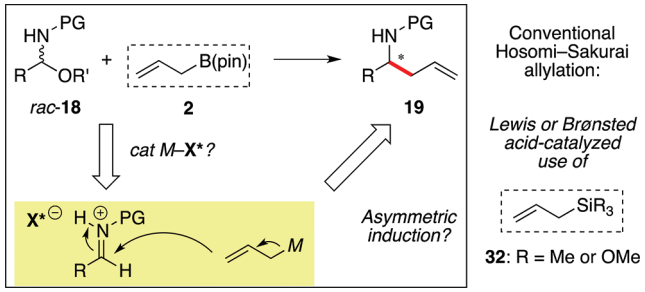
SCHEME 8. Scope for Cross-Coupling with Ethers[27]



SCHEME 9. C–C Bond Formation with Carbohydrates: Selected Example[28]



SCHEME 10. Asymmetric Borono Variant of the Hosomi–Sakurai Reaction?



times. These results highlight the remarkable reactivity of borane **29**. Metal triflates other than indium(I) were found to be significantly less efficient or did not afford **28a**.

Next, we investigated the scope of this new method (Scheme 8).[27] The cross-coupling proceeded smoothly with various primary, secondary, and tertiary benzylic, allylic, and propargylic ethers **27**. Importantly, a heteroaromatic moiety and functionalities such as aromatic bromo or methoxy and aliphatic chloro groups were tolerated.

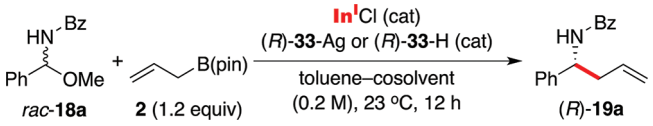
Although we cannot definitely exclude the possibility that the Lewis acidic boron atom of **29** may act as a stoichiometric Lewis acid to activate the C–OMe bond of ethers **27**, we propose a transmetalative S_N1 mechanism, in which indium(I) plays a dual role. This transformation represents a rare example of (i) a main group metal-catalyzed cross-coupling and (ii) the use of an allyl borane for C–C bond formation with C(sp^3) electrophiles.

Importantly, our concept of employing borane **29**, rather than boronate **2**,[27] proved to be applicable to carbohydrate chemistry, as demonstrated by the conversion **30** → **31** (Scheme 9).[28]

4.3. First Asymmetric Low-Oxidation State Indium Catalysis Directed by a Chiral Counteranion. Following an earlier *racemic* study (cf. Scheme 5),[26] we aimed to examine an *asymmetric* version. Initial metal screening for the reaction of *N,O*-aminal *rac*-**18a** with boronate **2** identified indium(I) as the best catalyst (R = Ph, PG = Bz, R′ = Me; Scheme 10).[26] On the other hand, the corresponding Hosomi–Sakurai allylation[23] with silicon-based reagents **32** hardly proceeded. The substantially higher reactivity of **2** over **32** under mild conditions constitutes a prerequisite for asymmetric catalysis. Postulating dual catalytic activation of *rac*-**18a** and **2** to generate iminium ion and allyl indium(I) intermediates (Scheme 10), we screened potential indium(I) catalysts bearing chiral *counteranions* rather than chiral *ligands*. In these experiments the combination of indium(I) chloride and chiral silver BINOL-phosphate (*R*)-**33a**–Ag[29] was found to be the most promising chiral catalyst system for the formation of product (*R*)-**19a** (Table 12). Here again, *silanes* **32** proved to be dramatically less effective than *boronate* **2** in terms of both reactivity and selectivity.

Next, we optimized the reaction conditions.[26] Screening of silver BINOL-phosphates identified (*R*)-**33b**–Ag as the best chiral source (Table 12, entries 1–5). Use of an apolar cosolvent and a slight excess of the chiral silver salt improved the asymmetric induction (entries 6–8). In the absence of indium(I) chloride, (*R*)-**33b**–Ag displayed both low reactivity and enantioselectivity (entry 10). The use of chiral Brønsted acid (*R*)-**33b**–H that may be generated in situ

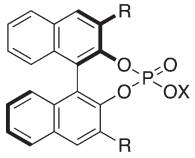
TABLE 12. Optimization and Control Experiments for Asymmetric Catalysis[26]



entry	**In^{I}**Cl (mol %)	(*R*)-**33** (mol %)	cosolvent	yield[a] (%)	*er*[b]
1[c]	10	(*R*)-**33a**–Ag (10)		81	88:12
2[c]	10	(*R*)-**33b**–-Ag(10)		96	94.5:5.5
3[c]	10	(*R*)-**33c**–Ag(10)		90	44.5:55.5
4[c]	10	(*R*)-**33d**–Ag (10)		91	49.5:50.5
5[c]	10	(*R*)-**33e**–Ag (10)		94	49.5:50.5
6[c]	10	(*R*)-**33b**–Ag (10)	CPME	96	95.5:4.5
7[c]	10	(*R*)-**33b**–Ag (13)	CPME	98	98.5:1.5
8[c,d]	5	(*R*)-**33b**–Ag (6.5)	CPME	96	97.5:2.5
9[d]	5		CPME	1	
10[d]		(*R*)-**33b**–Ag (6.5)	CPME	5	57:43
11[d]		(*R*)-**33b**–H (6.5)	CPME	NR[e]	
12[c,d]	5	(*R*)-**33b**–H (6.5)	CPME	88	62.5:37.5

[a]Isolated yield of **19a** after purification on silica gel (PTLC). [b]Enantiomeric ratio was determined by chiral high performance liquid chromatography (HPLC). [c]The chiral catalyst was preformed in toluene at rt. [d]Reaction time: 18 h. [e]NR = a reaction was not detected (^{1}H NMR spectroscopy).

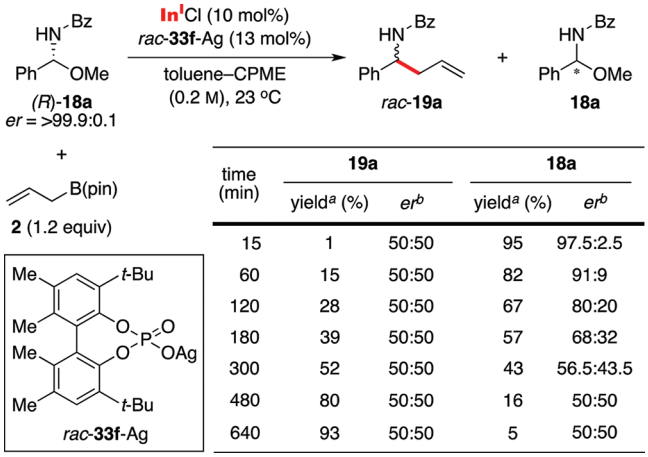
under the present conditions, without or with indium(I) chloride, did not lead to any reaction (entry 11) or provided low asymmetric induction (entry 12). Importantly, we confirmed that redox-disproportionation of indium(I)[2] did not occur in the present catalysis. Thus, the combination of indium(I) and (*R*)-**33b**–Ag was shown to be crucial for the highly enantioselective formation of (*R*)-**19a**. The results of our control experiments (entries 9–12) suggest the in situ generation of a *chiral low-oxidation state indium species as the active catalyst*.



(*R*)-**33a**-Ag: R = 3,5-(^{t}Bu)$_2$-C$_6$H$_3$, X = Ag
(*R*)-**33b**-Ag: R = 3,5-(^{t}Bu)$_2$-4-MeO-C$_6$H$_2$, X = Ag
(*R*)-**33b**-H: R = 3,5-(^{t}Bu)$_2$-4-MeO-C$_6$H$_2$, X = H
(*R*)-**33c**-Ag: R = 3,5-(Me)$_2$-C$_6$H$_3$, X = Ag
(*R*)-**33d**-Ag: R = 2,4,6-(^{i}Pr)$_3$-C$_6$H$_2$, X = Ag
(*R*)-**33e**-Ag: R = SiPh$_3$, X = Ag

Next, we carried out a mechanistic control experiment (Table 13).[26] We employed the optically enriched aminal (*R*)-**18a** (enantiomeric ratio (*er*) ≥ 99.9:0.1) and **2** under standard conditions using indium(I) chloride combined with racemic silver phosphate *rac*-**33f**–Ag as the catalyst system. This experiment was carefully analyzed over time by determining yields and enantiomeric ratios for both the generated product **19a** and the recovered substrate **18a**. The isolated product **19a** proved to be racemic at all stages, whereas the racemization of (*R*)-**18a** proceeded relatively slowly. These results strongly indicate an iminium ion intermediate for this

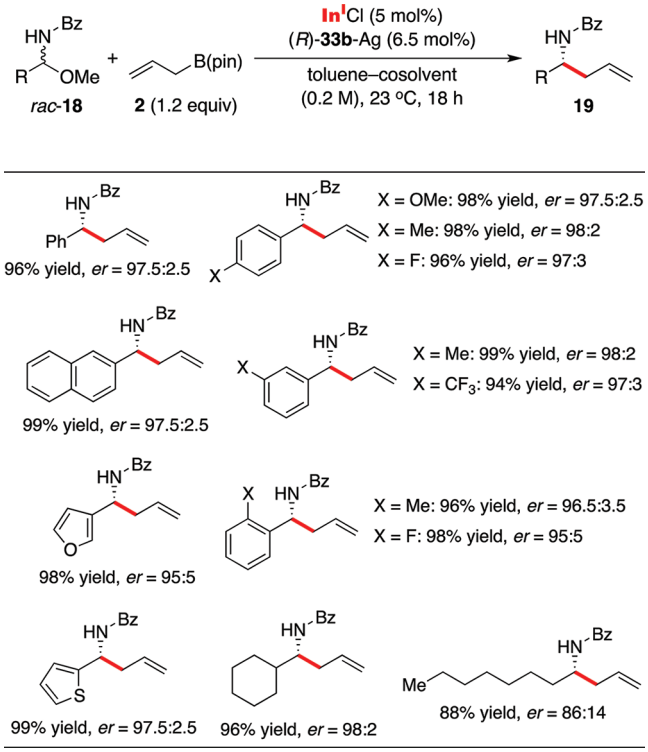
TABLE 13. Mechanistic Control Experiment[26]



time (min)	**19a** yield[a] (%)	**19a** *er*[b]	**18a** yield[a] (%)	**18a** *er*[b]
15	1	50:50	95	97.5:2.5
60	15	50:50	82	91:9
120	28	50:50	67	80:20
180	39	50:50	57	68:32
300	52	50:50	43	56.5:43.5
480	80	50:50	16	50:50
640	93	50:50	5	50:50

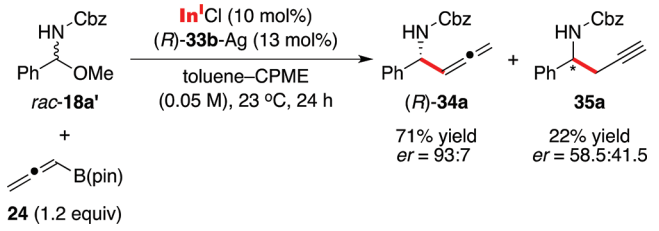
[a]Isolated yield of *rac*-**19a** and **18a** after purification on silica gel (PTLC). [b]Enantiomeric ratio was determined by chiral HPLC.

TABLE 14. Scope for Enantioselective Aminal Allylation[26]



reaction (S_N1 pathway). In turn, these data provide proof that the catalytic *asymmetric* version (cf. Table 12) proceeds via the postulated S_N1 mechanism with an iminium ion species as a key intermediate, thus confirming the critical role of the chiral counteranion (cf. Scheme 10). Overall, the present C–C bond-forming method relies on the generation of a chirally modified *electrophile* (*acyclic* transition state) and represents, therefore, an orthogonal approach compared with our

SCHEME 11. Enantioselective Aminal Allenylation



related earlier study,[15] in which we proposed a chirally modified *nucleophile* as a key intermediate (*cyclic* transition state).

We then examined the scope for this catalytic asymmetric transformation (Table 14).[26] Under optimized conditions the reactions between substituted aromatic, heteroaromatic, and aliphatic aminals *rac*-**18** and **2** proceeded smoothly to provide the desired products **19** with excellent asymmetric induction. Overall, we consider these results remarkable as the levels of asymmetric induction exceed or equal even those of the corresponding allylations of unactivated *aldimines* [C(sp^2) centers] with **2**[30] or **32**.[31]

In addition, we were pleased to find that this chiral catalyst system was applicable to asymmetric allenylation (Scheme 11).[26] The reaction of aminal *rac*-**18a**′ with **24** afforded mainly homoallenyl carbamate (*R*)-**34a** with high asymmetric induction. The minor regioisomer **35a** was separated by chromatography. This regioselectivity is unprecedented for the use of **24** in asymmetric catalysis.[32]

This chemistry features several notable characteristics. (i) Under mild conditions, *boronates* proved to be dramatically more reactive and selective than classic *silicon*-based reagents. (ii) The described transformations represent the first highly enantioselective Hosomi–Sakurai reactions with C(sp^3) centers.[23b,31,33] (iii) This study also constitutes the first main group metal-catalyzed activation of allyl boronates for *asymmetric* C–C bond formation with C(sp^3) centers. (iv) Chiral Brønsted acid catalysis with or without achiral metal salts proved to be inefficient. (v) In the context of *asymmetric intermolecular carbon–carbon bond formation*, the chemistry presented herein is a rare example not only of chiral counteranion-directed metal catalysis[29] but also of dynamic kinetic resolution.[34]

5. Summary and Outlook

In this account, we have described the development of (chiral) low-oxidation state indium catalysts for (asymmetric) carbon–carbon bond formation between boron-based pronucleophiles and various electrophiles. Indeed, indium(I) iodide was revealed to be an excellent catalyst for α-selective allylations of C(sp^2) electrophiles such as ketones and hydrazones. Importantly, catalytic asymmetric allylation, crotylation, and α-chloroallylation of hydrazones were established employing a chiral ligand. Furthermore, indium(I) triflate was found to be the best catalyst for allylation and propargylation of C(sp^3) electrophiles such as *O*,*O*-acetals, *N*,*O*-aminals, ethers, and carbohydrates. In addition, chiral counteranion-directed, catalytic asymmetric allylation and allenylation of *N*,*O*-aminals were developed. Overall, these discoveries demonstrate that low-oxidation state indium species are efficient catalysts in synthesis, including asymmetric catalysis. It is expected that these innovative concepts will be transferable (i) to other indium(I)-catalyzed processes and (ii) to other metal catalysts in their low-oxidation states.

We wish to thank cordially all co-workers for their significant contributions to the success of these projects. This work was partially supported by CREST, SORST, ERATO (JST), a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS), the Global COE Program, the University of Tokyo, and MEXT (Japan).

BIOGRAPHICAL INFORMATION

Shū Kobayashi studied at the University of Tokyo, receiving his Ph.D. in 1988 working under the direction of Professor T. Mukaiyama. Following an initial period as assistant professor, he was promoted to lecturer and then associate professor at Science University of Tokyo (SUT). In 1998, he moved to the Graduate School of Pharmaceutical Sciences, the University of Tokyo, as full professor. In 2007, he was appointed to his current position as professor of organic chemistry in the Department of Chemistry, Faculty of Science, the University of Tokyo, and is now Head of Department. He has held various visiting professorships, including the Universite Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), Philipps-University of Marburg (1997), and Paris-Sud (2010). Professor Kobayashi has wide-ranging research interests that include the development of new synthetic methods and novel catalysts, organic reactions in water, solid-phase synthesis, total synthesis of biologically interesting compounds, and organometallic chemistry. He has held numerous named lectureships and is a recipient of many prestigious awards, including the Chemical Society of Japan Award for Young Chemists (1991), Ciba-Geigy Research Foundation Award (1994), Springer Award in Organometallic Chemistry (1997), IBM Science Award (2001), Organic Reactions Lecturer (2002), Nagoya Silver Medal (2002), Mitsui Chemical Catalysis Science Award (2005), JSPS Prize (2005), the Arthur C. Cope Scholar Award from the American Chemical Society (2006), Howard Memorial Lecturer (2006), C.S. Hamilton Award (2007), and Merck-Cambridge Lecturer (2007).

Uwe Schneider is a Lecturer in the School of Chemistry at the University of Edinburgh, U.K. He was born and raised in Würzburg and studied Chemistry in Würzburg and Marburg, Germany, and in Lille and Lyon, France. Supported by FCI−Kekulé and ATER fellowships, he obtained his Ph.D. degree working with Professors Xavier Pannecoucke and Jean-Charles Quirion at IRCOF in Rouen, France (2003). In 2004, he moved to the University of Tokyo, Japan, to join the group of Professor Shū Kobayashi as a Research Associate (JST−ERATO). Subsequently, he was appointed as Group Leader (2006) and promoted to Assistant Professor (2007), before taking up his present position in September 2011. Uwe Schneider has diverse research interests: "green" chemistry; asymmetric catalysis; elements in low-oxidation and low-valence states; unexploited Lewis bases and acids; ambiphilic structures; and catalytic activation of strong bonns in small molecules. Recently, he has been the recipient of two GCOE Overseas Lectureships (2008 and 2010), a Thieme Chemistry Journal Award (2011), and a Marie Curie Career Integration Award (2012).

FOOTNOTES

*To whom correspondence should be addressed: shu_kobayashi@chem.s.u-tokyo.ac.jp.
The authors declare no competing financial interest.
‡The University of Edinburgh, EaStCHEM School of Chemistry, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, U.K.

REFERENCES

1 *Comprehensive Organometallic Chemistry III*; Crabtree, R., Mingos, M., Eds.; Elsevier Ltd.: Amsterdam, The Netherlands, 2006.

2 Review: Pardoe, J. A. J.; Downs, A. J. Development of the Chemistry of Indium in Formal Oxidation States Lower than +III. *Chem. Rev.* **2007**, *107*, 2–45.

3 Review: Augé, J.; Lubin-Germain, N.; Uziel, J. Recent Advances in Indium-Promoted Organic Reactions. *Synthesis* **2007**, 1739–1764.

4 Review: Chauhan, K. K.; Frost, C. G. Advances in Indium-Catalyzed Organic Synthesis. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015–3019.

5 Examples: (a) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. A Barbier Allylation and a Reformatsky Reaction of Carbonyl Compounds Mediated by Indium(I) Iodide. *J. Organomet. Chem.* **1989**, *369*, 291–296. (b) Fontana, G.; Lubineau, A.; Scherrmann, M.-C. Investigation of the Aqueous Transmetalation of π-Allyl Palladium with Indium Salt: The Use of the $Pd(OAc)_2$−TPPTS Catalyst. *Org. Biomol. Chem.* **2005**, *3*, 1375–1380.

6 Highlight: Aldridge, S. Platinum Complexes Featuring Terminally Bound Ga^+ and In^+ Ions. *Angew. Chem., Int. Ed.* **2006**, *45*, 8097–8099.

7 Wright, R. J.; Phillips, A. D.; Hardman, N. J.; Power, P. P. The "Diindene" ArInInAr (Ar = C_6H_3-2,6-$Dipp_2$, Dipp = C_6H_3-2,6-Pr^i_2). Dimeric versus Monomeric In(I) Aryls: para-Substituent Effects in Terphenyl Ligands. *J. Am. Chem. Soc.* **2002**, *124*, 8538–8539.

8 Schneider, U.; Kobayashi, S. Catalytic Activation of Pinacolyl Allyl Boronate with Indium(I): Development of a General Catalytic Allylboration of Ketones. *Angew. Chem., Int. Ed.* **2007**, *46*, 5909–5912.

9 Schneider, U.; Kobayashi, S. Unprecedented Catalytic Activation of Allyl Boronates with Indium(I) for General Catalytic Allylations of Ketones. *Poster Presentation*, OMCOS 14, Nara, Japan, August 2007.

10 Review: Sugiura, M.; Kobayashi, S. N-Acylhydrazones as Versatile Electrophiles for the Synthesis of Nitrogen-Containing Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 5176–5186.

11 Schneider, U.; Chen, I.-H.; Kobayashi, S. Development of General Catalytic Allylation of Acylhydrazones with Pinacolyl Allyl Boronate Using an Indium(I) Catalyst. *Org. Lett.* **2008**, *10*, 737–740.

12 Kobayashi, S.; Konishi, H.; Schneider, U. Indium(I) Iodide-Catalyzed Regio- and Diastereoselective Formal α-Addition of an α-Methylallyl Boronate to N-Acylhydrazones. *Chem. Commun.* **2008**, 2313–2315.

13 Examples: (a) Frazer, A.; Piggott, B.; Hursthouse, M. B.; Mazid, M. Synthesis and Crystal and Molecular Structure of [{Hydroboratotris(3′-phenylpyrazolyl)}indium]: An Air-Stable Monomeric Indium(I) Complex. *J. Am. Chem. Soc.* **1994**, *116*, 4127–4128. (b) Dias, H. V. R.; Jin, W. Monomeric Indium(I) and Silver(I) Complexes of a Polyfluorinated Tris(pyrazolyl)borate. *Inorg. Chem.* **1996**, *35*, 267–268. (c) Hill, M. S.; Hitchcock, P. B.; Pongtavornpinyo, R. A Linear Homocatenated Compound Containing Six Indium Centers. *Science* **2006**, *311*, 1904–1907. (d) Green, S. P.; Jones, C.; Stasch, A. "Dissolution" of Indium(I) Iodide: Synthesis and Structural Characterization of the Neutral Indium Sub-Halide Cluster Complex $[In_6I_8(tmeda)_4]$. *Angew. Chem., Int. Ed.* **2007**, *46*, 8618–8621. (e) Jurca, T.; Lummiss, J.; Burchell, T. J.; Gorelsky, S. I.; Richeson, D. S. Capturing In^+ Monomers in a Neutral Weakly Coordinating Environment. *J. Am. Chem. Soc.* **2009**, *131*, 4608–4609.

14 Andrews, C. G.; Macdonald, C. L. B. Crown Ether Ligation: An Approach to Low-Oxidation-State Indium Compounds. *Angew. Chem., Int. Ed.* **2005**, *44*, 7453–7456.

15 (a) Chakrabarti, A.; Konishi, H.; Yamaguchi, M.; Schneider, U.; Kobayashi, S. Indium(I)-Catalyzed Asymmetric Allylation, Crotylation, and α-Chloroallylation of Hydrazones with Rare Constitutional and High Configurational Selectivities. *Angew. Chem., Int. Ed.* **2010**, *49*, 1838–1841. (b) Schneider, U.; Chakrabarti, A.; Konishi, H.; Yamaguchi, M.; Kobayashi, S. Unprecedented Asymmetric Indium(I) Catalysis. *Poster Presentation*, OMCOS 16, Shanghai, China, July 2011.

16 Review: Kobayashi, S.; Mori, Y.; Fossey, J. S.; Salter, M. M. Catalytic Enantioselective Formation of C−C Bonds by Addition to Imines and Hydrazones: A Ten-Year Update. *Chem. Rev.* **2011**, *111*, 2626–2704.

17 Example: Hoffmann, R. W.; Weidmann, U. Zur "cis-Präferenz" bei der Addition von Butenyl-Metallverbindung an Ketone und Aldehyde. *J. Organomet. Chem.* **1980**, *195*, 137–146.

18 Example: Carosi, L.; Hall, D. G. Catalytic Enantioselective Preparation of α-Substituted Allyl Boronates: One-Pot Addition to Functionalized Aldehydes and a Route to Chiral Allylic Trifluoroborate Reagents. *Angew. Chem., Int. Ed.* **2007**, *46*, 5913–5915.

19 Tan, K. L.; Jacobsen, E. N. Indium-Mediated Asymmetric Allylation of Acylhydrazones Using a Chiral Urea Catalyst. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315–1317.

20 Example: Hoffmann, R. W.; Landmann, B. Transfer of Chirality in the Addition of Chiral α-Chloroallyl Boronate Esters to Aldehydes. *Angew. Chem., Int. Ed.* **1984**, *23*, 437–438.

21 Kennedy, J. W. J.; Hall, D. G. Dramatic Rate Enhancement with Preservation of Stereospecificity in the First Metal-Catalyzed Additions of Allyl Boronates. *J. Am. Chem. Soc.* **2002**, *124*, 11586–11587.

22 Example: Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. Catalytic Enantioselective Allylboration of Ketones. *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911.

23 Examples: (a) Hosomi, A.; Endo, M.; Sakurai, H. Chemistry of organosilicon compounds. 91. Allylsilanes as synthetic intermediates. II. Syntheses of homoallyl ethers from allylsilanes and acetals promoted by titanium tetrachloride. *Chem. Lett.* **1976**, 941–942. (b) Kampen, D.; Ladépêche, A.; Claßen, G.; List, B. Brønsted Acid-Catalyzed Three-Component Hosomi−Sakurai Reactions. *Adv. Synth. Catal.* **2008**, *350*, 962–966.

24 Schneider, U.; Dao, H. T.; Kobayashi, S. Unusual Carbon−Carbon Bond Formations between Allyl Boronates and Acetals or Ketals Catalyzed by a Peculiar Indium(I) Lewis Acid. *Org. Lett.* **2010**, *12*, 2488–2491.

25 Macdonald, C. L. B.; Corrente, A. M.; Andrews, C. G.; Taylor, A.; Ellis, B. D. Indium(I) Trifluoromethanesulfonate and Other Soluble Salts for Univalent Indium Chemistry. *Chem. Commun.* **2004**, 250–251.

26 Huang, Y.-Y.; Chakrabarti, A.; Morita, N.; Schneider, U.; Kobayashi, S. A Catalytic Asymmetric Borono Variant of Hosomi−Sakurai Reactions with N,O-Aminals. *Angew. Chem., Int. Ed.* **2011**, *50*, 11121–11124.

27 Dao, H. T.; Schneider, U.; Kobayashi, S. Indium(I)-Catalyzed Alkyl−Allyl Coupling between Ethers and an Allyl Borane. *Chem. Commun.* **2011**, *47*, 692–694.

28 Dao, H. T.; Schneider, U.; Kobayashi, S. "Design" of Boron-Based Compounds as Pro-Nucleophiles and Co-Catalysts for Indium(I)-Catalyzed Allyl Transfer to Various $C(sp^3)$-Type Electrophiles. *Chem. Asian. J.* **2011**, *6*, 2522–2529.

29 First use of a chiral silver BINOL-phosphate as a precatalyst: Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, D. F. A Powerful Chiral Counterion Strategy for Asymmetric Transition Metal Catalysis. *Science* **2007**, *317*, 496–499.

30 Example: Lou, S.; Moquist, P. N.; Schaus, S. E. Asymmetric Allylboration of Acyl Imines Catalyzed by Chiral Diols. *J. Am. Chem. Soc.* **2007**, *129*, 15398–15404.

31 Example: Momiyama, N.; Nishimoto, H.; Terada, M. Chiral Brønsted Acid Catalysis for Enantioselective Hosomi−Sakurai Reaction of Imines with Allyl Trimethylsilane. *Org. Lett.* **2011**, *13*, 2126–2129.

32 Example of opposite regioselectivity: Shi, S.-L.; Xu, L.-W.; Oisaki, K.; Kanai, M.; Shibasaki, M. Identification of Modular Chiral Bisphosphines Effective for Cu(I)-Catalyzed Asymmetric Allylation and Propargylation of Ketones. *J. Am. Chem. Soc.* **2010**, *132*, 6638–6639.

33 Seminal report of asymmetric allylation of $C(sp^3)$ electrophiles: Braun, M.; Kotter, W. Titanium(IV)-Catalyzed Dynamic Kinetic Asymmetric Transformation of Alcohols, Silyl Ethers, and Acetals under Carbon Allylation. *Angew. Chem., Int. Ed.* **2004**, *43*, 514–517.

34 Example: Pellissier, H. Organocatalyzed Dynamic Kinetic Resolution. *Adv. Synth. Catal.* **2011**, *353*, 659–676.