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Unusual Carbon−Carbon Bond Formations between Allylboronates and Acetals or Ketals Catalyzed by a Peculiar Indium(I) Lewis Acid

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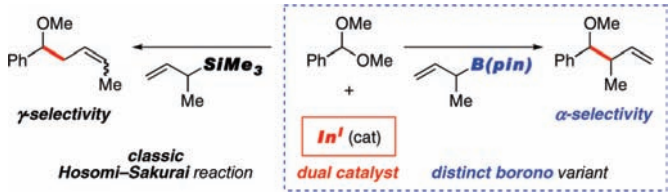
ABSTRACT



In^{I}OTf has been uncovered as an effective Lewis acid catalyst for unprecedented nucleophilic substitution of acetals or ketals with allylboronates. A transmetalative S_N1 mechanism is proposed in which a single In^{I} center acts as a dual catalyst to activate both reagents sequentially. Contrary to the classic γ-selectivity of allylsilanes (Hosomi−Sakurai reaction), this In^{I}-catalyzed borono variant displays distinct α-selectivity. Substrate scope and functional group tolerance proved to be excellent.

Innovative metal catalysis for selective bond formation plays a vital role in chemistry.[1] After pioneering reports,[2,3] allylboronates have been established among the most important nontoxic reagents for C−C coupling.[4] Originally, these species have been used for uncatalyzed 1,2-additions to aldehydes, which proceed via internal activation (C═O → B) in a cyclic transition state (γ-selectivity).[2−4] Following seminal metal-catalyzed aldehyde allylborations,[5] catalytic activation of allylboronates for 1,2-additions to ketones[6] and imines[7] has been explored.[8] Regarding indium(I) (In^{I}) catalysis we developed,[6c,7c,d] it is noted that this main group metal is appealing because In-based compounds have low toxicity, are safe, inexpensive, selective, and tolerant toward various functional groups.[9] Contrary to commonly employed In^{III} Lewis acids,[9] In^{I} catalysis is in its infancy.[6c,7c,d,10]

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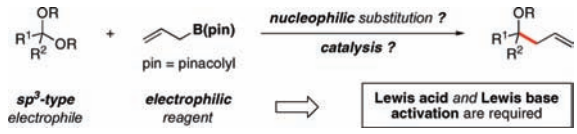
Acetals play a key role in nature[11] and chemistry;[12] acetal allylation is a useful carbon−carbon bond formation that can provide valuable homoallyl ethers.[13] Typically, this challenging C−C coupling proceeds via Lewis acid activation to form an oxocarbenium ion that can react with nucleophilic allylsilanes.[14] Lewis or Brønsted acid-catalyzed variants[15] have been developed,[16] but only some catalytic methods were found to be truly effective, practical, and general. Allylboronates are, in the absence of transition metals,[8] unreactive toward sp^3-type electrophiles (noncarbonyls); these boron reagents have been neglected, although they may offer significant advantages such as easier access, superior stability, and unique reactivity, and selectivity. In the quest for new electrophiles compatible with our In^I catalysis, we envisioned acetals for challenging nucleophilic substitution with allylboronates, an unprecedented process that would require Lewis acid *and* Lewis base activation (Scheme 1). We sought

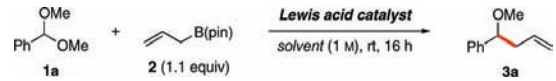
Scheme 1. Nucleophilic Substitution with an Allylboronate?



a single catalyst capable of activating both reagents and report here our preliminary results.

In initial experiments, the uncatalyzed reaction between acetal **1a** and allylboronate **2** did not occur, and catalytic use of indium(I) iodide[6c,7c,d] or other halides proved to be ineffective (Table 1, entries 1−3). To our surprise, when

Table 1. Screening of Lewis Acid Catalysts



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

[a] Conversions of **1a** to **3a** determined by ^1H NMR spectroscopic analysis of aliquots of the reaction mixtures. [b] Isolated yields of homoallyl ether **3a** after purification on silica gel (PTLC). nr = no reaction; nd = not determined (due to the formation of byproduct).

In^IOTf[17] (20 mol %) was employed, this C−C bond formation proceeded smoothly to provide homoallyl ether **3a** in 95% yield (entry 4). Strikingly, various other metal triflates including $In^{III}(OTf)_3$ were found to be inefficient (entries 5−9). This indicated that, contrary to classic allylsilanes, a strong Lewis acid, for the activation of **1a**, is not sufficient to promote this C−C coupling with **2**. Rather, the ability to activate both **1a** and **2** seems to be crucial. Note that (1) toluene was shown to be the best solvent of those examined (entries 10−13) and (2) the In^I catalyst loading could be reduced to 1 mol % (entry 14; 91% yield).

Next, we investigated the substrate scope (Figure 1). This reaction proceeded smoothly with acyclic or cyclic aromatic, heteroaromatic, and aliphatic acetals or ketals. It is noted that readily cleavable ethers such as product **3b** (R = Bn) are accessible and that the mild conditions tolerate reactive functional groups such as unprotected O−H and aliphatic C−Hal bonds (products **3c**, **3s**, and **3t**), which reveals the high appeal of this In^I catalysis for synthesis.

We then studied the mechanism by employing substituted allyl reagents (Scheme 2). As expected, use of α-methylallylsilane **4** provided the classic γ-product **7a**. In sharp contrast, use of α-methylallylboronate **5** resulted in the exclusive formation of the rarely obtained α-product **8a** in 83% yield. It should be noted that both crotylboronates (*E*)-**6** and (*Z*)-**6** gave an identical result with respect to regio- and

(9) Recent review on the use of indium for synthesis: Augé, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739.

(10) Selected *stoichiometric* examples for indium^I-mediated C−C bond formation: (a) Araki, S.; Ito, H.; Katsumura, N.; Butsugan, Y. *J. Organomet. Chem.* **1989**, *369*, 291. (b) Chan, T. H.; Yang, Y. *J. Am. Chem. Soc.* **1999**, *121*, 3228. (c) Yang, Y.; Chan, T. H. *J. Am. Chem. Soc.* **2000**, *122*, 402. (d) Araki, S.; Kamei, T.; Hirashita, T.; Yamamura, H.; Kawai, M. *Org. Lett.* **2000**, *2*, 847. (e) Babu, S. A.; Yasuda, M.; Shibata, I.; Baba, A. *Org. Lett.* **2004**, *6*, 4475.

(11) Selected examples: (a) Vinogradov, E.; Bock, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 671. (b) Milroy, L.-G.; Zinzalla, G.; Loiseau, F.; Qian, Z.; Prencipe, G.; Pepper, C.; Fegan, C.; Ley, S. V. *ChemMedChem* **2008**, *3*, 1922.

(12) Selected examples: (a) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430. (b) Dixon, D. J.; Foster, A. C.; Ley, S. V.; Reynolds, D. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1635. (c) See also ref 11b.

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(14) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941.

(15) Selected examples for catalytic Hosomi−Sakurai reactions: Lewis acids: (a) Sakurai, H.; Sasaki, K.; Hosomi, A. *Tetrahedron Lett.* **1981**, *22*, 745. (b) Yadav, J. S.; Reddy, B. V. S.; Srihari, P. *Synlett* **2001**, 673. (c) Wieland, L. C.; Zerth, H. B.; Mohan, R. S. *Tetrahedron Lett.* **2002**, *43*, 4597. (d) Braun, M.; Kotter, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 514. (e) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1150. (f) Spafford, M. J.; Anderson, E. D.; Lacey, J. R.; Palma, A. C.; Mohan, R. S. *Tetrahedron. Lett.* **2007**, *48*, 8665. (g) Brønsted acid: Kampen, D.; List, B. *Synlett* **2006**, 2589.

(16) Allylation of acetals with nucleophilic allyl trialkylborates (stoichiometric Si^{IV}): Hunter, R.; Michael, J. P.; Tomlinson, G. D. *Tetrahedron* **1994**, *50*, 871.

(17) Preparation of In^IOTf as a soluble indium(I) source: Macdonald, C. L. B.; Corrente, A. M.; Andrews, C. G.; Taylor, A.; Ellis, B. D. *Chem. Commun.* **2004**, 250.

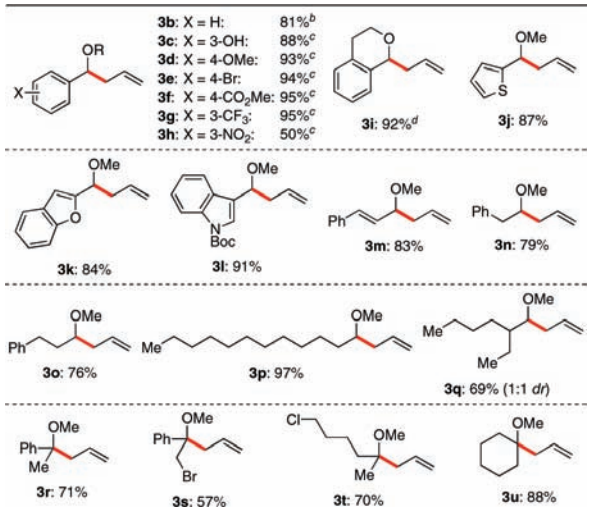
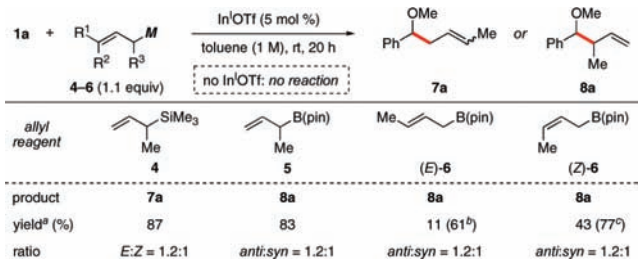


Figure 1. Scope for In^{I}OTf-catalyzed C−C bond formation. (a) Reaction conditions: In^{I}OTf (1−10 mol %), toluene or hexane, 25−30 °C, 14−40 h; isolated yields of homoallyl ethers **3b**−**u** after purification on silica gel (PTLC). (b) R = Bn. (c) R = Me. (d) Substrate **1i** is the corresponding methoxy acetal.

diastereoselectivity compared with **5**, suggesting the same reactive intermediate for all three boron reagents.[18] The α-selectivity with **5** may indicate catalytic B-to-In transmetalation, while the lower reactivity of (*E*)-**6** and (*Z*)-**6** may be explained with slower transmetalation due to steric demand at the γ-position.

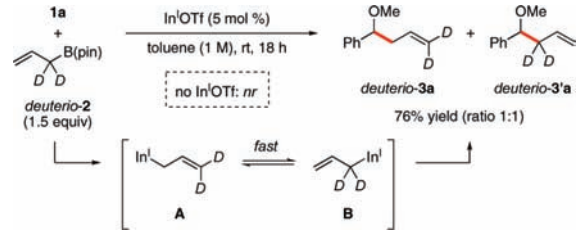
To test the B-to-In transmetalation hypothesis, the deuterated allylboronate *deuterio*-**2**[8a,b] was used (Scheme 3). If In^{I}OTf acts solely as a conventional Lewis acid, the reaction would proceed regiospecifically between **1a** and *deuterio*-**2** to form homoallyl ether *deuterio*-**3a** (acyclic transition state).[19] However, we observed the clean formation of an equimolar mixture of both regioisomers *deuterio*-**3a** and *deuterio*-**3′a**. This result supports the suggestion that transmetalation generates both nucleophilic allyl In^{I} isomers A and B (fast equilibrium),[20] thereby scrambling the deuterium label. Both isomers may react with the electrophile to provide the observed product mixture.

Scheme 2. Mechanistic Experiments



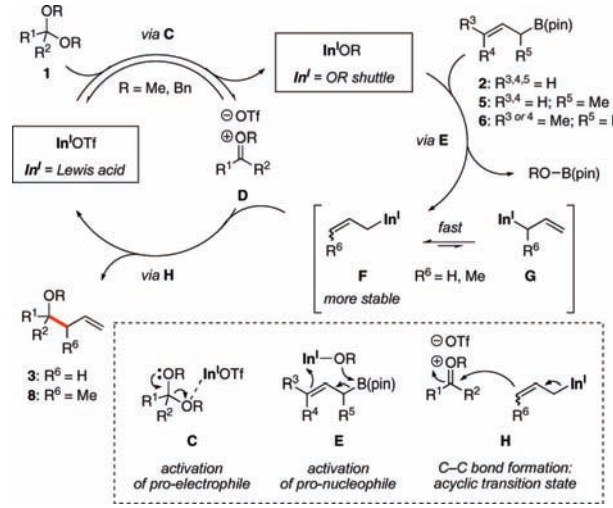
[a] Isolated yields of homoallyl ethers **7a** or **8a** after purification on silica gel (PTLC). [b] Conditions: (*E*)-**6** (1.5 equiv), 40 °C, 50 h. [c] Conditions: (*Z*)-**6** (1.5 equiv), rt, 50 h. M = B(pin) or SiMe$_3$; R^1, R^2, R^3 = H or Me.

Scheme 3. Deuterium Labeling Experiment



We then examined this B−In system by NMR spectroscopic analyses, which revealed that boronate **2** is stable in toluene-d_8 at rt in the presence of In^{I}OTf; no B-to-In transmetalation was detected even after 12 h. However, upon addition of acetal **1a**, the C−C coupling proceeded smoothly to form product **3a** in >99% NMR yield. In a preliminary kinetic study, a first-order dependence in catalyst (In^{I}OTf) was determined.[21] At present, we propose a transmetalative S_N1 mechanism in which In^{I} acts as a unique dual catalyst (Scheme 4). In^{I}OTf as a Lewis acid may activate **1** to form,

Scheme 4. Proposed Transmetalative S_N1 Mechanism



via **C**, oxonium ion **D** and In^{I}OR (R = Me, Bn). This alkoxide shuttle delivers the required Lewis base to activate the boronates **2**, **5**, or **6** to generate, via **E**, the nucleophilic In^{I} species **F** or **G** (fast equilibrium).[20] The more stable reagent **F** (if R^6 = Me) may react with **D** to provide, via **H**, homoallyl ethers **3** or **8**. The proposed S_N1 mechanism, including transmetalation and C−C coupling via an acyclic transition state, is consistent with both the α-selectivity of **5**

(18) Isomerization of allylboronates **5**, (*E*)-**6**, and (*Z*)-**6** or of products **7a** and **8a** via In^{I}OTf catalysis has not been observed.

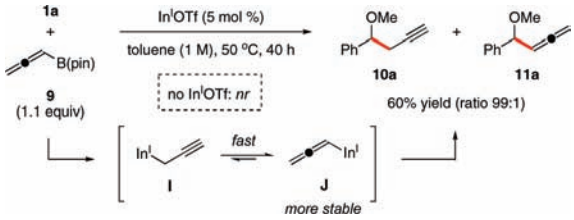
(19) In the absence of acetal **1a**, allylboronate *deuterio*-**2** proved to be stable under the reaction consitions; isomerization and/or decomposition did not occur.

(20) Isaac, M. B.; Chan, T. H. *Tetrahedron Lett.* **1995**, *36*, 8957.

(21) See the Supporting Information for details.

and diastereoselectivity; the almost identical result with (*E*)-**6** and (*Z*)-**6** may be explained with the more stable In^I species **F** (R^6 = Me) being the real nucleophile in all three cases.[18,20] The proposed mechanism is fully consistent with the fact that the weaker Lewis acid In^IOTf is substantially more active than $In^{III}(OTf)_3$. Indeed, although In^I is significantly larger than In^{III},[22] its acidity is sufficient to activate **1**. On the other hand, In^I may be more effective than In^{III} for several reasons: (1) The formed In^I-O bond within In^I-OR may be longer than in case of In^{III}; thus, the *O*-Lewis basicity is stronger, which accounts for an easier activation of the acidic boron atom (hard−hard). (2) The larger In^I is more suitable for transmetalation at the C=C double bond than In^{III} (soft−soft). (3) The generated In^I-C bond within the allyl In^I reagent is longer than in case of In^{III}; this nucleophile is more reactive.

Scheme 5. Regiospecific Propargylation of **1a** with **9**



Finally, allenylboronate **9** was converted regiospecifically into homopropargyl ether **10a**[23] (Scheme 5). This excellent result may also be ascribed to catalytic B-to-In transmetalation to form propargyl and allenyl In^I intermediates **I** and **J** (fast equilibrium). The more stable allenyl species **J**[24] may act as the real nucleophile, which may account for the regioselectivity in favor of **10a**.

This report introducing a new catalyst (In^IOTf) represents the first main group metal-catalyzed activation of allylboronates[8] for unprecedented carbon−carbon bond formation with noncarbonyls. The present catalytic indium(I) study is (1) distinct from earlier work with allylboronates and carbonyls[2−7] and (2) compares well with a related stoichiometric boron(III) protocol.[25] We propose a transmetalative S_N1 mechanism in which a single In^I center acts as a dual catalyst for sequential activation of both reagents. Contrary to the classic Hosomi−Sakurai reaction,[14,15] the present In^I-catalyzed borono variant displays distinct α-selectivity. This reaction proved to be tolerant toward various functional groups and is applicable to propargylation. Being aware of the possibilities opened up by this unusual In^I dual catalysis, we are currently investigating an asymmetric version, *C*-glycosylation, and other new transformations with nontoxic boron reagents.

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

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(22) Pauling ionic radii have been reported to be 104 pm (In^I) and 81 pm (In^{III}): http://www.webelements.com.

(23) This result constitutes a substantial advance compared with the best result obtained for an allenylsilane in a classic Hosomi−Sakurai reaction (3% yield for **10a**): Niimi, L.; Hiraoka, S.; Yokozawa, T. *Tetrahedron* **2002**, *58*, 245.

(24) Allenylindium species are more stable than propargylindium species: Miao, W.; Chung, L. W.; Wu, Y.-D.; Chan, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 13326.

(25) During the preparation of our manuscript, a related stoichiometric boron(III) method was reported: Mitchell, T. A.; Bode, J. W. *J. Am. Chem. Soc.* **2009**, *131*, 18057.