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"Design" of Boron-Based Compounds as Pro-Nucleophiles and Co-Catalysts for Indium(I)-Catalyzed Allyl Transfer to Various Csp^3-Type Electrophiles

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Abstract: We have recently uncovered a general indium(I)-catalyzed method for allylations and propargylation of acetals and ketals with a water- and air-stable allyl boronate. By using a more reactive allyl borane, we have successfully extended this methodology to the more challenging C–C coupling with ethers. Herein, we report an improved methodology for the indium(I)-catalyzed allylation of acetals and ethers, through combination of the allyl boronate with a commercially available "hard" Lewis acid, *B*-methoxy-9-BBN (BBN = borabicyclo[3.3.1]nonane), as an effective co-catalyst. Significantly, our work highlights for the first time the correlation between the Lewis acidity of "electrophilic" boron-based compounds and their "nucleophilic" reactivity in Csp^3–Csp^3 couplings, catalyzed by a "soft" low-oxidation main group metal. In addition, we also report several applications of these methodologies to the selective synthesis of various carbohydrate derivatives.

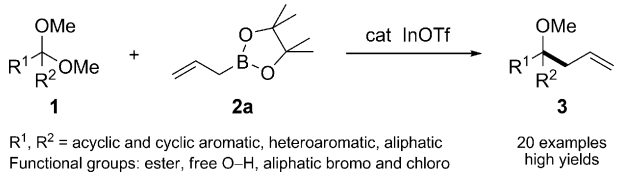
Keywords: allylation · boron · carbohydrates · C–C coupling · indium

Introduction

Innovative metal catalysis for C–C bond formation plays a vital role in organic chemistry.[1] In this context, boron-based compounds[2] are among the most important and appealing "standard" reagents in organic synthesis. Indeed, these molecules offer a unique combination of interesting properties. Whereas trivalent boron compounds have an "electrophilic" character owing to the vacant low-energy 2p orbital of the boron atom, they may display "nucleophilic" behavior after reaction with Lewis bases, thereby forming tetravalent boron–ate complexes.[2c,d] Moreover, boron-based reagents are attractive because of high functional group tolerance, low toxicity, and convenient handling.[2]

The allylation of organic substrates is among the most important carbon–carbon bond-forming reactions in organic synthesis.[3] While allylation of Csp^2-type electrophiles, such as carbonyl compounds and imines, has been extensively studied,[4] the coupling of allyl reagents with Csp^3-type electrophiles is relatively underexplored. Typically, this challenging transformation proceeds by Lewis or Brønsted acid activation of the electrophile to form an oxocarbenium or carbenium ion that can react with nucleophiles such as allyl silanes (Hosomi–Sakurai allylation).[5]

Recently, we have disclosed a general catalytic method for allylation of acetals and ketals with allyl boronates using an indium(I) catalyst (Scheme 1).[6] To the best of our knowledge, this work represents the first main group metal-catalyzed activation of allyl boronates for C–C bond formation with noncarbonyls. This methodology features a broad functional group tolerance, and is applicable to both allylations and propargylation.



Scheme 1. Indium(I)-catalyzed allylation of acetals and ketals with allyl boronate **2a**.

With detailed insight into the reaction mechanism, we have successfully extended this dual activation concept to the more challenging coupling with ethers, by switching from allyl boronate **2a** to allyl borane **2b** (Scheme 2).[7] Our present contribution provides a full account on issues relat-

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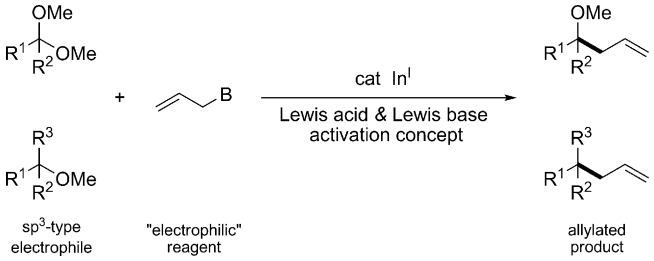


Scheme 2. Concept of dual catalytic activation for "nucleophilic" substitution reactions with sp^3-type electrophiles employing "electrophilic" allyl boron reagents.

ed to allyl boron reagents for the alkyl–allyl coupling with Csp^3-type electrophiles, in order to 1) address limitations in scope and 2) gain further mechanistic insight. We also report applications in carbohydrate chemistry.

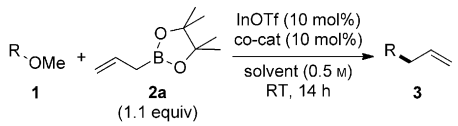
Results and Discussion

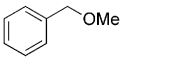
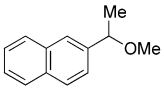
While surveying the scope for the InOTf-catalyzed allylation of acetals and ketals with allyl boronate **2a**, we detected for certain substrates the formation of diallylated products in trace amounts. It was reasoned that these by-products might be formed by further allylation of the initially generated homoallylic ethers.[8] This observation prompted us to investigate the C–C coupling between **2a** and ethers, another class of Csp^3-type electrophiles. However, owing to the relatively strong C–O bond, allylation of ethers is expected to be significantly more challenging than that of acetals and ketals.[5,9] Indeed, the InOTf-catalyzed reactions of several ethers **1** with **2a**, under optimized conditions for acetal allylation, did not afford the desired C–C bond-formed products **3** (Table 1, entries 1, 2, and 6), or only a very low yield for **3** (Table 1, entry 8).

To overcome this higher energy barrier, our initial plan was to facilitate the C–O bond activation by employing metal Lewis acids, such as $InCl_3$, $In(OTf)_3$, and $Ga(OTf)_3$, as co-catalysts (Table 1, entries 3–5, 7, 9, and 10). However, the use of these stronger Lewis acids in toluene resulted only in messy mixtures, which contained Friedel–Crafts-type side-products. The formation of these undesired compounds suggests that the activation of the C–O bond indeed occurred to afford both the corresponding carbenium ions and the corresponding metal methoxide species. However, in contrast to indium(I) methoxide, these intermediates may not be able to deliver the required methoxide to activate allyl boronate **2a**, which is a prerequisite for the postulated transmetalation mechanism. In addition, kinetic studies for the allylation of acetals with **2a** revealed that the transmetalation was the rate-determining step in the catalytic cycle. Therefore, facilitation of this boron Lewis acid-involving step might be the key for the acceleration of the coupling with less reactive Csp^3-type electrophiles, such as ethers. Based on this assumption, we uncovered that, in contrast to allyl boronate **2a**, the more reactive 9-BBN-derived (BBN = Borabicyclo-[3.3.1]nonane), allyl borane **2b** worked as an effective pronucleophile in the challenging C–C bond formation with ethers.

Various metal Lewis acids were tested for the allylation of ether **1a** with allyl borane **2b**, and the results are summarized in Table 2. With the exception of $Bi(OTf)_3$ (Table 2, entry 2), all other metal triflates were found to be significantly less effective than InOTf (Table 2, entry 1 vs entries 3–11), or did not afford at all the desired product **3a** (Table 2, entries 12–14). Among these catalysts, stronger

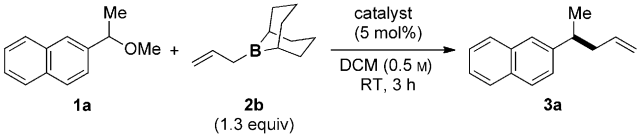
Table 1. Screening of metal co-catalysts for the allylation of **1** with allyl boronate **2a**.



Entry	Ether **1**	Co-Catalyst	Solvent	Conversion[a]
1		–	toluene	n.r.
2		–	DCM	n.r.
3		$InCl_3$	toluene	messy[b]
4		$In(OTf)_3$	toluene	messy[b]
5		$GaCl_3$	toluene	messy[b]
6		–	toluene	n.r.
7		$InCl_3$	toluene	messy[b]
8		–	DCM	<20%
9		$In(OTf)_3$	DCM	messy
10		$GaCl_3$	DCM	messy

[a] The conversion of ethers **1** was determined by ^1H NMR analysis of aliquots of the reaction mixtures. [b] Friedel–Crafts-type by-products were obtained. n.r. = no reaction.

Table 2. Screening of metal catalysts for the allylation of ether **1a** with allyl borane **2b**.



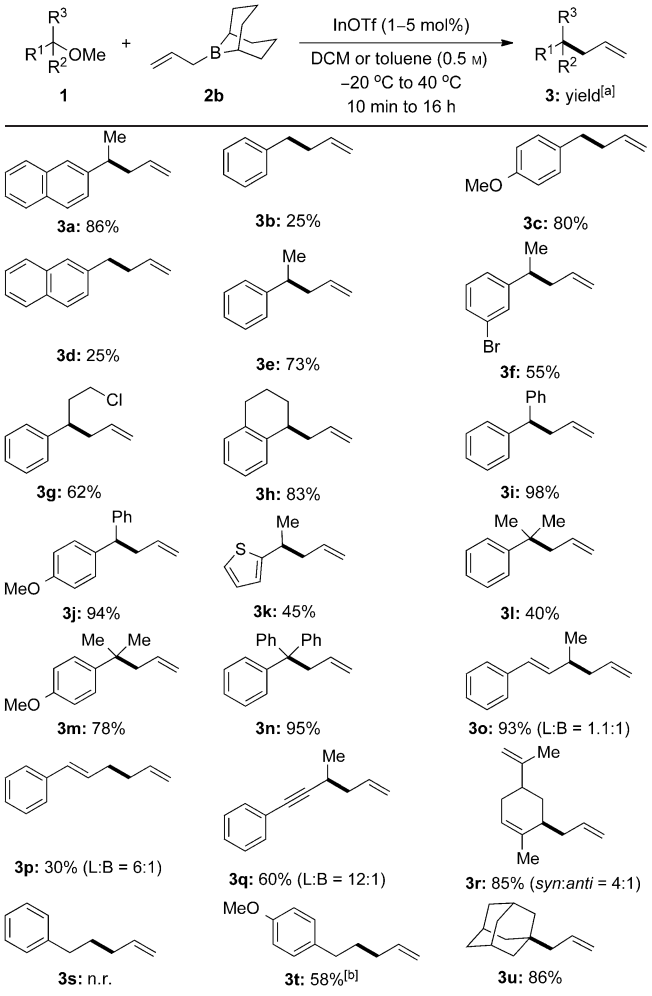
Entry	Catalyst	Yield [%][a]	Entry	Catalyst	Yield [%][a]
1	InOTf	86	9	$Cu(OTf)_2$	26
2	$Bi(OTf)_3$	70	10	$Al(OTf)_3$	25
3	$Sc(OTf)_3$	52	11	$Fe(OTf)_2$	12
4	$In(OTf)_3$	45	12	$Zn(OTf)_2$	n.r.[b]
5	$Ga(OTf)_3$	41	13	$Mg(OTf)_2$	n.r.[b]
6	$Hf(OTf)_4$	35	14	$Sm(OTf)_3$	n.r.[b]
7	AgOTf	26	15	$TfOSiMe_3$	43[c]
8	CuOTf[d]	27	16	TfOH	12[c]

[a] Yield of isolated product after purification on silica gel (PTLC). [b] Determined by ^1H NMR analysis of aliquots of the reaction mixtures and by TLC monitoring of crude mixtures. [c] 10 mol% of the catalyst was added at −78 °C, then warming to RT. [d] Used as a toluene (0.5 equiv) complex.

Lewis acids such as $Al(OTf)_3$ may suffer from undesired reactions, while other metal triflates, such as $Mg(OTf)_2$, may not successfully activate the C–O bond of **1a**, or the corresponding metal methoxide intermediates may not be able to deliver the required methoxide to activate allyl borane **2b**. Interestingly, metal-free acids, such as trimethylsilyl triflate and triflic acid, also catalyzed the model reaction, albeit in moderate and low yields (Table 2, entries 15 and 16).

Scope and limitation for the InOTf-catalyzed allylation of ethers **1** with **2b** are shown in Table 3. The present catalytic alkyl–allyl cross-coupling showed good substrate generality

Table 3. Scope and limitation for the allylation of ethers **1** with allyl borane **2b**.



[a] Yield of isolated product after purification on silica gel (PTLC or column chromatography). [b] Neat, 60 °C, 48 h.

including various primary, secondary, and tertiary benzylic, allylic, and propargylic ethers, thereby providing the corresponding allylated products in good to excellent yields in most cases.[7]

We have proposed a transmetalative S_N1 mechanism, in which indium(I) plays a dual role, as shown in Figure 1.[7] First, InOTf acts as a Lewis acid to activate the C–O bond,

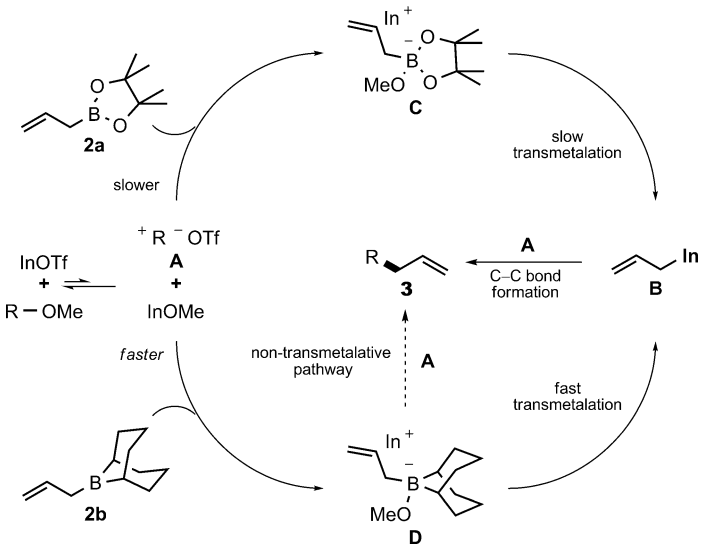


Figure 1. InOTf-catalyzed alkyl–allyl cross-coupling: boronate **2a** versus borane **2b.**

thereby forming a carbenium ion species **A** (an oxocarbenium ion species in the case of acetals) and indium(I) methoxide. The in situ-formed InOMe then triggers B-to-In transmetalation with borane **2b** (or boronate **2a**) to generate the nucleophilic allyl indium(I) species (**B**), which subsequently reacts with electrophile **A** to give the desired allylated product **3**. For the reaction using allyl boronate **2a**, we believe that this transformation exclusively follows the above transmetalative pathway (via boron–ate complex **C**).[6] In the case of allyl borane **2b**, however, we cannot rule out a non-transmetalative pathway, which involves the direct reaction of the more reactive boron–ate complex **D** with electrophile **A**. Particularly, in the reactions catalyzed by metal-free compounds ($TfOSiMe_3$ and TfOH; Table 2, entries 15 and 16), the non-transmetalative mechanism should be the major pathway for the formation of the allylated product **3a**.[10]

The nature of the substituents on the boron atom of a trivalent boron compound determines its Lewis acidity, and thus its electrophilicity.[2e,11] The relative strength in Lewis acidity of boron-based compounds can be estimated by the chemical shift δ in ^{11}B NMR spectroscopy, which is a common tool for monitoring reactions involving boron-containing reagents.[11] Although this method seems to be very appealing for the prediction of the reactivity of boron-based molecules, there have been only sporadic reports on the correlation between ^{11}B NMR values (boron Lewis acidity) and the reactivity of boron-based compounds, such as 1,2-additions to aldehydes[12] or transition metal-triggered transmetalation.[11] In the present indium(I) catalysis, we observed a substantial improvement in reactivity by switching from allyl boronate **2a** to allyl borane **2b** (Figure 1). Judging from our ^{11}B NMR data, the Lewis acidity of the boron atom of borane **2b** ($\delta_{2b}=85$ ppm) is expected to be significantly higher than that of boronate **2a** ($\delta_{2a}=32$ ppm; Figure 2).

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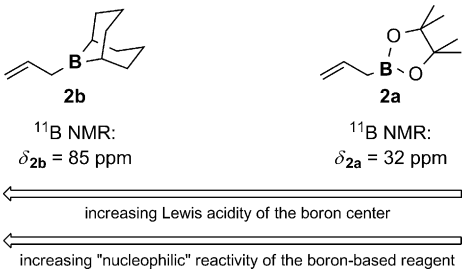


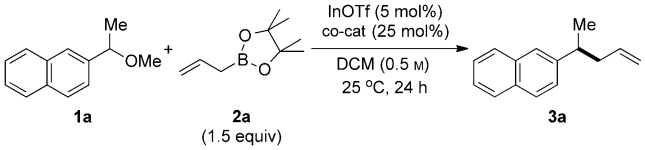
Figure 2. Correlation between Lewis acidity ("electrophilicity") and "nucleophilicity" of boron-based reagents.

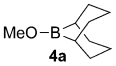
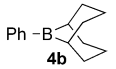
Therefore, allyl borane **2b** would have a substantially increased affinity toward the in situ-formed Lewis base, indium(I) methoxide, thus resulting in a faster generation of boron–ate complex **D** (compared with the formation of complex **C** from **2a**). This notable change may push the equilibrium in the first step of our mechanism to the right side, thus leading to rate acceleration. In addition, boron–ate complex **D** should also be more reactive than complex **C** in the transmetalation step, or **D** as a nucleophile may undergo a direct reaction with **A**. These combined effects explain why allyl borane **2b** is a significantly more reactive pro-nucleophile than allyl boronate **2a**. Overall, **2b** can react with less reactive electrophiles, including primary ethers (Table 3).

Being exceedingly reactive, thanks to its highly Lewis acidic nature, allyl borane **2b** exhibits a relatively low tolerance toward functionalities, such as hydroxy and ester groups.[2c] Moreover, **2b** is not very convenient in terms of both preparation and storage, compared with the water- and air-stable allyl boronate **2a**. In addition, we experienced some difficulties in cleanly synthesizing derivatives of **2b**. In view of C–C bond formations with challenging Csp^3-type electrophiles (such as less reactive acetals and secondary ethers), we sought an improved catalytic method to replace allyl borane **2b** with the more environmentally benign allyl boronate **2a** and derivatives thereof.

Based on the proposed mechanism in Figure 1, we envisioned a "hard" Lewis acid co-catalyst to be appropriate to "trap" in situ-formed indium(I) methoxide, which may force the equilibrium in the first step to the formation of carbenium ions **A**, thus accelerating the catalytic cycle with the less reactive allyl boronate **2a**. In this context, we screened various boron Lewis acids (Table 4). To our delight, when the commercially available "hard" boron Lewis acid, *B*-methoxy-9-BBN (**4a**), was employed in a catalytic amount, the yield was substantially improved (Table 4, entry 1 vs entry 2). A similar rate enhancement was observed for the catalytic use of boranes **4b** and **4c** (Table 4, entries 3 and 4), while triethyl borane (**4d**) did not show any positive effect (Table 4, entry 5). Strikingly, strong Lewis acids, such as $BF_3{\cdot}OEt_2$ (**4e**) and the perfluorinated borane **4f**, afforded only low isolated yields of product **3a** (Table 4, entries 6 and 7).

Table 4. Screening of metal-free co-catalysts for the allylation of **1a** with **2a**.



Entry	Co-Catalyst	Yield [%][a]
1	–	14
2	 **4a**	55[b]
3	 **4b**	44
4	BPh_3 (**4c**)	41
5	BEt_3 (**4d**)[c]	14
6	$BF_3{\cdot}OEt_2$ (**4e**)[d]	19
7	$B(C_6F_5)_3$ (**4f**)	5

[a] Yield of isolated product after purification on silica gel (PTLC). [b] Reaction time: 36 h; 61% yield. [c] A solution (1 M in hexane) was used. [d] The co-catalyst was added at 0 °C.

Next, we turned our attention to the mechanism of this unprecedented indium(I)/boron(III) co-catalysis. With the aim to investigate the role of the most effective co-catalyst, borinic ester **4a**, we conducted ^1H NMR studies. In deuterium labeling experiments, our model substrate, ether **1a**, was combined with an equimolar amount of borinic ester [D_3]**4a**, in the absence and in the presence of indium(I) triflate (Figure 3). These reactions were monitored with time by ^1H NMR analysis (15 min; 3 h; 16 h); the obtained spectra were then compared with the data for reference **4a**.

In the absence of InOTf, even after 16 h, there was no change in the ^1H NMR spectra of the mixture containing **1a** and [D_3]**4a** (Figure 3a). Compound **4a** was not detected; thus, scrambling of the deuterium label did not occur. On the other hand, in the presence of 20 mol% of InOTf, an increasing amount of compound **4a** was formed with time (Figure 3b). Thus, scrambling of the deuterium label must have occurred to convert **1a** and [D_3]**4a** into [D_3]**1a** and **4a**. These results suggest that InOTf, rather than the boron Lewis acid **4a**, catalytically activates the C–O bond of ether **1a**. For the deuterium scrambling to occur, the in situ-formed InOMe may be trapped by [D_3]**4a** to form the corresponding boron–ate complex [D_3]**5a** (Figure 4a). This complex may serve as a deuterio-methoxide source ($^-OCD_3$) that reacts with the generated carbenium ion **A** to form [D_3]**1a** and **4a**. Therefore, in our catalytic reaction system, borinic ester **4a** may facilitate the first equilibrium by forming the boron–ate complex **5a** (Figure 4b). This complex may work as an effective methoxide source ($^-OCH_3$) to deliver the required Lewis base, in view of the activation of allyl boronate **2a** for B-to-In transmetalation. Stronger boron Lewis acids, such as **4e** and **4f**, may be able to "trap" the methoxide species to generate the corresponding boron–ate complexes, but those may not effectively transfer the methoxide to **2a**.[13] Finally, it is noted that we cannot rule

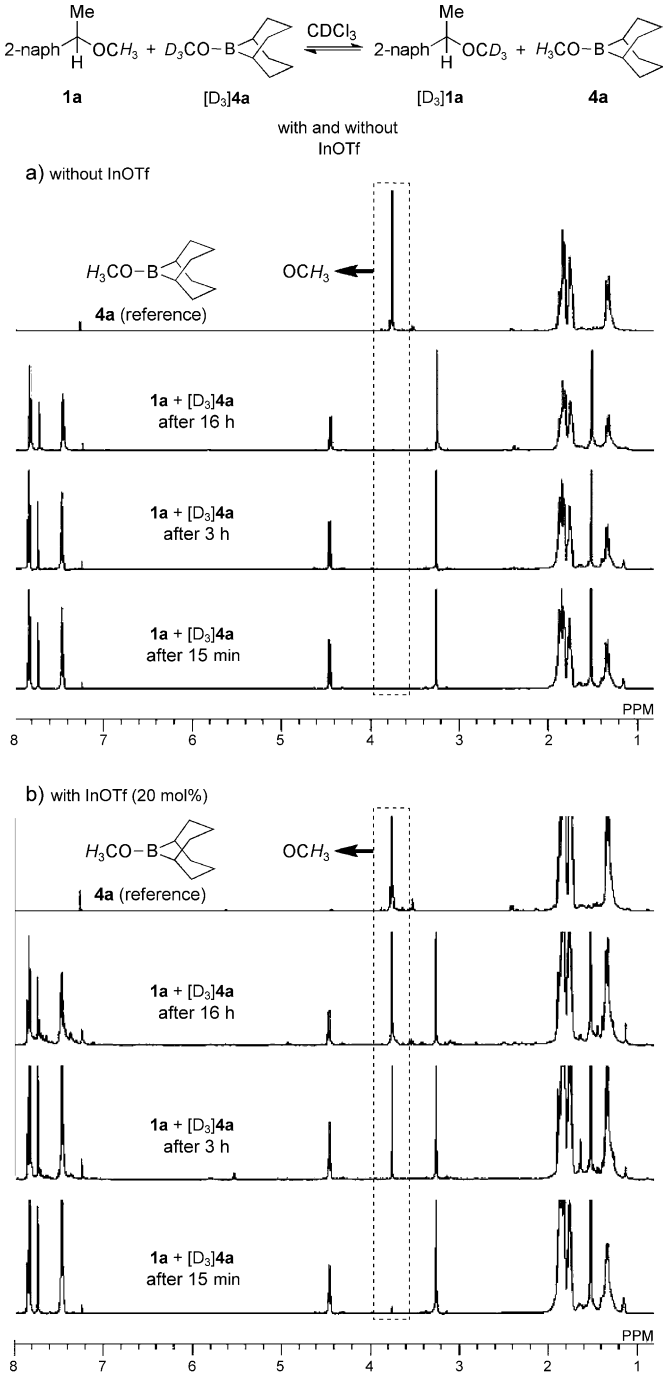


Figure 3. Labeling experiments with ether **1a** and borinic ester [D_3]**4a** (a) without and (b) with InOTf.

out the possibility of a B-to-B "transmetalation" to form the more reactive boron–ate complex **D** (Figure 4c). This complex may serve as a precursor for allyl indium(I) ($E^+ = In^+$), or may be the active nucleophile in the C–C bond formation (E^+ = carbenium ion R^+).

Next, we investigated the scope for electrophiles by employing allyl boronate **2a** with the new indium(I)/boron(III) dual catalyst system (Table 5). Under standard conditions [InOTf (5 mol%) + **4a** (25 mol%)], a substantial rate enhancement was observed for the secondary ethers **1e**, **1i**, and **1p**. The reaction with the more reactive dibenzylic ether **1j** proceeded smoothly, even without the boron co-catalyst; a rate acceleration was not observed. In the case of the particularly challenging primary ether **1b**, the desired product was not obtained, even at an elevated temperature. Finally, borinic ester **4a** was also found to be an effective co-catalyst for the allylation of the less reactive acetals **1v–x**.

We then studied the scope for boronates **2** in catalytic C–C bond formations with ether **1a** (Table 6). In the absence of co-catalyst **4a**, the indium(I)-catalyzed reaction with α-methylallyl boronate **2c** afforded exclusively α-adduct **6** in 45% yield (Table 6, entry 2). This yield was improved to 70% by employing an additional 25 mol% of borinic ester **4a**; the excellent constitutional selectivity was maintained

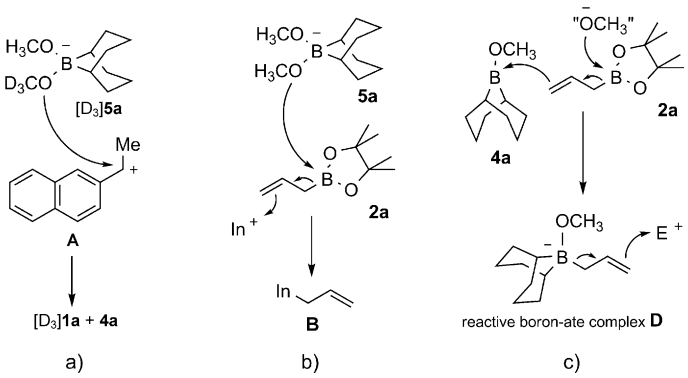
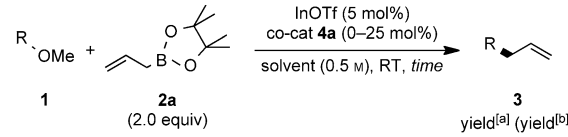
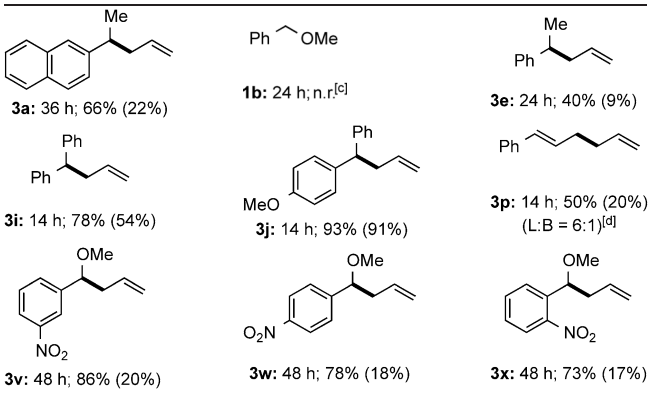


Figure 4. Plausible mechanisms: a) scrambling of the deuterium label; b) boron-to-indium transmetalation; c) boron-to-boron "transmetalation".

Table 5. Scope for the allylation of ethers and acetals **1** with allyl boronate **2a**.

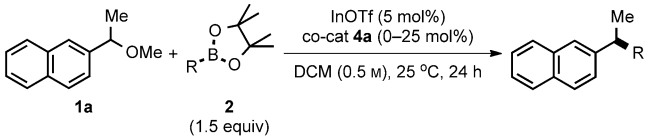


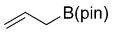
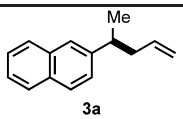
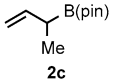
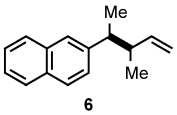
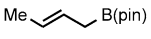
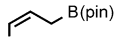
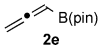
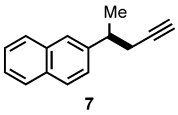
1 | 2a (2.0 equiv) | 3 yield[a] (yield[b])



Yield of isolated product after purification on silica gel (PTLC): [a] 25 mol% of **4a** was used; [b] **4a** was not used. [c] A reaction was not detected even at 50°C. [d] The secondary allylic ether **1p′** (1-methoxy-1-phenylpropene) was employed.

Table 6. Scope for boronates **2** in C–C bond formations with ether **1a**.



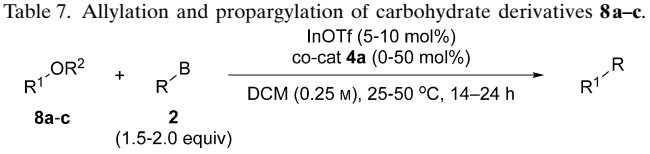
Entry	Pro-Nucleophile	Product	Yield[a] (Yield[b])
1	 **2a**	 **3a**	60% (20%)
2	 **2c**	 **6**	70%[c] (45%)[c]
3	 (*E*)-**2d**	messy	n.d.[d]
4	 (*Z*)-**2d**	messy	n.d.[d]
5	 **2e**	 **7**	65%[e] (5%)

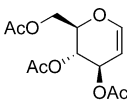
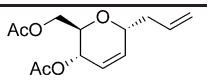
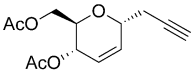
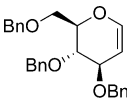
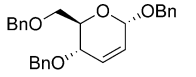
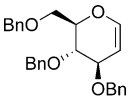
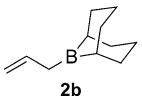
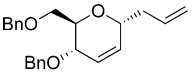
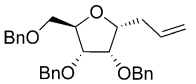
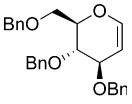
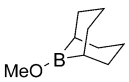
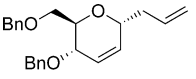
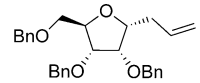
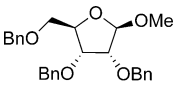
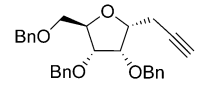
Yield of isolated product after purification on silica gel (PTLC): [a] 25 mol% of **4a** was used; [b] **4a** was not used. [c] Reaction time: 14 h. [d] A reaction was not detected even at 50°C. [e] Propargylation/allenylation = > 20:1. n.d. = not detected.

(Table 6, entry 2). This rare α-selectivity with **2c** is a strong indicator for catalytic B-to-In transmetalation prior to C–C bond formation. The reactions using crotyl boronates (*E*)-**2d** and (*Z*)-**2d** gave only messy mixtures even in the presence of **4a** (Table 6, entries 3 and 4). The low reactivity of these boronates is consistent with our previous work, and may be explained by a particularly slow transmetalation owing to steric congestion at the γ-position.[6] Finally, without **4a**, the reaction with allenyl boronate **2e** hardly proceeded (Table 6, entry 5). On the other hand, in the presence of **4a** (25 mol%), boronate **2e** reacted with **1a** regiospecifically to afford the homopropargylic product **7** in 65% yield (Table 6, entry 5). These improved results highlight the appeal of the present indium(I)/boron(III) dual catalysis for synthetic purposes.

Having developed three general methodologies for Csp^3–Csp^3 couplings of boron-based reagents with Csp^3-type electrophiles, we aimed at applying these methods to *C*-glycosylation, in view of the selective synthesis of carbohydrates. *C*-Glycosides are versatile building blocks for the preparation of many biologically active compounds. This class of molecules has the potential to serve as carbohydrate analogs resistant to metabolic processes, and is a potential source for therapeutic agents in view of various clinical applications.[14] In this context, allylic and propargylic glycosides are attractive because the terminal, unsaturated C–C bond can be easily functionalized to generate other carbohydrate derivatives.[15]

Table 7. Allylation and propargylation of carbohydrate derivatives **8a–c**.



Substrate	Method	Product
 **8a**	"Method 1"[a]  **2a** or  **2e**	 **9a:** 60% (*d.r.* = 10:1)[d]  **10a:** 55% (*d.r.* = 3:1)[d]
 **8b**		 **8b'**: 40% (*d.r.* = 9:1)[d]
 **8b**	"Method 2"[b]  **2b**	 **9b:** 58% (*d.r.* = 9:1)[d]  **9c:** 75% (*d.r.* = 16:1)[d]
 **8b**	"Method 3"[c]  **2a** or  **2e** and  **4a** (co-catalyst)	 **9b:** 44% (*d.r.* = 9:1)[d]  **9c:** 35% (*d.r.* = 11:1)[d]
 **8c** (*d.r.* = 6:1)		 **10c:** 25% (*d.r.* = >10:1)[d]

[a] Conditions ("method 1"): **8a** or **8b** (0.4 mmol, 1.0 equiv), **2a** or **2e** (1.5 equiv), InOTf (5 mol%), DCM (0.25 M), 25°C, 16 h. [b] Conditions ("method 2"): **8b** or **8c** (0.2 mmol, 1.0 equiv), **2b** (2.0 equiv), InOTf (5 mol%), DCM (0.25 M), 25°C, 14 h. [c] Conditions ("method 3"): **8b** or **8c** (0.2 mmol, 1.0 equiv), **2a** or **2e** (2.0 equiv), InOTf (10 mol%), co-catalyst **4a** (50 mol%), DCM (0.25 M), 50°C, 24 h. [d] Diastereomeric ratios were determined by ^{1}H NMR analysis.

The application of the above catalytic methodologies to carbohydrate chemistry is summarized in Table 7. Treatment of 3,4,5-tri-*O*-acetyl-D-glucal (**8a**) with allyl boronate **2a**, in the presence of indium(I) triflate (5 mol%), resulted in the formation of 2,3-unsaturated allyl glycoside **9a** in good yield with high diastereoselectivity ("method 1"). Similarly, glucal **8a** smoothly reacted with allenyl boronate **2e** to provide the corresponding propargylic *C*-pseudoglycal **10a** in good yield with moderate diastereoselectivity. However, when 3,4,5-tri-*O*-benzyl-D-glucal (**8b**) was reacted under "method 1" conditions, only the Ferrier rearrangement-type side-product

8b′ was obtained in moderate yield. These results suggest that the C–O bond activation in **8b** occurred, but the B-to-In transmetalation may be too slow compared with the undesired rearrangement. In addition, **8b′** may be less reactive, and can therefore not be activated under the conditions of "method 1". However, when the more reactive borane **2b** was employed, we obtained the desired product **9b** in good yield with high diastereoselectivity ("method 2"). In analogy, 1-*O*-methyl-2,3,5-tri-*O*-benzylpentofuranose (**8c**) did not undergo allylation with "method 1", while providing high yields and high diastereoselectivities with "method 2". Importantly, the challenging substrates **8b** and **8c** can indeed be reacted with allyl boronate **2a** when the newly developed "method 3" was selected, although a higher loading of the co-catalyst **4a** (50 mol%) and an elevated temperature (50°C) were required. Interestingly, by employing "method 3", carbohydrate **8c** and allenyl boronate **2e** could be selectively converted into the desired propargylic product **10c**, whereas this compound would definitely not be accessible with "method 1" or "method 2".

Conclusions

We have uncovered an interesting rate enhancement for indium(I)-catalyzed allylations and propargylation of Csp^3-type electrophiles with boronate reagents, through the use of borinic ester **4a** as a "hard" Lewis acid co-catalyst. Our work not only represents a significant advance compared with our earlier studies in terms of scope,[6,7] but also sheds further light on the involved reaction mechanism. In addition, we have achieved the application of the present methodologies to selective allylation and propargylation of carbohydrate derivatives. Most importantly, we report here for the first time the relationship between the Lewis acidity of "electrophilic" boron-based compounds and their "nucleophilic" reactivity in Csp^3–Csp^3 couplings, catalyzed by a "soft" low-oxidation main group metal (Figure 5). We believe that these findings will 1) provide more insight into the understanding of boron-based pro-nucleophiles and potential co-catalysts and 2) significantly expand their utility in various domains of organic synthesis. Further investigations with the aim to apply this concept to asymmetric catalysis are now ongoing in our laboratory.

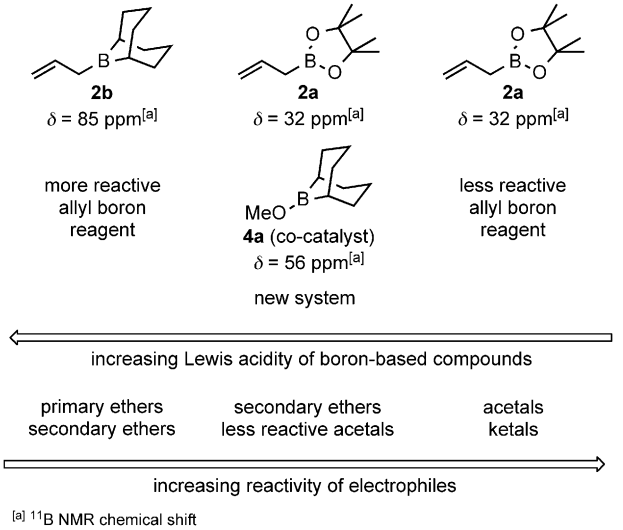


Figure 5. Correlation between the Lewis acidity of "electrophilic" boron-based compounds and their "nucleophilic" reactivity toward Csp^3-type electrophiles.

Experimental Section

General

NMR spectra were recorded on a JEOL ECX-400, an ECA-500, or an ECA-600 spectrometer, operating at 400, 500, or 600 MHz for ^{1}H NMR, and at 100, 125, or 150 MHz for ^{13}C NMR, and at 128 MHz for ^{11}B NMR. Chemical shifts are reported downfield from tetramethylsilane (TMS). IR spectra were measured using a JASCO FTIR-610 spectrometer. HRMS were recorded using a JEOL JMS-T100TD spectrometer (DART). Preparative thin-layer chromatography (PTLC) was carried out using Wakogel B-5F from WAKO. All organic solvents used were commercially available dry solvents, which were distilled appropriately under an argon atmosphere and stored over molecular sieves prior to use in an argon box. Indium(I) triflate (InOTf) was prepared according to a reported procedure, and stored in an argon box at −30°C.[16] Ethers **1a–u** were prepared from the corresponding alcohols. Acetals **1v–x**[17] and carbohydrates **8b–c**[18] were synthesized following reported methods. Carbohydrate **8a** (Aldrich) and boron Lewis acids **4c**, **4d** (1 M in hexane), and **4e** are commercially available (all TCI), and were used without further purification. *B*-Methoxy-9-BBN (**4a**; 1 M in hexane) is commercially available (Aldrich); the solvent was removed prior to its use. Allyl boronate **2a**,[19] allyl borane **2b**,[20] α-methylallyl boronate **2c**,[21] crotyl boronates (*E*)-**2d** and (*Z*)-**2d**,[19] allenyl boronate **2e**,[22] and borane **4b**[20] were prepared by slightly modified procedures of reported methods. Allylations and propargylation were performed according to the general procedure. Products **3a–3r**, **3t–u**,[6] **3v**,[7] **3w**,[23] **8b′**,[24] **9a**,[18a] **9b**,[25] **9c**,[26] and **10a**[27] are literature-known compounds. Their analyses are in full agreement with the reported data. The analytical data for unreported compounds **3x**, **6**, **7**, and **10c** are provided below.

General Procedures

Indium(I) triflate (5–10 mol%), dry DCM or dry $CDCl_3$ (0.25–0.50 M), and the corresponding substrate **1a–x** or **8a–c** were combined in a flame-dried 5 mL-screw vial with magnetic stirring bar in an argon box. After successive addition of the corresponding boron-based reagent **2a**, **2b**, **2c**, (*E*)-**2d**, (*Z*)-**2d**, or **2e** (1.5–2.0 equiv) and co-catalyst **4a** (25–50 mol%, if applicable), the reaction mixture was stirred at the indicated temperature for the indicated time. Quenching with aqueous K_2CO_3 (1 M) yielded the crude reaction mixture, which was then purified by preparative thin-layer chromatography (PTLC; eluant: hexane→hexane/ethyl acetate = 85:15; in a small scale, the product may be purified without quenching).

*1-(1-Methoxybut-3-en-1-yl)-2-nitrobenzene (**3x**)*

Prepared from acetal **1x** (0.4 mmol) and allyl boronate **2a** according to the general method (eluant for PTLC: hexane/ethyl acetate = 95:5). Pale yellow liquid; yield: 73%; ^{1}H NMR (600 MHz, [D$_1$]chloroform, 20°C, TMS): δ = 2.44–2.49 (m, 1H), 2.55–2.59 (m, 1H), 3.23 (s, 3H), 4.85–4.88 (m, 1H), 5.06–5.09 (m, 2H), 5.85–5.92 (m, 1H), 7.43 (t, 1H, J = 7.6 Hz), 7.65 (t, 1H, , J = 7.6 Hz), 7.72 (d, 1H, J = 8.3 Hz), 7.94 ppm (d, 1H, J = 7.6 Hz); ^{13}C NMR (150 MHz, [D$_1$]chloroform, 20°C, TMS, both diastereoisomers): δ = 42.0, 57.4, 78.6, 117.6, 124.4, 128.2, 128.2, 133.5, 134.2, 138.0, 148.9 ppm; IR (neat): $\tilde{\nu}$ = 3077, 2932, 1526, 1345, 1102 cm^{-1}; HRMS (DART): calculated for $C_{11}H_{14}N_1O_3^+ = [M+H]^+$: m/z = 208.09737, found: m/z = 208.09816.

*2-(1,2-Dimethyl-3-buten-1-yl)-naphthalene (**6**)*

Prepared from ether **1a** (0.4 mmol) and α-methylallyl boronate **2c** according to the general method (eluant for PTLC: hexane). Colorless liquid; yield: 70%; ^{1}H NMR (600 MHz, [D$_1$]chloroform, 20°C, TMS): δ = 0.78 and 0.94 (both diastereoisomers; d, 3H, J = 6.2 Hz and 6.9 Hz), 1.22 and 1.26 (both diastereoisomers; d, 3H, J = 7.6 Hz and 7.6 Hz), 1.42 (s, 1H), 2.32–2.40 (both diastereoisomers; m, 1H), 2.58–2.78 (m, 1H), 4.79–4.98 (both diastereoisomers; m, 2H), 5.58–5.71 (both diastereoisomers; m, 1H), 7.24–7.26 (m, 1H), 7.32–7.37 (m, 2H), 7.49–7.51 (m, 1H), 7.67–7.72 ppm (m, 3H); ^{13}C NMR (150 MHz, [D$_1$]chloroform, 20°C, TMS; both diastereoisomers): δ = 16.8, 18.1, 19.2, 19.9, 43.8, 44.9, 45.0, 45.6, 113.6, 114.0, 125.1, 125.7, 125.8, 126.0, 126.1, 126.2, 126.8, 127.4, 127.5, 127.5, 127.6, 127.7, 132.1, 132.2, 133.4, 133.5, 142.7, 143.1, 143.2, 143.9 ppm.

*2-(1-Methyl-3-butyn-1-yl)-naphthalene (**7**)*

Prepared from ether **1a** (0.4 mmol) and allenyl boronate **2e** according to the general method (eluant for PTLC: hexane). Colorless liquid; yield: 65%; ^{1}H NMR (600 MHz, [D$_1$]chloroform, 20°C, TMS): δ = 1.46 (d, 3H, J = 6.9 Hz), 1.51 (s, 1H), 1.97 (t, 1H, J = 2.8 Hz), 2.47–2.52 (m, 1H), 2.56–2.60 (m, 1H), 3.13–3.17 (m, 1H), 7.37–7.46 (m, 3H), 7.66 (s, 1H), 7.78–7.80 ppm (m, 3H); ^{13}C NMR (150 MHz, [D$_1$]chloroform, 20°C, TMS; both diastereoisomers): δ = 20.8, 27.5, 39.0, 69.6, 83.0, 125.0, 125.4, 125.5, 125.9, 127.6, 127.7, 128.0, 132.4, 133.5, 143.0 ppm.

*3-(2,3,5-Tri-O-benzyl-α-D-ribofuranosyl)-1-propyne (**10c**)*

Prepared from carbohydrate **8b** (0.2 mmol) and allenyl boronate **2e** according to the general method (eluant for PTLC: hexane/ethyl acetate = 85:15, three times). Colorless liquid; yield: 25%; ^{1}H NMR (600 MHz, [D$_1$]chloroform, 20°C, TMS): δ = 1.99 (s, 1H), 2.61–2.63 (m, 1H), 2.64–2.71 (m, 1H), 3.49–3.51 (m, 1H), 3.60–3.62 (m, 1H), 4.07–4.09 (m, 1H), 4.12–4.13 (m, 1H), 4.21–4.24 (m, 2H), 4.47 (d, 2H, J = 11.0 Hz), 4.58 (t, 2H, J = 11.7 Hz), 4.67 (d, 1H, J = 11.7 Hz), 4.79 (d, 1H, J = 11.0 Hz), 7.26–7.39 ppm (m, 15H); ^{13}C NMR (150 MHz, [D$_1$]chloroform, 20°C, TMS; both diastereoisomers): δ = 20.0, 69.5, 69.9, 72.5, 73.4, 73.7, 79.0, 79.4, 80.0, 81.4, 127.6, 127.7, 127.7, 127.7, 127.8, 127.9, 128.3, 138.1, 138.2 ppm; IR (neat): $\tilde{\nu}$ = 3030, 2916, 2862, 1453, 1122, 1087, 1048, 1026, 736, 698 cm^{-1}; HRMS (DART): calculated for $C_{29}H_{31}O_4^+ = [M+H]^+$: m/z = 443.22010, found: m/z = 443.22223.

Acknowledgements

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[1] *Comprehensive Organometallic Chemistry III* (Eds.: R. Crabtree, M. Mingos), Elsevier Ltd., Amsterdam, **2006**.

[2] a) W. R. Roush in *Comprehensive Organic Synthesis* (Ed.: B. M. Trost), Pergamon Press, Oxford, UK, **1991**; b) D. S. Matteson in *Stereodirected Synthesis with Organoboranes*, Springer, Berlin, **1995**; c) *Science of Synthesis: Houben-Weyl Methods of Molecular Transformation, Organometallics*, *Vol. 6* (Eds.: D. E. Kaufmann, D. S. Matteson), Thieme, **2005**; d) J. W. J. Kennedy, D. G. Hall, in *Boronic Acids*, *Vol. 11* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, **2005**, pp. 241; e) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457.

[3] Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207.

[4] a) R. W. Hoffmann, W. Ladner, *Tetrahedron Lett.* **1979**, *20*, 4653; b) R. W. Hoffmann, *Angew. Chem.* **1982**, *94*, 569; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 555; c) R. W. Hoffmann, *Pure Appl. Chem.* **1988**, *60*, 123; d) Y. Yamamoto, T. Komatsu, K. Maruyama, *J. Am. Chem. Soc.* **1984**, *106*, 5031; e) S. E. Denmark, N. G. Almstead, in *Modern Carbonyl Chemistry*, *Vol. 10* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, pp. 299; f) S. R. Chemler, W. R. Roush in *Modern Carbonyl Chemistry*, *Vol. 11* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, pp. 403.

[5] a) A. Hosomi, T. Imai, M. Endo, H. Sakurai, *J. Organomet. Chem.* **1985**, *285*, 95; b) G. Kaur, M. Kaushik, S. Trehan, *Tetrahedron Lett.* **1997**, *38*, 2521; c) M. Rubin, V. Gevorgyan, *Org. Lett.* **2001**, *3*, 2705; d) S. H. Kim, C. Shin, A. N. Pae, H. Y. Koh, M. H. Chang, B. Y. Chung, Y. S. Cho, *Synthesis* **2004**, 1581; e) S. K. De, R. A. Gibbs, *Tetrahedron Lett.* **2005**, *46*, 8345; f) M. Yasuda, T. Saito, M. Ueba, A. Baba, *Angew. Chem.* **2004**, *116*, 1438; *Angew. Chem. Int. Ed.* **2004**, *43*, 1414; g) T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2006**, *71*, 8516.

[6] U. Schneider, H. T. Dao, S. Kobayashi, *Org. Lett.* **2010**, *12*, 2488.

[7] H. T. Dao, U. Schneider, S. Kobayashi, *Chem. Commun.* **2011**, *47*, 692.

[8] Double allylation of acetals has also been reported: H. Tanaka, S. Yamashita, Y. Ikemoto, S. Torii, *Tetrahedron Lett.* **1988**, *29*, 1721.

[9] T. Saito, Y. Nishimoto, M. Yasuda, A. Baba, *J. Org. Chem.* **2007**, *72*, 8588.

[10] For an example of a stoichiometrically formed boron–ate complex that reacts with carbenium ion centers, see: R. Hunter, G. D. Tomlinson, *Tetrahedron Lett.* **1989**, *30*, 2013.

[11] K. Matos, J. A. Soderquist, *J. Org. Chem.* **1998**, *63*, 461.

[12] H. C. Brown, U. S. Racherla, P. J. Pellechia, *J. Org. Chem.* **1990**, *55*, 1868.

[13] Boranes **4e** and **4f** may work as hard Lewis acids for the catalytic activation of C–O bonds.

[14] *The Chemistry of C-Glycosides* (Eds.: D. E. Levy, C. Tang), Pergamon Press, Oxford, UK, **1995**.

[15] G. J. McGarvey, C. A. LeClair, B. A. Schmidtmann, *Org. Lett.* **2008**, *10*, 4727.

[16] C. L. B. Macdonald, A. M. Corrente, C. G. Andrews, A. Taylor, B. D. Ellis, *Chem. Commun.* **2004**, 250.

[17] R. Kumar, D. Kumar, A. K. Chakraborti, *Synthesis* **2007**, 299.

[18] a) R. Nakamura, K. Tanino, M. Miyashita, *Org. Lett.* **2003**, *5*, 3583; b) G. Xu, K. D. Moeller, *Org. Lett.* **2010**, *12*, 2590.

[19] W. R. Roush, M. A. Adam, A. E. Walts, D. J. Harrish, *J. Am. Chem. Soc.* **1986**, *108*, 3422.

[20] G. F. Fang, O. A. Wallner, N. Di Blasio, X. Ginesta, J. N. Harvey, V. K. Aggarwal, *J. Am. Chem. Soc.* **2007**, *129*, 14632.

[21] R. W. Hoffmann, J. J. Wolff, *Chem. Ber.* **1991**, *124*, 563.

[22] K. Tonogaki, K. Itami, J.-i. Yoshida, *J. Am. Chem. Soc.* **2006**, *128*, 1464.

[23] M. Barbero, S. Bazzi, S. Cadamuro, S. Dughera, C. Piccinini, *Synthesis* **2010**, 315.

[24] P. Nagaraj, N. G. Ramesh, *Eur. J. Org. Chem.* **2008**, 4607.

[25] J. S. Yadav, B. V. S. Reddy, K. Srinivasa Reddy, L. Chandraiah, V. Sunitha, *Synthesis* **2004**, 2523.

[26] T. Mukaiyama, S. Kobayashi, *Carbohydr. Res.* **1987**, *171*, 81.

[27] M. Isobe, W. Phoosaha, R. Saeeng, K. Kira, C. Yenjai, *Org. Lett.* **2003**, *5*, 4883.

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