Homogeneous Catalysis

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Double Molecular Recognition with Aminoorganoboron Complexes: Selective Alcoholysis of β-Dicarbonyl Derivatives**

*Shunsuke Oishi and Susumu Saito**

Artificial molecular recognition systems play an important role in organic, bioorganic, and supramolecular chemistry.[1–7] In particular, molecular recognition of carbonyl compounds has attracted a great deal of attention because of their synthetic utility.[6,7] However, an artificial system for precise recognition and activation of two different chemical entities, namely, a neutral nucleophile and its coupling partner such as carbonyl compound, for addition/elimination reactions, remains essentially undeveloped. Herein we report on aminoorganoboron (AOB) complexes (Figure 1)[8,9] which are able

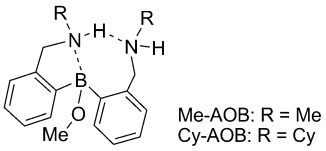
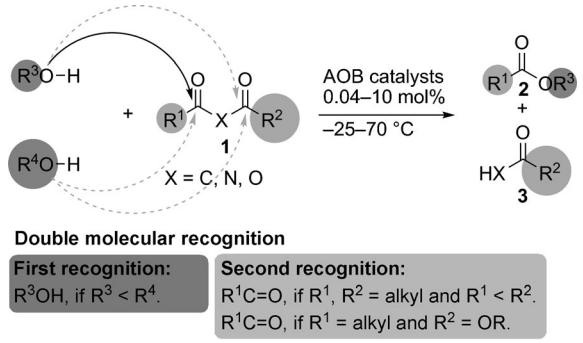


Figure 1. AOB complexes. Cy = cyclohexyl.

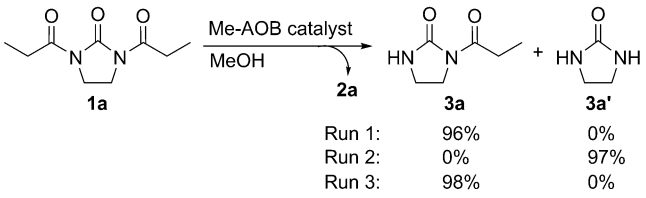
to recognize a smaller alcohol (first recognition) and β-dicarbonyl units (second recognition), and then facilitate chemo- and site-selective alcoholysis of the β-dicarbonyl unit at near neutral pH conditions[10] through activation of both reaction partners (Scheme 1). β-Dicarbonyl structures are, without a doubt, among the most versatile synthetic equivalents in natural product synthesis and asymmetric catalysis.[11]

The alcoholysis procedure for β-dicarbonyl derivatives is simple and straightforward: treatment of a MeOH solution of Me-AOB (1 mol%; [Me-AOB] = 10 mM) with dipropionylimidazolidinone (**1a**) under an argon atmosphere (1 atm) at 25 °C for less than 15 minutes gave, after column chromatography on silica gel, the corresponding methanolysis product



Scheme 1. Representative scheme of alcoholysis of **1** catalyzed by AOBs. The basis of the selectivity of the recognition by the AOB of the alcohol (first recognition) and of the dicarbonyl unit (second recognition) is shown. R^1 and R^2 differ in steric size, electronic nature, and functional groups. Dashed arrows denote relatively unfavorable nucleophilic attack.

3a in a yield of 96% (Scheme 2, run 1). One of the two ethylcarbonyl groups remained completely unreacted. In control reactions using other reagent(s) instead of Me-AOB



Scheme 2. Methanolysis of **1a**. Product **2a** is methyl propionate. Run 1: Me-AOB (1 mol%), 25 °C, < 15 min; Run 2: Me-AOB (2 mol%), 50 °C, 15 h; Run 3: Me-AOB (0.04 mol%), 25 °C, 21 h.

[a] $BnNH_2$ (2 mol%), b) (±)-1,2-diphenylethylenediamine (DPEN; 1 mol%), c) $PhB(OH)_2$ (1 mol%), d) $BnNH_2$ (2 mol%), $PhB(OH)_2$ (1 mol%), or e) DPEN, $PhB(OH)_2$ (1 mol% each)] less than 1% of **1a** was uniformly consumed after 15 minutes at 25 °C. In contrast, by increasing the reaction temperature to 50 °C the two ethylcarbonyl groups were fully removed, thus giving **3a′** in 97% yield (Scheme 2, run 2). Although **3a** and **3a′** remained in the reaction mixture as an NH acid throughout the reaction, these weak acids were not detrimental to the catalytic activity of the AOB. An attempt to decrease the catalyst loading from 1 mol% to 0.04 mol% also resulted in a satisfactory result (turnover number ≈ 2500; Scheme 2, run 3). This sustainable catalytic activity is due to the near neutral pH conditions as well as the favorable discrimination of β-dicarbonyl or tricarbonyl units from other functional groups.

[*] S. Oishi, Dr. S. Saito
Department of Chemistry, Graduate School of Science
Nagoya University, Chikusa, Nagoya 464-8602 (Japan)
E-mail: saito.susumu@f.mbox.nagoya-u.ac.jp
Homepage: http://noy.chem.nagoya-u.ac.jp/S_Saito_E/Saito.html
Dr. S. Saito
Institute for Advanced Research, Nagoya University
Chikusa, Nagoya 464-8601 (Japan)

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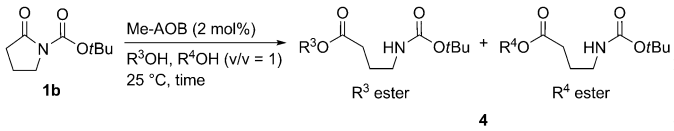
The Me-AOB complex can also promote the alcoholysis of β-dicarbonyl compound **1b** through a subtle change in the steric environment of the alcohols, and leads to attack at the amide carbonyl carbon atom only (Table 1). When MeOH and EtOH were used as a mixed solvent (v/v = 1), MeOH cleaved the C–N bond of **1b** preferentially, thus giving the methyl ester **4b** as the major product (entry 1). Differentiation between two different alcohols (MeOH versus *i*PrOH and EtOH versus *i*PrOH) was also successful (entries 2 and 3). The reactivity of alcohols decreases in the order of MeOH > EtOH > *i*PrOH.

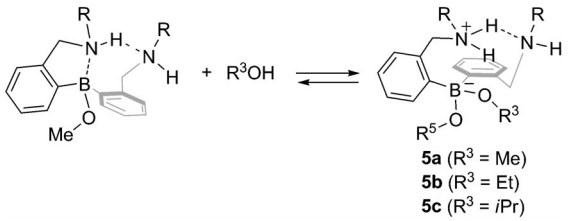
Table 1: Determination of the reactivity of different alcohols.[a]



	R^3OH	R^4OH	*t* [h]	Yield [%]	R^3/R^4 ester
1	MeOH	EtOH	36	**4b** (R^3 = Me) + **4b′** (R^4 = Et): 95	6.3:1
2	MeOH	*i*PrOH	24	**4b** (R^3 = Me) + **4b″** (R^4 = *i*Pr): > 99	> 99:1
3	EtOH	*i*PrOH	48	**4b′** (R^3 = Et) + **4b″** (R^4 = *i*Pr): 64	31:1

[a] Unless specified otherwise, the reaction was carried out with **1b** (1 mmol), Me-AOB (0.02 mmol) in R^3OH and R^4OH (2 mL, v/v = 1) at 25 °C.

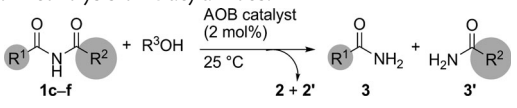
To elucidate the mechanism of the Me-AOB recognition of alcohols, NMR studies were carried out using Me-AOB with different alcohols (Scheme 3). The ^{11}B NMR spectrum of Me-AOB showed a signal at $\delta = 7.7$ ppm (broad singlet) in anhydrous DMSO ([Me-AOB]$_0$ = 10 mM). In contrast, the signal was shifted upfield ($\delta = 6.4$ ppm, broad singlet) in the mixed solvent MeOH/DMSO (1:1, v/v; [Me-AOB]$_0$ = 10 mM). This signal is assigned to **5a**, which results from σ-bond metathesis. There are few catalysts reported based on the boron-"ate" complex.[9d,e] Furthermore, a combination of two broad singlets—a major signal at $\delta = 7.7$ ppm, and a less intense signal at $\delta = 5.3$ ppm—was detected for Me-AOB in *i*PrOH/DMSO (1:1, v/v; [Me-AOB]$_0$ = 10 mM). The major signal was assigned to the nitrogen-coordinated tetragonal boron atom of free (unbound) Me-AOB, and the minor signal corresponds to **5c**, which is formed upon σ-bond metathesis between Me-AOB and *i*PrOH. The appearance of two different signals upon treatment of AOB complexes with alcohols was observed in relevant systematic studies.[9c,f] When MeOH was added to an *i*PrOH/DMSO solution of Me-AOB (MeOH/*i*PrOH/DMSO = 1:1:1, v/v; [Me-AOB]$_0$ = 6.7 mM), the signals at $\delta = 5.3$ and 7.7 ppm disappeared and a new broad singlet appeared at $\delta = 5.6$ ppm. Similarly, an intense peak and a second of medium intensity were observed in the ^{11}B NMR spectrum of Me-AOB in EtOH/DMSO, and they coalesced in MeOH/EtOH/DMSO.[12] These ^{11}B NMR data suggest that smaller alcohols are preferentially incorporated into AOB complexes (Scheme 3).

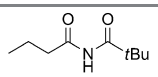
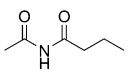
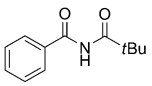
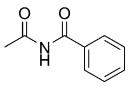


Scheme 3. Proposed incorporation of alcohols into AOB. R = Me or Cy; $R^5 = R^3$ or Me.

Given the important discovery that smaller alcohols are more favorably activated, thus leading to subsequent alcoholysis of β-dicarbonyl units, other β-dicarbonyl derivatives (**1c**–**1n**) were tested, and the results are listed in Tables 2 and 3. The chemo- and site selectivity of the methanolysis depends upon the steric size, electronic nature, and substitution pattern of the β-dicarbonyl units. For the *N*-acylamides **1c**–**f**, alcoholysis took place selectively at the sterically less hindered carbonyl carbon atom (Table 2). Methanolysis of **1c**, bearing the *tert*-butyl group, gave the corresponding **3′** with excellent site selectivity (entry 1). In contrast, such site selectivity was consistently only moderate in the Me-AOB-mediated methanolysis of **1d–f**, and was marginally improved

Table 2: Alcoholysis of *N*-acylamides.[a]

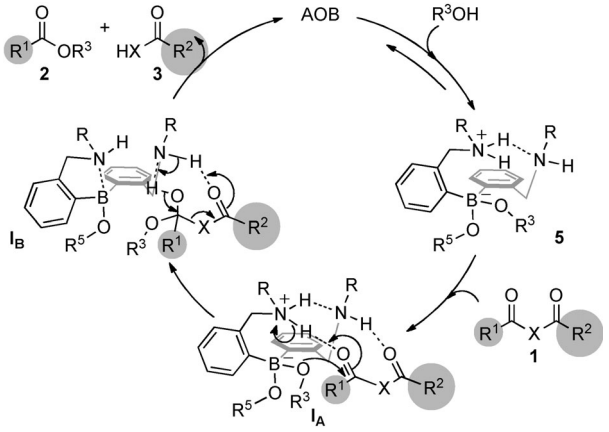


Entry	*N*-acylamide **1**	AOB catalyst	R^3OH	Yield [%][b]	**3**/**3′**
					
1	**1c** (R^1 = *n*Pr, R^2 = *t*Bu)	Me-AOB	MeOH	> 99	1: > 99
					
2	**1d** (R^1 = Me, R^2 = *n*Pr)	Me-AOB	MeOH	> 99	1:1.6
3[c]		Cy-AOB	MeOH	99	1:1.7
4[d]		Me-AOB	EtOH	> 99	1:4.6
5[e]		Cy-AOB	EtOH	93	1:7.5
					
6[f]	**1e** (R^1 = Ph, R^2 = *t*Bu)	Me-AOB	MeOH	> 99	1:5.7
7[c]		Cy-AOB	MeOH	> 99	1:12
8[d]		Me-AOB	EtOH	> 99	1:10
9[e]		Cy-AOB	EtOH	76	1:14
					
10	**1f** (R^1 = Me, R^2 = Ph)	Me-AOB	MeOH	> 99	1:6.1
11[c]		Cy-AOB	MeOH	99	1:8.0
12[d]		Me-AOB	EtOH	> 99	1:13
13[e]		Cy-AOB	EtOH	85	1:20

[a] **2** = $R^2CO_2R^3$; **2′** = $R^1CO_2R^3$. Unless specified otherwise, the reaction was carried out with **1** (1 mmol), Me-AOB or Cy-AOB (0.02 mmol) in R^3OH (1 mL) at 25 °C for 4 h. [b] Yield of **3** and **3′** combined. [c] 14 h. [d] 30 h. [e] 45 °C, 40 h. [f] 6 h.

by the use of Cy-AOB, which has sterically bulkier substituents on the nitrogen atoms (entries 3, 7, and 11). The selectivity was additionally improved when using EtOH and Me-AOB (entries 4 and 12). These results can be accounted for by the larger steric congestion imposed on the catalytically active site of **5b** upon binding of EtOH to Me-AOB. Accordingly, it is reasonable to use a combination of Cy-AOB and EtOH, which was in fact the most effective in discriminating the sterically less hindered carbonyl group (entries 5, 9, and 13).

On the basis of these experiments and interpretation of the results, a plausible catalytic cycle for the alcoholysis is depicted in Scheme 4. The incorporation of R^3OH into an AOB complex occurs to give **5** prior to the alcoholysis. As a result, an ionic pair consisting of $[Ar_2B(OMe)_2]^-$ and $[(Bn)(R)H_2N–H–NR(Bn)]^+$ is produced intramolecularly. As shown in $\mathbf{I_A}$, this ionic pair recognizes the β-dicarbonyl compound **1**, binds preferentially to carbonyl group bearing the less sterically demanding R group, and activates it for reaction. The sterically more hindered carbonyl group of **1** is therefore more exposed to prevent severe steric repulsion within the active site. Nucleophilic attack of $[Ar_2B(OMe)_2]^-$ on the sterically less congested carbonyl carbon center occurs, thus producing the tetrahedral intermediate $\mathbf{I_B}$. Finally **2** and **3** are released and reformation of hydrogen bonds regenerates AOB. The point of this overall scenario is that the hydrogen atoms of **5** that are the secondary coordination (outer) sphere[1a,13] are the primary location where a carbonyl group(s) could have a direct interaction for its activation. The alignment of elements [O(δ−)–B(δ+)–N(δ−)–H(δ+)–N(δ−)–H(δ+)] inherent in AOB complexes serves as a prototype for encouraging hydrogen-bond-promoted catalysis.

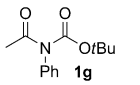
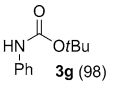
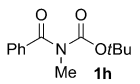
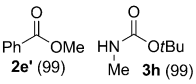
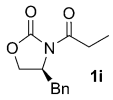
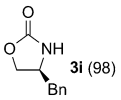
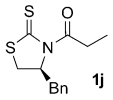
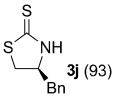
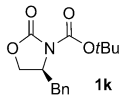
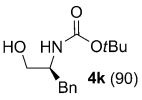
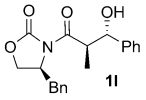
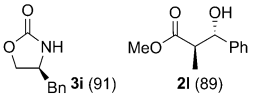
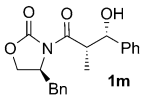
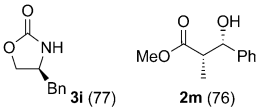
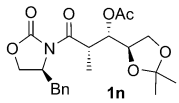
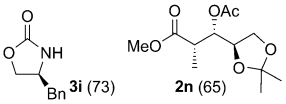


Scheme 4. Plausible catalytic cycle for alcoholysis.

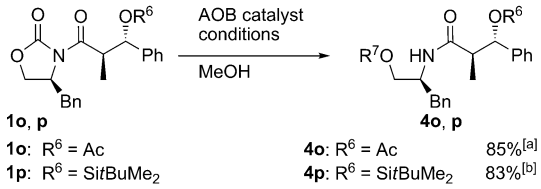
When either R^1 or R^2 in **1** was substituted by a heteroatom (such as O or S), the other side of the carbonyl group was the favored reaction site (Table 3). One exception is the methanolysis of **1k**, bearing two different carbamate moieties, which took place at the less hindered carbonyl carbon atom to give the ring-opening product **4k** as the sole isomer (entry 5). For the *N*-Boc-protected amides, methanolysis gave *N*-Boc amines **3g** and **3h** in excellent yields, and the *N*-Boc groups remained intact (entries 1 and 2). This protocol is also applicable to 2-acyl oxazolidinones and 2-acyl-2-thiazolidinethione derivatives, which are frequently used in chiral auxiliary mediated asymmetric synthesis.[11b,d,h,k] In practice, **1i** and **1j** underwent deacylation to give **3i** and **3j**, respectively, in high yields (entries 3 and 4). Methanolysis of the aldol adducts **1l**, **1m**, and **1n** yielded methyl esters **2l**, **2m**, and **2n**, respectively, without epimerization at the stereogenic carbon centers (entries 6–8). The Cy-AOB was more effective than the Me-AOB in the site-selective methanolysis of **1l** and **1m**, substrates with unprotected OH groups (entries 6 and 7). The chiral auxiliary **3i** was recovered in almost quantitative yields in both cases. In contrast, methanolysis of **1l** with NaOMe (5 mol%; $[NaOMe]_0 = 25$ mM) proceeded less selectively, thus giving **3i** in 64% yield and **2l** in 62% yield. More-neutral AOB catalysts gave a selectivity superior to NaOMe, which facilitated fragmentation of the cyclic framework of **1l**.

A series of AOB complexes was also able to recognize small changes in the functional group of the β-oxo-δ-oxycarbonyl units (**1o**,**p**; Scheme 5). For example, the *endo*-C–N bond was cleaved predominantly at 25 °C when the δ-hydroxy group was protected ($R^6 \neq H$) by either an acetyl (Ac) or *tert*-butyldimethylsilyl (Si*t*BuMe$_2$) group; in contrast, when $R^6 =$ H, *exo*-C–N bond cleavage occurred preferentially at −25 °C (Table 3, entries 6 and 7). Of note is that the Ac and Si*t*BuMe$_2$

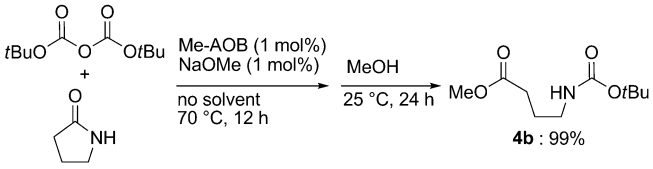
Table 3: C–N bond cleavage of activated amides.[a]

Entry	1	t [h]	Products (yield [%][b])
1	 **1g**	18	 **3g** (98)
2	 **1h**	10	 **2e'** (99) **3h** (99)
3	 **1i**	< 1	 **3i** (98)
4	 **1j**	6	 **3j** (93)
5	 **1k**	13	 **4k** (90)
6[c]	 **1l**	48	 **3i** (91) **2l** (89)
7[c]	 **1m**	48	 **3i** (77) **2m** (76)
8[d]	 **1n**	12	 **3i** (73) **2n** (65)

[a] Unless otherwise specified, the reaction was carried out with **1** (1 mmol), and Me-AOB (0.02 mmol) in MeOH (2 mL) at 25 °C. [b] Yield of isolated product. [c] Cy-AOB (0.05 mmol) was used at −25 °C. [d] Me-AOB (0.10 mmol) was used at −25 °C.



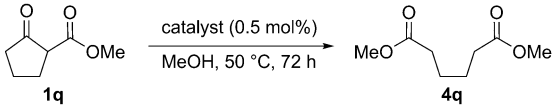
Scheme 5. Discrimination of β-oxo-δ-oxycarbonyl units. Reaction conditions: Me-AOB (2 mol%), 25 °C, 26 h. [a] R^7 = -(C=O)OMe. [b] R^7 is a mixture of H and -(C=O)OMe (2.2:1).



Scheme 7. C–O bond cleavage in a β-dicarbonyl unit and formal alcoholysis of deactivated amides using modified AOB. 2-pyrrolidinone/Boc_2O/Me-AOB/NaOMe/MeOH = 1.1:1:0.01:0.01:30.

groups are labile under basic and acidic conditions, respectively; however, each group remained unreacted under identical reaction conditions, thus suggesting that near neutral pH environments were preserved throughout the reaction.

The retro-Dieckmann condensation[14] of the β-ketoester **1q** was also facilitated by a slightly modified AOB complex (Scheme 6). In the presence of 0.5 mol% each of Me-AOB



Scheme 6. C–C bond cleavage (retro-Dieckmann condensation) catalyzed by modified or native AOB. Run 1: [Me-AOB + NaOMe]$_0$ = 2.5 mM, 83%; Run 2: [NaOMe]$_0$ = 2.5 mM, 31%; Run 3: [Me-AOB]$_0$ = 2.5 mM, 19%.

and NaOMe, the carbon–carbon bond was cleaved smoothly to give the dimethyl adipate (**4q**) in 83% yield at 25 °C. Me-AOB itself had relatively low reactivity (19%). In comparison, when the more basic NaOMe (0.5 mol%) alone was used under otherwise identical conditions, the yield of **4q** upon isolation was decreased significantly (31%) even after a prolonged reaction time. However, the Me-AOB and NaOMe were not functioning independently, since the sum of the yields obtained using NaOMe alone and Me-AOB alone is only about two-thirds of the 83% obtained when using the mixture of the two. In any event, such a new catalytic species[15] is a weaker base but more effective than NaOMe.[16a]

Me-AOB can also catalyze the scission of the C–O bond in Boc_2O upon reaction with 2-pyrrolidinone to give **1b** in quantitative yield (2-pyrrolidinone/Boc_2O/Me-AOB = 1.1:1:0.02).[16b] This result, obtained under near neutral pH conditions, is in contrast to the amine-base-catalyzed reactions.[17] Since **1b** was readily transformed into the *N*-Boc-γ-amino ester **4b** (Table 1), these two different reaction steps can be combined to provide a unique method for the alcoholysis of deactivated amides, a reaction that is otherwise difficult to attain under relatively neutral pH conditions. Indeed, this consecutive process is accomplished in a one-pot operation using the Me-AOB/NaOMe catalyst (Scheme 7).

In summary, AOB complexes have been shown to react highly selectively depending on differences in the size of the alcohols, and discriminate between a broad spectrum of β-dicarbonyl units and other functional groups. This behavior facilitated the chemo- and site-selective alcoholysis of the β-dicarbonyl functional group, thus enabling C–C, C–N, and C–O bond-cleavage reactions. This methodology not only provides a conceptually new method for molecular recognition of multifunctional substrates but also has potential applications in the selective bond cleavage of many synthetically relevant intermediates under near neutral pH conditions.

Experimental Section

A 1.0 M methanol solution of sodium methoxide (10 μL, 10 μmol) was added to a solution of the precursor of Me-AOB, $C_{16}H_{20}BClN_2$[8a] (2.9 mg, 10 μmol), in anhydrous methanol (1.0 mL) at room temperature under argon, and the reaction mixture was stirred at room temperature for 15 min. *N,N'*-dipropionylimidazolidin-2-one (**1a**; 1.0 mmol, 198 mg) was added to the methanol solution of the resulting Me-AOB. The reaction mixture was stirred for 15 min at room temperature under argon. The mixture was quenched with one drop of a saturated aqueous NH_4Cl using a Pasteur pipette and then concentrated in vacuo. The resulting oil was purified by flash chromatography on silica gel (ethyl acetate/*n*-hexane = 1:2 to 1:1 as eluent) to give pure **3a** (129 mg, 96%). For spectral and analytical data of product **3a**, see the Supporting Information.

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[12] See the Supporting Information (Figures S1–S6).

[13] In prospective intermediates $\mathbf{I_A}$ and $\mathbf{I_B}$, an alternating alignment of two different types of chemical bonds, one undergoing bond breaking and the other undergoing bond making, provides cyclic linkages among multiple elements. Such an alignment facilitates a "push and pull" movement of electrons in catalysis (formally delineated by curved arrows), which corresponds to relatively low-barrier processes involving "low-barrier hydrogen bonds (LBHB)".[18] Such a natural movement of electrons would not be well arranged if direct and strong binding of a carbonyl group to the primary coordination sphere (the boron in the case of AOB) were involved; such binding is unlikely as a part of the primary path of the catalysis. For a similar secondary coordination system, see also: a) Y. Du, S. Oishi, S. Saito, *Chem. Eur. J.* **2011**, *17*, 12262 – 12267; b) M. Rakowski DuBois, D. L. DuBois, *Chem. Soc. Rev.* **2009**, *38*, 62 – 72; c) C. A. Sandoval, T. Okuma, K. Muniz, R. Noyori, *J. Am. Chem. Soc.* **2003**, *125*, 13490 – 13503.

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[15] During the formation of the new active species (Me-AOB/NaOMe = 1:1), NaOMe should be incorporated into Me-AOB through a metathesis process similar to that shwon in Scheme 3 to form a more active species, or should deprotonate the NH in Me-AOB with subsequent metathesis with MeOH. Either process should give the same structure, which affords a ^{11}B NMR signal at $\delta = 6.0$ ppm (broad singlet) in teh mixed solvent MeOH/DMSO (1:1, v/v; $[\text{Me-AOB}]_0 = 10$ mM).

[16] a) When DPEN (0.5 mol%) or DPEN + $PhB(OH)_2$ (0.5 mol% each) was used, the yields of **4q** were less than 1%; b) DPEN (2 mol%) and DPEN + $PhB(OH)_2$ (2 mol% each) showed scant catalytic activity (**1b**: 29% and < 1%, respectively) under otherwise identical reaction conditions.

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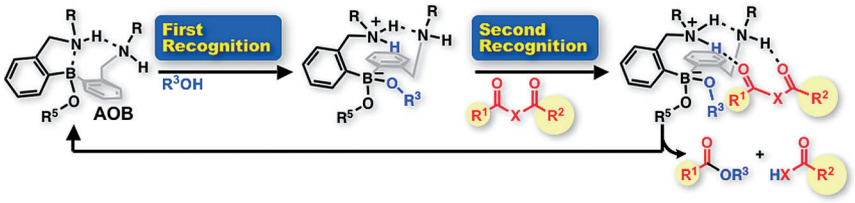
Communications

Homogeneous Catalysis

S. Oishi, S. Saito* _____ ■■■■–■■■■

Double Molecular Recognition with Aminoorganoboron Complexes: Selective Alcoholysis of β-Dicarbonyl Derivatives



Double duty: Aminoorganoboron (AOB) complexes recognize alcohol and β-dicarbonyl units, and thereby facilitate chemo- and site-selective alcoholysis of the latter (see scheme). The complex activates both reaction partners. This strategy enables C–C, C–N, and C–O bond cleavage in addition/elimination reactions under near neutral pH conditions and provides a new method for functional group conversions.