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Development of a Simple Adjustable Zinc Acid/Base Hybrid Catalyst for C–C and C–O Bond-Formation and C–C Bond-Cleavage Reactions

Yasuhiro Yamashita,[a] Kodai Minami,[a] Yuki Saito,[a] and Shū Kobayashi*[a]

Dedication ((optional))

Abstract: A newly designed zinc Lewis acid/base hybrid catalyst was developed. By adjusting the Lewis acidity of the zinc center, aldol-type additions of 2-picolylamine Schiff base to aldehydes proceeded smoothly to afford *syn*-aldol adduct equivalents, *trans*-*N*,*O*-acetal adducts, in high yields with high selectivities. NMR experiments including microchanneled cell for synthesis monitoring (MICCS) NMR analysis revealed that *anti*-aldol adducts were formed at the initial stage of the reactions under kinetic control, but that the final products were the *trans*-(*syn*)-*N*,*O*-acetal adducts that were produced through a retro-aldol process under thermodynamic control. In the whole reaction process, the zinc catalyst played three important roles: promotion of the aldol process (C–C bond formation), the cyclization process to the *N*,*O*-acetal product (C–O bond formation), and the retro-aldol process from the *anti*-aldol adduct to the *syn*-aldol adduct (C–C bond cleavage and C–C bond formation).

The development of well-designed, conceptually advanced catalysts with high reactivity and selectivity that can be used to realize efficient synthesis of organic molecules is strongly desired. Lewis acid/Brønsted base-catalyzed carbon–carbon (C–C) bond-forming reactions are useful, fundamental, and atom-economical methods to construct the basic framework of complex molecules.[1] We have been focusing on the development of simple Lewis acid/Brønsted base catalysts and investigating metal amides as highly reactive, simple one-molecule acid/base catalysts.[2] In synthetic organic chemistry, metal amides have long been mainly used as strong Brønsted bases to deprotonate acidic hydrogen atoms stoichiometrically to form anion species; their use as highly reactive catalysts in C–C bond-forming reactions is very limited. We have previously revealed that chiral silver or copper amides worked well as highly reactive catalysts in catalytic asymmetric [3+2] cycloadditions.[3] Furthermore, we have quite recently developed indium Lewis acid/metal amide hybrid catalysts, $In(N(SiMe_3)_2)_2X$ {$In(HMDS)_2X$, X= Cl, OTf}, as a new type of catalyst for addition reactions of terminal alkynes to nitrones.[4] The Lewis acidity on the metal center is adjusted by the electron-withdrawing group, chloride or triflate, which activates the nitrones (less reactive electrophiles), and at the same time the amide moiety deprotonates the terminal alkynes effectively. Here, we show another Lewis acid/metal amide hybrid based on the new concept (Figure 1); the new Zn catalyst efficiently promotes C–C and C–O bond-forming reactions as well as C–C bond-cleavage reactions. [5]

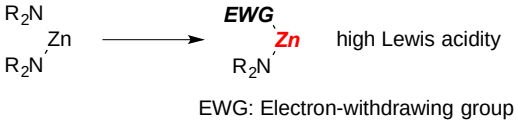

Figure 1 Zinc Lewis acid/metal amide hybrid

Heteroaryl-substituted alkylamine units are often observed in biologically active compounds; among them, 1-(2-pyridyl)-1,2-aminoalcohols are interesting synthetic components in a number of drug candidates.[6] Although the syntheses of these compounds have been investigated,[7,8] efficient and versatile methods that involve catalytic C–C bond formation have been very limited. Enders *et al.* reported a catalytic stereoselective Mannich-type reaction of an imine derived from 2-pyridinecarboxyaldehyde with 2,2-dimethyl-1,3-dioxan-5-one by using an organocatalyst;[8g] however, it is difficult to synthesize 2-alkyl or 2-aryl-substituted 1-(2-pyridyl)-1,2-aminoalcohols directly by using this reaction. To provide a versatile method to synthesize these compounds, a catalytic direct aldol reaction of protected 2-picolylamine is promising; however, to our knowledge, this type of catalytic aldol reaction has rarely been reported.[7,9]

First, we investigated the aldol reaction of Schiff base **2**, derived from 2-picolylamine, by using zinc amide catalysts (Table 1; for details see Table S1 in the Supporting Information (SI)).[10] Interestingly, the reaction of **2** with benzaldehyde (**1a**) proceeded in THF in the presence of a zinc Lewis acid/metal amide hybrid, Zn(HMDS)OTf. In contrast, the use of either $Zn(HMDS)_2$[11] or $Zn(OTf)_2$ did not afford any products (entries 1–3). This is a remarkable advantage of a Lewis acid/metal amide hybrid system compared with a simple Lewis acid or a simple metal amide catalyst.[12] It was also found that the major product of the reaction was not aldol adduct **4a** but *N*,*O*-acetal adduct **3a**. The structure of **3a**, which was determined by X-ray single-crystal structure analysis, indicated that the configuration of **3a** was *trans*, corresponding to *syn*-aldol adduct (*syn*-**4a**).[13,14] Screening of solvents was then conducted to improve the yield of the *N*,*O*-acetal adduct, and 1,2-dichloroethane (DCE) was found to give both high yield and high *trans*-(*syn*)-selectivity (entry 4). Control of the reaction temperature was important: conducting the reaction at 0 °C led to higher selectivity (entry 5).

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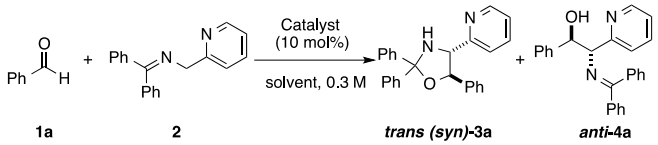
Supporting information for this article is given via a link at the end of the document.

Further optimization of concentrations and ratios of substrates improved the yield to 85% (entry 7). Under the optimal conditions, the catalyst loading could be reduced to 5 mol% to afford the desired product in high yield with high selectivity, albeit in a longer reaction time (entries 8 and 9). Interestingly, it was found that the selectivity was increased by simply extending the reaction time (*vide infra*).

Table 1 Catalytic Aldol-Type Additions of **1a** with **2**[a]



1a **2** ***trans (syn)*-3a** ***anti*-4a**

Entry	Cat.	Solvent	Temp. (°C)	Total yield (%)[b]	*Trans* /*anti*[c]
1[d]	$Zn(OTf)_2$	THF	40	trace	–
2[d]	$Zn(HMDS)_2$	THF	40	trace	–
3	Zn(HMDS)OTf	THF	20	59 (48)	92:8
4	Zn(HMDS)OTf	DCE	20	79 (69)	91:9
5	Zn(HMDS)OTf	DCE	0	83 (74)	94:6
6[e]	Zn(HMDS)OTf	DCE	0	79	94:6
7[e]	Zn(HMDS)OTf	DCE[f]	0	85 (77)	93:7
8[e,g]	Zn(HMDS)OTf	DCE[f]	0	59	92:8
9[e,g,h]	Zn(HMDS)OTf	DCE[f]	0	88 (83)	95:5

[a] The reaction of 0.3 M **1a** (0.33 mmol) with **2** (0.30 mmol) was conducted for 18 h at the temperature described in the presence of Zn catalyst (10 mol%) unless otherwise noted. Zn(HMDS)OTf was prepared *in situ* by mixing $Zn(OTf)_2$ and KHMDS (1:1) in THF just before use (see supporting information). [b] Determined by ^{1}H NMR analysis of the crude mixture using durene as an internal standard. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] 0.4 M. [e] **1a** (0.30 mmol) and **2** (0.36 mmol) were used. [f] 0.6 M. [g] 5 mol% of the Zn catalyst was used. [h] The reaction was conducted for 48 h.

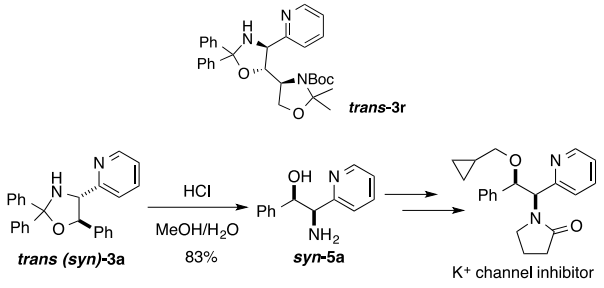
The substrate scope of the aldol-type addition reaction was then examined (Table 2). Tolaldehydes **1b**–**d** were also successfully employed in the reaction, and the desired *N*,*O*-acetal adducts were obtained in good yields with high selectivities (entries 2–4). Benzaldehydes bearing either electron-donating or electron-withdrawing groups also worked well to afford the desired products in good yields with high selectivities, although reactivities were sometimes not very high (entries 5–9). Other aromatic aldehydes, **1j** and **1k**, gave similar good results (entries 10 and 11). Aliphatic aldehydes were also successfully employed, and, except for pivalaldehyde (**1l**), the desired products were obtained in high yields. Although primary aliphatic aldehydes **1o**–**q** gave slightly lower selectivities (entries 15–17), bulky aliphatic aldehydes **1l**–**n** gave excellent selectivities (entries 12–14). An asymmetric aldol-type reaction with Garner's aldehyde **1r** also proceeded in good yield with high selectivities (entry 18). It should be noted that wide substrate scope was observed in the reaction. Simple hydrolysis of these compounds could give potential precursors of biologically active compounds, for example, a K^+ channel inhibitor (Scheme 1).[6]

During optimization of the reaction conditions, it was found that the selectivity increased as the reaction time was prolonged for some substrates, especially for aliphatic aldehydes. This observation suggested that isomerization under thermodynamic

Table 2 Substrate Scope[a]

Entry	R (**1**)	**3**	Total yield (%)[b]	Yield of *trans*-**3** (%)[c]	*trans*-**3**/*anti*-**4**[d]
1	Ph (**1a**)	**3a**	87	83	95:5
2[e]	*o*-MeC_6H_4 (**1b**)	**3b**	77	72	94:6
3	*m*-MeC_6H_4 (**1c**)	**3c**	73	67	92:8
4	*p*-MeC_6H_4 (**1d**)	**3d**	70	66	94:6
5[e]	*p*-$MeOC_6H_4$ (**1e**)	**3e**	77	73	95:5
6[e,f]	*p*-BrC_6H_4 (**1f**)	**3f**	79	72	91:9
7	*o*-$O_2NC_6H_4$ (**1g**)	**3g**	61	54	88:12
8[f]	*m*-$O_2NC_6H_4$ (**1h**)	**3h**	74	69	93:7
9[f]	*p*-$O_2NC_6H_4$ (**1i**)	**3i**	80	75	94:6
10[f,g]	2-naphthyl (**1j**)	**3j**	75	71	94:6
11[e]	2-thiophenyl (**1k**)	**3k**	68	62	91:9
12[g]	^{t}Bu (**1l**)	**3l**	47	47	>99:1
13[g]	^{i}Pr (**1m**)	**3m**	81	79	98:2
14[e]	Cyclohexyl (**1n**)	**3n**	89	86	99:1
15[e]	^{i}Bu (**1o**)	**3o**	85	73	86:14
16[g]	C_7H_{15} (**1p**)	**3p**	80	69	87:13
17[g]	C_3H_7 (**1q**)	**3q**	91	77	85:15
18[f,g,h]	Garner's aldehyde (**1r**)	**3r**	73	62[i]	96:4 (91:9)[j]

[a] The reactions of 0.6 M RCHO **1** (0.30 mmol) and **2** (0.36 mmol) were conducted in DCE at 0 °C for 48 h in the presence of Zn(HMDS)OTf (0.015 mmol, 5.0 mol%) unless otherwise noted. Zn(HMDS)OTf was prepared *in situ* by mixing $Zn(OTf)_2$ and KHMDS (1:1) in THF just before use. [b] Determined by ^{1}H NMR analysis of the crude mixture using durene as an internal standard. [c] Isolated yield. [d] Determined by ^{1}H NMR analysis of the crude mixture. [e] At 25 °C. [f] 10 mol% Zn(HMDS)OTf was used. [g] At 40 °C. [h] 0.3 M. [i] Isolated yield of major diastereomer of *trans*-**3r**. [j] Diastereomer ratio of *trans*-**3r**.



Scheme 1 Synthesis of a K^+ channel inhibitor

control might occur to change the selectivity. To clarify the detailed reaction profile, we followed the progress of reaction by using ^{1}H NMR analysis (details are provided in the SI). The reaction of **1a** with **2** proceeded smoothly in around 30% conversion at room temperature even in 1 h, and the *trans(syn)*-*N*,*O*-acetal adduct **3a** was formed preferentially with high selectivity (>9:1) during the initial stage of the reaction (Chart 1). On the other hand, a similar investigation using cyclohexanecarboxaldehyde (**1n**) showed a different tendency; in this case, the *anti*-aldol adduct was observed as the major

product during the initial stage of the reaction, although the final major product was *trans*-*N*,*O*-acetal adduct **3** (Chart 2). A possible explanation was that the reaction of aromatic aldehyde **1a** was obtained under kinetic control and that the reaction of aliphatic aldehyde **1n** was formed under thermodynamic control. However, we thought that this was not likely based on a consideration of similar types of aldol reactions. Another possible explanation was that the rate of the isomerization in the reaction of **1a** was too fast to be observed on the time scale of the NMR experiments shown in Chart 1.

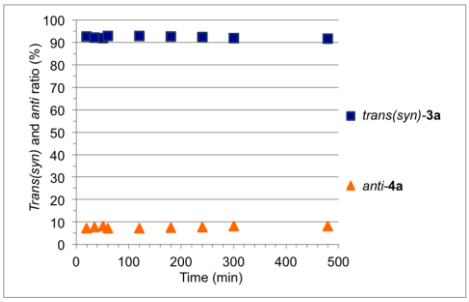


Chart 1 Change of the *trans*-**3a**/*anti*-**4a** ratio at the initial stage of the addition reaction of **1a** with **2** in DCM-d_2 at 25 °C in the presence of Zn(HMDS)OTf (10 mol%) measured with a standard NMR spectrometer.

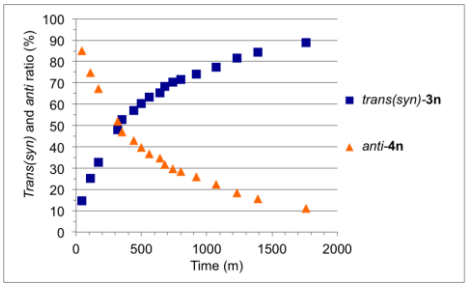


Chart 2 Change of the *trans*-**3n**/*anti*-**4n** ratio at the initial stage of the addition reaction of **1n** with **2** in DCM-d_2 at 25 °C in the presence of Zn(HMDS)OTf (10 mol%) measured with a standard NMR spectrometer.

To elucidate the interesting phenomena of the isomerization, we then conducted ^{1}H microchanneled cell for synthesis monitoring (MICCS) NMR analysis to observe the very early stage of the reaction of **1a** (Chart 3).[15] The reaction of **1a** with **2** was monitored in the presence of Zn(HMDS)OTf with a MICCS system. Interestingly, the results revealed that *anti*-aldol product **4a** was obtained preferentially at the very early stage of the reaction. This result strongly suggested that the kinetically favored product in the reaction of **1a** was also *anti*-**4a**, and the *trans*-*N*,*O*-acetal adduct **3a** corresponding to *syn*-aldol adduct was a thermodynamically favored product. In the reaction of **1a**, isomerization of **4a** to **3a** would be very fast compared with the reactions of aliphatic aldehydes, presumably because the aromatic group affects the acidity of the hydroxyl groups of the aldol adducts to enhance the retro-aldol process.[9g] From these experiments, it was suggested that the addition reaction of **1** with **2** would proceed kinetically to afford the *anti*-aldol product selectively (Figure S3), but that the product would isomerize during the reaction to give the *trans*-*N*,*O*-acetal adduct with high selectivity. High levels of stereoselectivity are usually obtained under kinetic control in typical base-catalyzed direct-type aldol reactions because of the easy retro-aldol processes,[9] but the present case appears to be a rare example of a highly stereoselective aldol-type reaction that proceeds under thermodynamic control. A key factor might be that the cyclization product *cis*-**3** is not formed from *anti*-aldol product **4**.[16]

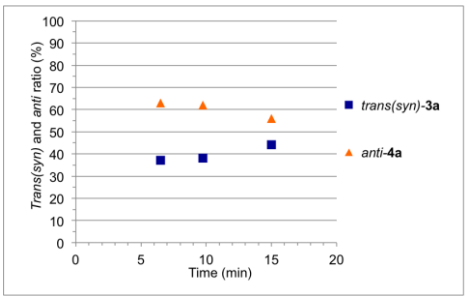
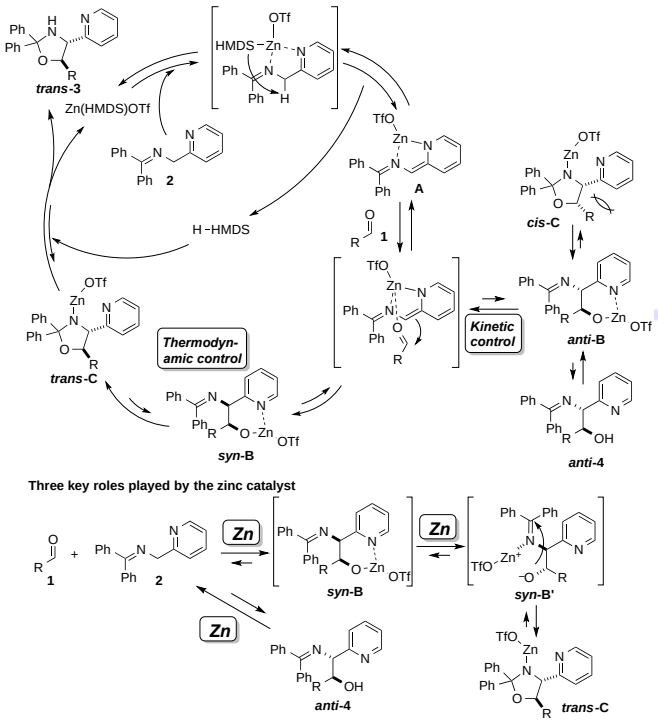


Chart 3 Change of the *trans*-**3a**/*anti*-**4a** ratio at the initial stage of the addition reaction of **1a** with **2** in DCE at 25 °C in the presence of Zn(HMDS)OTf (20 mol%) determined by MICCS-NMR analysis. In the MICCS system, the rate of change in the *trans*/*anti* ratio was slower than that in a standard NMR experiment because the low mixing efficiency of the components led to lower levels of conversion (MICCS-NMR: 15 min, 2.4% yield / standard NMR: 20 min, 5% yield).



Scheme 2 Proposed catalytic cycle and key roles of the zinc catalyst

A proposed reaction mechanism is shown in Scheme 2. Schiff base **2** is deprotonated to form zinc anion intermediate **A**, which reacts with aldehyde **1** to afford *anti*-aldol intermediate *anti*-**B** under kinetic control. Intermediate *anti*-**B** further gives *anti*-aldol adduct *anti*-**4** after protonation before cyclization to form sterically unstable *cis*-**C**. However, the thermodynamic stability of the *anti*-aldol adduct *anti*-**4** is not sufficient under the reaction conditions; therefore, a retro-aldol process from *anti*-**4** through deprotonation by the catalyst occurs to form intermediate **A** again. This retro-aldol process was also confirmed by NMR spectroscopic analysis (Scheme S2 and Figure S1).

Intermediate **A** reacts with **1** in a stepwise aldol addition/cyclization pathway through formation of *syn*-aldol intermediate *syn*-**B** to afford *N*,*O*-acetal intermediate *trans*-**C** under thermodynamic control.[17] The intermediate *trans*-**C** was further protonated to afford *N*,*O*-acetal adduct *trans*-**3** with regeneration of Zn(HMDS)OTf. Enhanced Lewis acidity of the Zn hybrid species might accelerate the addition step efficiently.[18] In the catalytic cycle, it was revealed that Zn(HMDS)OTf played three major roles (Scheme 2, bottom scheme). The first is promoting the desired aldol reaction to afford *syn*-aldol intermediate *syn*-**B** through C–C bond formation. The second is promoting the intramolecular cyclization of *syn*-**B** into *trans*-**C**. The third is promoting the retro-aldol process through C–C bond-cleavage reaction of the *anti*-aldol adduct *anti*-**4**.

In summary, we have developed a newly designed zinc Lewis acid/metal amide hybrid catalyst for aldol-type additions of 2-picolylamine Schiff base to aldehydes. It was found that only the hybrid catalyst Zn(HMDS)OTf showed high activity; neither Lewis acid $Zn(OTf)_2$ nor metal amide $Zn(HMDS)_2$ had catalyst activity. The desired reactions proceeded smoothly in the presence of Zn(HMDS)OTf to afford the *trans*-*N*,*O*-acetal adducts as *syn*-aldol adduct equivalents, in good to high yields with high selectivities. The obtained *N*,*O*-acetal adduct was converted into a precursor of a biologically active compound. Whereas initial NMR experiments suggested an apparent inconsistency in the results, final MICCS NMR analysis indicated that the observed high stereoselectivities were generated under thermodynamic control rather than under kinetic control. This is a rare example of highly stereoselective aldol-type reaction under thermodynamic control. Furthermore, in this study we have revealed the strong potential of Lewis acid/metal amide hybrid catalysts as highly efficient, simple one-molecule acid/base catalysts. Further investigations including asymmetric catalysis and the development of other hybrid catalysts are ongoing.

Keywords: Lewis acid • metal amide • catalyst • aldol-type addition • MICCS

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[12] KHMDS could also promote the reaction, but the selectivity was lower than Zn(HMDS)OTf. See Table S1 in the Supporting Information (SI).

[13] The data have been deposited with the Cambridge Crystallographic Data Centre as CCDC 1433949.

[14] See also ref. 9h for a related cyclic product.

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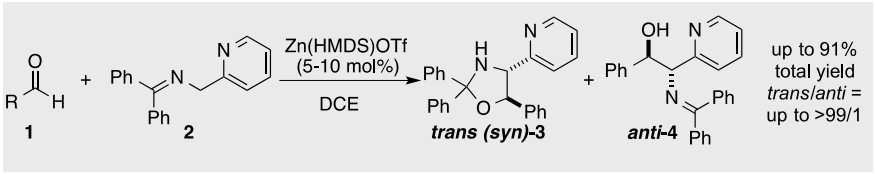
[16] In aldol-type reactions of glycine Schiff bases, both *trans*- and *cis*-cyclic products could form (ref. 9h), which did not go back to the corresponding aldol intermediates under typical catalytic reaction conditions. See also ref. 9g.

[17] In this step, it is difficult to distinguish between a stepwise aldol addition/cyclization pathway and a concerted 1,3-dipole [3+2] cycloaddition pathway at the current stage; however, judging from the exclusive formation of *trans*-*N*,*O*-acetal adduct and *anti*-aldol adduct (without formation of any *cis*-*N*,*O*-acetal adduct and *syn*-aldol adduct), it is reasonable to consider that the reaction would proceed through a stepwise pathway.

[18] Lewis acidity of Zn(HMDS)OTf was evaluated by DFT calculations of $Zn(NH_2)_2$, $Zn(NH_2)OTf$ and $Zn(OTf)_2$. Lewis acidity of $Zn(NH_2)OTf$ was stronger than $Zn(NH_2)_2$ but weaker than $Zn(OTf)_2$. See Supporting Information.

Layout 2:

COMMUNICATION



A newly designed zinc Lewis acid/base catalyzes aldol-type additions of 2-picolylamine Schiff base to afford *syn*-aldol adduct equivalents, *trans*-*N*,*O*-acetal adducts, as major products in high yields with high selectivities. The zinc catalyst plays three important roles: promotion of the aldol process (C–C bond formation), the cyclization process to the *N*,*O*-acetal product (C–O bond formation), and the retro-aldol process from the *anti*-aldol adduct to the *syn*-aldol adducts (C–C bond cleavage and C–C bond formation).

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Development of a Simple Adjustable Zinc Acid/Base Hybrid Catalyst for C–C and C–O Bond-Formation and C–C Bond-Cleavage Reactions