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Catalytic Asymmetric Aza-Morita−Baylis−Hillman Reaction of Methyl Acrylate: Role of a Bifunctional La(O-*i*Pr)$_3$/Linked-BINOL Complex

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Abstract: The catalytic asymmetric aza-Morita−Baylis−Hillman reaction using unactivated methyl acrylate is described. A simple Lewis acidic metal catalyst, such as La(OTf)$_3$, was not suitable for the reaction, but rare earth metal alkoxide/linked-BINOL complexes possessing bifunctional Lewis acid and Brønsted base properties efficiently promoted the reaction in combination with an achiral nucleophilic organocatalyst. The combined use of a La(O-*i*Pr)$_3$/(*S*,*S*)-TMS-linked-BINOL complex with a catalytic amount of DABCO promoted the aza-Morita−Baylis−Hillman reaction of a broad range of *N*-diphenylphosphinoyl imines. Products from aryl, heteroaryl, and alkenyl imines were obtained in 67−99% yield and 81−95% ee. It is noteworthy that isomerizable alkyl imines could be employed as well, giving products in 78−89% yield and 94−98% ee. Initial rate kinetic studies as well as kinetic isotope effect experiments using α-deuterio-methyl acrylate support the importance of both the nucleophilicity of La-enolate and the Brønsted basicity of a La-catalyst for promoting the reaction.

1. Introduction

The catalytic asymmetric aza-Morita−Baylis−Hillman (aza-MBH) reaction, i.e. the nucleophile-catalyzed reaction of electron-deficient alkenes with imines, provides direct access to functionalized chiral β-amino carbonyl compounds.[1,2] Shi,[3] Sasai,[4] and others[5] have reported various bifunctional hydrogen bond/nucleophile organocatalysts that realize highly enantioselective aza-MBH reactions using enones as nucleophiles. Highly enantioselective examples (>90% ee) using less reactive acrylates as nucleophiles, however, are limited.[6−8] Jacobsen[6] reported a chiral thiourea combined with a stoichiometric amount of DABCO for nonisomerizable aryl and heteroaryl imines in combination with unactivated methyl acrylate. Excellent enantioselectivity was achieved for the first time with acrylates, but the product yields were not satisfactory. Recently, Zhu and Masson[7a] achieved notable advances using bifunctional β-isocupreidine derivatives as catalysts. High enantioselectivity and high yield were realized for aryl and heteroaryl imines with an activated naphthyl acrylate. In 2010, Zhu and Masson also successfully realized good yield and excellent enantioselectivity with isomerizable alkyl imines for the first time,[7b] but the use of an activated acrylate was still essential. Compared with activated acrylates, methyl acrylate is by far the cheapest and readily available reagent. Consequently, the development of a new strategy to overcome the poor reactivity of methyl acrylate in the aza-MBH reaction is highly desirable. Herein, we describe the successful application of a chiral Lewis acid/Brønsted base bifunctional rare earth metal catalyst in combination with a nucleophilic organocatalyst. The combination of bifunctional La(O-*i*Pr)$_3$/(*S*,*S*)-linked-BINOL **1** (Figure 1) complexes[9,10] with DABCO provides good yields and enantioselectivities for aryl,

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(1) General review on aza-MBH reactions and their applications: Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2009**, *109*, 1.
(2) Reviews on catalytic enantioselective aza-MBH reactions: (a) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 4614. (b) Shi, Y.-L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905.
(3) (a) Shi, M.; Xu, Y.-M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507. (b) Shi, M.; Xu, Y.-M.; Shi, Y.-L. *Chem.—Eur. J.* **2005**, *11*, 1794. (c) Shi, M.; Chen, L.-H.; Li, C.-Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790. (d) Liu, Y.-H.; Chen, L.-H.; Shi, M. *Adv. Synth. Catal.* **2006**, *348*, 973. (e) Shi, Y.-L.; Shi, M. *Adv. Synth. Catal.* **2007**, *349*, 2129. (f) Guan, X.-Y.; Jiang, Y.-Q.; Shi, M. *Eur. J. Org. Chem.* **2008**, 2150. (g) Qi, M.-J.; Ai, T.; Shi, M.; Li, G. *Tetrahedron* **2008**, *64*, 1181. See also ref 2b.
(4) (a) Matsui, K.; Takizawa, S.; Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680. (b) Matsui, K.; Takizawa, S.; Sasai, H. *Synlett* **2006**, 761.
(5) For selected recent examples, see: (a) Abermil, N.; Masson, G.; Zhu, J. *Org. Lett.* **2009**, *11*, 4648. (b) Garnier, J.-M.; Liu, F. *Org. Biomol. Chem.* **2009**, *7*, 1272. (c) Gausepohl, R.; Buskens, P.; Kleinen, J.; Bruckmann, A.; Lehmann, C. W.; Klankermayer, J.; Leitner, W. *Angew. Chem., Int. Ed.* **2006**, *45*, 3689. For other examples, see refs 1 and 2.
(6) Raheem, I. T.; Jacobsen, E. N. *Adv. Synth. Catal.* **2005**, *347*, 1701.
(7) (a) Abermil, N.; Masson, G.; Zhu, J. *J. Am. Chem. Soc.* **2008**, *130*, 12596. (b) Abermil, N.; Masson, G.; Zhu, J. *Adv. Synth. Catal.* **2010**, *352*, 656.
(8) For partially successful early trials using acrylates, see ref 3a,c. See also: (a) Balan, D.; Adolfsson, H. *Tetrahedron Lett.* **2003**, *44*, 2521. (b) Kawahara, S.; Nakano, A.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103.

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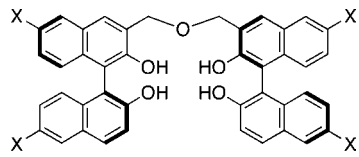


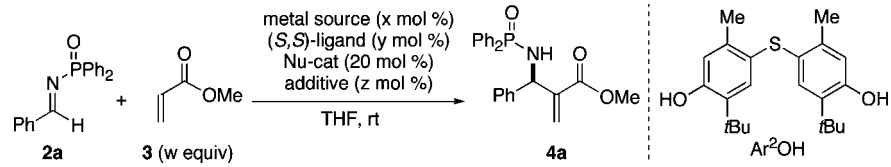
Figure 1. Structures of (*S*,*S*)-linked-BINOL **1a** and (*S*,*S*)-TMS-linked-BINOL **1b**.

heteroaryl, alkenyl, and even isomerizable alkyl imines using unactivated methyl acrylate (up to 99% yield and up to 98% ee). Mechanistic studies indicated that the simple Lewis acidic metal catalysis is not sufficient for the effective promotion of the aza-MBH reaction and shed light on the properties of metal catalysts crucial for fast and selective reaction.

2. Results and Discussion

2.1. Development of the Catalytic Asymmetric Aza-MBH Reaction of Methyl Acrylate. The previously reported organocatalytic asymmetric aza-MBH reactions required the use of either activated acrylates or excess DABCO for activating methyl acrylate. To realize good reactivity with unactivated methyl acrylate, we investigated the combined use of a chiral metal catalyst with an achiral nucleophilic organocatalyst. Initial trials to use Lewis acidic rare earth triflates for activating methyl acrylate, however, failed.[11] In the previous reports on organocatalytic aza-MBH reactions, the rate-limiting step was postulated to be the intramolecular proton transfer step following C−C bond formation.[6] Thus, we hypothesized that the use of metal catalysts with Brønsted basic properties would be effective to accelerate the aza-MBH reaction. Among the catalysts screened, Lewis acid/Brønsted base bifunctional[12] rare earth metal alkoxide/linked-BINOL **1a** complexes gave promising results. The optimization studies are summarized in Table 1. The combined use of a La(O-*i*Pr)$_3$/(*S*,*S*)-linked-BINOL **1a** = 1:1 complex with DABCO promoted the reaction of *N*-diphenylphosphinoyl imine **2a** with acrylate **3** to give the aza-MBH adduct **4a** in 88% ee, albeit in modest yield (46%, entry 1).[13] To improve the reactivity, an achiral nucleophilic catalyst (entry 2, Ph$_3$P) and various rare earth metal sources (entries 3−6) were screened but resulted in an even less satisfactory yield and/or enantioselectivity. By increasing the amount of ligand **1a** to 15 mol %, the yield was improved to 90% (entry 7). Because the enantioselectivities in entries 1 and 7 were almost the same, we speculated that the same chiral La-complex would be working in both entries and that excess ligand **1a** was not acting as a ligand to change the structure of the La-species, but rather as a proton source to accelerate the reaction.[14] Thus, sterically hindered achiral phenolic additives were investigated using 10 mol % of ligand **1a**. The use of 30 mol % of 2,6-di-*t*-Bu-4-Me-phenol (Ar^{1}OH) effectively improved the yield (91%), while maintaining good enantioselectivity (entry 1 vs entry 8). Among the additives screened,[15] 10−30 mol % of 4,4′-thiobis(6-*t*-Bu-*m*-cresol) (Ar^{2}OH)[16] gave a slightly better enantioselectivity (entries 9−10). When performing the reaction using a 1:1 ratio of imine and methyl acrylate, comparably good enantioselectivity was achieved, but the reaction did not complete even after 48 h (entry 11, 83% yield and 89% ee). To improve the reactivity, quinuclidine,[17] which is known as a superior catalyst to DABCO in the racemic reaction of aldehydes with methyl acrylate, was investigated in entry 12. High reactivity was observed as expected (99% yield after 22 h), but the enantioselectivity decreased to 81% ee, possibly due to the competitive racemic pathway without participation of the chiral La-catalyst. Control experiments (entries 13−14) suggested that neither the La(O-*i*Pr)$_3$/**1a** complex alone nor DABCO with chiral Brønsted acid **1a** was suitable to promote the reaction in good yield and enantioselectivity. Finally, the

Table 1. Optimization of Reaction Conditions



entry	metal source (*x* mol %)	ligand (*y* mol %)	Nu-cat.	additive (*z* mol %)	**3** (*w* equiv)	time (h)	% yield[a]	% ee
1	La(O-*i*Pr)$_3$ (10)	**1a** (10)	DABCO	none	2.0	26	46	88
2	La(O-*i*Pr)$_3$ (10)	**1a** (10)	Ph$_3$P	none	2.0	26	0	—
3	La(OTf)$_3$ (10)	**1a** (10)	DABCO	none	2.0	26	0	—
4	La(HMDS)$_3$ (10)	**1a** (10)	DABCO	none	2.0	26	23	55
5	Sm(O-*i*Pr)$_3$ (10)	**1a** (10)	DABCO	none	2.0	26	42	78
6	Gd(O-*i*Pr)$_3$ (10)	**1a** (10)	DABCO	none	2.0	26	34	81
7	La(O-*i*Pr)$_3$ (10)	**1a** (15)	DABCO	none	2.0	26	90	89
8	La(O-*i*Pr)$_3$ (10)	**1a** (10)	DABCO	Ar^{1}OH (30)[b]	2.0	26	91	88
9	La(O-*i*Pr)$_3$ (10)	**1a** (10)	DABCO	Ar^{2}OH (30)[b]	2.0	26	92	91
10	La(O-*i*Pr)$_3$ (10)	**1a** (10)	DABCO	Ar^{2}OH (10)[b]	2.0	26	96	90
11	La(O-*i*Pr)$_3$ (10)	**1a** (10)	DABCO	Ar^{2}OH (10)[b]	1.0	48	83	89
12	La(O-*i*Pr)$_3$ (10)	**1a** (10)	quinuclidine	Ar^{2}OH (10)[b]	2.0	22	99	81
13	La(O-*i*Pr)$_3$ (10)	**1a** (10)	none	Ar^{2}OH (10)[b]	2.0	26	0	—
14	none	**1a** (10)	DABCO	Ar^{2}OH (10)[b]	2.0	26	13	0
15	La(O-*i*Pr)$_3$ (10)	**1b** (10)	DABCO	Ar^{2}OH (10)[b]	2.0	24	92[c]	93

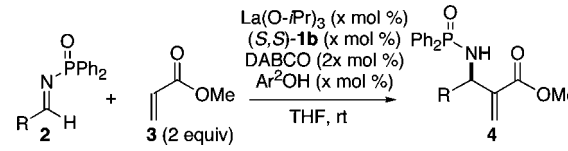
[a] Determined by ^{1}H NMR analysis of crude mixture. [b] Ar^{1}OH = 2,6-di-*t*-Bu-4-Me-phenol; Ar^{2}OH = 4,4′-thiobis(6-*t*-Bu-*m*-cresol). [c] Isolated yield of **4a** after purification by silica gel column chromatography.

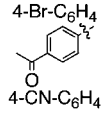
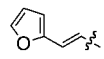
best enantioselectivity (93% ee) was achieved by changing the chiral ligand to (*S*,*S*)-TMS-linked-BINOL **1b** (entry 15).

The substrate scope of the reaction is summarized in Table 2.[18] The optimized reaction conditions were applicable to various nonisomerizable aryl and heteroaryl imines. Good enantioselectivity was achieved for aryl imines with either an electron-withdrawing or an electron-donating substituent at the *para*-, *meta*-, or *ortho*-positions (entries 2−9, 90−93% ee). Functionalized imines **4j** and **4k**, with a methyl ketone moiety and a nitrile group at the *para*-position, were also applicable, but the enantioselectivity was somewhat lower (entry 10: 84% ee; entry 11: 81% ee). With heteroaryl imines, products **4l**−**4o** were obtained with an even higher enantioselectivity (entries 12−15, 92−95% ee). Catalyst loading was successfully reduced to 5 mol %, while maintaining good yield and enantioselectivity (entry 16). The present system was also applicable to alkenyl and alkyl imines (entries 17−23). Notably, the desired reaction proceeded nicely even with isomerizable alkyl imines, including linear alkyl imine **2s** and sterically hindered α-branched alkyl imine **2v**, to afford products in 78−89% yield and 94−98% ee (entries 19−23). The results in entries 19−23 indicated the high chemoselectivity of the present system, promoting the desired aza-MBH reaction while avoiding competitive isomerization of imines to enamides.

2.2. Mechanistic Studies. In the present reaction, Lewis acidic $La(OTf)_3$ did not afford product **4a**, even in the presence of DABCO (Table 1, entry 3 in THF). Thus, a simple chiral Lewis acid metal complex together with DABCO was not suitable to efficiently promote the aza-MBH reaction in THF. Kinetic isotope effect experiments using α-deuterio-methyl acrylate resulted in $k_H/k_D = 1.0$ (Figure 2).[19] The result is different from that observed in

Table 2. Catalytic Asymmetric Aza-MBH Reaction of Various *N*-Dpp Imines with Methyl Acrylate[a]



entry	imine R: **2**		catalyst (x mol %)	Product **4**	time (h)	% yield[b]	% ee
1	Ph	**2a**	10	**4a**	24	92	93
2	2-Me-C_6H_4	**2b**	10	**4b**	48	82	90
3	3-Me-C_6H_4	**2c**	10	**4c**	48	89	92
4	4-Me-C_6H_4	**2d**	10	**4d**	48	77	93
5	3-MeO-C_6H_4	**2e**	10	**4e**	36	98	93
6	3-F-C_6H_4	**2f**	10	**4f**	24	99	92
7	4-F-C_6H_4	**2g**	10	**4g**	24	99	91
8	4-Cl-C_6H_4	**2h**	10	**4h**	24	94	91
9	4-Br-C_6H_4	**2i**	10	**4i**	24	94	90
10		**2j**	10	**4j**	24	87	84
11	4-CN-C_6H_4	**2k**	10	**4k**	24	83	81
12	2-furyl	**2l**	10	**4l**	36	92	92
13	2-thienyl	**2m**	10	**4m**	36	90	94
14	3-furyl	**2n**	10	**4n**	36	89	93
15	3-thienyl	**2o**	10	**4o**	36	96	95
16[c]	3-thienyl	**2o**	5	**4o**	48	95	92
17		**2p**	10	**4p**	48	73	89
18	cyclopropyl	**2q**	10	**4q**	36	67	94
19	$PhCH_2CH_2$	**2r**	10	**4r**	48	89	96
20	*n*Pr	**2s**	10	**4s**	60	82	94
21	*t*Bu	**2t**	10	**4t**	48	85	96
22	*c*-hexylCH$_2$	**2u**	10	**4u**	48	84	98
23	*c*-hexyl	**2v**	10	**4v**	60	78	96

[a] Reaction was run using 1 equiv of **2**, 2 equiv of **3**, in THF (1.0 M) at room temperature. Ar^2OH = 4,4′-thiobis(6-*t*-Bu-*m*-cresol). [b] Isolated yield after purification by column chromatography. [c] 5 mol % of La(O-*i*Pr)$_3$/(*S*,*S*)-**1b**, 20 mol % of DABCO, and 10 mol % of Ar^2OH were used.

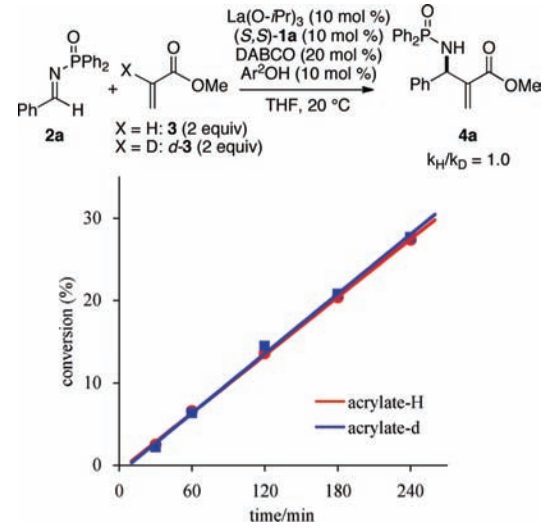


Figure 2. Kinetic isotope effect study using deuterated methyl acrylate *d*-**3**.

Jacobsen's system ($k_H/k_D = 3.8$),[6] indicating that the proton transfer step following C−C bond formation is not the rate-determining step in this system. On the other hand, kinetic isotope effect

(9) La(O-*i*Pr)$_3$/linked-BINOL **1a** complex as a Lewis acid/Brønsted base bifunctional catalyst for asymmetric Michael reaction of malonates: (a) Kim, Y. S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 6506. (b) Takita, R.; Ohshima, T.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 4661.

(10) For synthesis of linked-BINOLs, see **1a**: (a) Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252. **1b**: (b) Harada, S.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4365. (c) Sugita, M.; Yamaguchi, A.; Yamagiwa, N.; Handa, S.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2005**, *7*, 5339.

(11) In striking contrast, a chiral $La(OTf)_3$ complex with DABCO was reported as an efficient system for the reaction of *aldehydes* with acrylates. (a) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* **2003**, *68*, 915.

(12) For reviews on acid/base bifunctional asymmetric catalysis, see: (a) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566. (b) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (c) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (d) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471. (e) Shibasaki, M.; Kanai, M.; Matsunaga, S.; Kumagai, N. *Acc. Chem. Res.* **2009**, *42*, 1117.

(13) Initial screening with other BINOL derivatives resulted in poor enantioselectivity.

(14) For positive effects of achiral Brønsted acids to accelerate catalytic asymmetric aza-MBH reaction, see refs 3e,5a, and 7. The effects of the proton source in Morita−Baylis−Hillman reactions of *aldehydes* were investigated in detail; see: Robiette, R.; Aggarwal, V. K.; Harvey, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 15513, and references therein.

(15) 2,6-Di-*t*Bu-phenol, 2,6-di-*t*Bu-4-MeO-phenol, 2-*t*Bu-phenol, and 2-*t*Bu-4-MeO-phenol also had positive effects, and **4a** was obtained in greater than 80% yield and 87−89% ee. 4,4′-Thiobis(6-*t*-Bu-*m*-cresol) was selected for further studies, because it gave the highest enantioselectivity.

(16) For the utility of 4,4′-thiobis(6-*t*-Bu-*m*-cresol) as a radical inhibitor in organic synthesis, see: (a) Kishi, Y.; Aratani, M.; Tanino, H.; Fukuyama, T.; Goto, T.; Inoue, S.; Sugiura, S.; Kakoi, H. *J. Chem. Soc., Chem. Commun.* **1972**, 64. For the utility as an antioxidant for stabilizing polymers, see: (b) Gordon, D. A.; Rothstein, E. C. *Polym. Eng. Sci.* **1966**, *6*, 231.

(17) Aggarwal, V. K.; Emme, I.; Fulford, S. Y. *J. Org. Chem.* **2003**, *68*, 692.

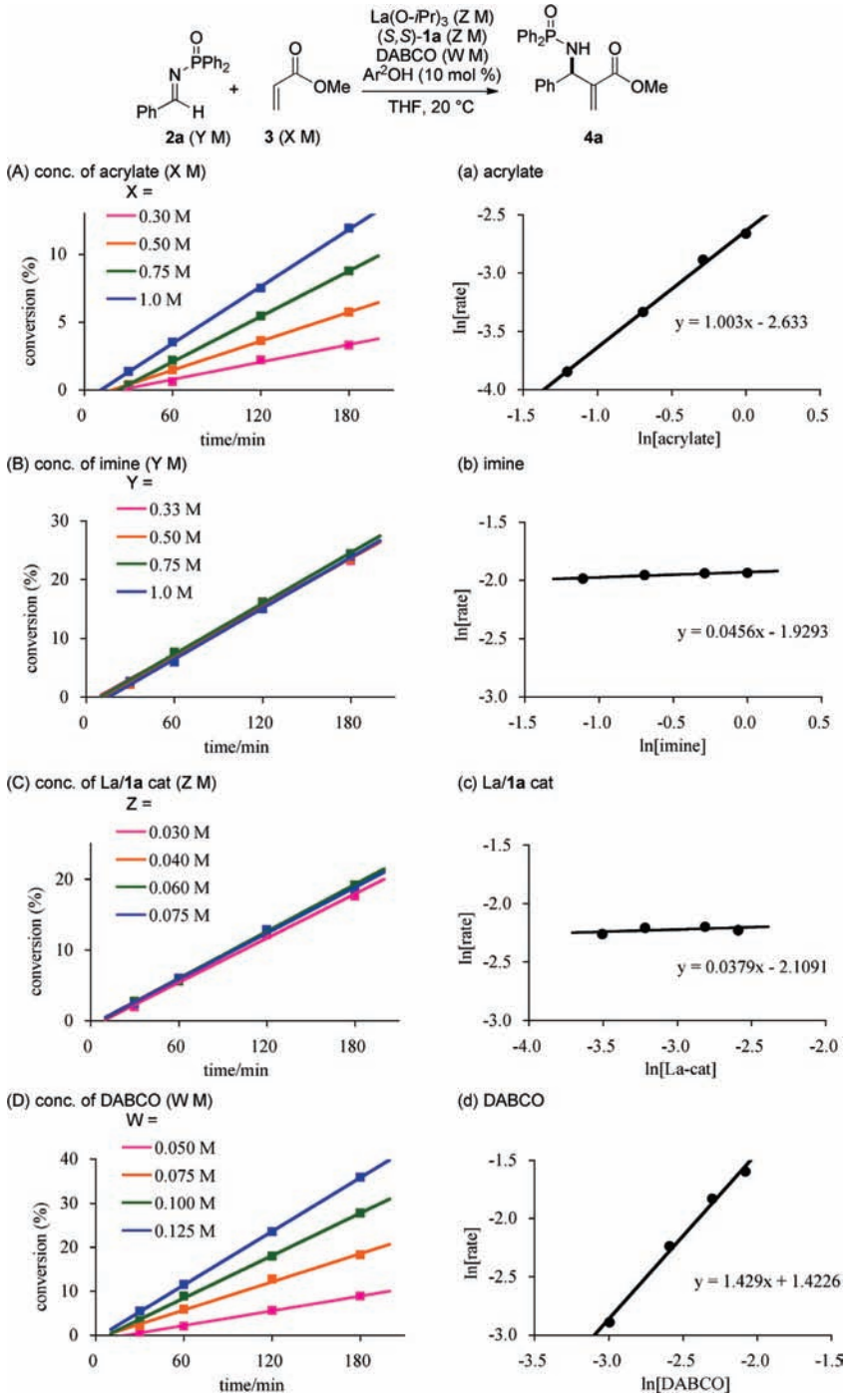


Figure 3. (A–D) Reaction profiles of catalytic asymmetric aza-MBH reactions; (a–d) rate dependency on each component.

experiments using *d*-**3** in the *absence* of an achiral proton source (Ar^2OH) resulted in $k_H/k_D = 2.5$,[20] suggesting the importance of the proton source in the proton transfer step. To obtain further information on the catalytic cycle, we performed initial rate kinetic studies. The reaction profile of the catalytic asymmetric aza-MBH reaction and the rate dependency on each component are summarized in Figure 3. The reaction rate had a first-order dependency on acrylate (Figure 3a), a zeroth-order dependency on imine (Figure 3b), a zeroth-order dependency on the La(O-*i*Pr)$_3$/linked-BINOL complex (Figure 3c), and 1.4th-order dependency on DABCO (Figure 3d).

The proposed catalytic cycle, based on the kinetic data summarized in Figures 2 and 3, is shown in Figure 4. The results of the kinetic studies suggest that the rate-determining step is the 1,4-addition of DABCO to methyl acrylate. Apparently, the chiral La-catalyst — showing a zeroth-order dependency — is not participating in the rate-limiting 1,4-addition of DABCO to acrylate (**I**). Thus, Lewis acid activation of methyl acrylate does

(18) The absolute configuration of **4a** was determined by comparing the sign of the optical rotation with the reported data reported in ref 8b.
(19) 85% deuterated **3** was used for the experiments depicted in Figure 2. The degree of deuteration of **3** did not change under the reaction conditions in Figure 2 as confirmed by NMR.
(20) See Supporting Information for experimental data.

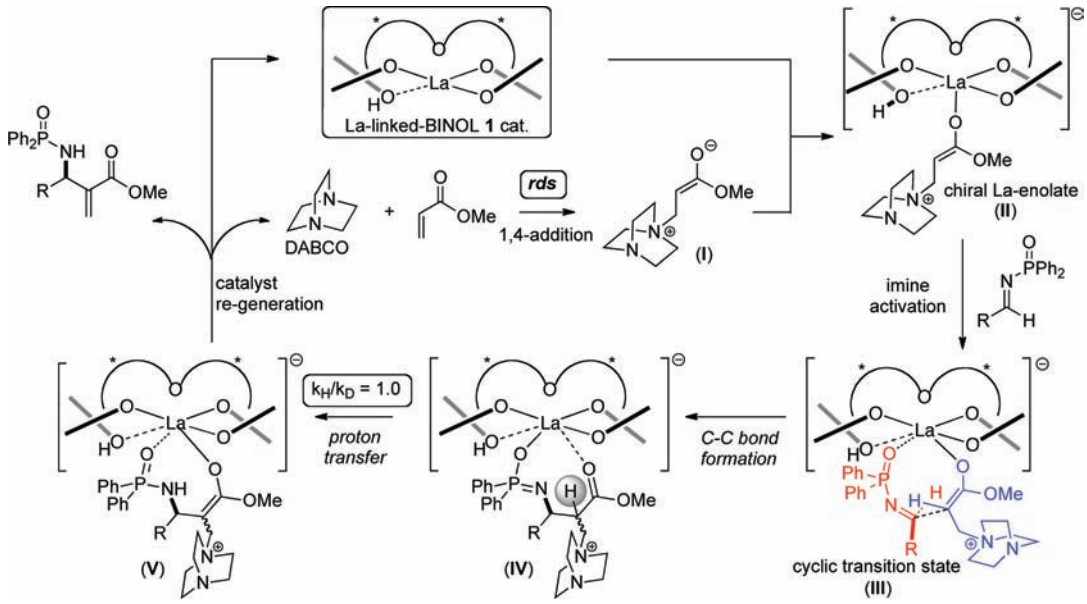


Figure 4. Postulated catalytic cycle.

not appear to be involved in our aza-MBH reaction. To induce enantioselectivity, the chiral La(O-*i*Pr)$_3$/linked-BINOL complex needs to be involved in the enantio-discriminating step, possibly the C−C bond formation.[21] We propose that the La/linked-BINOL complex interacts with the zwitterionic enolate species to generate a La-enolate (**II**). Simple Lewis acidic La(OTf)$_3$ did not promote the reaction (Table 1, entry 3), possibly because the La-enolate derived from La(OTf)$_3$ was of lower nucleophilicity compared to that derived from the La(O-*i*Pr)$_3$/linked-BINOL complex. The La(O-*i*Pr)$_3$/linked-BINOL complex would also work as a Lewis acid to activate the imine component for C−C bond formation via the cyclic transition state (**III**), thereby inducing high enantioselectivity. In contrast to other organocatalytic aza-MBH reactions, kinetic isotope effect experiments indicated that the proton transfer step following C−C bond formation is fast. We assume that the Brønsted basicity of the La-species (**IV**) would play a key role, accelerating the proton transfer step from (**IV**) to generate a La-enolate intermediate (**V**). The role of the achiral proton source to accelerate the proton transfer step is not clear. But, we speculate that the protonation of the La-intermediate (**IV**) might change the conformation of the intermediate (**IV**), thereby accelerating the deprotonation of the α-proton by a Brønsted basic La-catalyst. The elimination of DABCO from the zwitterionic intermediate (**V**) regenerates the La(O-*i*Pr)$_3$/linked-BINOL catalyst as well as DABCO.

3. Conclusion

In summary, we described the utility of a chiral rare earth metal catalyst in combination with an achiral nucleophilic catalyst for the aza-MBH reaction using unactivated methyl acrylate as a donor. Simple Lewis acidic La(OTf)$_3$ was not suitable for promoting the asymmetric aza-MBH reaction, and the use of a bifunctional rare earth metal catalyst was important. The La(O-*i*Pr)$_3$/(*S*,*S*)-TMS-linked-BINOL **1b**/DABCO system was applicable to a broad range of aryl, heteroaryl, alkenyl, and alkyl imines at ambient temperature, giving products in 67−99% yield and 81−98% ee. Mechanistic studies pointed to the importance of the nucleophilicity of an intermediate La-enolate species as well as the Brønsted basicity of metal catalyst, rather than its Lewis acidity, for accelerating the enantioselective aza-MBH reaction. In addition to their preparative importance, the results reported herein are expected to pave the way for the design of other and potentially more active chiral metal/organocatalyst combinations for aza-MBH reactions using methyl acrylate.

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Supporting Information Available: Experimental procedures, spectral data of new compounds, determination of the absolute configuration, and detailed reaction profiles in kinetic studies and kinetic isotope effect studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Possibility of the enantio-differentiation at the proton transfer step, which is often postulated in other systems (see ref 6), cannot be excluded. But, we speculate that the enantioselectivity would be kinetically determined at the C−C bond-formation step, because the proton transfer step is fast in the present system.