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Enantioselective aza-Diels–Alder reaction of Brassard's diene with aldimines catalyzed by chiral *N,N′*-dioxide–Yb(OTf)$_3$ complex

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ABSTRACT

The chiral *N,N′*-dioxide–Yb(OTf)$_3$ complex-catalyzed enantioselective aza-Diels–Alder reaction of Brassard's diene with aldimines has been developed, giving the corresponding α,β-unsaturated δ-lactam derivatives in moderate yields with good enantioselectivities (up to 81% ee and up to 99% ee by single recrystallization) under mild conditions. Isolation of the reaction intermediate indicates that this asymmetric aza-Diels–Alder reaction proceeds through a stepwise Mannich-type pathway.

The α,β-unsaturated δ-lactams are important intermediates of highly functionalized piperidine derivatives,[1,2] which are widely spread in nature mainly as alkaloids, peptides, and aza sugars. Besides, they are also key subunits of many useful compounds with biological activities.[3] The aza-Diels–Alder reaction[4] of Brassard's diene[5] with imines provides one of the most convenient protocols for the preparation of chiral α,β-unsaturated δ-lactams.

Brassard's diene has attracted more and more attentions in recent years toward the synthesis of many useful compounds.[6] For the catalytic asymmetric version, Ding's and our group[7] have developed highly enantioselective hetero-Diels–Alder reaction of Brassard's diene with aldehydes.[8] However, compared to the achievement on the enantioselective reactions of aldehydes, the reaction of Brassard's dienes with imines[9] is still less developed.[4b] Although a few diastereoselective reactions of Brassard's diene with chiral imines have been described,[10] to the best of our knowledge, only Akiyama and co-workers[11] reported the catalytic enantioselective aza-Diels–Alder reaction of Brassard's diene with imines using chiral Brønsted acid as catalyst until now. Thus, searching for effective metal catalysts for the aza-Diels–Alder reaction of Brassard's diene with simple imines would be highly challenging as well as interesting task.

The chiral *N,N′*-dioxide complexes[12,13] have emerged as a new class of effective catalysts for a variety of asymmetric reactions. Also as part of our ongoing program after highly enantioselective hetero-Diels–Alder reaction of Brassard's diene with aldehydes, we wish to describe herein that the chiral *N,N′*-dioxide–Yb(OTf)$_3$ complexes catalyzed enantioselective aza-Diels–Alder reaction of Brassard's diene with aldimines.

Two mechanistic pathways have generally been considered for a Lewis acid-catalyzed aza-Diels–Alder reaction (Scheme 1), which are (i) a traditional Diels–Alder-type cycloaddition reaction and (ii) formation of the aza-Diels–Alder adduct by a Mannich reaction path.[4b]

In our initial studies we found that *N,N′*-dioxide/metal complexes could promote the reaction of Brassard's diene **1** with imine **2a** with asymmetric induction. Only the Mannich product **3a** was observed in the reaction mixture. Its structure was confirmed by NMR as the Mannich product, and the stereochemistry of the olefine was predominantly a (*E*) form verified by NOE. The cyclic intermediate isolated by Midland[10a] seemed not to form in our initial studies. Still, the expected lactam **4a** could be achieved by heating the secondary amine **3a** with benzoic acid. The facts mentioned above indicated that the aza-Diels–Alder reaction catalyzed by *N,N′*-dioxide–metal complexes proceeded via a Mannich-type pathway rather than a traditional DA cycloaddition pathway.

Among metals we studied,[14] Sc(OTf)$_3$, previously shown to be effective for the aza-Diels–Alder reaction of Danishefsky's diene, gave only 26% yield and 36% ee in this reaction, when complexed with **L1** (Table 1, entry 1). The double substitution at the Brassard's diene terminus seems to have deleterious consequences upon the enantioselectivity of the cycloaddition reaction.[8e] Fortunately, a significant improvement of yield and ee values was obtained when other rare earth metals[15] were used (Table 1, entries 1–5). Especially, Yb(OTf)$_3$ gave the best results affording 56% yield with 73% ee (Table 1, entry 5).

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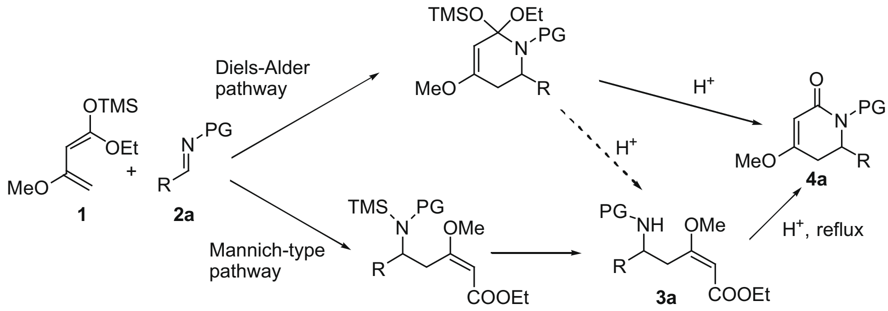
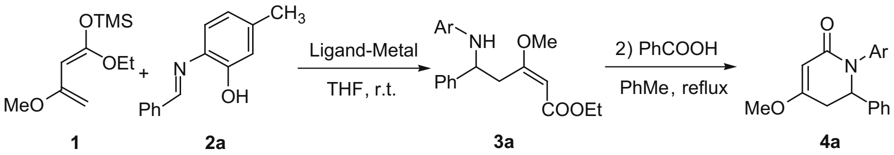


Scheme 1. Two possible mechanisms of the aza-Diels–Alder reaction.

Table 1
Enantioselective aza-Diels–Alder reaction between Brassard's diene **1** and aldimine **2a** under the indicated conditions[a]



Entry	L	Metal	Total yield of **4a**[b] (%)	ee[c] (%)
1	**L1**	$Sc(OTf)_3$	26	36
2	**L1**	$Sm(OTf)_3$	41	57
3	**L1**	$Y(OTf)_3$	46	64
4	**L1**	$La(OTf)_3$	30	68
5	**L1**	$Yb(OTf)_3$	56	73
6	**L2**	$Yb(OTf)_3$	33	59
7	**L3**	$Yb(OTf)_3$	32	−9
8	**L4**	$Yb(OTf)_3$	43	72
9	**L5**	$Yb(OTf)_3$	44	63
10[d]	**L1**	$Yb(OTf)_3$	58	76
11[e]	**L1**	$Yb(OTf)_3$	47	70

[a] Unless otherwise noted, all reactions were carried out with *N,N′*-dioxide (5 mol %), metal (5 mol %), imine **2a** (0.1 mmol), and Brassard diene **1** (0.185 mmol) in THF (0.5 mL) at rt for 22 h, then isolation was followed by adding PhCOOH (0.1 mmol) at 110 °C in PhMe for 12 h.
[b] Yield after flash chromatography.
[c] ee of **4a** determined by HPLC.
[d] The ratio of **L1**:$Yb(OTf)_3$ was 1.1:1.
[e] The ratio of **L1**:$Yb(OTf)_3$ was 1.2:1.

Then, a series of *N,N′*-dioxides combined with ytterbium triflate were examined for the addition reaction (**L1–L5**, Fig. 1). It was found that the steric bulk of the amide moiety played a crucial role on the asymmetric induction of the aza-Diels–Alder reaction (Table 1, entries 5–7). Decreasing the size of the amide moiety led to a dramatic reduction of the enantioselectivity. When sterically much less demanding aniline-derived *N,N′*-dioxide **L3** was used, only 9% ee was observed and the absolute configuration of the product was even opposite. As for the chiral backbone of *N,N′*-dioxides, **L4** (derived from L-proline) and **L5** (derived from L-ramipril acid) were inferior to the (*S*)-pipecolic acid-derived **L1** (Table 1, entries 8 and 9 vs entry 5). Subsequent screening of the molar ratio of ligand to central metal showed that the use of slight excess ligand gave better results (Table 1, entries 10 vs 5). However, further increase of ligand caused adverse results (Table 1, entry 11). After extensive investigation, we found that the optimized conditions were 5 mol % **L1**–Yb(III) complex (molar ratio: 1.1:1), 0.1 mmol aldimine, and 0.185 mmol Brassard's diene in 0.5 mL THF.

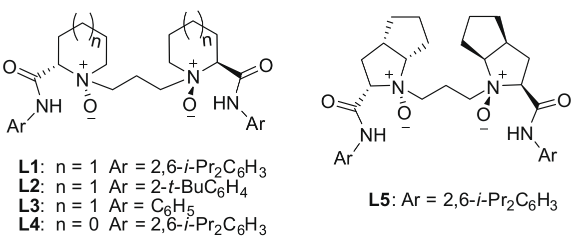


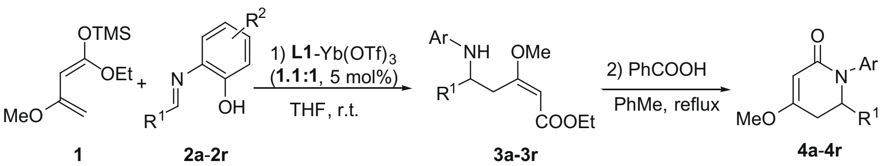
Figure 1. *N,N′*-Dioxide ligands evaluated.

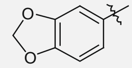
Under the optimized conditions, aldimines with other protecting groups (**2b** and **2c**) were investigated (Table 2, entries 2 and 3). The results varied as the imines derived from different 2-aminophenols. Imines **2a** and **2b** gave better results in both yields and selectivities compared to imine **2c** with 5-methyl substituent on the phenyl group.

The asymmetric aza-Diels–Alder reaction of Brassard's diene **1** with a variety of aldimines (**2d–2q**) was probed under the optimized reaction conditions. As shown in Table 2, aromatic, heteroaromatic, condensed-ring aldimines were converted to the corresponding α,β-unsaturated δ-lactams (**4d–4q**) with moderate to good yields and up to 81% ee (up to >99% ee after single recrystallization). Various aromatic aldimines,[16] bearing either electron-donating (Table 2, entries 4–8, 14, and 15) groups or electron-withdrawing (Table 2, entries 9–13) groups showed good enantioselectivities. In the case of heteroaromatic aldimine **2p**, 81% ee was obtained (Table 2, entry 16).

Table 2

Enantioselective aza-Diels–Alder reaction between Brassard's diene **1** and aldimines[a]



Entry	R^1	R^2	Total yield[b](%)	ee[c](%)
1	Ph	4-Me	58 (**4a**)	76
2	Ph	H	48 (**4b**)	66
3	Ph	5-Me	34 (**4c**)	59(*S*)[d]
4	2-MeC$_6$H$_4$	4-Me	54 (**4d**)	72 (>99)[e]
5	3-MeC$_6$H$_4$	4-Me	48 (**4e**)	80
6	4-MeC$_6$H$_4$	4-Me	54 (**4f**)	70
7	4-MeOC$_6$H$_4$	4-Me	50 (**4g**)	64
8	3-MeOC$_6$H$_4$	4-Me	50 (**4h**)	77
9	4-FC$_6$H$_4$	4-Me	39 (**4i**)	67
10	4-ClC$_6$H$_4$	4-Me	45 (**4j**)	70
11	4-BrC$_6$H$_4$	4-Me	48 (**4k**)	71
12	3-ClC$_6$H$_4$	4-Me	51 (**4l**)	73
13	3-NO$_2$C$_6$H$_4$	4-Me	42 (**4m**)	68
14	3-PhOC$_6$H$_4$	4-Me	35 (**4n**)	78
15		4-Me	33 (**4o**)	77
16	2-Thienyl	4-Me	30 (**4p**)	81 (>99)[e]
17	2-Naphthyl	4-Me	56 (**4q**)	75

[a] Unless otherwise noted, all reactions were carried out with *N*,*N'*-dioxide **L1** (5.5 mol %), Yb(OTf)$_3$ (5 mol %), imine **2** (0.1 mmol), and Brassard diene **1** (0.185 mmol) in THF (0.5 mL) at rt for 22 h, then isolation was followed by adding PhCOOH (0.1 mmol) at 110 °C in PhMe for 12 h.

[b] Isolated yield of **4**.

[c] Determined by HPLC using commercial chiral columns.

[d] The absolute configuration was determined by comparison of the optical rotation values in the literature.

[e] After a single recrystallization from hexane/ethyl acetate.

In conclusion, the enantioselective aza-Diels–Alder reaction of Brassard's diene with aldimines has been achieved using chiral *N*,*N'*-dioxide–Yb(OTf)$_3$ complex as the catalyst. Under mild conditions, the reaction proceeds smoothly to afford the corresponding α,β-unsaturated δ-lactam derivatives in moderate to good yields with good enantioselectivities (up to 81% ee, up to >99% ee after single recrystallization). On the basis of the isolated intermediates, a Mannich-cyclization pathway is indicated. Further efforts will be devoted to the study of the reaction mechanism and applications of this methodology to natural product synthesis.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.009.

References and notes

1. (a) Weinreb, S. M. Hetero Dienophile Additions to Dienes. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 401; (b) Kobayashi, S.; Jørgensen, K. A. *Cycloaddition Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2002; (c) Waldmann, H. *Synthesis* **1994**, 535.
2. (a) Clive, D. L. J.; Bergstra, R. J. *J. Org. Chem.* **1991**, *56*, 4976; (b) Comins, D. L.; LaMunyon, D. H.; Chen, X. H. *J. Org. Chem.* **1997**, *62*, 8182; (c) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633.
3. (a) Senda, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2001**, *66*, 6852; (b) Nakao, Y.; Chen, J. S.; Imanaka, H.; Hiyama, T.; Ichikawa, Y.; Duan, W.-L.; Shintani, R.; Hayashi, T. *J. Am. Chem. Soc.* **2007**, *129*, 9137; (c) Xie, Y. L.; Raffo, A.; Ichise, M.; Deng, S. X.; Harris, P. E.; Landry, D. W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5111.
4. For reviews, see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (b) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558; (c) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099; (d) Reymond, S.; Cossy, J. *Chem. Rev.* **2008**, *108*, 5359.
5. Savard, J.; Brassard, P. *Tetrahedron Lett.* **1979**, *20*, 4911.
6. (a) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1229; (b) Tapia, R. A.; Alegría, L.; Valderrama, J. A.; Cortés, M.; Pautet, F.; Fillion, H. *Tetrahedron Lett.* **2001**, *42*, 887; (c) Krohn, K.; Vitz, J. *Eur. J. Org. Chem.* **2004**, 209; (d) Ohmori, K.; Tamiya, M.; Kitamura, M.; Kato, H.; Oorui, M.; Suzuki, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 3871; (e) Van, T. N.; Verniest, G.; Claessens, S.; Kimpe, N. D. *Tetrahedron* **2005**, *61*, 2295; (f) Tewierik, L. M.; Dimitriadis, C.; Donner, C. D.; Gill, M.; Willems, B. *Org. Biomol. Chem.* **2006**, *4*, 3311; (g) Ashburn, B. O.; Carter, R. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 6737; (h) Ashburn, B. O.; Carter, R. G.; Zakharov, L. N. *J. Am. Chem. Soc.* **2007**, *129*, 9109; (i) Lucas, B. S.; Gopalsamuthiram, V.; Burke, S. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 769; (j) Ashburn, B. O.; Carter, R. G. *Org. Biomol. Chem.* **2008**, *6*, 255; (k) Mroß, G.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2009**, *65*, 3910.
7. (a) Du, H. F.; Zhao, D. B.; Ding, K. L. *Chem. Eur. J.* **2004**, *10*, 5964; (b) Fan, Q.; Lin, L. L.; Liu, J.; Huang, Y. Z.; Feng, X. M.; Zhang, G. L. *Org. Lett.* **2004**, *6*, 2185; (c) Fan, Q.; Lin, L. L.; Liu, J.; Huang, Y. Z.; Feng, X. M. *Eur. J. Org. Chem.* **2005**, 3542; (d) Lin, L. L.; Fan, Q.; Qin, B.; Feng, X. M. *J. Org. Chem.* **2006**, *71*, 4141; (e) Lin, L. L.; Chen, Z. L.; Yang, X.; Liu, X. H.; Feng, X. M. *Org. Lett.* **2008**, *10*, 1311; The scope of the reaction can be expanded by combining with Winkler's one-step synthesis of 2,3-dihydro-4*H*-pyran-4-ones: (f) Winkler, J. D.; Oh, K. *Org. Lett.* **2005**, *7*, 2421.
8. (a) Midland, M. M.; Graham, R. S. *J. Am. Chem. Soc.* **1984**, *106*, 4294; (b) Midland, M. M.; Afonso, M. M. *J. Am. Chem. Soc.* **1989**, *111*, 4368; (c) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 4647; (d) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1990**, *55*, 5058; (e) Togni, A. *Organometallics* **1990**, *9*, 3106; (f) Bläser, E.; Kolar, P.; Fenske, D.; Goesmann, H.; Waldmann, H. *Eur. J. Org. Chem.* **1999**, 329; (g) Pierres, C.; George, P.; van Hijfte, L.; Ducep, J.-B.; Hibert, M.; Mann, A. *Tetrahedron Lett.* **2003**, *44*, 3645.
9. For recent examples of highly enantioselective aza-Diels–Alder reaction of Danishefsky's diene with imines, see: (a) Kobayashi, S.; Kusakabe, K.-i.; Ishitani,

H. *Org. Lett.* **2000**, *2*, 1225; (b) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435; (c) Josephsohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 4018; (d) Mancheño, O. G.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2004**, *126*, 456; (e) Guillarme, S.; Whiting, A. *Synlett* **2004**, 711; (f) Yamashita, Y.; Mizuki, Y.; Kobayashi, S. *Tetrahedron Lett.* **2005**, *46*, 1803; (g) Akiyama, T.; Tamura, Y.; Itoh, J.; Morita, H.; Fuchibe, K. *Synlett* **2006**, 141; (h) Newman, C. A.; Antilla, J. C.; Chen, P.; Predeus, A. V.; Fielding, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7216; (i) Bari, L. D.; Guillarme, S.; Hanan, J.; Henderson, A. P.; Howard, J. A. K.; Pescitelli, G.; Probert, M. R.; Salvadori, P.; Whiting, A. *Eur. J. Org. Chem.* **2007**, 5771; (j) Shang, D. J.; Xin, J. G.; Liu, Y. L.; Zhou, X.; Liu, X. H.; Feng, X. M. *J. Org. Chem.* **2008**, *73*, 630.

10. (a) Midland, M. M.; McLoughlin, J. I. *Tetrahedron Lett.* **1988**, *29*, 4653; (b) Midland, M. M.; Koops, R. W. *J. Org. Chem.* **1992**, *57*, 1158; (c) Waldmann, H.; Braun, M.; Dräger, M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1468; (d) Waldmann, H.; Braun, M.; Dräger, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1231; (e) Kawęcki, R. *Tetrahedron* **2001**, *57*, 8385.
11. Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 4796.
12. For reviews of chiral *N*-oxides, see: (a) Malkov, A. V.; Kočovský, P. *Curr. Org. Chem.* **2003**, *7*, 1737; (b) Chelucci, G.; Murineddu, G.; Pinna, G. A. *Tetrahedron: Asymmetry* **2004**, *15*, 1373; (c) Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29. and references cited therein.
13. (a) Kokubo, M.; Ogawa, C.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6909; (b) Zheng, K.; Shi, J.; Liu, X. H.; Feng, X. M. *J. Am. Chem. Soc.* **2008**, *130*, 15770; (c) Tan, C.; Liu, X. H.; Wang, L. W.; Wang, J.; Feng, X. M. *Org. Lett.* **2008**, *10*, 5305; (d) Yu, Z. P.; Liu, X. H.; Dong, Z. H.; Xie, M. S.; Feng, X. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1308; (e) Li, X.; Liu, X. H.; Fu, Y. Z.; Wang, L. J.; Zhou, L.; Feng, X. M. *Chem. Eur. J.* **2008**, *14*, 4796; (f) Chen, S. K.; Hou, Z. R.; Zhu, Y.; Wang, J.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Chem. Eur. J.* **2009**, *15*, 5884; (g) Zhou, X.; Shang, D. J.; Zhang, Q.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Org. Lett.* **2009**, *11*, 1401; (h) Liu, Y. L.; Shang, D. J.; Zhou, X.; Liu, X. H.; Feng, X. M. *Chem. Eur. J.* **2009**, *15*, 2055.
14. For use of other metals, see Supplementary data.
15. For reviews of rare earth metal complexes in asymmetric reactions, see: (a) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187; (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. *Chem. Rev.* **2002**, *102*, 2227; For the catalytic diastereoselective synthesis of tetrahydroquinoline derivatives using imine as an azadiene: (c) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357; (d) Xie, M. S.; Chen, X. H.; Zhu, Y.; Gao, B.; Lin, L. L.; Liu, X. H.; Feng, X. M. *Angew. Chem., Int. Ed.* in press, doi:10.1002/anie.201000590.
16. Unfortunately, for aliphatic imines, the results were not good, and only 17% yield and 42% ee were obtained for the aldimine derived from cyclohexanecarboxaldehyde.