Asymmetric Catalysis

DOI: 10.1002/anie.200704759

An *N*,*N*′-Dioxide/In(OTf)$_3$ Catalyst for the Asymmetric Hetero-Diels–Alder Reaction Between Danishefsky's Dienes and Aldehydes: Application in the Total Synthesis of Triketide**

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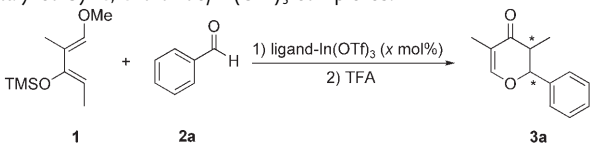
Highly substituted dihydropyranones are key structural elements in many bioactive natural products and important pharmaceuticals,[1] and asymmetric hetero-Diels–Alder (HDA) reactions between Danishefsky's dienes and carbonyl compounds have been shown to be the most powerful and straightforward approach to these optically active dihydropyranones.[2] Great effort has been devoted to this area in the last two decades and a number of successful methods have been reported.[2,3] Despite these excellent catalysts, however, In^{III}, which is a strong activator of carbonyl compounds, has rarely been employed as an asymmetric catalyst of these reactions,[4] therefore the development of In^{III}-based catalysts is of great potential interest. *N*,*N*′-Dioxide/metal complexes are excellent chiral scaffolds,[5,6] especially for metals such as indium,[4d] cadmium,[5b] copper,[5d,e] and scandium,[5c] and have exhibited great potential in many asymmetric reactions. Herein we present a novel and efficient chiral catalyst system based on *N*,*N*′-dioxide/In(OTf)$_3$ complexes and its application in the asymmetric HDA reaction.

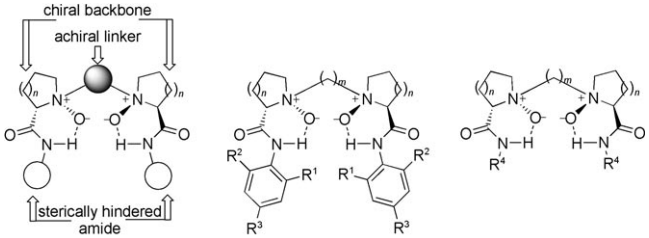
Our preliminary investigation revealed that treatment of **2a** with diene **1** (1.5 equiv) in the presence of 5 mol% of an aromatic amide derived *N*,*N*′-dioxide/In(OTf)$_3$ (1:1) complex (Table 1, entries 1–8) in THF gave compounds (2*S*,3*S*)-**3a** (16–84% *ee*) as the major HDA product. A similar reaction in the presence of aliphatic amide derived complexes (Table 1, entries 9–12) showed the opposite stereoinduction and gave (2*R*,3*R*)-**3a** (20–66% *ee*) as the major product. As for the chiral backbone moiety, (*S*)-pipecolic acid derived *N*,*N*′-dioxides (Scheme 1) were found to be superior to L-proline derived ones (up to 84% *ee*; entries 1 vs. 2 and 6 vs. 8 in Table 1). These results indicate that a three-carbon linkage is best. Although a five-carbon linkage affords a comparable

Table 1: The asymmetric HDA reaction of benzaldehyde with diene **1** catalyzed by *N*,*N*′-dioxide/In(OTf)$_3$ complexes.[a]



Entry	L	*x*	Solvent	Yield [%][b]	*trans*/*cis*	*ee* [%][c]
1	**L1**	5	THF	55	1:3	28
2	**L2**	5	THF	64	1:3.7	53
3	**L3**	5	THF	54	1:4.7	52
4	**L4**	5	THF	48	1:4.3	16
5	**L5**	5	THF	50	1:3.2	47
6	**L6**	5	THF	61	1:2.1	74
7	**L7**	5	THF	11	1:7.5	77
8	**L8**	5	THF	54	1:1.2	84
9	**L9**	5	THF	56	1:1.8	20[d]
10	**L10**	5	THF	37	1:1.3	54[d]
11	**L11**	5	THF	80	1:4.2	39[d]
12	**L12**	5	THF	73	1:2.8	66[d]
13[e]	**L8**	2.5	THF	52	1:1.2	84
14[e]	**L8**	1	THF	<5	n.d.	80
15[f]	**L8**	5	*t*BuOMe	85	1:6	96
16[f]	**L8**	5	*m*-xylene	86	<1:20	84
17[f]	**L8**	5	PhOMe	93	1:15	97
18[f,g]	**L8**	5	PhOMe	96	<1:20	98

[a] Unless otherwise noted, the reactions were performed with *N*,*N*′-dioxide/In(OTf)$_3$ (1:1) complexes prepared in situ at 0°C for 48 h (0.25 M). TFA = Trifluoro acetic acid. [b] Yield of isolated *cis* isomer. [c] Configuration of *cis* isomer was (2*S*,3*S*) as determined by HPLC. [d] (2*R*,3*R*) configuration. [e] Reaction time: 72 h. [f] The catalyst was pre-prepared (0.125 M). [g] 4-Å molecular sieves were added.



L1: $R^1 = R^2 = R^3$ = H, *n* = 1, *m* = 3
L2: $R^1 = R^2 = R^3$ = H, *n* = 2, *m* = 3
L3: $R^1 = R^2$ = H, R^3 = Me, *n* = 2, *m* = 3
L4: $R^1 = R^3$ = H, R^2 = Me, *n* = 2, *m* = 3
L5: $R^1 = R^2$ = *i*Pr, R^3 = H, *n* = 1, *m* = 2
L6: $R^1 = R^2$ = *i*Pr, R^3 = H, *n* = 1, *m* = 3
L7: $R^1 = R^2$ = *i*Pr, R^3 = H, *n* = 1, *m* = 5
L8: $R^1 = R^2$ = *i*Pr, R^3 = H, *n* = 2, *m* = 3
L9: R^4 = cyclohexyl, *n* = 1, *m* = 3
L10: R^4 = 1-adam, *n* = 1, *m* = 3
L11: R^4 = cyclohexyl, *n* = 2, *m* = 3
L12: R^4 = 1-adam, *n* = 2, *m* = 3

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

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[**] We are grateful to the National Natural Science Foundation of China (grant Nos. 20732003 and 20472056) for financial support. We also thank the Sichuan University Analytical & Testing Center for performing the NMR analysis.

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enantioselectivity and better diastereoselectivity, the yield of the reaction is very poor (Table 1, entry 6 vs. entries 5 and 7). Accordingly, the sterically hindered amide **L8** was chosen as the most promising ligand. Reducing the catalyst loading to 1 mol% produced no significant loss in *ee* value but the overall yield was lower (Table 1, entries 13 and 14).

A remarkable improvement was achieved by varying the reaction solvent. THF was used to prepare the catalyst in situ and then replaced by a different reaction solvent.[7] Thus, *t*BuOMe showed excellent enantioselectivity (up to 96% *ee*, Table 1, entry 15), while *m*-xylene showed excellent diastereoselectivity (up to 1:20; Table 1, entry 16). Anisole appears to combine the merits of *t*BuOMe and *m*-xylene (up to 97% *ee* and 1:15 d.r.; Table 1, entry 17), although the best result was obtained upon adding 4-Å molecular sieves (Table 1, entry 18).[8]

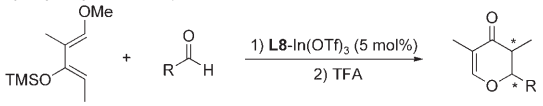
A wide range of aromatic, aliphatic, and heterocyclic aldehydes were investigated under the optimized conditions and trisubstituted dihydropyranones **3** were obtained with excellent enantioselectivity (up to 99% *ee*) and high diastereoselectivity (Table 2, entries 1–31). Significantly, *m*-hydroxybenzaldehyde, which has a reasonably acidic hydroxy group, undergoes an HDA reaction to afford the product with up to 96% *ee* and 1:20 d.r. (Table 2, entry 23). It is noteworthy that the system **L8**/In(OTf)$_3$ leads to excellent enantioselectivities for the HDA reactions between diene **1** and aliphatic aldehydes (up to 98% *ee*; Table 2, entries 24–31), which could allow the preparation of various key natural-product frameworks, especially those of beetle pheromone.[1a–c]

To extend the diene scope, our further examination of the substrate generality focused on the HDA reaction of diene **4** and several representative aldehydes. The results in Table 3 show that the reactions with aromatic aldehydes furnish the dihydropyranones in more than 92% yield and up to 98% *ee* in a shorter time (Table 3, entries 1–4),[3m] although the *ee* values obtained with straight-chain aliphatic aldehydes are not so good (Table 3, entries 5–7). The α-branched aliphatic aldehyde (Table 3, entry 8) shows a high reactivity (up to 82% yield) and good enantioselectivity (up to 92% *ee*), and the HDA reaction with (*E*)-cinnamaldehyde gave a quantitative yield and up to 97% *ee* (Table 3, entry 9).

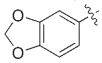
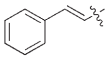
From a practical point of view, the catalyst stability was determined on a gram scale by mixing **L8**/In(OTf)$_3$ with 4-Å molecular sieves in THF and removing the solvent to give a stable white solid. The activity of the catalyst was found to remain unchanged even after more than half a year.[9]

We applied this reaction to the synthesis of triketide in an effort to show its practical utility.[1f,g,10] Our approach involved the addition of diene **1** to **2aa** on a sub-gram scale catalyzed

Table 2: Substrate scope of the asymmetric HDA reaction with diene **1** and **L8**/In(OTf)$_3$ as catalyst.[a]

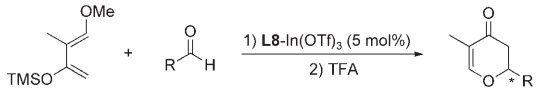


1 **2a-2ah** **3a-3ah**

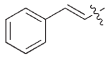
Entry	R	Yield [%][b]	*trans*/*cis*	*ee* [%][c]
1	Ph	96 (**3a**)	<1:20	98 (2*S*,3*S*)
2	4-ClC$_6$H$_4$	89 (**3b**)	<1:20	98
3	3-ClC$_6$H$_4$	98 (**3c**)	<1:20	99
4	2-ClC$_6$H$_4$	80 (**3d**)	1:4[d]	78
5	3,4-Cl$_2$C$_6$H$_3$	93 (**3e**)	1:16	99
6	2,4-Cl$_2$C$_6$H$_3$	84 (**3f**)	1:8[d]	90
7	4-MeC$_6$H$_4$	96 (**3g**)	<1:20	98
8	3-MeC$_6$H$_4$	97 (**3h**)	<1:20	97
9	2-MeC$_6$H$_4$	33 (**3i**)	n.d.	93
10	4-FC$_6$H$_4$	96 (**3j**)	<1:20	99
11	4-BrC$_6$H$_4$	90 (**3k**)	1:16	96
12	3-BrC$_6$H$_4$	96 (**3l**)	<1:20	97
13	4-NO$_2$C$_6$H$_4$	83 (**3m**)	1:10	95
14	3-NO$_2$C$_6$H$_4$	90 (**3n**)	1:20	97
15		83 (**3o**)	1:18	98
16	4-MeOC$_6$H$_4$	66 (**3p**)	1:3	92
17	1-naphthyl	80 (**3q**)	1:10	98
18	2-naphthyl	91 (**3r**)	<1:20	96
19	3-PhOC$_6$H$_4$	95 (**3s**)	<1:20	98
20	4-PhC$_6$H$_4$	81 (**3t**)	1:17	97
21	4-PhCH$_2$C$_6$H$_4$	55 (**3u**)	1:10	98
22	2-furyl	89 (**3v**)	1:9[d]	99
23	3-HOC$_6$H$_4$	96 (**3w**)	1:20[d]	96
24[e]	Et	70 (**3aa**)	1:9	98[f]
25[e]	*i*Bu	20 (**3ab**)	n.d.	96[f]
26[e]	*n*Bu	52 (**3ac**)	1:10	98[f]
27[e]		58 (**3ad**)	1:10	98[f]
28[e]	pentyl	52 (**3ae**)	1:11	97[f] (2*R*,3*S*)
29[e]	hexyl	52 (**3af**)	1:12	98[f]
30	cyclohexyl	33 (**3ag**)	n.d.	98
31		92 (**3ah**)	1:17	98 (2*R*,3*S*)

[a] Unless otherwise noted, all reactions were carried out with aldehyde (0.25 mmol) and diene **1** (1.5 equiv) in PhOMe (2.0 mL) at 0°C for 48 h. The catalyst was pre-prepared in the presence of 4-Å molecular sieves. [b] Yield of *cis* isomer isolated. [c] Determined by HPLC. [d] d.r. determined by HPLC. The absolute configurations were determined by comparison with literature data.[3l] [e] Reaction time: 60 h. [f] Determined by GC.

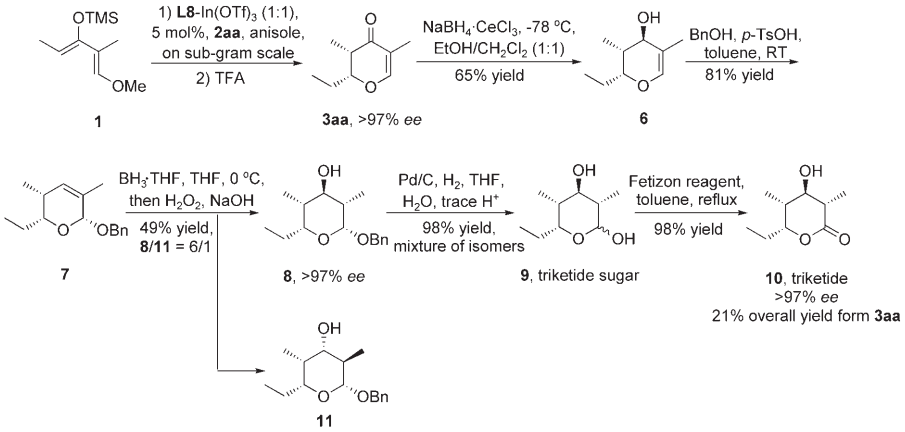
Table 3: Substrate generality of the asymmetric HDA reactions of diene **4** with **L8**/In(OTf)$_3$ as catalyst.[a]



4 **2** **5a-5i**

Entry	R	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	30	99 (**5a**)	98
2	1-naphthyl	30	92 (**5b**)	88
3	2-ClC$_6$H$_4$	24	97 (**5c**)	84
4	3-ClC$_6$H$_4$	24	99 (**5d**)	95
5	Et	32	82 (**5e**)	80
6	pentyl	32	76 (**5f**)	81
7	hexyl	32	95 (**5g**)	81
8	cyclohexyl	32	82 (**5h**)	92
9		30	99 (**5i**)	97

[a] Unless otherwise noted, all reactions were carried out with aldehyde (0.25 mmol) and diene **4** (1.5 equiv) in PhOMe (2.0 mL) at 0°C. The catalyst was pre-prepared in the presence of 4-Å molecular sieves. [b] Yield of isolated product. [c] Determined by HPLC.



Scheme 2. A concise catalytic enantioselective synthesis of triketide.

by the pre-prepared complex and gave the product in up to 72% yield with 97% *ee*.[9] As depicted in Scheme 2, the chiral inductive reduction of pyranone **3aa** to cyclic allylic alcohol **6** occurs by a Lüche reduction in the presence of $CeCl_3 \cdot 7H_2O$.[3j] A subsequent Ferrier-type rearrangement[11] of alcohol **6** gives the α,β-unsaturated acetal **7**. Although hydroboration–oxidation occurs in only moderate yield, it occurs without any loss of the optical purity and provides isomeric benzyl-protected triketide sugars **8** and **11**.[10a,g] Deprotection of **8** by a Pd/C catalyzed hydrogenolysis gives **9** as a mixture of isomers, which is then oxidized into triketide **10** by treatment with the Fetizon reagent (Ag_2CO_3/Celite).[12] The overall yield of **10** was 21% with 97% *ee*. This reaction is reminiscent of one reported by Danishefsky,[13] although with several advantages. Thus, the Ferrier-type rearrangement of **6** furnishes **7**, which has great potential in natural product synthesis owing to its C=C double bond, in 81% yield. Similarly, products **8** and **11** can be considered as stable precursors of triketide sugars.[10g]

In conclusion, we have developed a novel *N*,*N*′-dioxide/$In(OTf)_3$ catalyst that catalyzes the HDA reaction with an extremely broad range of substrates and produces highly substituted chiral pyranones in good yields with up to 99% *ee*. The stability of the catalyst facilitates its practical usage, and this reaction has been successfully applied on a sub-gram scale to the synthesis of triketide. Future efforts will focus on the application of this system to the development of an asymmetric C–C bond forming reaction as well as natural product synthesis.

Experimental Section

Typical experimental procedure: The prepared catalyst (5 mol%; see Supporting Information) was stirred in anisole (2.0 mL) in a dry reaction tube under nitrogen. This mixture was cooled to 0°C and the aldehyde (0.25 mmol) and diene **1** (100 μL) were added. The mixture was stirred at 0°C for 48 h and then TFA (0.1 mL) was added. Work-up was performed as described in the Supporting Information.

Received: October 15, 2007
Published online: January 4, 2008

Keywords: aldehydes · asymmetric catalysis · cycloaddition · indium · nitrogen oxide

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