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Chiral Catalyst Optimization Using Both Solid-Phase and Liquid-Phase Methods in Asymmetric Aza Diels–Alder Reactions

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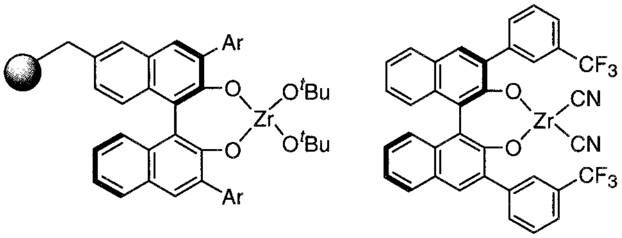
ABSTRACT



In the presence of 1–5 mol % of a chiral zirconium catalyst, aza Diels–Alder reactions of aldimines with Danishefsky's dienes proceeded smoothly to afford the corresponding piperidine derivatives in high yields with high enantioselectivities. For the catalyst optimization, solid-phase and liquid-phase methods were successfully used. In the solid-phase approach, polymer-supported (*R*)-1,1′-binaphthols (BINOLs) have been synthesized and rapid optimization using the solid-phase reactions has been achieved. On the other hand, novel chiral zirconium cyanides were developed as excellent catalysts using the liquid-phase approach.

Asymmetric reactions using chiral catalysts provide one of the most promising and powerful methods for construction of chiral molecules.[1] In these reactions, development of chiral catalysts is crucial, and in particular, development of efficient methods for catalyst optimization is strongly desired. In this paper, we disclose a truly efficient new method for chiral catalyst optimization using both solid-phase and liquid-phase approaches in asymmetric aza Diels−Alder reactions.

Catalytic aza Diels−Alder reactions provide one of the most powerful methods for the synthesis of chiral nitrogen-containing heterocycles.[2] While rather fruitful results have been reported in catalytic asymmetric Diels−Alder reactions,[3] successful results are limited in catalytic asymmetric aza Diels−Alder reactions. In 1996, we reported the first examples of catalytic asymmetric aza Diels−Alder reactions using a chiral ytterbium catalyst.[4] This report showed examples of asymmetric reactions using azadienes (iminodienes). After that, we also disclosed reactions of azadienophiles (imino dienophiles) with Danishefsky's diene using chiral zirconium−binaphthol complexes.[5,6] While high yields and selectivities were attained in these reactions in several cases, further optimization of the catalyst structure was desired. In addition, another problem was the rather high

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(1) (a) Ojima, I., Ed. *Catalytic Asymmetric Syntesis*; VCH: New York, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*, John Wiley & Sons: New York, 1994.

(2) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069.

(3) For example, Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.

(4) Ishitani, H.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 7357.

(5) (a) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979. (b) Kobayashi, S.; Kusakabe, K.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220. Cf. (c) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153. (d) Hattori, K.; Yamamoto, H. *Tetrahedron* **1993**, *49*, 1749.

(6) Other examples of catalytic asymmetric aza-Diels−Alder reactions: (a) Jnoff, E.; Ghosez, L. *J. Am. Chem. Soc.* **1999**, *121*, 2617. (b) Yao, S.; Johannsen, M.; Hazell, R. G.; Jϕrgensen, K. A. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121. (c) Bromidge, S.; Wilson, P. C.; Whiting, A. *Tetrahedron Lett.* **1998**, *39*, 8905.

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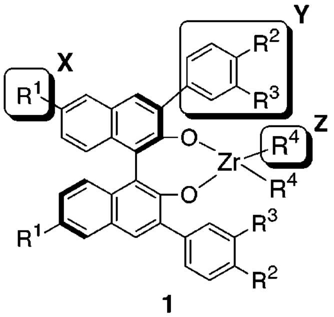
loading of the catalyst (10−20 mol %). To address these issues, we planned to optimize the catalyst structure using both solid-phase and liquid-phase methods.[7]

We divided the catalyst into three parts (X, Y, Z in Scheme 1). First, to optimize Y, polymer-supported (*R*)-1,1′-binaphthol (BINOL) derivatives were prepared.[8] The synthetic route is shown in Scheme 2. 6-Tethered (*R*)-BINOL derivative **2** was prepared according to the literature.[9] After MOM protection (**3**), the ester moiety of **3** was reduced using lithium aluminum hydride ($LiAlH_4$) to give **4**, whose hydroxyl group was protected by its *tert*-butyldimethylsilyl (TBS) ether (**5**). The 3,3′-positions of **5** were then brominated via an aromatic lithium intermediate to afford **6**, and after deprotection of the TBS ether (**7**), 1% divinylbenzene-cross linked chloromethylated polystyrene (Merrifield resin) was used as a polymer support to form **8**. A key step to introduce aryl substituents at the 3,3′-positions of **8** was carried out using the Suzuki reaction with boronic acids under the influence of a palladium catalyst.[10] After deprotection of the MOM groups, the desired polymer-supported BINOL derivatives (**10**) were obtained successfully. All the solid-phase reactions were monitored by ^1H and ^{13}C swollen-resin magic angle spinning (SR-MAS) NMR.[11]

Scheme 1



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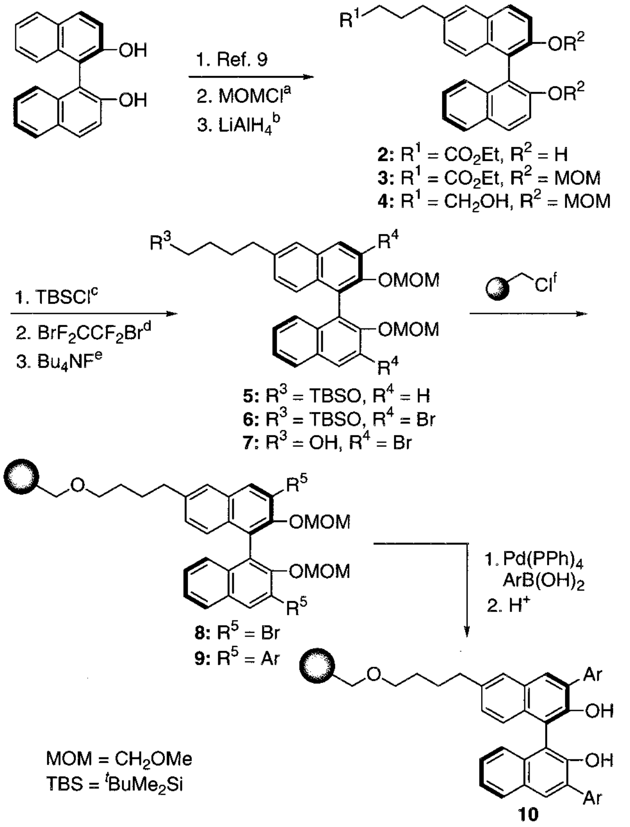
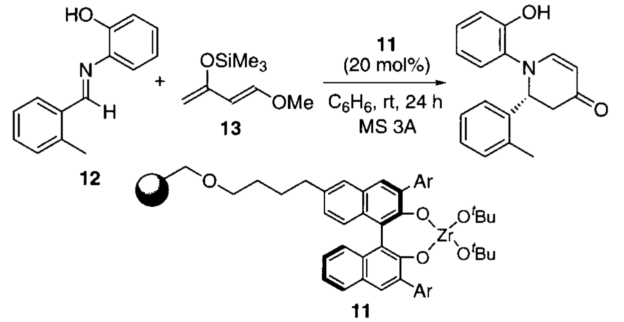
Scheme 2. Synthesis of Polymer-Supported BINOLs[a]



[a](a) MOMCl, NaH, DMF, rt, 95%; (b) $LiAlH_4$, THF/Et_2O, rt, quant; (c) TBSCl, imidazole, DMF, rt, 98%; (d) 1. BuLi; 2. BrF_2CCF_2Br, 90%; (e) Bu_4NF, THF, rt, 95%; (f) Merrifield resin, NaH, Bu_4NI, 81%.

Polymer-supported BINOLs thus prepared were treated with $Zr(O^tBu)_4$ to form polymer-supported zirconium **11**. In the presence of 20 mol % of various zirconium **11**, the model aza Diels−Alder reactions of aldimine **12** with Danishefsky's diene (**13**)[12] were performed, and the results of selected examples are shown in Table 1. While the 4-*tert*-butylphenyl group gave lower enantiomeric excess (ee), higher ees were obtained when 3,5-xylyl, 4-biphenyl, 4-fluorophenyl, and 3-trifluoromethylphenyl groups were introduced at the 3,3′-positions of the BINOLs. Among them, the 4-fluorophenyl

Table 1. Catalyst Optimization Using **11** in the Reaction of **12** with **13**



Ar	yield/%	ee/%
phenyl	61	77
m-tolyl	80	73
o-tolyl	80	72
4-*tert*-butylphenyl	58	48
3,5-xylyl	70	82
4-biphenyl	59	80
2-naphthyl	74	74
6-methoxy-2-naphthyl	61	70
4-fluorophenyl	80 (78)[a]	83 (88)[a]
3,4-difluorophenyl	82	71
3-trifluoromethylphenyl (**11a**)	87 (>99)[a]	80 (91)[a]
3,5-bis(trifluoromethyl)phenyl	92	60
3-methoxyphenyl	75	76
4-methoxyphenyl	75	41
3,4-dimethoxyphenyl	82	60
4-ethoxyphenyl	63	59
2-thienyl	61	44

[a]1-Methoxy-2-methyl-3-trimethylsiloxy-1,3-butadiene was used instead of **13**.

and 3-trifluoromethylphenyl groups were the most promising in both yields and selectivities. One advantage using polymer-supported BINOLs is that the ligand can be easily recovered by simple filtration and reused. For example, in the reaction of **12** with 1-methoxy-2-methyl-3-(trimethylsiloxy)-1,3-butadiene in the presence of 20 mol % of **11a** (Ar = 3-trifluoromethylphenyl); first run, >99% yield, 91% ee; second run, 97% yield, 90% ee; third run, 97% yield, 90% ee. It is also noted that many chiral ligands were synthesized and optimized rapidly using the solid-phase methods.

We next optimized the X and Z parts using liquid-phase methods. We prepared several zirconium catalysts, which were tested in the model reaction of **12** with **13**, and the results are summarized in Table 2. It was found that higher selectivities were obtained when electron-withdrawing cyano groups were introduced at the R^4 positions. Higher selectivities were also observed when electron-withdrawing groups such as fluoro and trifluoromethyl groups were employed at the R^2 and R^3 positions. In addition, it was revealed that a slow addition of the substrates to the catalyst was effective. Finally, 94% ee of the aza Diels−Alder adduct was obtained when only 2 mol % of the catalyst (**1f**) was employed.

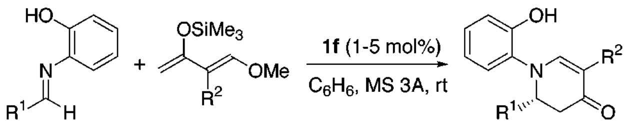
Table 2. Catalyst Optimization Using **1** in the Reaction of **12** with **13**

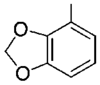
R^1	R^2	R^3	R^4	catalyst /mol%	yield/%	ee/%
H	H	H	^{t}BuO (**1a**)	20	92	77
Br	H	H	^{t}BuO (**1b**)	20	93	91
Br	H	H	^{t}BuO (**1b**)	10	81	77
Br	H	H	^{t}BuO (**1b**)	5	75	52
Br	H	H	CN (**1c**)	20	94	94
Br	H	H	CN (**1c**)	10	90	88
Br	H	H	CN (**1c**)	5	84 (92)[a]	68 (92)[a]
Br	H	H	CN (**1c**)	2	77 (83)[a]	47 (80)[a]
H	F	H	CN (**1d**)	2	59	73
Br	F	H	CN (**1e**)	2	70 (70)[a]	77 (85)[a]
H	H	CF_3	CN (**1f**)	2	73 (68)[a]	87 (94)[a]
Br	H	CF_3	CN (**1g**)	2	74	88

[a] A mixture of **12** and **13** was added to the catalyst over 1 h.

Several examples of the catalytic asymmetric aza Diels−Alder reactions are shown in Table 3.[13] In all cases, the reaction proceeded smoothly to afford the corresponding piperidine derivatives in good to high yields with high enantiomeric excesses using 1−5 mol % of the chiral zirconium catalyst.

Table 3. Catalytic Asymmetric Aza Diels−Alder Reactions



R^1	R^2	catalyst/mol%	yield/%	ee/%
Ph	H	5	76	92
Ph	Me	5	81	91
o-MePh	H	5	93	91
o-MePh	H	2	68	94
o-MePh	H	1	64	83
o-MePh	Me	2	72	88
α-Nap	H	5	80	92
α-Nap	H	2	67	86
α-Nap	Me	2	71	84
	H	5	75	90
	Me	2	68	90
2-thiophene	H	2	61	83
c-C_6H_{11}	Me	5	75	84[a]

[a] The imine was prepared from cyclohexanecarboxaldehyde and 2-amino-3-methylphenol.

In summary, a novel chiral zirconium complex for asymmetric aza Diels−Alder reactions has been developed by efficient catalyst optimization using both solid-phase and liquid-phase approaches. High yields, high selectivities, and low loading of the catalyst have been achieved, and the effectiveness of chiral catalyst optimization using a combination of solid-phase and liquid-phase methods has been demonstrated.

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Supporting Information Available: Experimental details and physical data of the catalysts and the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Solid-phase and liquid-phase methods have advantages and disadvantages, and we believe that combining the advantages of these methods leads to the most efficient catalyst optimization.

(8) For chiral catalyst optimization using solid-phase methods, see (a) Francis, M. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 937. (b) Porte, A. M.; Reibenspies, J.; Burgess, K. *J. Am. Chem. Soc.* **1998**, *120*, 9180. (c) Gilbertson, S. R.; Wang, X. *Tetrahedron Lett.* **1996**, *37*, 6475. (d) Shimizu, K. D.; Cole, B. M.; Krueger, C. A.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1703, and references cited therein.

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(11) Kobayashi, S.; Akiyama, R.; Furuta, T.; Moriwaki, M. *Molecules* **1998**, *2*, 35. Conversions from **9** to **10** are >95%.

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(13) Details are shown in Supporting Information.