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Asymmetric Intramolecular [3 + 2] Cycloaddition Reactions of Acylhydrazones/Olefins Using a Chiral Zirconium Catalyst

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The [3 + 2] cycloaddition reaction provides one of the most efficient methods for constructing five-membered ring systems.[1] Indeed, cycloadditions of 1,3-dipolars such as nitrones, nitrile oxides, and so forth with olefins affording isoxazoline derivatives have been well studied, and some highly enantioselective reactions using catalytic amounts of chiral Lewis acids have been developed.[2] On the other hand, cycloaddition of hydrazones such as 1,3-dipolars with olefins is a useful reaction to afford pyrazolidine derivatives, which can be easily converted to 1,3-diamines after N−N bond cleavage. Chiral 1,3-diamines are versatile components not only as chiral ligands in asymmetric catalysis but also as biologically important compounds such as cisplatin derivatives.[3] However, this type of [3 + 2] cycloaddition has not been well developed previously despite its potential usefulness. It was reported that strongly acidic conditions[4] or high temperature (thermal conditions)[5] were required to achieve this cycloaddition, and no asymmetric catalysis has been reported.

In the course of our investigations to develop novel reactions using hydrazones,[6] we have found that Lewis acids such as Sc(OTf)$_3$ and Zr(OTf)$_4$ effectively catalyzed [3 + 2] cycloaddition of acylhydrazones.[7,8] As an extension of this finding, we undertook a project to develop asymmetric intramolecular [3 + 2] cycloaddition reactions using a chiral Lewis acid.

In our initial investigation, we conducted an intramolecular [3 + 2] cycloaddition reaction of 4-nitrobenzoylhydrazone (**1a**) derived from 3-methylcitronellal as a model substrate in the presence of a chiral zirconium/BINOL complex, which has been shown to be an efficient catalyst for asymmetric Mannich-type reactions,[9] aza Diels−Alder reactions,[10] Strecker reactions,[11] allylation reactions of imines,[12] Mukaiyama aldol reactions,[13] and hetero Diels−Alder reactions (Scheme 1).[14] It was found that a chiral zirconium catalyst prepared from Zr(O^{t}Bu)$_4$ and (*R*)-3,3′-dibromo-1,1′-bi-2-naphthol ((*R*)-3,3′-Br$_2$BINOL, (*R*)-**2b**)[9d] gave a promising result of affording the desired pyrazolidine derivative as a sole *trans*-isomer in 86% yield with 75% ee (Table 1, entry 2). A zirconium complex prepared from Zr(O^{t}Bu)$_4$ and (*R*)-6,6′-Br$_2$BINOL ((*R*)-**2a**) resulted in a much lower yield and selectivity (entry 1). Addition of propanol (PrOH) to this catalyst system led to dramatic improvements in both the yield and selectivity (entry 3). When Zr(OPr)$_4$−PrOH was used instead of Zr(O^{t}Bu)$_4$ as a zirconium source, almost the same result was obtained (entry 4). The selectivity was slightly improved, but the reactivity decreased when toluene or benzene was used as a solvent. The catalyst prepared from (*R*)-3,3′-I$_2$BINOL, ((*R*)-**2c**) showed similar high selectivity (entry 5). Finally, it was found that a complex prepared from Zr(OPr)$_4$−PrOH and (*R*)-3,3′,6,6′-I$_4$BINOL ((*R*)-**2d**), in which iodo groups were introduced at the 6,6′-positions of (*R*)-3,3′-I$_2$BINOL as electron-withdrawing groups,[13b] showed an excellent catalyst ability; the cyclization occurred in 99% yield with excellent selectivity (96% ee) (entry 6).

Scheme 1. Intramolecular [3 + 2] Cycloaddition of Hydrazones

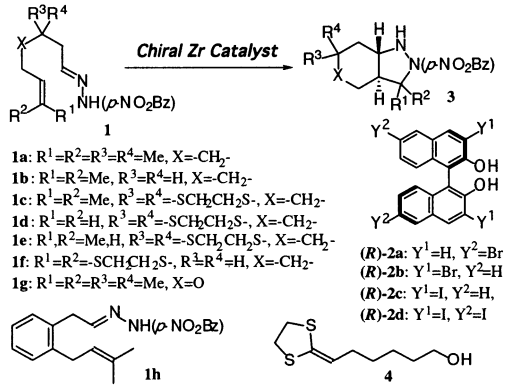

Table 1. Reaction Conditions Tested[a]

entry	Zr(OR)$_4$[b]	BINOL/mol %	additive	yield/%	ee/%
1	Zr(O^{t}Bu)$_4$	**2a**/20	-	35	9
2	Zr(O^{t}Bu)$_4$	**2b**/20	-	86	75
3	Zr(O^{t}Bu)$_4$	**2b**/12	PrOH [c]	92	93
4	Zr(OPr)$_4$	**2b**/12	-	82, 56[d],86[e]	92, 93[d],95[e]
5	Zr(OPr)$_4$	**2c**/12	-	86	92
6	Zr(OPr)$_4$	**2d**/12	PrOH [c]	99	96

[a] The reactions were performed in CH_2Cl_2 at room temperature for 4−11 h, unless otherwise noted. [b] 10 mol %. [c] 50 mol %. [d] Benzene was used as a solvent. [e] Toluene was used as a solvent.

Table 2. Asymmetric Intramolecular [3 + 2] Cycloaddition Reactions of Hydrazones Using a Chiral Zirconium Catalyst[a]

entry	hydrazone	solvent, time	yield/% (*cis*/*trans*)	ee/% (*trans*)
1	**1a**	CH_2Cl_2, 4.5 h	99 (<1/>99)	96
2[b]	**1a**	CH_2Cl_2, 12 h	87 (<1/>99)	90
3[b]	**1a**	benzene, 28 h	70 (<1/>99)	95
4[c]	**1b**	benzene-CH_2Cl_2, 64 h	62 (29/71)	92
5[c]	**1c**	CH_2Cl_2, 12 h	91 (<1/>99)	97
6	**1f**[d]	benzene, 1 h	57[e] (<1/>99)	72
7[c,f]	**1g**	benzene, 21 h	38 (<1/>99)	81
8[c,g]	**1h**	benzene, 1 h	73 (11/89)	90

[a] Unless otherwise noted, the catalyst was prepared from Zr(OPr)$_4$ (10 mol %), (*R*)-**2d** (12 mol %) and PrOH (50 mol %), and the asymmetric reaction was performed at room temperature. In entries 5, 6, (*R*)-**2c** was used instead of (*R*)-**2d**. [b] Catalyst (5 mol %). [c] Catalyst (20 mol %). [d] Unpurified. [e] Yield was determined based on the starting material **4**. [f] 40 °C. [g] 60 °C.

We then tested other substrates, and the results are summarized in Table 2. In the reaction of **1a**, 5 mol % of the zirconium catalyst worked well, and a high yield and selectivity were obtained (entries 2, 3). On the other hand, the reaction of substrate **1b**, which

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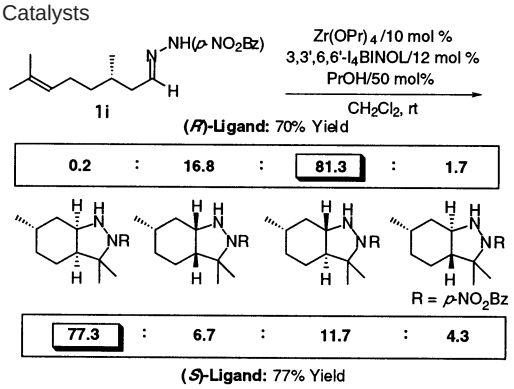
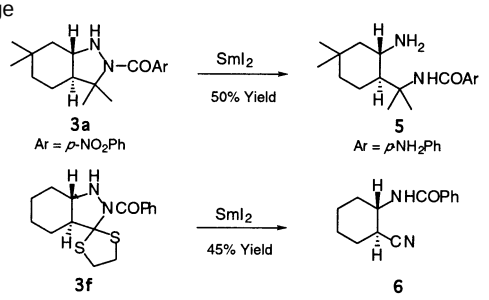
Scheme 2. Correlation between the Chiral Substrate and the Chiral Catalysts



Scheme 3. Transformation of the Products by N−N Bond Cleavage



contained no methyl group at the β-position of the hydrazone, proceeded slowly, and moderate diastereoselectivity and high enantioselectivity were observed in the presence of 20 mol % of catalyst. This lower reactivity could be explained by the Ingold−Thorpe effect.[15] When hydrazone **1c** having a thioketal moiety was employed, the reaction proceeded smoothly to afford the desired cyclic adduct in high yield with high diastereo- and enantioselectivities (entry 4). It was also found that the substituents at the terminal position affected the reactivity significantly, and the reactions proceeded sluggishly in the cases of mono and no substituted substrates **1d** and **1e**. On the other hand, hydrazone **1f** having a ketene dithioacetal moiety at the terminal position reacted smoothly to afford the desired pyrazolidine derivative with good selectivity. It should be noted that these thioacetal moieties can be readily converted to carbonyl and other functional groups.[16] Moreover, both ether-type hydrazone/olefin **1g** and hydrazone **1h** possessing an aromatic ring cyclized efficiently with high selectivity in the presence of the chiral Zr catalyst (entries 7, 8).

We then investigated the reaction of chiral hydrazones /olefins. In the presence of a chiral zirconium complex prepared from Zr(OPr)$_4$−PrOH and (*R*)-**2d**, intramolecular [3 + 2] cycloaddition of 4-nitrobenzoylhydrazone **1i** derived from (*S*)-citronellal proceeded to afford the *trans*-pyrazolidine derivative with high selectivity. On the other hand, when (*S*)-**2d** was used under the same reaction conditions, the corresponding *cis*-adduct was obtained with good selectivity. Although precise reaction pathways in these reactions are not clear at this stage, it should be noted that the *cis*/*trans* selectivity was controlled by the chirality of the chiral catalysts (Scheme 2). The pyrazolidine derivatives obtained by this [3 + 2] cycloaddition reaction can be readily transformed to 1,3-diamine derivatives via N−N bond cleavage with samarium iodide (SmI_2) (Scheme 3).[17] Interestingly, synthetically useful nitrile **6** was formed when pyrazolidine derivative **3f** having a thioketal moiety was treated with SmI_2.

In summary, we have demonstrated the first example of catalytic asymmetric intramolecular [3 + 2] cycloaddition of hydrazones/olefins. The cycloaddition proceeded in the presence of a chiral zirconium complex as a catalyst under mild conditions. While the adducts, chiral pyrazolidine derivatives, are a biologically interesting class of compounds, the N−N bonds of the adducts have been shown to be readily cleaved under reductive conditions to afford chiral diamine derivatives.

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra of the products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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