Zirconium-Catalyzed Enantioselective [3+2] Cycloaddition of Hydrazones to Olefins Leading to Optically Active Pyrazolidine, Pyrazoline, and 1,3-Diamine Derivatives

Yasuhiro Yamashita and Shū Kobayashi*

*Contribution from the Graduate School of Pharmaceutical Sciences,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

Received January 28, 2004; E-mail: skobayas@mol.f.u-tokyo.ac.jp

Abstract: Asymmetric [3+2] cycloaddition of hydrazones to external olefins has been successfully conducted in high yields with high enantioselectivities using a chiral zirconium catalyst. These reactions open ways to synthetically and biologically important pyrazoline, pyrazolidine, and 1,3-diamine derivatives. Further, several experiments suggested that the reactions proceeded via concerted pathways.

Introduction

Asymmetric [3+2] cycloaddition of 1,3-dipoles to olefins provides powerful methods for the synthesis of various optically active five-membered ring systems containing heteroatoms. Recently, catalytic enantioselective versions of this reaction using chiral Lewis acids have been studied, and several highly stereoselective [3+2] cycloaddition reactions of nitrones, nitrile oxides, and azomethine ylides, etc., leading to optically active isoxazolidine, isoxazoline, and pyrrolidine derivatives, have been reported.[1] On the other hand, catalytic asymmetric [3+2] cycloaddition of azomethine imines, diazoalkanes, and nitrile imines, which affords optically active five-membered rings containing two adjacent nitrogen atoms, has not been well investigated despite the potential usefulness for synthesis of many biologically active compounds, and only a few examples of enantioselective synthesis have been reported.[2] Kanemasa et al. reported catalytic enantioselective cycloaddition of diazoalkanes to electron-deficient olefins using Lewis-acid catalysts modified by chiral DBFOX ligands.[2a] Fu et al. also reported recently that fused azomethine imines reacted with terminal alkynes in high enantioselectivity in the presence of a chiral Cu(I) catalyst.[2b]

Our group has been interested in an acylhydrazone as an imine equivalent and revealed that benzoylhydrazones and its derivatives reacted with several nucleophiles in the presence of a Lewis-acid catalyst such as Sc(OTf)₃ or a Lewis-base promoter.[3] On the basis of these findings, we focused on the use of acylhydrazones as general 1,3-dipolars and found that [3+2]
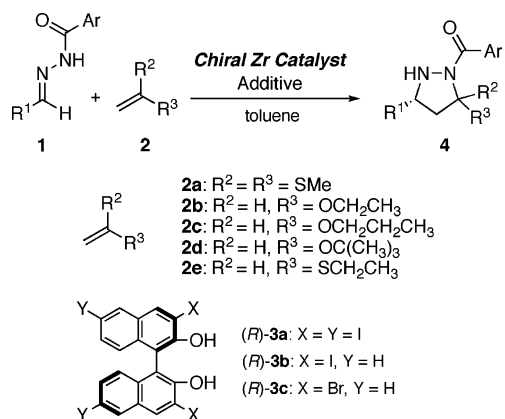
cycloaddition reactions[4] of acylhydrazones with olefins proceed smoothly under the influence of a catalytic amount of a Lewis acid.[5] Furthermore, asymmetric intramolecular [3+2] cyclo-addition reactions of acylhydrazones using a chiral Lewis acid have been disclosed recently.[6] However, the substrates were restricted, and the reactions were limited to only an intramolecular fashion. Herein, we report highly enantioselective catalytic asymmetric intermolecular [3+2] cycloaddition of hydrazones to olefins (Scheme 1). The synthesis of optically active pyrazolidine, pyrazoline, and 1,3-diamine derivatives is also described.

Results and Discussion

We initially investigated the cycloaddition of *p*-nitrobenzoyl-hydrazone **1a** of 3-phenylpropionaldehyde to ketene dimethyl dithioacetal **2a** (Table 1). The reaction proceeded in the presence of a chiral zirconium catalyst prepared from zirconium propoxide (Zr(OPr)₄), (*R*)-3,3′,6,6′-I₄BINOL (**3a**), and propanol (PrOH) to afford the desired product in moderate yield with moderate enantioselectivity (entry 1). When the reaction was conducted using a catalyst prepared from (*R*)-3,3′-I₂BINOL (**3b**), the enantioselectivity was slightly improved (entry 2). The yield and selectivity were slightly decreased when the catalyst was prepared without PrOH (entry 3). Furthermore, the enantio-

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Scheme 1. Asymmetric Intermolecular [3+2] Cycloaddition of Hydrazones to Olefins

2a: $R^2 = R^3 = SMe$
2b: $R^2 = H$, $R^3 = OCH_2CH_3$
2c: $R^2 = H$, $R^3 = OCH_2CH_2CH_3$
2d: $R^2 = H$, $R^3 = OC(CH_3)_3$
2e: $R^2 = H$, $R^3 = SCH_2CH_3$

(*R*)-**3a**: X = Y = I
(*R*)-**3b**: X = I, Y = H
(*R*)-**3c**: X = Br, Y = H

Table 1. Asymmetric Intermolecular [3+2] Cycloaddition of Hydrazones to Ketene Dimethyl Dithioacetal **2a**[a]

1a: Ar = *p*-NO$_2$C$_6$H$_4$
1b: Ar = Ph

entry	hydrazone	2a (equiv)	(*R*)-3	yield[b] (%)	ee (%)
1	**1a**	1.2	**3a**	67	67
2	**1a**	1.2	**3b**	84	70
3[c]	**1a**	1.2	**3b**	74	66
4	**1b**	1.2	**3b**	71	97
5	**1b**	1.5	**3b**	85	97
6	**1b**	2.0	**3b**	87	97

[a] The reaction was performed in toluene at 0 °C for 18 h in the presence of a zirconium catalyst (10 mol %) prepared from Zr(OPr)$_4$ (10 mol %), (*R*)-**3** (12 mol %), and PrOH (50 mol %). [b] Isolated yield. [c] Additional PrOH (50 mol %) was not used.

selectivity was dramatically improved to 97% when benzoyl-hydrazone **1b** was employed (entry 4). The amount of the ketene dimethyl dithioacetal also affected the reactivity, and the yield was improved to 87% by using 2 equiv of the ketene dimethyl dithioacetal (entry 6).

We then investigated the reactions of other hydrazones, and the results are summarized in Table 2. In all cases, the intermolecular [3+2] cycloadditions proceeded smoothly in the presence of a catalytic amount of the chiral zirconium catalyst to afford the desired pyrazolidine derivatives in high yields with excellent ee's. It is noted that hydrazones derived from a β-branched aldehyde (entry 2), a sterically hindered aldehyde (entry 3), an enolizable aldehyde (entry 6), and a functionalized aldehyde (entry 7) reacted with the olefin without any side reactions and that high levels of enantioselectivity were achieved.[7]

We next studied the reactions with vinyl ethers as olefins. The products expected are pyrazoridines containing a N,O-acetal structure, which would be further modified by Lewis-acid-mediated carbon−carbon bond formation. In preliminary investigations it was found that benzoylhydrazone **1b** was not

(7) The absolute configuration of the cycloadduct **5nc** was determined by converting the product to MS-153. The absolute configuration of other adducts was determined by analogy.

Table 2. Asymmetric Intermolecular [3+2] Cycloaddition of Hydrazones to **2a**[a]

entry	R (1)	product	yield (%)[b]	ee (%)
1	PhCH$_2$CH$_2$ (**1b**)	**4ba**	87	97
2	(CH$_3$)$_2$CHCH$_2$ (**1c**)	**4ca**	84	98
3	*c*-C$_6$H$_{11}$ (**1d**)	**4da**	74	95
4[c]	CH$_3$(CH$_2$)$_4$ (**1e**)	**4ea**	79	97
5[c]	CH$_3$(CH$_2$)$_2$ (**1f**)	**4fa**	60	96
6	PhCH$_2$ (**1g**)	**4ga**	90	97
7[c]	*t*BuMe$_2$SiOCH$_2$CH$_2$ (**1h**)	**4ha**	77	97

[a] The reaction was performed in toluene at 0 °C for 18 h in the presence of a zirconium catalyst (10 mol %) prepared from Zr(OPr)$_4$ (10 mol %), (*R*)-**3b** (12 mol %), and PrOH (50 mol %). [b] Isolated yield. [c] Additional PrOH was not used.
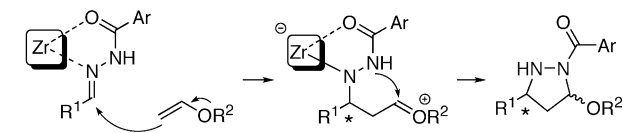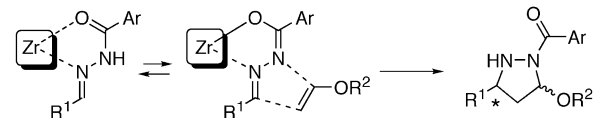
Table 3. Asymmetric Intermolecular [3+2] Cycloaddition of Hydrazones to Vinyl Ethers **2b**−**e**[a]

entry	R^1 (1)	R^2 (2)	product	yield (%)[b]	dr[c]	ee (%) (major/minor)
1	PhCH$_2$CH$_2$ (**1a**)	OEt (**2b**)	**5ab**	94	52/48	92/98
2	PhCH$_2$CH$_2$ (**1a**)	OPr (**2c**)	**5ac**	95	54/46	92/98
3	PhCH$_2$CH$_2$ (**1a**)	O*t*Bu (**2d**)	**5ad**	90	81/19	87/93
4	PhCH$_2$CH$_2$ (**1a**)	SEt (**2e**)	**5ae**	38	76/24	92/92
5	(CH$_3$)$_2$CHCH$_2$ (**1i**)	OPr (**2c**)	**5ic**	86	58/42	99/99
6	*c*-C$_6$H$_{11}$ (**1j**)	OPr (**2c**)	**5jc**	95	67/33	92/99
7	CH$_3$(CH$_2$)$_4$ (**1k**)	OPr (**2c**)	**5kc**	65	59/41	93/96
8[d]	PhCH$_2$ (**1l**)	OPr (**2c**)	**5lc**	84	68/32	84/98
9[e]	Ph (**1m**)	OPr (**2c**)	**5mc**	70	50/50	42/81

[a] The reaction was performed in toluene at 0 °C for 18 h in the presence of a zirconium catalyst (10 mL%) prepared from Zr(OPr)$_4$ (10 mol %) and (*R*)-**3a** (12 mol %). [b] Isolated yield. [c] Determined by ¹H NMR analysis. [d] The reaction was performed at 10 °C. [e] The reaction was performed at 20 °C for 24 h in the presence of a Zr catalyst prepared from Zr(O*t*Bu)$_4$ (20 mol %) and (*R*)-**3c** (24 mol %).

suitable for the present reaction because of its low reactivity. When a catalyst prepared from Zr(OPr)$_4$ and 3,3′,6,6′-I$_4$BINOL was employed in the reaction of **1a** with ethyl vinyl ether (**2b**) or propyl vinyl ether (**2c**), the desired pyrazolidines were obtained in high yields with high enantioselectivities, albeit with moderate diastereoselectivities (Table 3, entries 1 and 2). The reaction with a bulky vinyl ether, *tert*-butyl vinyl ether (**2d**), showed a slightly higher diastereoselectivity, although enanti-oselectivities of both diastereomers were somewhat lower (entry 3). Ethyl vinyl sulfide (**2e**) was found to be less reactive (entry 4). We then examined the reactions of other hydrazones with **2c**. The hydrazones of α-branched and β-branched aliphatic aldehydes also reacted with **2c** smoothly to afford the corresponding adducts in high yields with high enantioselectivities (entries 5 and 6).[7] Although diastereoselectivity was moderate, it is noteworthy that both diastereomers showed excellent enantioselectivity in most cases and that the lower diastereo-selectivity was not a serious drawback from a synthetic point of view (vide infra). In the reaction of **1m** (aromatic hydrazone),

Scheme 2. Transformation of the Products[a]
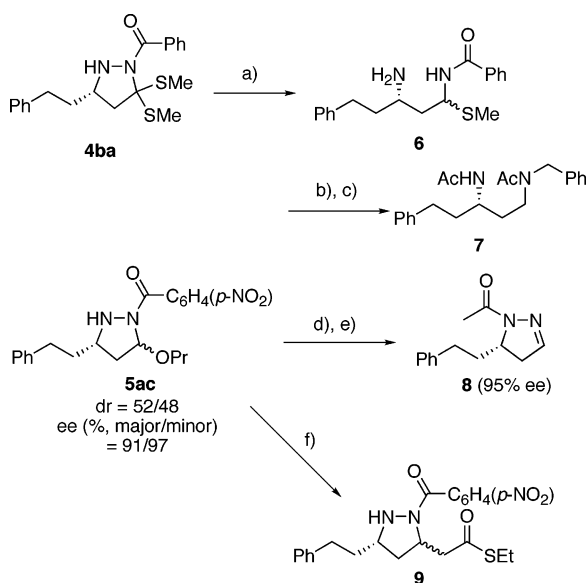
[a] Reagents and conditions: (a) SmI$_2$, THF-MeOH, −78 °C, 83%; (b) LiAlH$_4$, THF, reflux; (c) Ac$_2$O, pyridine, rt, 95% (2 steps); (d) LiAlH$_4$, THF, −78 °C; (e) AcCl, pyridine, DMAP, CH$_2$Cl$_2$, rt, 76% (2 steps); (f) Me$_3$SiOTf, H$_2$C=C(OSiMe$_3$)SEt, CH$_3$CN, 0 °C, 68% (dr = 86:14).

the desired cycloaddition product was obtained in good yield but the stereoselectivities were a little lower (entry 9).

The products obtained were converted to several valuable compounds (Scheme 2). Transformation of pyrazolidines to 1,3-diamines is an important method to afford useful chelating agents. The N−N bond of product **4ba** was cleaved by SmI$_2$ to give N,S-acetal **6** in high yield as a diastereomer mixture.[3b,f] This compound was converted to 1,3-diamine **7** by reduction with LiAlH$_4$ and acetylation in high yield. On the other hand, product **5ac** was converted to acetylated 2-pyrazoline **8** in good yield with high optical purity (95% ee).[8] This result indicates that the starting diastereomers have the same absolute configurations regarding the asymmetric centers derived from the C=N double bonds of the hydrazones and that the moderate diastereoselectivity obtained in the cycloaddition was not a serious issue in further transformation of the product. Moreover, **5ac** reacted with the silyl enol ether derived from *S*-ethyl ethanethioate in the presence of trimethylsilyl triflate to afford synthetically useful compound **9** in good yield with good diastereoselectivity.[9]

In the current [3+2] cycloaddition of the hydrazones to olefins, two reaction mechanisms are proposed (Scheme 3). One is a stepwise pathway, nucleophilic addition to the imine moiety and successive cyclization, and the other is a [3+2] concerted pathway, simultaneous cyclization of a 1,3-dipole equivalent with an olefin. In addition to the above information that both diastereomers of the products have the same absolute configurations at the carbon atoms connected to the R^1 substituents, we conducted several experiments to clarify the reaction mechanism. When the reaction of hydrazone **1a** with vinyl ether **2c** was carried out in toluene at 0 °C for 3 h using the standard

(8) This imine formation by removal of the acyl group using LiAlH$_4$ is rare. See: Biswas, K. M.; Mallik, H.; Halder, S. *Monatsh. Chem.* **1997**, *128*, 1283.

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Scheme 3. Proposed Reaction Mechanisms

Stepwise pathway

Concerted pathway

Scheme 4. Synthesis of *ent* MS-153[a]
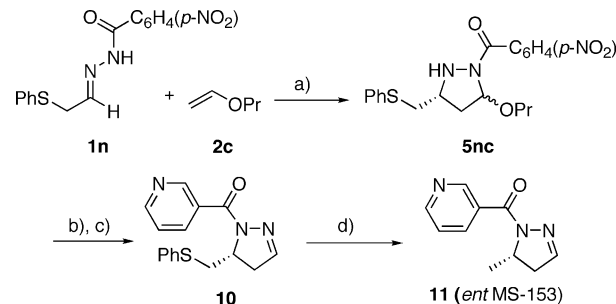
[a] Reagents and conditions: (a) Zr(OPr)$_4$ (20 mol %), (*R*)-3,3′-I$_2$BINOL (24 mol %), toluene, 10 °C, 48 h, 76%, dr = 62/38, 84% ee (major)/97% ee (minor); (b) LiAlH$_4$, THF, −78 °C; (c) nicotinoyl chloride hydrochloride, ^{i}Pr$_2$NEt, DMAP, rt, 68% (2 steps); (d) Raney-Ni (W-2), EtOH−acetate buffer (pH = 5.2) (2:1), rt, 29% (88% ee).

chiral zirconium catalyst (10 mol %) shown in Table 3, the desired cycloaddition adduct (**5ac**) was obtained in 57% yield with moderate diastereoselectivity (ds = 54/46) and high enantioselectivity (91% ee (major)/98% ee (minor)). These selectivities are almost the same as those of the reaction for 18 h (Table 3, entry 2), suggesting that epimerization of the product (having a N,O-acetal moiety) did not occur during the reaction course. Further, we conducted several experiments in the reaction of **1a** with **2c** by changing several reaction parameters (temperature, ligands of the zirconium catalyst, loading amounts of the catalyst). In these experiments, the diastereomer ratio was 54/46−63/37 and the enantioselectivity was 91−93% ee (major) and 96−98% ee (minor), showing that the ee's of the major and minor isomers are clearly different. This difference is also observed in almost all entries in Table 3 (remarkably observed in entry 9). If the reaction proceeded via the stepwise pathway, the enantioselectivity of the major and minor diastereomers might be the same, and therefore, the above results suggest that the present reaction would proceed via the concerted pathway. We also performed the reaction of hydrazone **1a** with 2-methoxypropene as a representative of a 1-alkyl-substituted vinyl ether, and it was revealed that the reaction proceeded sluggishly under the standard reaction conditions. This result also suggests that the reaction would proceed via the concerted pathway, because an alkyl substituent at the 1-position of a vinyl ether would increase the nucleophilic addition of the vinyl ether to a hydrazone in the stepwise pathway but decrease the reactivity in the concerted pathway due to the steric hindrance.

Finally, synthesis of a biologically important compound, MS-153, and its derivatives was investigated (Scheme 4). MS-153 is a cerebroprotecting agent and is employed as a biological

tool;[10] however, its asymmetric synthesis has not hitherto been reported. The [3+2] cycloaddition of hydrazone **1n** to **2c** proceeded smoothly to afford pyrazolidine **5nc** in good yield with high enantioselectivity. The *p*-nitrobenzoyl group was removed by reduction using LiAlH₄ followed by nicotinoylation. The adduct **10** thus obtained was a useful intermediate for the synthesis of MS-153 derivatives. In fact, after removal of the phenylthio group, *ent* MS-153 (**11**) was obtained with high enantioselectivity.[11]

Conclusion

In summary, we demonstrated that asymmetric [3+2] cycloaddition of hydrazones to olefins successfully proceeds in high yields with high enantioselectivities in the presence of a chiral zirconium catalyst. This is the first example of catalytic enantioselective [3+2] cycloaddition of hydrazones to external olefins. These reactions open ways to synthetically and biologically important pyrazoline, pyrazolidine, and 1,3-diamine derivatives. For the reaction mechanism, [3+2]-concerted pathways have been proposed based on several experiments. Further applications of these reactions to the synthesis of other biologically important compounds are now in progress.

Experimental Section

Experimental Procedures for Asymmetric Intermolecular [3+2] Cycloaddition of Benzoylhydrazones to Ketene Dimethyl Dithioacetal 2a Using a Chiral Zirconium Catalyst Prepared from (*R*)-3b. A typical experimental procedure is described for the reaction of **1b** with **2a**. To a suspension of (*R*)-3,3′-I₂BINOL (**3b**, 0.048 mmol) in toluene (0.3 mL) was added Zr(OPr)₄ (0.040 mmol) in toluene (0.4 mL) at room temperature. The mixture was stirred for 0.5 h at the same

temperature, and propanol (0.2 mmol) in toluene (0.3 mL) was added. The mixture was stirred for additional 0.5 h. The catalyst solution was transferred to another vessel using toluene (0.5 mL), in which hydrazone **1b** (0.40 mmol) was placed, and the mixture was stirred at 0 °C. Ketene acetal **2a** in toluene (0.5 mL) was then added to the suspension, and the whole was stirred at the same temperature for 18 h. After water was added to quench the reaction, the mixture was extracted three times with CH₂Cl₂. The organic phases were combined and dried over anhydrous Na₂SO₄. After filtration and concentration under reduced pressure, the crude product was purified by column chromatography (aluminum oxide) to afford the desired pyrazolidine derivative (**4ba**). The optical purity of this adduct was determined by HPLC analysis using a chiral column.

Experimental Procedures for Asymmetric Intermolecular [3+2] Cycloaddition of *p*-Nitrobenzoylhydrazones to Vinyl Ethers 2b−d Using a Chiral Zirconium Catalyst Prepared from (*R*)-3a. A typical experimental procedure is described for the reaction of **1a** with **2c**. To a suspension of (*R*)-3,3′,6,6′-I₄BINOL (**3a**, 0.048 mmol) in toluene (0.3 mL) was added Zr(OPr)₄ (0.040 mmol) in toluene (0.4 mL) at room temperature. The mixture was stirred for 3 h at the same temperature. The catalyst solution was transferred to another vessel using toluene (0.8 mL), in which hydrazone **1a** (0.40 mmol) was placed, and the mixture was stirred at 0 °C. Vinyl ether **2c** (4.0 mmol) in toluene (0.5 mL) was then added to the suspension, and the whole was stirred at the same temperature for 18 h. After water was added to quench the reaction, the mixture was extracted three times with CH₂Cl₂. The organic phases were combined and dried over anhydrous Na₂SO₄. After filtration and concentration under reduced pressure, the crude product was purified by column chromatography (aluminum oxide) to afford the desired pyrazolidine derivative (**5ac**). The diastereomer ratio was determined by ¹H NMR analysis, and the optical purity of this adduct was determined by HPLC analysis using a chiral column.

Supporting Information Available: Full experimental section (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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