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Enantioselective Preparation of *cis*-β-Azidocyclopropane Esters by Cyclopropanation of Azido Alkenes Using a Chiral Dirhodium Catalyst

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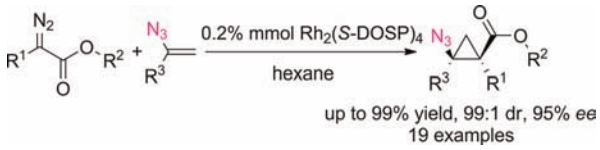
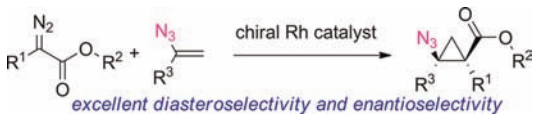
ABSTRACT



A diastereo- and enantiocontrolled preparation of the conformationally restricted *cis*-β-azidocyclopropane esters have been developed. The Rh_2(*S*-DOSP)$_4$ was found to be an efficient catalyst in hexane for the cyclopropanation of azido alkenes with diazo esters, and 19 *cis*-β-azidocyclopropane esters were prepared in excellent yields. The value of the diastereomer ratio was up to 99:1, and the enantiomeric excess was up to 95%. Furthermore, the relative and absolute configuration was confirmed by X-ray analysis.

Cyclopropanation of olefins with diazoalkanes in the presence of metal catalysts has been extensively explored.[1] Among the cyclopropanes, the β-N-functionalized cyclopropane esters have attracted particular interest from bio-organic chemists in peptide syntheses.[2,3] However, the most sensitive approach to enantioenriched β-N-functionalized cyclopropane esters by catalytic asymmetric cyclopropanation of enamine derivatives with a chiral dirhodium catalyst could only give poor control of the relative and absolute configuration.[4] In this paper, we report the first efficient diastereo- and enantioselective preparation of *cis*-β-azidocyclopropane esters[5] by cyclopropanation of azido alkenes with diazo esters using a chiral dirhodium catalyst (Scheme 1).

Scheme 1. Asymmetric Cyclopropanation of Azido Alkenes with Diazo Esters



The β-azidocyclopropane esters incorporating two stereogenic centers on the ring possess a restricted

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(1) For selected reviews on cyclopropanation of olefins, see: (a) Pellissier, H. *Tetrahedron* **2008**, *64*, 7041–7095. (b) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977–1050. (c) Davies, H. M. L.; Antoulinakis, E. *Org. React.* **2001**, *57*, 1–326. (d) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911–936.

(2) For a review, see: Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603–1623.

(3) For selected recent examples, see: (a) Koglin, N.; Zorn, C.; Beumer, R.; Cabrele, C.; Bubert, C.; Sewald, N.; Reiser, O.; Beck-Sickinger, A. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 202–205. (b) De Pol, S.; Zorn, C.; Zerbe, O.; Reiser, O. *Angew. Chem., Int. Ed.* **2004**, *43*, 511–514. (c) Urman, S.; Gaus, K.; Yang, Y.; Strijowski, U.; Sewald, N.; De Pol, S.; Reiser, O. *Angew. Chem., Int. Ed.* **2007**, *46*, 3976–3978.

(4) (a) Miller, J. A.; Hennessy, E. J.; Marshall, W. J.; Scialdone, M. A.; Nguyen, S. T. *J. Org. Chem.* **2003**, *68*, 7884–7886. (b) Melby, T.; Hughes, R. A.; Hansen, T. *Synlett* **2007**, 2277–2279. (c) Paulini, K.; Reissig, H.-U. *Liebigs Ann. Chem.* **1991**, 455–461.

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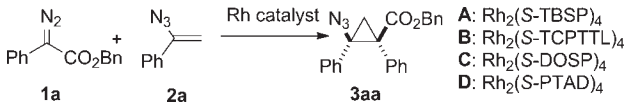
conformation, and two types of diastereomers (*cis* and *trans*) are derived from the orientations of the azido and carboxyl groups. The synthesis of β-azidocyclopropane esters must address diastereoselectivity as well as enantioselectivity. We are more interested in the *cis*-β-azidocyclopropane esters as they could be regarded as precursors of *cis*-β-aminocyclopropane carboxylic acids (*cis*-β-ACCs), which were widely used in peptide syntheses.[3] Furthermore, the β-azidocyclopropane esters have two potential chelating groups oriented in the same direction, offering the possibility of chiral ligand design.

The asymmetric cyclopropanation of N-protected enamines gave *trans*-β-aminocyclopropane esters in poor diastereo- and enantioselectivities using chiral dirhodium catalysts.[4] Moreover, the attempted cyclopropanation of a Boc-protected enamine by Doyle's catalyst led to no conversion.[4a] As prior solvents for many cyclopropanations with rhodium catalysts were hydrocarbons, we considered that the low yields and diastereoselectivities as well as enantioselectivities for the cyclopropanation of the N-protected enamines with the diazo esters by chiral dirhodium catalysts might be due to the following situations: the steric hindrance from the protection group, the nucleophilicity of the protected-enamine nitrogen, and poor solubility of the protected enamine in hydrocarbons. The azido group was smaller than the protected-amino group, and it generally showed weak nucleophilicity when it existed in organic azide under neutral conditions.[6] Moreover the alkyl azide was revealed to be better incorporated with hydrocarbon solvents than protected enamine. With this in mind, we envisioned that the azido alkenes would be more suitable substrates than the protected-enamine analogues for stereocontrolled cyclopropanation, which would generate high enantioenriched β-N-functionalized cyclopropane esters. In order to attain the more conformationally restricted β-azidocyclopropane esters, we decided to install two quaternary carbons on the cyclopropane ring. One of the quaternary carbons was designed to attach to the carbonyl group, and the other one was bound to the azido nitrogen. The *cis*-β-azidocyclopropane esters would be obtained when α-azido-styrene analogues were used, as the ester was the directing group in the cyclopropanation. For the preparation of the enantioenriched β-azidocyclopropane esters to be successful, there were two central issues to be addressed: (1) could the azido alkenes be suitable for cyclopropanation as no such alkenes were employed previously;[7] (2) would the cyclopropanation proceed in a good stereocontrolled manner in the presence of a chiral dirhodium catalyst, as poor diastereo- and enantioselectivities were observed when α-substituted styrenes were used for the cyclopropanation.[8]

To test our proposal, the first attempt to attain the *cis*-β-azidocyclopropane ester employed the cyclopropanation of the benzyl diazophenylacetate (BnDPA) **1a** and α-azido-styrene **2a** (Table 1). Several commercially available chiral dirhodium catalysts were screened (Table 1, entries 1−4). Among them, Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTAD)$_4$ gave positive results in hexane. The Rh_2(*S*-DOSP)$_4$-catalyzed (0.2 mol %) cyclopropanation of diazo ester **1a** in the presence of azido alkene **2a** (5 equiv) at room temperature afforded the *cis*-β-azidocyclopropane ester **3aa** in 79% yield (entry 3), and the diastereoselectivity (96:4 dr) as well as the enantioselectivity (85% ee) were controlled. The product from the Rh_2(*S*-PTAD)$_4$-catalyzed reaction was obtained in an even higher yield (89%) and enantioselectivity (89% ee); however, the diastereoselectivity (83:17 dr) was imperfect (entry 4). It should be noted that opposite enantioselectivity was observed in this case, and a similar situation was reported by Davies's group with the cyclopropanation of 4-chlorostyrene with α-aryl-α-diazoketone.[9] Further experiments using Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTAD)$_4$ in hexane at −5 °C revealed that Rh_2(*S*-DOSP)$_4$ was better than Rh_2(*S*-PTAD)$_4$ (entry 5 vs 6). The yield of **3aa** was improved to 95%, and the diastereoselectivity (98:2 dr) and enantioselectivity (89% ee) were slightly increased. If the temperature was lowered (−10 °C), insolubility of diazo ester **1a** took place. After the catalyst was identified as Rh_2(*S*-DOSP)$_4$, various solvents including diethyl ether, toluene, DCM, and THF were investigated at −5 °C (entries 7−10); however, no better results could be obtained than that in hexane.

Table 1. Optimization of the Cyclopropanation[a] of **1a** and **2a**



entry	Rh	solvent	*t* (°C)	yield[b] (%)	dr[c] (*c*:*t*)	ee[d] (%)
1	A	hexane	rt	61	96:4	83
2	B	hexane	rt	83	67:33	82
3	C	hexane	rt	79	96:4	85
4	D	hexane	rt	89	83:17	89
5	**C**	**hexane**	**−5**	**95**	**98:2**	**89**
6	D	hexane	−5	32	83:17	85[e]
7	C	Et2O	−5	63	99:1	78
8	C	toluene	−5	87	95:5	81
9	C	DCM	−5	80	87:13	52
10	C	THF[f]	−5	trace	–	–

[a] Cyclopropanation of diazo ester **1a** (0.2 mmol) and azido alkene **2a** (1.0 mmol) in the presence of chiral dirhodium catalyst (0.0004 mmol) for 3 h under the conditions mentioned in the table. [b] Isolated yield after purification. [c] Determined from the crude reaction mixture by ^{1}H NMR. [d] Determined by chiral HPLC. [e] Enantioselectivity of the product was observed to be opposite to that of other catalysts. [f] Trace product was obtained after 24 h.

(5) For the preparation of racemic β-azidocyclopropane esters in moderate yield by the Michael initiated ring closure reaction, see: (a) Mangelinckx, S.; Kimpe, N. D. *Synlett* **2006**, 369–374. (b) Su, J.; Qiu, G.; Liang, S.; Hu, X. *Synth. Commun.* **2005**, *35*, 1427–1433.

(6) The azido group shows nucleophilicity under acidic conditions; for a selected example, see: Aubé, J.; Milligan, G. L. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966.

(7) We had examined the cyclopropanation of 2-nitroethenylbenzene with various diazo esters using many dirhodium catalysts but failed to obtain any desired β-nitrocyclopropane ester.

With the optimal conditions established above (in bold, Table 1), the scope of diazo esters was explored (Table 2). The cyclopropanations of the azido alkene **2a** with the analogues of the diazophenylacetate (**1b**–**1i**) were investigated. In all cases, the diastereoselectivities of the reaction were well controlled (> 90:10 dr). First, three diazophenylacetates **1b**–**1d** were examined (entries 1–3). Ethyl diazophenylacetate **1b** gave better control in enantioselectivity than diazo ester **1a** (91% vs 89% ee), but the yield (82% vs 95%) and diastereoselectivity (90:10 vs 98:2 dr) decreased. Introduction of *para*-substituents on the benzyl group effected little change in the diastereoselectivity (entries 2 and 3), and 4-bromobenzyl diazophenylacetate **1c** could maintain the yield (92%) and improve the enantioselectivity (95% ee), while methoxybenzyl diazophenylacetate **1d** caused a drop in yield (84%) and maintained the enantioselectivity (90% ee). The relative and absolute configuration[10] of **3ca** was assigned to be (1*R*,2*S*) by X-ray crystallographic analysis (Figure 1). Further experiments focused on modification of the aromatic ring neighboring a diazo unit (entries 4 and 5).

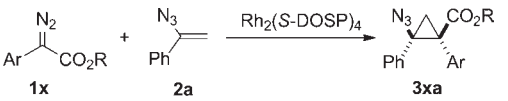
Reaction of diazo 4-bromophenyl acetate **1e** resulted in comparable diastereoselectivity (99:1 dr) and enantioselectivity (91% ee) but gave cyclopropane in a slightly lower yield (86%, entry 4). Cyclopropanation of diazo 4-methoxyphenyl acetate **1f** delivered cyclopropane **3fa** in 99% yield (entry 5) with good diastereoselectivity (95:5 dr), but the enantioselectivity (75% ee) was affected. Because the 4-bromobenzyl diazo ester resulted in good enantioselectivity for cyclopropanation compared to that of benzyl diazo ester (entry 2 vs 3), diazo ester **1g** was expected to give a better enantiocontrolled cyclopropane than that of **1f**, which did occur (92% vs 75% ee, entry 6 vs 5). An even higher enantioselectivity was expected by employing diazo ester **1h**, and a comparable stereocontrolled cyclopropanation (99:1 dr, 93% ee) was obtained (entry 7). The naphthalene analogue **1i** was also examined but did not give a better result (entry 8).

A series of azido alkenes **2b**–**2f** were investigated for asymmetric cyclopropanation with diazo ester **1a** and **1h** (Table 3). In all cases, the azido alkenes underwent asymmetric cyclopropanation with high diastereoselectivities.

Generally, the cyclopropanes from the azido alkenes and diazo ester **1a** were obtained in better yields than that of diazo ester **1h**. The enantioselectivities were also well controlled for different kinds of alkenes besides the 4-cyanophenyl alkene **2e** (entries 7 and 8). The poor enantioselectivities for the reactions of alkene **2e** partly resulted from the poor solubility in hexane at −5 °C, which agreed with our assumption on the poor enantioselectivity in the cyclopropanation of protected enamines above. Finally, the reactions were conducted at room temperature, which might affect the selectivities.

The gram-scale cyclopropanation of alkene **2d** with diazo ester **1a** at rt for 17 h gave cyclopropane **3ad** in the same yield and with similar diastereoselectivity when compared with that of the general scale reaction at −5 °C, while the enantioselectivity was slightly lower (86% vs 92%). The gram-scale reaction required a longer reaction time

Table 2. Scope of Diazo Esters in the Cyclopropanation[a]



entry	diazo ester	product	yield (%)[b]	dr[c]	ee (%)[d]
1	**1b** Ar = Ph; R = Et	**3ba**	82	90:10	91
2	**1c** Ar = Ph; R = 4-Br-Bn	**3ca**	92	99:1	95
3	**1d** Ar = Ph; R = 4-OMe-Bn	**3da**	84	99:1	90
4	**1e** Ar = 4-Br-C_6H_4; R = Bn	**3ea**	86	99:1	91
5	**1f** Ar = 4-OMe-C_6H_4; R = Bn	**3fa**	99	95:5	75
6	**1g** Ar = 4-Br-C_6H_4; R = 4-OMe-Bn	**3ga**	70	99:1	92
7	**1h** Ar = 4-Br-C_6H_4; R = 4-Br-Bn	**3ha**	97	99:1	93
8	**1i** Ar = Naphth; R = Bn	**3ia**	91	94:6	85

[a] Cyclopropanation of azido alkene 2a (1.0 mmol) with diazo ester **1x** (0.2 mmol) in the presence of Rh_2(S-DOSP)$_4$ (0.7 mg, 0.0004 mmol) for 3 h in hexane at −5 °C. [b] Isolated yield after purification. [c] Determined from the crude reaction mixture by ^{1}H NMR. [d] Determined by chiral HPLC.

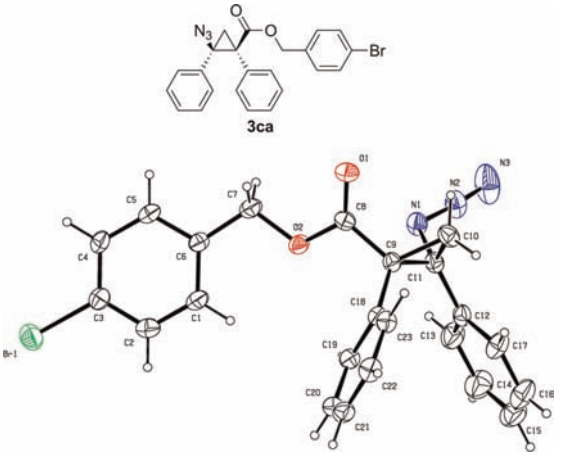


Figure 1. X-ray crystal structure of **3ca**.

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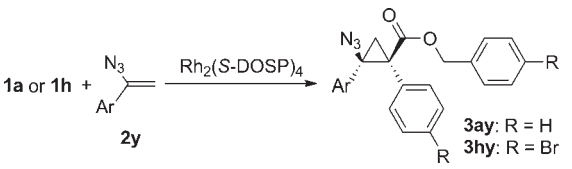
(9) Denton, J. R.; Davies, H. M. L. *Org. Lett.* **2009**, *11*, 787–790.

(10) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897–6907.

Table 3. Scope of Azido Alkenes in the Cyclopropanation[a]



entry	azido alkene	prod	yield[b]	dr[c]	ee[d]
1	**2b** Ar = 4-Br-C_6H_4	**3ab**	99	99:1	91
2	**2b**	**3hb**	68	94:6	88
3	**2c** Ar = 4-OMe-C_6H_4	**3ac**[e]	90	99:1	91
4	**2c**	**3hc**[e]	99	96:4	90
5	**2d** Ar = 4-F-C_6H_4	**3ad**	92 (92)[f]	96:4 (96:4)[f]	92 (86)[f]
6	**2d**	**3hd**	76	97:3	90
7	**2e** Ar = 4-CN-C_6H_4	**3ae**[g]	97	93:7	85
8	**2e**	**3he**[g]	80	95:5	73
9	**2f** Ar = Naphth	**3af**	99	95:5	90
10	**2f**	**3hf**	99	95:5	93

[a] Cyclopropanation of azido alkene **2y** (1.0 mmol) with diazo ester **1a** or **1h** (0.2 mmol) in the presence of Rh_2(*S*-DOSP)$_4$ (0.7 mg, 0.0004 mmol) for 3 h in hexane at −5 °C. [b] Isolated yield after purification. [c] Determined from the crude reaction mixture by ^{1}H NMR. [d] Determined by chiral HPLC. [e] Cyclopropanation of azido alkene **2c** completed in 12 h. [f] Gram-scale cyclopropanation at rt. [g] Cyclopropanation at rt.

and high temperature to complete, which might slightly decrease the enantioselectivity.

In conclusion, we have designed and realized a practical diastereo- and enantiocontrolled preparation of conformationally restricted *cis*-β-azidocyclopropane esters. The reaction conditions were investigated, and Rh_2(*S*-DOSP)$_4$ was proven to be an efficient promoter in hexane at −5 °C. The scopes of the diazo esters and azido alkenes were explored, and 19 *cis*-β-azidocyclopropane esters were prepared in excellent yields. The stereoselectivities were well controlled, the value of the diastereomer ratio was up to 99:1, and the enantiomeric excess was up to 95%. Currently, extensive conversion of the β-azidocyclopropane esters and application of the cyclopropanes in synthesis of constrained peptides and natural products are underway in our laboratory.

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Supporting Information Available. Experimental procedures and spectroscopic data for the reaction products and X-ray crystallographic data for compound **3ca**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.