Asymmetric Synthesis

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trans-Directing Ability of Amide Groups in Cyclopropanation: Application to the Asymmetric Cyclopropanation of Alkenes with Diazo Reagents Bearing Two Carboxy Groups**

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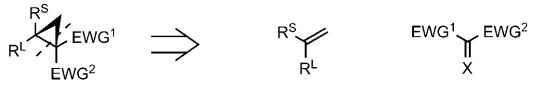
The cyclopropane unit is an integral component of many natural products and synthetic drugs.[1] In addition, cyclopropanes bearing two geminal electron-withdrawing groups (for example, **1**–**3**, Scheme 1) are suitable precursors of



1 : $EWG^1 = EWG^2 = CO_2R$
2 : $EWG^1 = NO_2$, $EWG^2 = CO_2Me$
3 : $EWG^1 = CN$, $EWG^2 = CO_2R$
4 : $EWG^1 = CONR_2$, $EWG^2 = CO_2R$

5a : $EWG^1 = EWG^2 = CO_2R$, X = N_2
5b : $EWG^1 = EWG^2 = CO_2R$, X = IPh

Scheme 1. Synthesis of cyclopropane derivatives bearing two electron-withdrawing groups (EWG). R^L and R^S are large and small R groups, respectively.

biologically important cyclopropyl α- and β-amino acids.[2,3] This important class of cyclopropane derivatives is also known for its unique electrophilicity.[4] For example, cyclopropane 1,1-diesters, such as **1**, have been shown to undergo cycloaddition reactions or react with nucleophiles with complete preservation of the stereochemical information.[5–9] Among the methods to generate cyclopropane *gem*-diesters, transition metal-catalyzed intermolecular cyclopropanation of readily available alkenes with the corresponding diazo reagent is an efficient and straightforward strategy (Scheme 1).

However, to achieve this transformation asymmetrically remains a formidable challenge, especially with diazo reagents bearing two geminal carboxy groups.[10] For example, direct access to **1** (R = Me) using diazo reagent **5a** (R = Me) gave low enantiocontrol in the cyclopropanation of styrene (44% *ee*) using $[Rh_2(4S\text{-meaz})_4]$.[11] To date, the highest enantioselectivity for the cyclopropanation of styrene is 82% *ee* which was obtained using precursor **5b** (Scheme 1, R = Me) and $[Rh_2\{4\text{-Br}(S\text{-nttl})\}_4]$.[12] Currently, the most efficient and reliable means to generate enantioenriched cyclopropane 1,1-diesters requires several steps using the Sharpless dihydroxylation,[13] a Davies cyclopropanation[14] or a kinetic resolution of the racemate.[7a] Herein, we report a novel stereoselective synthesis of cyclopropane bearing geminal dicarboxy groups with excellent enantio- and diastereocontrol utilizing the unprecedented *trans*-directing ability of an amide [Eq. (1)].

(1)

The asymmetric cyclopropanation of electron-rich alkenes using unsubstituted α-diazoesters in the presence of Cu, Rh, and Ru complexes bearing chiral ligands involves the two competing transition state structures **A** and **B** (Figure 1). Many Cu- and Ru-based catalysts are very effective at blocking one of the two prostereogenic faces (α) of the metal carbene thus leading to formation of the *trans* isomer in high enantiomeric excess. The level of diastereoselectivity

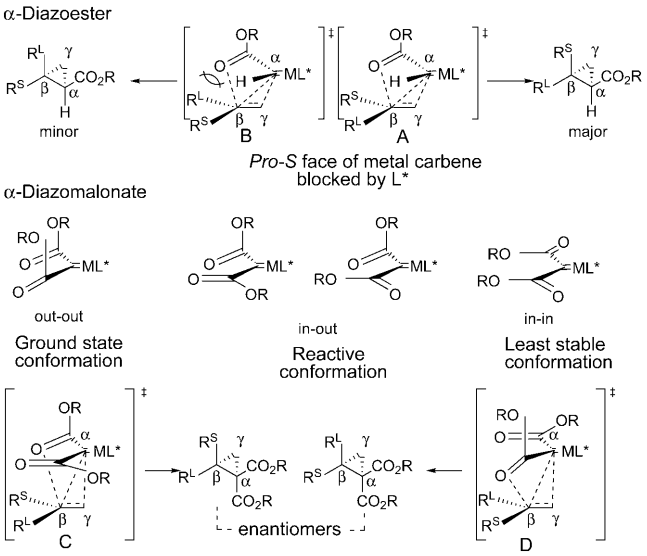


Figure 1. Transition-state structures for Cu- and Rh-catalyzed cyclopropanation.

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usually depends on the bulkiness of the ester group. It has been postulated that the ester prefers to adopt an out-of-plane conformation that leads to a stabilization of the developing partial positive charge on the β carbon of the alkene, and thus acting as a *trans*-directing group.[15] The asymmetric cyclopropanation of a metal carbene derived from α-diazomalonate is slightly more complex, since the metal carbene can exist in three different conformations. X-ray crystal structures of Ru carbenes derived from malonates[16] are consistent with the postulate that the most stable conformation is that in which both ester groups are out-of-plane (out–out) relative to the carbene.[17]

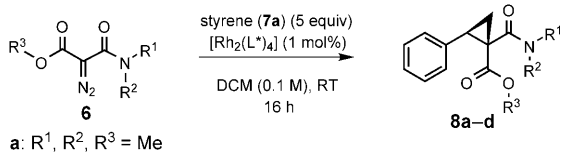
For steric reasons, it is believed that out–out is not the reactive conformation in the cyclopropanation reaction. It can also be assumed that the reaction does not proceed through the in–in conformer (both ester groups in the plane of the metal carbene), since it should be significantly higher in energy owing to the conjugation of two electron-withdrawing substituents, and its resultant inability to stabilize the developing positive charge.[15]

We postulate that in–out will be the preferred conformation in the transition state, as it provides increased electrophilicity of the metal carbene, owing to conjugation of the electron-withdrawing group, and allows stabilization of the partial positive charge on the alkene. The alkene will attack the electrophilic carbene by orienting its largest substituent on the side of the in-plane ester group. However in the case of a symmetric malonate derivative, the metal carbene α carbon is not prostereogenic. The design of chiral ligands that will discriminate between the two transition state structures **C** and **D** is quite challenging even if the catalyst is very effective at blocking one face of the metal carbene, and it probably explains why low enantioselectivities have been reported thus far in cyclopropanations using α-diazomalonates. Our proposed solution for the cyclopropanation of α-diazomalonate derivatives was to use an α-diazodicarboxy derivative possessing two carboxy groups with different *trans*-directing abilities, to discriminate between **C** and **D**, and a chiral catalyst effective at blocking one prostereogenic face of the metal carbene. In this context, our initial work aiming to establish a relative scale of the "*trans*-directing ability" of various carboxy derivatives led to the use of α-amido-α-diazoacetate derivatives. Indeed this class of compounds led to very high diastereoselectivities when various α-diazo-1,3-dicarboxy derivatives were treated with rhodium(II) octanoate (Scheme 2) with a general trend of *trans*-directing ability in cyclopropanation being amide > ketone > ester.

Encouraged by the result obtained using the amide, chiral rhodium complexes and various structurally related α-amido-α-diazoacetate compounds were screened (Table 1, Figure 2).[18]

$[Rh_2(S\text{-nttl})_4]$ was the most promising catalyst, giving 75% *ee* and >30:1 d.r. when using diazo reagent **6a**. The methyl ester of the diazo **6a** offered a better enantioselectivity than that for the ethyl ester **6d** (Table 1, entries 2 and 7). Exchanging the *N*,*N*-dimethyl amide for the *N*-ethyl-*N*-methyl amide **6c** increased the enantioselectivity to 85% *ee* but lowered the yield to 35% (Table 1, entry 6). The use of pyrrolidine amide **6b** led to outstanding enantio- and diasteroselectivities (95% *ee*, >30:1 d.r.) (Table 1, entry 5). Slightly higher enantioselectivities were obtained if the

Table 1: Optimization of the asymmetric cyclopropanation using α-amido diazoacetates.



a: R^1, R^2, R^3 = Me
b: R^1, R^2 = -$(CH_2)_4$-; R^3 = Me
c: R^1, R^3 = Me; R^2 = Et
d: R^1, R^2 = Me; R^3 = Et

Entry	Diazo Reagent	$[Rh_2(L^*)_4]$	Yield [%][a]	d.r.[b] *cis*/*trans*	*ee* [%] *cis*[c]
1	**6a**	$[Rh_2(S\text{-ntv})_4]$	83	>30:1	54
2	**6a**	$[Rh_2(S\text{-nttl})_4]$	71	>30:1	75
3	**6a**	$[Rh_2(S\text{-ptv})_4]$	69	>30:1	30
4	**6a**	$[Rh_2(S\text{-pttl})_4]$	76	>30:1	70
5	**6b**	$[Rh_2(S\text{-nttl})_4]$	71	>30:1	95
6	**6c**	$[Rh_2(S\text{-nttl})_4]$	35	>30:1	85
7	**6d**	$[Rh_2(S\text{-nttl})_4]$	48	>30:1	54
8[d]	**6b**	$[Rh_2(S\text{-nttl})_4]$	75	>30:1	96
9[e]	**6b**	$[Rh_2(S\text{-nttl})_4]$	79	>30:1	96

[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by super fluid chromatography (SFC) on chiral stationary phase. [d] Reaction carried out in dichloroethane (DCE). [e] Using diazo compound (3 equiv) and styrene (1 equiv) in DCE.

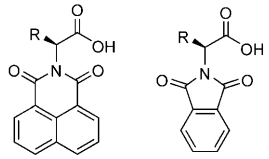
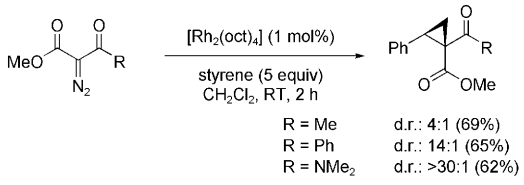


Figure 2. Ligands (L*H) for $[Rh_2(L^*)_4]$-catalyzed cyclopropanation. nttl = *N*-1,8-naphthoyl-*tert*-leucine; pttl = *N*-phthaloyl-*tert*-leucine; ntv = *N*-1,8-naphthoylvaline; ptv = *N*-phthaloylvaline.

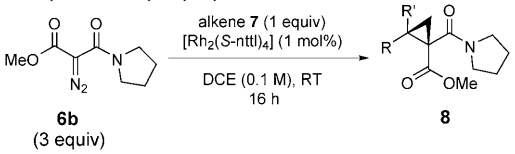


Scheme 2. Diastereoselective cyclopropanation of various α-diazo-1,3-dicarboxy derivatives.

reaction was run in 1,2-dichloroethane (DCE, Table 1, entry 8). Similar levels of enantioselectivity and efficiency were detected if the alkene was used as the limiting reagent (Table 1, entry 9).

Employing the optimal conditions (**6b** (three equivalents), $[Rh_2(S\text{-nttl})_4]$ (1 mol%), alkene (one equivalent, 0.1M solution in DCE) at room temperature), the scope of the cyclopropanation was investigated (Table 2). Excellent yields

Table 2: Scope of the Cyclopropanation.

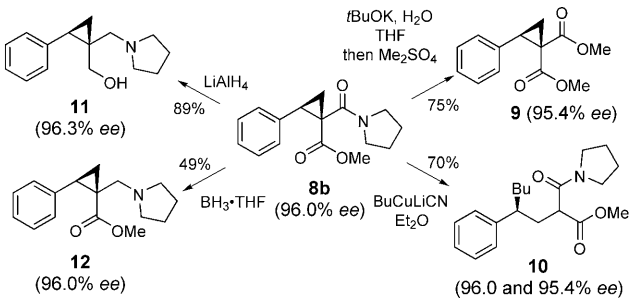


Entry	Alkene	Yield [%][a]	d.r.[b] *cis*/*trans*	*ee* [%] *cis*[c]
1	$PhCH{=}CH_2$ (**7a**)	79	>30:1	96
2	4-*t*BuPhCH=CH_2 (**7e**)	89	>30:1	96
3	4-FPhCH=CH_2 (**7f**)	77	>30:1	97
4	4-ClPhCH=CH_2 (**7g**)	81	>30:1	96
5	4-MeOPhCH=CH_2 (**7h**)	92	>30:1	93
6	4-MePhCH=CH_2 (**7i**)	82	>30:1	96
7	indene (**7j**)	51	>30:1	84
8[d]		63	>30:1	89
9	Ph(Me)C=CH_2(**7k**)	63	>30:1	95
10	1-napthylCH=CH_2 (**7l**)	86	>30:1	95
11[e]	2-BrPhCH=CH_2 (**7m**)	24 [85][f]	>30:1	94
12	*(E)*-PhCH=CHCH=CH_2 (**7n**)	78	9:1	87
13	BuOCH=CH_2 (**7o**)	70	9:1	89
14	*N*-Me-2-(CH=CH_2)-pyrrole (**7p**)	31	>30:1	90

[a] Yield of the isolated *cis* isomer. [b] Determined by ^1H NMR spectroscopy of the crude mixture. [c] Determined by SFC on chiral stationary phase. [d] 2 mol% of catalyst was used. [e] Reaction carried out at 50°C. [f] Yield based on recovered starting material.

(92%) and enantioselectivities (93% *ee*) were observed with styrene derivatives substituted with electron-donating groups (Table 2, entry 5). 1,2-Disubstituted *Z*-alkenes such as indene **7j** (Table 2, entry 7) gave slightly lower enantioselectivity. 1,1-Disubstituted α-methylstyrene **7k** gave an excellent 95% *ee* (Table 2, entry 9). Sterically hindered 1-naphthyl **7l** afforded the cyclopropane in good yield (86%, Table 2, entry 10)). Using 2-bromostyrene (**7m**) dramatically diminished the yield of isolated product, but a high level of enantiocontrol was still achieved (24% yield, 94% *ee*, Table 2, entry 11). The same substrate was reported to give low enantiocontrol as a result of the proximity to the double bond of the basic *ortho* Br.[19] Aliphatic olefins gave only trace amounts of the corresponding cyclopropane under these conditions. This problem could be overcome by the selective cyclopropanation of the less-hindered double bond of diene **7n** followed by hydrogenation (H_2, $Pd(OH)_2/C$, EtOAc, 20 min, 94%) to afford alkylsubstituted cyclopropane in good yield and enantiomeric excess (Table 2, entry 12). Enol ether **7o** (Table 2, entry 13) and heteroaromatic olefin *N*-methyl-2-vinylpyrrole (Table 2, entry 14) also reacted under these conditions to afford the corresponding cyclopropanes with high enantiocontrol and good to excellent diastereocontrol. It should be emphasized that diazo reagents **6a–d** are stable for prolonged periods (>5 months) at 0°C and can be readily used without additional purification with no adverse effect on yields or enantioselectivities.

To demonstrate the versatility of these novel cyclopropanes, **8b** was transformed into the corresponding diester **9** with preservation of the enantiomeric purity of the starting material (Scheme 3). Furthermore, **8b** is sufficiently electrophilic to give the corresponding linear chain **10** upon reaction with BuCuLiCN. Alternatively, treatment of **8b** with $LiAlH_4$ afforded the corresponding amino alcohol **11**. These compounds have been shown to be selective serotonin reuptake inhibitors.[20]



Scheme 3. Derivatization of cyclopropane **8b**.

Chemoselective reduction of the amide in the presence of the ester[21] could be carried out using borane–THF complexes, giving the β-aminocarboxy ester **12** containing a cyclopropane ring.[2b]

In summary, a highly enantio- and diastereoselective synthesis of cyclopropane 1,1-dicarboxylic derivatives has been developed. The diazo reagent **6b** reacts with a variety of mono- and disubstituted alkenes in good to excellent yields. The resulting cyclopropanes are useful scaffolds for further synthetic transformations. Other applications of this *trans*-directing ability of amides in cyclopropanation will be reported in due course.

Experimental Section

General procedure for the synthesis of enantioenriched cyclopropanes (Table 2): DCE (1 mL) and the corresponding alkene (0.20 mmol, 1.00 equiv) were added to $[Rh_2(S\text{-nttl})_4]$ (2.9 mg, 0.002 mmol, 1 mol%) in a sealed, argon-purged 10 mL microwave tube. The diazo compound (0.60 mmol, 3.00 equiv) dissolved in DCE (1 mL) was added to the reaction mixture over a period of 2 h using a syringe pump (Chemyx Fusion 200) at room temperature. Following complete addition, the resulting mixture was stirred for an additional 14 h at room temperature. After complete consumption of the diazo reagent, the reaction mixture was purified by column chromatography on silica gel (gradient elution, 100% hexane to 100% Et_2O). In cases where the rhodium dimer is complexed to the product, the green mixture was dissolved in DCM and poly(4-vinylpyridine) (50 mg) was added. The color changed from green to red, and the mixture was then

filtered through Celite to afford a rhodium-free product after concentration under reduced pressure.

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