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Expedient Synthesis of Cyclopropane α -Amino Acids by the Catalytic Asymmetric Cyclopropanation of Alkenes Using Iodonium Ylides Derived from Methyl Nitroacetate

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The asymmetric synthesis of cyclopropane α -amino acids is an important process due to the occurrence of this moiety in natural products¹ and in several bioactive unnatural analogues.² The sterically restrained cyclopropane amino acid is known to induce changes in conformation^{2b} such as β -turns^{2c} and to bring stability toward enzymatic hydrolysis.^{2d,e} Although several approaches have been designed toward their asymmetric synthesis,^{3,4} the transformation remains a great synthetic challenge since control of both diastereoselectivity and enantioselectivity in the cyclopropane formation step is required. Moreover, few methods allow expedient preparation of a wide series of derivatives from readily available starting materials. Furthermore, the related chiral aminocyclopropanes⁵ are widely found in potential drugs (Figure 1).⁶

Our research group has been developing a general expedient approach for the synthesis of the cyclopropyl amino acid unit, using either diazo (**2b**) or phenyliodonium ylide (**2a**) derivatives of α -nitro ester **1** (Scheme 1).⁷ The Rh- or Cu-catalyzed cyclopropanation of these species with alkenes affords substituted 1-nitro-cyclopropyl carboxylates^{7,8} in good yields and diastereocontrol but with poor enantiocontrol ($\leq 72\%$ ee).^{7d}

This is not surprising since, even though the transition-metal-catalyzed cyclopropanation reactions of metal carbenes bearing either an acceptor group (EWG) (**A**) or both acceptor and donor (EDG) groups (**B**)^{4d} have provided high enantiocontrol, similar reactions of metal carbenes substituted by two acceptor groups (**C**) have given much lower ee's (Figure 2).^{3a}

We herein report that a Cu(I)–bis(oxazoline) complex is highly efficient in the catalytic asymmetric cyclopropanation of phenyliodonium ylides.⁹

This study was initiated using styrene, $\text{PhI}=\text{O}$, and molecular sieves to scavenge water. Commercially available isopropylidene bis(4-phenyl-2-oxazoline) (**5**) and $\text{Cu}(\text{MeCN})_4\text{PF}_6$ were used as catalyst precursors (Table 1, entry 1).

An encouraging 10% yield (22% conversion + remaining unreacted **1a**) of the desired cyclopropanation adduct was obtained using 5 mol % of the catalyst, which showed that the presence of iodosobenzene, an oxidizing agent, did not shut down the Cu(I) catalytic pathway. Furthermore, the enantioselectivities (75% ee) were similar to those previously observed with the parent diazo compound with **5** as the ligand.^{7d} Our next goal was to find conditions to fully consume methyl nitroacetate **1a**. The use of Na_2CO_3 (2.3 equiv) as an additive was found to be optimal for the full consumption of the starting material, although no improvement in the yield was observed. It was assumed that the low catalyst activity was responsible for the low yield (entry 3). In contrast to the cyclopropanation reaction of the parent diazo compound, use of ethyl diazoacetate (EDA) was not required to activate the Cu(I) catalyst (entry 2). Upon screening the Cu(I) source, we observed a tremendous effect of the catalyst counterion on the reactivity.¹⁰ Among those tested, the hexafluoroantimonate (SbF_6) counterion

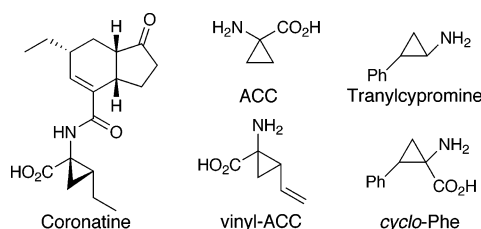


Figure 1. Important cyclopropane amino acids and amines.

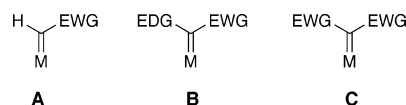


Figure 2. Various classes of metal (M) carbenes in cyclopropanations.

Scheme 1. Approach toward Cyclopropyl Amino Acids

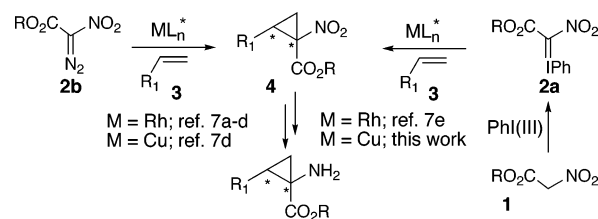
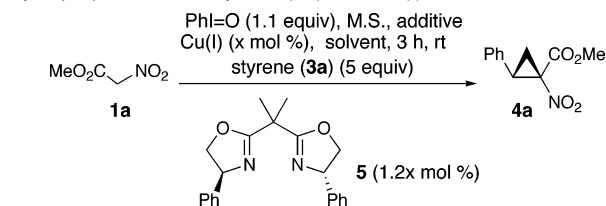


Table 1. Optimization of Reaction Conditions for the Cyclopropanation of Styrene (**3a**) with Cu(I)



entry	additive	solvent	Cu(I) (x mol %)	yield ^a	dr ^b	ee ^c
1	none	CH_2Cl_2	$\text{Cu}(\text{MeCN})_4\text{PF}_6$ (5)	10	85:15	75
2	EDA (0.2) ^d	CH_2Cl_2	$\text{Cu}(\text{MeCN})_4\text{PF}_6$ (5)	13	85:15	75
3	Na_2CO_3 (2.3)	CH_2Cl_2	$\text{Cu}(\text{MeCN})_4\text{PF}_6$ (5)	11	92:8	74
4	Na_2CO_3 (2.3)	CH_2Cl_2	CuSbF_6 (5) ^e	58	92:8	82
5	Na_2CO_3 (2.3)	toluene	CuSbF_6 (5)	65	92:8	89
6	Na_2CO_3 (2.3)	<i>o</i> -xylene	CuSbF_6 (5)	35	92:8	90
7	Na_2CO_3 (2.3)	C_6H_6	CuSbF_6 (5)	73	93:7	91
8	Na_2CO_3 (2.3)	C_6H_6	CuSbF_6 (2)	79	93:7	91
9	Na_2CO_3 (2.3)	C_6H_6	CuSbF_6 (1)	52	93:7	91

^a Isolated yield. ^b Diastereomeric ratio was determined by ^1H NMR. ^c Enantiomeric excesses (ee) were determined by SFC on chiral stationary phase. ^d Ethyl diazoacetate was premixed with the catalyst. ^e CuSbF_6 was generated from CuCl (1 equiv) and AgSbF_6 (1.2 equiv).

resulted in an increased yield (58%) of the resulting cyclopropane and improved enantioselectivity (82% ee) (entry 4). The solvent effect on the enantioselectivity was then studied, and several trends were observed. Acetonitrile (either added or from $\text{Cu}(\text{MeCN})_4\text{PF}_6$)

Table 2. Scope for the Cyclopropanation of Alkenes (**3a–j**) with Cu(I)

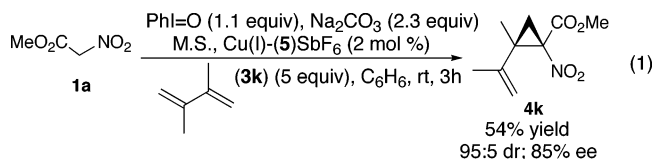
$\text{MeO}_2\text{C}-\text{CH}_2-\text{NO}_2 \xrightarrow[\text{alkene (3) (5 equiv), C}_6\text{H}_6, \text{rt, 3 h}]{\text{PhI=O (1.1 equiv), M.S., Na}_2\text{CO}_3 (2.3 \text{ equiv})} \text{R}-\text{C}(\text{CO}_2\text{Me})_2-\text{NO}_2$				
entry	alkene	yield ^a	dr ^b	ee ^c
1	PhCH=CH ₂ (3a)	82 ^e	94:6	91
2	4-Cl-PhCH=CH ₂ (3b)	45	92:8	91
3	4-MeO-PhCH=CH ₂ (3c)	71 ^f	93:7	68 ^d
4	4-Me-PhCH=CH ₂ (3d)	76	93:7	92
5	1-NaphthCH=CH ₂ (3e)	53	93:7	91
6	2-NaphthCH=CH ₂ (3f)	74	91:9	91
7	2,4,6-Me ₃ C ₆ H ₂ CH=CH ₂ (3g)	54	95:5	93
8	4-T _{Bu} -PhCH=CH ₂ (3h)	80	93:7	90
9	indene (3i)	72	95:5	98 ^d
10	1,3-butadiene (3j)	84	82:18	90

^a Isolated yield. ^b Diastereomeric ratio was determined by ¹H NMR. ^c Enantiomeric excesses (ee) were determined by SFC on chiral stationary phases. ^d Enantiomeric excesses (ee) were determined on a derivative. ^e Reaction was performed on 10 mmol scale. ^f Yield by ¹H NMR with internal standard.

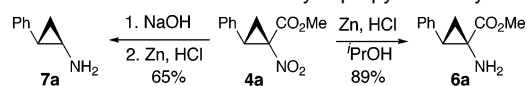
lowered the enantioselectivities, whereas nonpolar solvents improved both the conversions and the enantioselectivities. Benzene, toluene, and *o*-xylene turned out to be the optimal solvents both in terms of yield and enantioselectivity (Table 1, entries 5–7). The catalyst loading could be lowered to 2 mol % without affecting the isolated yield, the diastereoselectivity or the enantioselectivity of the reaction. The absolute stereochemistry (1*R*,2*S*) was unambiguously established by comparison with authentic amine **7a**.¹¹

Several alkenes were then submitted to the optimized conditions (Table 2). 4-Chlorostyrene was cyclopropanated in lower yield (45%) but with excellent enantiocontrol (entry 2), whereas 4-methoxystyrene afforded the cyclopropane adduct **4c** in 71% yield but with lower enantioselectivity (entry 3). Substitution of the aromatic ring could be accomplished with success, as the cyclopropanation of sterically hindered 2,4,6-trimethylstyrene led to the desired product in 54% yield and 93% ee (entry 7). Indene (**3i**) also furnished excellent yield, diastereoselectivity, and enantioselectivity of the corresponding cyclopropane (entry 9).

A high asymmetric induction was also observed with 1,3-butadiene, although the diastereoselectivity was slightly reduced (entry 10). Much to our surprise, high diastereo- and enantiocontrol were maintained using 2,3-dimethyl-1,3-butadiene, which provided an adduct with two contiguous quaternary centers (eq 1).¹²



To demonstrate the versatility of the nitrocyclopropyl carboxylates **4** as chiral building blocks, methyl 1-nitro-2-phenylcyclopropyl carboxylate (**4a**) was converted into important unnatural cyclopropanes **6a**^{2c} and **7a**^{6a} (Scheme 2). A simple two-step process was used to decarboxylate and reduce the nitroester **4a** into the amine **7a**. The most stable trans isomer of the 1-aminocyclopropane **7a** was obtained through thermodynamic equilibration of the 1-nitrocyclopropane. Similarly, the aminoester **6a** was obtained in high yield from **4a** by a simple Zn-mediated reduction.^{7a} In both cases, the high enantioselectivity was preserved.

Scheme 2. Derivatization of 1-Nitrocyclopropyl Carboxylate **4a**

In conclusion, a three-step synthesis of enantiomerically enriched cyclopropane α-amino acid esters was developed using the Cu(I)-catalyzed asymmetric cyclopropanation reaction of phenyliodonium ylides with alkenes. The method is efficient and practical, and it should find wide application in synthesis. Efforts to access the other diastereomeric cyclopropane α-amino acids are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures for the preparation of all the compounds and characterization data for each reaction and detailed structural assignment. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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