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Enantioselective Synthesis of Diarylcyclopropanecarboaldehydes by Organocatalysis

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ABSTRACT

An efficient synthetic method for chiral trisubstituted diarylcyclopropanecarboaldehydes has been developed from substituted benzyl chloride and α,β-unsaturated aldehydes. The reactions were catalyzed by chiral amine catalyst under mild condition to afford the chiral diarylcyclopropanecarboaldehydes in good to high yields and up to excellent enantioselectivities.

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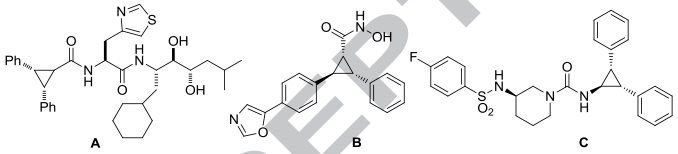
Cyclopropane, particular chiral cyclopropane, is one of the most important privileged core structures in natural products and biologically active compounds,[1] which has inspired extensive synthetic effect for obtaining asymmetric multi-substituted cyclopropanations.[2] Simmons-Smith cyclopropanation with chiral promoters could afford substituted cyclopropanes with high enantioselectivities.[3,4] However, the methods rely significantly on metal catalysis, including Rh,[5] Te ylide,[6] Cu,[7] Zn,[8] Co,[9] and Ru.[10] In the last decade, organocatalysis, which is more environmental friendly than metal catalysis, has emerged as a new methodology to afford asymmetric cyclopropanes. For example, ammonium ylides was converted to cyclopropanes catalyzed by cinchona alkaloid.[11] Iminium catalyzed cyclopropanation between enals and ylides could afford chiral trisubstituted cyclopropanes.[12] Cyclopropanation of nitrostyrenes, enals or 2-arylidene-1,3-indandiones with halomalonates generated asymmetric cyclopropanes with good to high enatioselectivities.[13-15]

Among cyclopropanes, trisubstituted diarylcyclopropanes present special biological activities. For example, trisubstituted diphenyl cyclopropane amide derivative **A** is a potent inhibitor of purified renin (Scheme 1).[16] Trisubstituted diarylcyclopropanehydroxamic acid derivative **B** has been developed as potent and selective class IIa histone deacetylase (HDAC) inhibitor for potential treatment of Huntington's disease.[17] Trisubstituted diarylcyclopropane urea derivative **C** has been reported as potent orally available soluble epoxide hydrolase (sEH) inhibitor.[18] However, efficient synthetic methods for constructing trisubstituted diarylcyclopropanes were still very rare. Recently, an improved Zn-catalyzed Simmons-Smith reaction was developed to synthesize 1,2,3-trisubstituted diarylcyclopropanes.[19] Very recently, asymmetric synergistic catalysis of the *cis*-cyclopropanation of benzoxazoles has been reported.[20]

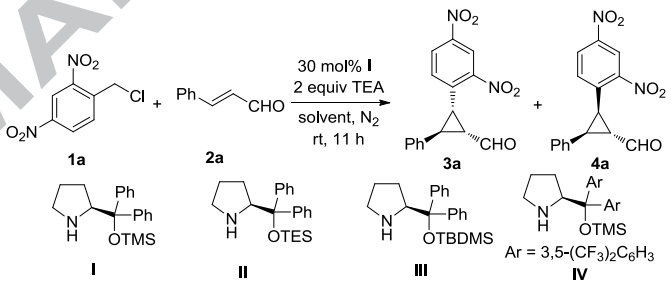
Scheme 1. Trisubstituted diphenyl cyclopropane derivatives with biological activities.



Our research focuses on the development of efficient methodology for construction of chiral scaffolds. For chiral cyclopropane synthesis, in 2007, we reported cascade Michael-alkylation reaction of α,β-unsaturated aldehydes with bromomalonates for synthesis of chiral diester substituted cyclopropanes.[21] Later on, electron-deficient arylmethanes were also demonstrated to react with α,β-unsaturated aldehydes and form cyclopropanes.[22] Based on our previous work, we envisioned that chiral trisubstituted diarylcyclopropanes could be constructed from electron-deficient benzyl chloride and α,β-unsaturated aldehydes.[23]

To test out our hypothesis, we initially tried reaction between 1-(bromomethyl)-2,4-dinitrobenzene **1a'** (0.33 mmol) and cinnamaldehyde **2a** (0.28 mmol) in CH_3CN using diphenylprolinol TMS ether **I** (30 mol%) as the organo-catalyst and trimethylamine (TEA) as base under ambient air and temperature. Interestingly, the reaction for 11 h gave mainly a mixture of 2,4-dinitrobenzaldehyde from hydrolysis and oxidation of **1a'** and a nucleophilic substitution product formed between **1a'** and amine catalyst **I**. (table 1, entry 1). To avoid side reactions due to substitution and oxidation, the less reactive benzyl chloride **1a** was used instead at same condition. To our delight, cyclopropane products (**3a** and **4a**) were isolated in 32% yield with some 2,4-dinitrobenzaldehyde obtained as well (entry 2). The reaction yield was further improved to 51% as well as good enantioselectivities for both **3a** and **4a** (92% and 81% ee, respectively, entry 3) when **1a** was added in four portions and reaction was performed under N_2 atmosphere. When this reaction was performed at different solvents, it generally afforded two diasteromeric cyclopropane products in moderate yields and high enantioselectivities (entries 3-6). Reaction in diethyl ether gave the highest reaction yield but with compromised enantioselectivities (entry 7), while in toluene or dioxane, no cyclopropane products were separated (entries 8 and 9). For all solvents tested, 1,2-dichloroethane (DCE) seemed to give the best combination of yield, enantioselectivity and diastereoselectivity (entry 4). Therefore, DCE was chosen as the best reaction solvent. In terms of organocatalyst, four catalysts were screened. The more steric catalysts **II** and **III** afforded much higher yields while still retaining good enantioselectivities (entries 10 and 11). The enhanced yield was likely caused by the minimized nucleophilic substitution side reaction due to increased steric effects. By increasing the amount of **1a** to 2 equiv., the reaction catalyzed by **III** gave the products in good yields with excellent enantioselectivities (entry 12). However, the reaction catalyzed by more steric catalyst **IV** gave much lower enantioselectivities (entry 13). Other bases such as 2,6-lutidine and NaOAc could not afford the product.

Table 1. Screening of the reaction conditions[a]



entry	cat.	solvent	yield%[b] (**3a**+**4a**)	ee% (**3a**/**4a**)[c]	dr (**3a**:**4a**)[d]
1[e,f]	**I**	CH_3CN	trace	-	-
2[f]	**I**	CH_3CN	32	-	-
3	**I**	CH_3CN	51	92/81	2:1
4	**I**	$Cl(CH_2)_2Cl$	55	92/89	2:1
5	**I**	$CHCl_3$	42	93/75	1:1
6	**I**	THF	54	95/87	1:1
7	**I**	Et_2O	66	68/67	3:2
8	**I**	toluene	-	-	-
9	**I**	dioxane	-	-	-
10	**II**	$Cl(CH_2)_2Cl$	75	85/82	1:1
11	**III**	$Cl(CH_2)_2Cl$	72	88/85	2:1
12[g]	**III**	$Cl(CH_2)_2Cl$	74	96/94	2:1
13	**IV**	$Cl(CH_2)_2Cl$	65	25/39	3:2

[a] Reaction conditions: unless specified, a mixture of **2a** (0.33 mmol), TEA (0.56 mmol) and catalyst (0.084 mmol) in 1.6 mL solvent was added the solution of **1a** (0.28 mmol) in 4 mL solvent for 4 times and stirred for 11 h at rt.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis.

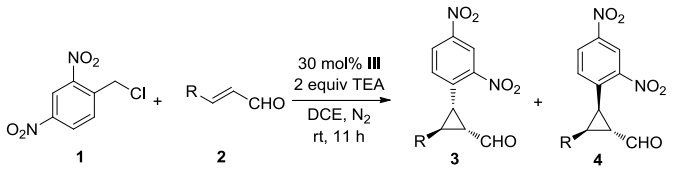
[d] Determined by ^{1}H NMR.

[e] 2,4-Nitro benzyl bromide **1a'** was used.

[f] **1** was added in one port under air.

[g] **2a** (0.56 mmol) was used.

Table 2. Scope of the synthesis of chiral cyclopropanes[a]



entry	R	yield%[b] (**3**+**4**)	ee% (**3**/**4**)[c]	dr (**3**:**4**)[d]
1	Ph (**a**)	74	96/94	2:1
2	4-BrC_6H_4 (**b**)	66	90/95	2:1
3	4-ClC_6H_4 (**c**)	74	95/90	1.5:1
4	4-MeC_6H_4 (**d**)	76	95/94	2:1
5	4-MeOC_6H_4 (**e**)	68	93/86	1:1
6	3-FC_6H_4 (**f**)	81	91/92	1.7:1

[a] Reaction conditions: unless specified, a mixture of **2** (0.56 mmol), TEA (0.56 mmol) and catalyst (0.084 mmol) in 1.6 mL DCE was added the solution of **1a** (0.28 mmol) in 4 mL DCE for 4 times and stirred for 11 h at rt.

[b] Isolated yield.

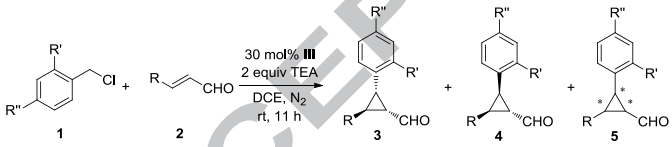
[c] Determined by chiral HPLC analysis.

[d] Determined by ^{1}H NMR.

With the optimal reaction condition in hand, we then focused on exploration of reactant scope of α,β-unsaturated aldehydes for this asymmetric cyclopropanation reaction (Table 2). The results showed that α,β-unsaturated aldehydes with substituted group at *para*- and *meta*- position of the phenyl ring afforded cyclopropane products **3** and **4** in modest to good yields and excellent enantioselectivities. Unfortunately, the diastereoselectivities of cyclopropanation products were not so attractive due to high structural similarity between two aromatic groups on the cyclopropane ring. Electron-withdrawing groups at *para*- position of the phenyl ring gave similar results as the unsubstituted cinnamaldehyde (entries 2 and 3). Electron-donating groups at *para*- position of the phenyl ring also reacted smoothly to afford two products (entries 4 and 5). For 4-methoxycinnamaldehyde, diastereoselectivity was decreased to 1:1 (entry 5). The reaction yield could reach to 81% when 3-fluorocinnamaldehyde was used (entry 6).

Interestingly, when 2-substituted cinnamaldehydes reacted with 1-(chloromethyl)-2,4-dinitrobenzene **1a**, the third diastereomer **5** was detected as the minor product (Table 3). α,β-Unsaturated aldehydes with electron-withdrawing groups at the *ortho*- position of the phenyl ring gave all three products in good yields and enantioselectivities (entry 1 and 2). For 2-methoxy cinnamaldehyde, cyclopropane products were obtained in a high yield of 86% with high enantioselectivities for only two products: **3i** and **4i**. The enantioselectivity of the other product **5i** dropped significantly (39% ee, entry 3). When a less electron-withdrawing methoxycarbonyl group replaced one nitro group in disubstituted benzylchlorides reacted with 2-methoxycinnamaldehyde, no cyclopropane products were obtained. To our delight, for these less reactive disubstituted benzylchlorides including 1-(chloromethyl)-2-nitro-4-(trifluoromethyl)benzene **1j**, methyl 2-(chloromethyl)-5-nitrobenzoate **1k**, and methyl 4-(chloromethyl)-3-nitrobenzoate **1l**, 4-chlorocinnamaldehyde reacted smoothly to give acceptable reaction yields and high enantioselectivities, though extended reaction time up to several days were needed (entries 4-6). However, the reactions between benzylchloride and alkyl substituted α,β-unsaturated aldehydes could not proceed under these reaction conditions, presenting a limitation for this method.

Table 3. Scope of the synthesis of chiral cyclopropanes[a]



Entry	R', R''	R	yield%[b] (**3**+**4**+**5**)	Ee% (**3**/**4**/**5**)[c]	dr (**3**:**4**:**5**)[d]
1	NO_2, NO_2	2-BrC_6H_4 (**g**)	70	96/94/86	2.5:1:1.5
2	NO_2, NO_2	2-ClC_6H_4 (**h**)	74	90/95/94	3.4:2.4:1
3	NO_2, NO_2	2-MeOC_6H_4 (**i**)	86	95/94/39	3:1:1.3
4[e]	NO_2, CF_3	4-ClC_6H_4 (**j**)	76	96/90/85	1.5:1.3:1
5[e]	CO_2Me, NO_2	4-ClC_6H_4 (**k**)	61	88/91/70	1:1.7:1.1
6[f]	NO_2, CO_2Me	4-ClC_6H_4 (**l**)	61	96/90/80	1.9:1.5:1

[a] Reaction conditions: unless specified, a mixture of **2** (0.56 mmol), TEA (0.56 mmol) and catalyst (0.084 mmol) in 1.6 mL DCE was added the solution of **1** (0.28 mmol) in 4 mL DCE for 4 times and stirred for 11 h at rt.

[b] Isolated yield.

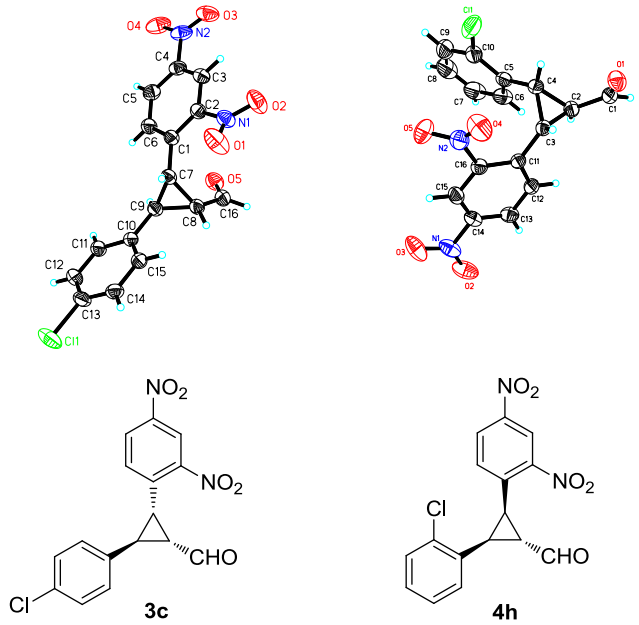
[c] Determined by chiral HPLC analysis.

[d] Determined by ^{1}H NMR.

[e] The reaction was stirred for 7 d at rt.

[f] The reaction was stirred for 4 d at rt.

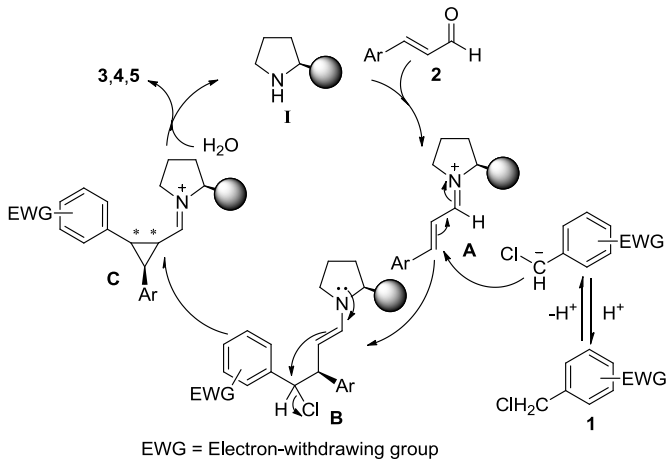
Scheme 2. The absolute configurations of **3c** and **4h**.



The absolute configurations of product **3** and **4** were determined by single crystal X-ray diffraction analysis based on compound **3c** and **4h** (Scheme 2). Unfortunately, we were not able to get good crystal of product **5** and solve its absolute configuration.

The proposed mechanism is described in Scheme 3. Activation of *α,β*-unsaturated aldehyde **2** by a chiral organocatalyst **III** produces iminium **A**. Conjugate addition of a nucleophilic anion from **1**, to the resulting active iminium **A**, triggers a Michael process to afford intermediate **B**. Then a nucleophilic substitution results in cyclopropane intermediate **C**. Probably, the nucleophilic substitution can happen from both directions due to chloride at achiral β position to give poor diastereoselectivities. Finally, water enters to recycle the catalyst **III** and afford products **3**, **4** and **5**.

Scheme 3. The proposed mechanism.



In summary, we have developed an efficient method for the synthesis of chiral trisubstituted diarylcyclopropanecarboaldehydes from substituted benzyl chloride and α,β-unsaturated aldehydes. The reactions were catalyzed by chiral diphenylprolinol TBDMS ether under mild condition to give chiral diarylcyclopropanecarboaldehydes in good to high yields and overall excellent enantioselectivities. For α,β-unsaturated aldehydes with substitutions at both *para*- and *meta*- position of the phenyl ring reacting with 1-(chloromethyl)-2,4-dinitrobenzene afforded only two cyclopropane products, while the reactions of cinnamaldehyde with substitution at *ortho*-position or other disubstituted benzylchlorides generated three diastereomers. Further exploration of this methodology in synthetic applications towards biologically relevant molecules are under investigation in our laboratory.

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Supplementary Material

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC 1500758 and 1500817. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.UK). All experimental procedures, spectroscopic data associated with this article can be found, in the online version. at http://dx.doi.org/ .

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Highlights

Chiral trisubstituted diarylcyclopropanecarboaldehydes have been synthesized by organocatalysis.

The enantioselectivities of trisubstituted diarylcyclopropanecarboaldehydes are very high.

The reactions can be proceeded under the mild conditions.