Sidearm effects in the enantioselective cyclopropanation of alkenes with aryldiazoacetates catalyzed by trisoxazoline/Cu(I)

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A highly enantioselective cyclopropanation of alkenes with phenyldiazoacetates catalyzed by $CuPF_6(CH_3CN)_4$/trisoxazoline has been developed.

The metal catalyzed cyclopropanation between diazo compounds and alkenes is one of the most important methods for the synthesis of cyclopropane derivatives and has been widely applied in organic synthesis.[1] Since Nozaki *et al.*[2] reported the first example of its asymmetric version, a number of excellent chiral catalysts[3–8a] such as BOX/Cu(I) complexes[4] and rhodium prolinates[5] have also been designed and synthesized for such reactions. Of the asymmetric metal-catalyzed cyclopropanation of alkenes with diazo compounds developed, most α-substituted diazoacetates gave the desired products with moderate diastereoselectivities[6] except for the diazoacetates[3,4] used in some cases. Recently, several rhodium catalysts[7] were reported to promote the cyclopropanation of styrene with aryldiazoacetates well, in which both good diastereoselectivity and enantioselectivity are achieved. However, poor enantioselection was observed in this reaction when non-rhodium catalysts were used.[7a]

Very recently, Gade *et al.*[8] and our laboratory[9] independently found that bisoxzolines with pendant donor groups are more efficient than the parent bisoxazolines in several enantioselective reactions. The strong sidearm effects[8,9] observed encouraged us to explore the Cu(I)-catalyzed enantioselective cyclopropanation of alkenes with aryldiazoacetates. It was found that only moderate ees were observed when both *tert*-butyl and *iso*-propyl bisoxazoline/$CuPF_6$, excellent catalysts for the cyclopropanation of diazoacetates,[4] were used (eqn 1 and 2 in Scheme 1). To our delight, the introduction of a pendant oxazoline on bisoxazoline improved greatly both the yield and enantioselectivity of the reaction of styrene with ethyl phenyldiazoacetate, providing an easy access to highly optically active multi-substituted cyclopropanes (Scheme 1). In this paper, we wish to report the preliminary results.

In the presence of 5 mol% $CuPF_6$/trisoxazoline **6** or **7**, styrene could react with α-phenyldiazoacetate to afford the cyclopropanation product smoothly. Further studies found that the reaction conditions influenced strongly both the yield and enantioselectivity (Table 1). In both hexane and toluene, no cyclopropanation product was obtained. DCM gave moderate enantioselectivity (entry 1, Table 1). Under the screened conditions, EtOAc gave the best enantioselectivity (91% ee, entries 4–7, Table 1). The substituents on the pendant oxazoline proved to influence the enantioselectivity slightly. For example, the *tert*-butyl derived-oxazoline **7** gave 92% ee and the isopropyl derived-oxazoline **6** gave 91% ee (entries 7 and 8).

Further studies showed that the generality of this reaction was pretty good. As shown in Table 2,† the diastereoselectivities were

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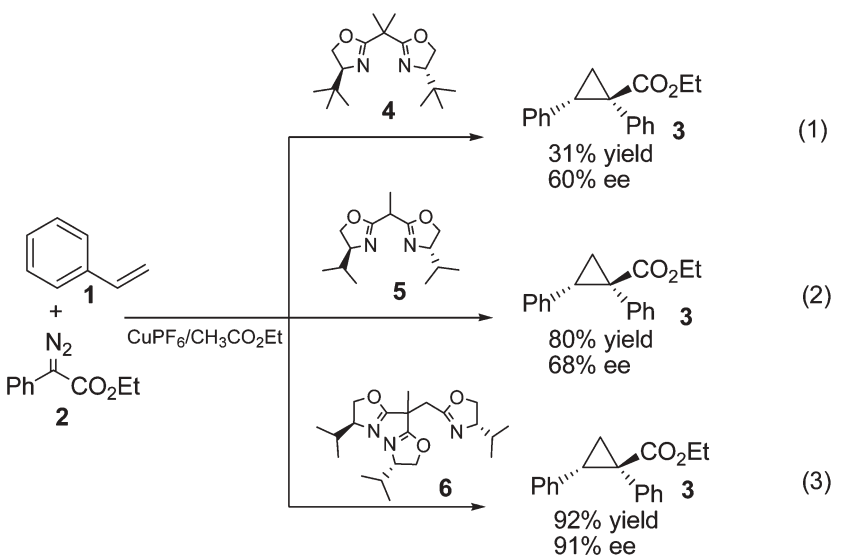
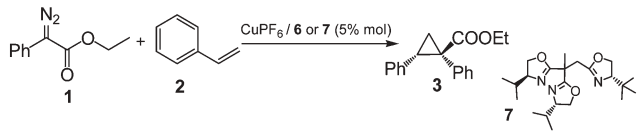


Scheme 1 The effects of the pendant oxazoline on the cyclopropanation.

Table 1 Effects of reaction conditions on cyclopropanation of styrene and ethyl phenyldiazoacetate

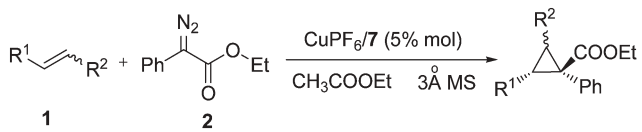


Entry	Ligand	Solvent	T/°C	t/h	Yield (%)[a]	ee (%)[b]
1	**6**	CH_2Cl_2	15	12	64	69
2	**6**	Hexane	15	24	0	—
3	**6**	Toluene	15	24	0	—
4	**6**	EtOAc	15	24	50	91
5[c]	**6**	EtOAc	15	24	79	91
6[c]	**6**	EtOAc	25	15	99	91
7[c]	**6**	EtOAc	40	8	91	91
8[c]	**7**	EtOAc	40	8	92	92

[a] Isolated yield. [b] Determined by chiral HPLC and GC. [c] 3 Å MS was added.

outstanding and only single diastereomers were observed in all cases. Various styrene derivatives are good substrates for this reaction. The substituents on the benzene ring of the styrenes influenced both the yields and enantioselectivities slightly (entries 1–4). For example, 4-methoxystyrene gave the highest enantioselectivity (95% ee, entry 4) in 94% yield (entry 4) and 4-chlorostyrene also gave 91% ee in 97% yield (entry 2). 1-Phenyl-1,3-butadiene was also a suitable substrate and gave *trans*-phenylvinylcyclopropane with excellent chemoselectivity and high enantioselectivity in 99% yield (entry 5). *cis*-1-Phenyl-1-propylene and indene afforded 1,1,2,3-tetrasubstituted

Table 2 Asymmetric cyclopropanation of alkenes



Entry	Alkene	T/°C	Yield (%)[a]	ee (%)[b,c]
1	Ph (**1a**)	40	92	92
2	*p*-ClC$_6$H$_4$ (**1b**)	40	97	91
3	*p*-CH$_3$C$_6$H$_4$ (**1c**)	40	99	93
4	*p*-CH$_3$OC$_6$H$_4$ (**1d**)	40	94	95
5	Ph (**1e**)	40	99	89
6	(**1f**)	40	85	87
7	Ph (**1g**)	40	51	82
8	BuO (**1h**)	20	99	82
9	O (**1i**)	20	80	83
10	O (**1j**)	20	86	90

[a] Isolated yield. [b] Determined by chiral HPLC and GC. [c] dr > 99/1.

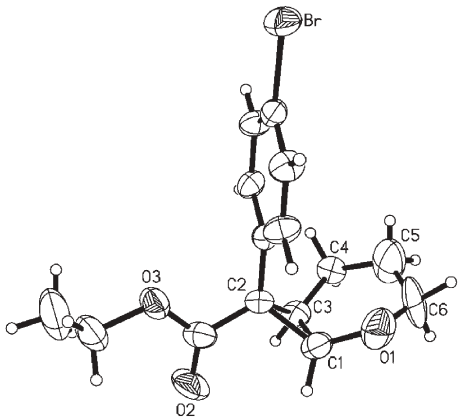
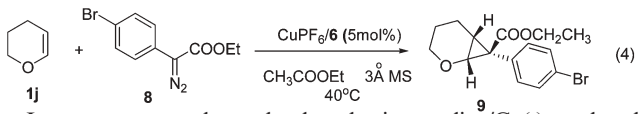


Fig. 1 ORTEP drawing (35% ellipsoids) for **9** (note that C(6) is disordered over two sets of positions with 0.5 : 0.5 occupancies and only one conformer is shown for clarity).

cyclopropanes with high diastereoselectivities and good enantioselectivities in moderate to good yields (entries 6 and 7). Alkoxyl alkenes also worked well to afford donor–acceptor cyclopropane derivatives with good enantioselectivities (ee up to 90%) in high yields (entries 8–10), which could undergo many chemical transformations[10] and were widely used in organic synthesis.[11] 1-Hexene was inactive to this cyclopropanation.

The products were characterized by ^{1}H NMR, ^{13}C NMR, IR as well as mass spectra. The relative configurations of the cyclopropanes were determined by comparision of their NMR spectra with the known compounds'.[12] The relative configuration of cyclopropane **9** was determined by X-ray diffraction analysis (Fig. 1).‡



In summary, we have developed trisoxazoline/Cu(I)-catalyzed cyclopropanation of alkenes with aryldiazoacetate, providing an efficient method for the synthesis of tri- or tetra-substituted cyclopropane derivatives with high diastereoselectivities and enantioselectivities in high yields. Comparing with bisoxazoline **4** and **5**, the corresponding trisoxazolines **6** and **7** gave much higher ees and yields, demonstrating a strong sidearm effect of ligand in this cyclopropanation. The readily available trisoxazoline and the high enantioselectivities as well as diastereoselectivities make the present method potentially useful. The studies on further improvement of enantioselectivity and understanding the mechanism are in progress in our laboratory.

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Notes and references

† **Representive procedure**. A mixture of $CuPF_6(CH_3CN)_4$ (7.7 mg, 0.021 mmol), trisoxazoline **7** (9.0 mg, 0.023 mmol), styrene **1a** (0.2 mL, 1.9 mmol, 5 equivalents) in ethyl acetate (1 mL) was stirred at room temperature for 2 h. The resulting mixure was heated to 40 °C and then 3 Å MS (200 mg) was added. To this solution was injected ethyl phenyldiazoacetates (78 mg, 0.42 mmol) in 2 mL of ethyl acetate *via* a syringe pump

within 6 h. After the reaction was complete (monitored by TLC), the mixture was filtered rapidly through a glass funnel with a thin layer of silica gel and eluted with dichloromethane. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography (silica gel, petroleum ether/ethyl acetate) to afford the desired product **3a**. Yield: 112 mg (92%); ee 92% (determined by chiral GC analysis: t_r (major) = 128.05 min, t_r (minor) = 129.50 min and chiral GC). $[\alpha]_D^{20} = 22.5^\circ$ (c 1.05, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.78–7.15 (m, 10H), 4.09–4.20 (m, 2H), 3.13 (dd, J = 7.5, 9.3 Hz, 1H), 2.16 (dd, J = 4.8, 9.6 Hz, 1H), 1.89 (dd, J = 4.8, 7.5 Hz, 1H), 1.20 (t, J = 6.9 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 173.45, 136.15, 134.51, 131.61, 127.73. 127.37, 127.29, 126.60, 125.94, 60.96, 37.28, 32.62, 19.88, 13.88; LRMS-EI (m/e): 266 (M^+, 64.2), 191 (100.0).

‡ *Crystal data*: for **9**, $C_{15}H_{17}BrO_3$, M = 325.2, rhombohedral, space group $R(-3)$, a = 34.229(2), c = 6.488(1) Å, V = 6583.1(9) Å^3, D_c = 1.477 g cm^{-3}, Z = 18, T = 293 K, $2\theta_{max}$ = 50.06°, $F(000)$ = 2988, μ(Mo-K$_\alpha$) = 2.811 mm^{-1}, 2594 reflections used, 1887 unique, R_1 = 0.078 ($I > 2\sigma(I)$), wR_2 = 0.177 on F^2. CCDC 630801. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b617967c

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