

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 $\text{CuPF}_6(\text{CH}_3\text{CN})_4$ /trisoxazoline has been developed.

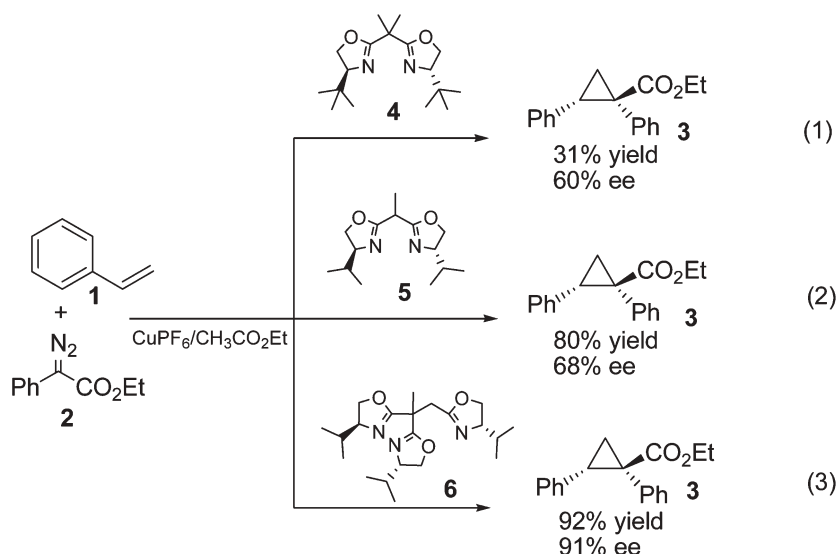
The metal catalyzed cyclopropanation between diazo compounds and alkenes is one of the most important methods for the synthesis of cyclopropane derivatives and has been widely applied in organic synthesis.¹ Since Nozaki *et al.*² reported the first example of its asymmetric version, a number of excellent chiral catalysts^{3–8a} such as BOX/Cu(I) complexes⁴ and rhodium prolinates⁵ 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 diastereoselectivities⁶ except for the diazoacetates^{3,4} used in some cases. Recently, several rhodium catalysts⁷ 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 laboratory⁹ independently found that bisoxazolines 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/CuPF₆, 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% CuPF₆/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



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

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, CHCl₃); ¹H NMR (300 MHz, CDCl₃) 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) ¹³C NMR (75 MHz, CDCl₃): 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**, C₁₅H₁₇BrO₃, $M = 325.2$, rhombohedral, space group $R(-3)$, $a = 34.229(2)$, $c = 6.488(1)$ Å, $V = 6583.1(9)$ Å³, $D_c = 1.477$ g cm⁻³, $Z = 18$, $T = 293$ K, $2\theta_{\max} = 50.06^\circ$, $F(000) = 2988$, $\mu(\text{Mo-K}\alpha) = 2.811$ 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

- For reviews, please see: (a) A. Padaw and S. F. Hornbuckle, *Chem. Rev.*, 1991, **91**, 263; (b) T. Ye and M. A. Mckerverey, *Chem. Rev.*, 1994, **94**, 1091; (c) M. P. Doyle and D. C. Forbes, *Chem. Rev.*, 1998, **98**, 911; (d) H. Lebel, J. F. Marcous, C. Molinaro and A. B. Charette, *Chem. Rev.*, 2003, **103**, 977.
- (a) H. Nozaki, S. Moriuti, H. Takaya and R. Noyori, *Tetrahedron Lett.*, 1966, **7**, 5239; (b) H. Nozaki, S. Moriuti, H. Takaya and R. Noyori, *Tetrahedron Lett.*, 1968, **24**, 3655.
- (a) H. Fritsch, U. Leutenegger and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, 1986, **25**, 1005; (b) H. Nishiyama, Y. Itoh, H. Matsumoto, S. B. Park and K. Itoh, *J. Am. Chem. Soc.*, 1994, **116**, 2223; (c) I. J. Munslow, K. M. Gillespie, R. J. Deeth and P. Scott, *Chem. Commun.*, 2001, 1638; (d) T. Niimi, T. Uchida, R. Irie and T. Katsuki, *Adv. Synth. Catal.*, 2001, **343**, 79; (e) Y. Li, J. S. Huang, Z. Y. Zhou, C. M. Che and X. Z. You, *J. Am. Chem. Soc.*, 2002, **124**, 13185; (f) M. M. Diaz-Requejo, A. Caballero, T. R. Belderrain, M. C. Nicasio, S. Trofimenko and P. J. Perez, *J. Am. Chem. Soc.*, 2002, **124**, 978; (g) P. Müller and A. Ghanem, *Org. Lett.*, 2004, **6**, 4347; (h) L. R. Marcini, D. J. Denhart and R. J. Mattson, *Org. Lett.*, 2005, **7**, 2651; (i) J. A. Miller, B. A. Gross, M. A. Zhuravel, W. Jin and S. T. Nguyen, *Angew. Chem., Int. Ed.*, 2005, **44**, 3885; (j) T. M. Weathers, Jr., M. P. Doyle and M. D. Carducci, *Adv. Synth. Catal.*, 2006, **348**, 449; (k) D. Bykowski, K.-H. Wu and M. P. Doyle, *J. Am. Chem. Soc.*, 2006, **128**, 16038; (l) For a review, please see ref. 1d.
- (a) D. A. Evans, K. A. Woerpel, M. M. Hinman and M. M. Faul, *J. Am. Chem. Soc.*, 1991, **113**, 726; (b) D. A. Evans, K. A. Woerpel and M. J. Scott, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 430; (c) M. P. A. Lyle and P. D. Wilson, *Org. Lett.*, 2004, **6**, 855; (d) M. Itagaki, K. Masumoto and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 3292.
- (a) H. M. L. Davies and D. K. Hutcheson, *Tetrahedron Lett.*, 1993, **34**, 7243; (b) M. P. Doyle, Q. L. Zhou, S. H. Simonsen and V. Lynch, *Synlett*, 1996, 697; (c) M. P. Doyle, S. B. Davies and W. Hu, *Org. Lett.*, 2000, **2**, 1145; (d) P. Müller, G. Bernardinelli, Y. F. Allenbach, M. Ferri and H. D. Flack, *Org. Lett.*, 2004, **6**, 1725; (e) Y. Lou, M. Horikawa, R. A. Kloster, N. A. Hawayluk and E. J. Corey, *J. Am. Chem. Soc.*, 2004, **126**, 8916.
- (a) T. Ikeno, M. Sato and T. Yamada, *Chem. Lett.*, 1999, 1345; (b) C. M. Che, H. L. Kwong, W. C. Chu, K. F. Cheng, W. S. Lee, H. S. Yu, C. T. Yeung and K. K. Cheung, *Eur. J. Inorg. Chem.*, 2002, 1456; (c) Y. Chen and X. P. Zhang, *J. Org. Chem.*, 2004, **69**, 2431.
- (a) M. P. Doyle, Q. L. Zhou, C. Charnsangavej and M. A. Longoria, *Tetrahedron Lett.*, 1996, **37**, 4129; (b) H. M. L. Davies, P. R. Bruzinski and M. J. Fall, *Tetrahedron Lett.*, 1996, **37**, 4133; (c) H. M. L. Davies and S. A. Panaro, *Tetrahedron*, 2000, **56**, 4871; (d) T. Nagashima and H. M. L. Davies, *J. Am. Chem. Soc.*, 2001, **123**, 2695; (e) H. M. L. Davies, T. Nagashima and J. L. Kilino, *Org. Lett.*, 2000, **2**, 823; (f) T. Nagashima and H. M. L. Davies, *Org. Lett.*, 2002, **4**, 1989; (g) H. M. L. Davies and C. Venkataramani, *Org. Lett.*, 2003, **5**, 1403; (h) H. M. L. Davies and A. M. Walji, *Org. Lett.*, 2005, **7**, 2941; (i) A. Biffis, M. Braga, S. Cadamuro, C. Tubaro and M. Basato, *Org. Lett.*, 2005, **7**, 1841.
- (a) S. Bellemin-Laponnaz and L. H. Gade, *Angew. Chem., Int. Ed.*, 2002, **41**, 3473; (b) C. Foltz, B. Stecker, G. Marconi, S. Bellemin-Laponnaz, H. Wadepohl and L. H. Gade, *Chem. Commun.*, 2005, 5115; (c) B. D. Ward, S. Bellemin-Laponnaz and L. H. Gade, *Angew. Chem., Int. Ed.*, 2005, **44**, 1668; (d) M. Seitz, C. Capacchione, S. Bellemin-Laponnaz, H. Wadepohl, B. D. Ward and L. H. Gade, *Dalton Trans.*, 2006, 193.
- (a) J. Zhou and Y. Tang, *J. Am. Chem. Soc.*, 2002, **124**, 9030; (b) M.-C. Ye, J. Zhou, Z.-Z. Huang and Y. Tang, *Chem. Commun.*, 2003, 2554; (c) Z.-Z. Huang, Y.-B. Kang, J. Zhou and Y. Tang, *Org. Lett.*, 2004, **6**, 1677; (d) J. Zhou, M.-C. Ye, Z.-Z. Huang and Y. Tang, *J. Org. Chem.*, 2004, **69**, 1309; (e) M.-C. Ye, B. Li, J. Zhou, X.-L. Sun and Y. Tang, *J. Org. Chem.*, 2005, **70**, 6108.
- For a review, please see: H. U. Reissig and R. Zimmer, *Chem. Rev.*, 2003, **103**, 1151.
- (a) B. M. Trost and J. Y. L. Chung, *J. Am. Chem. Soc.*, 1985, **107**, 4586; (b) S. C. Bobzin and D. J. Faulkner, *J. Nat. Prod.*, 1991, **54**, 225; (c) A. K. Gosh, J. F. Kincaid, D. E. Walters, Y. Chen, N. C. Chaudhuri, W. J. Thompson, C. Culberson, P. M. D. Fitzgerald, H. Y. Lee, S. P. Mckee, P. M. Munson, T. T. Duong, P. L. Darke, J. A. Zugay, W. A. Schleif, M. G. Axel, J. Lin and J. R. Huff, *J. Med. Chem.*, 1996, **39**, 3278.
- H. M. L. Davies and G. H. Lee, *Org. Lett.*, 2004, **6**, 1233.