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Bis(oxazoline)·copper(I)-catalyzed enantioselective cyclopropanation of cinnamate esters with diazomethane

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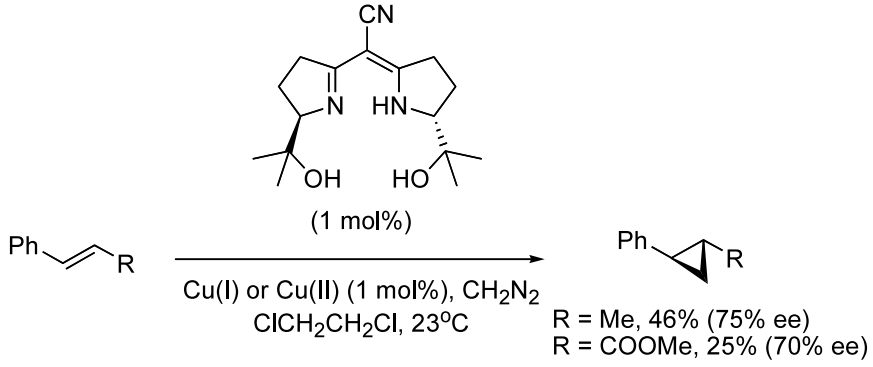
Abstract—Chiral bis(oxazoline)–copper(I) complexes were found to be effective catalysts for the enantioselective cyclopropanation reaction of *trans*-cinnamate esters exploiting an argon flow mediated diazomethane addition method. After optimization of the catalyst structure, good yields and enantiomeric excesses were obtained with electron-poor methyl cinnamate derivatives. Sterically demanding esters gave lower yields and enantioselectivities. The correlation between the product enantiopurities and the σ^+ values of the aromatic *para*-substituents was shown to be linear in a Hammet-type plot.

1. Introduction

The addition of a metal carbene or carbenoid complex to an alkene is one of the most widely used methods for the synthesis of cyclopropane units.[1] Our research group has been interested for some time in the catalytic enantioselective cyclopropanation of allylic alcohols using zinc carbenoids.[2] Kobayashi and Denmark have also made important contributions to this field.[3] In contrast to zinc carbenoids, the catalytic enantioselective cyclopropanation of alkenes via decomposition of diazo compounds is not limited to substrates bearing oxygen directing groups.[1] However, up to now, efficient and highly enantioselective intermolecular cyclopropanations have only been observed with diazo ester compounds.[1a,b,c] Diazoalkanes are known to react with transition metal complexes[4] and diazomethane (the simplest diazoalkane) has been used extensively for the racemic or diastereoselective cyclopropanation of alkenes.[5] Interestingly, the cyclopropanation of *E* or *Z* alkenes employing diazomethane leads to *trans* or *cis* cyclopropanes, respectively.[5] Extensive efforts have been directed towards the development of a catalytic enantioselective cyclopropanation reaction using diazomethane and transition metal complexes.[6] Pfaltz has shown that a chiral semicorrin–copper complex (Eq. (1))[1c,6a] catalyzed the cyclopropanation of β-methyl styrene (46% yield, 75% e.e.) and methyl *trans*-cinnamate (25% yield, 70% e.e.) with modest yields using the Gaspar–Roth[7] method (an inert gas flow mediated addition of diazomethane).[8] In contrast, chiral bis(oxazoline)–palladium catalysts were reported by Denmark to produce only racemic cyclopropane products.[6b]



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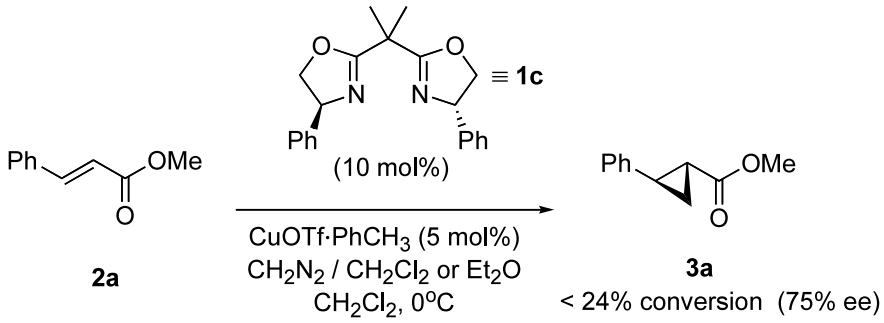


(2)

Our interest in developing new stereoselective methods using diazomethane for the cyclopropanation of alkenes led us to survey a wide range of catalytic systems. In light of previously reported unsuccessful attempts using various chiral palladium catalysts, we focused our efforts on copper salts as catalysts. It is well precedented that chiral ligands such as salicylaldimines, diketones, phosphites, phosphoramidites, bis(oxazolines), semicorrins, bipyridines, diamines and diimines derivatives bind copper salts leading to complexes that can efficiently catalyze enantioselective reactions.[9] Herein, we report our findings on the screening of bis(oxazoline) ligands for the enantioselective cyclopropanation of alkenes involving chiral copper(I)triflate complexes and diazomethane.

2. Results and discussion

2.1. Technical considerations for the addition of diazomethane

Low yields (less than 24%, 75% e.e.) of the cyclopropanated product **3a**[10] are observed (Eq. (2)).[11] when 10 mol% of a 2:1 or 1:1 bis(oxazoline) **1c**-copper(I)triflate complex was treated with a solution of diazomethane in dichloromethane (caution: appropriate precautions must be taken when using diazomethane)[12,13] in the presence of methyl *trans*-cinnamate **2a** at 0°C.

We postulated that a slow addition of diazomethane would reduce carbene dimerization, polymerization or diazomethane attack on the metal carbene, thus leading to the desired cyclopropane with greater efficiency.[14] Since the slow addition of diazomethane is technically challenging due to its low boiling point (–23°C), an alternative delivery system is required. The Gaspar–Roth method is an attractive way to control the rate of diazomethane addition into reaction mixtures.[7] In addition, this method prevents the dilution of the reaction mixture, even if a large excess of diazomethane is required.

Our adaptation of the Gaspar–Roth method involved passing a flow of argon over a cooled (0°C) diazomethane solution (Fig. 1). This flow was then directed into the reaction via cannula. When 5 mol% of a 1:1 ratio of bis(oxazoline) **1c**–copper(I)triflate complex was treated with a dichloromethane solution of diazomethane in the presence of methyl *trans*-cinnamate in dichloromethane at –40°C, the cyclopropanated product was isolated in 80% yield and 72% e.e. (Eq. (3)). When the reaction was carried out at 0°C, the yield dropped slightly to 74% (72% e.e.) but the temperature variation had no effect on the enantioselectivity.[15]

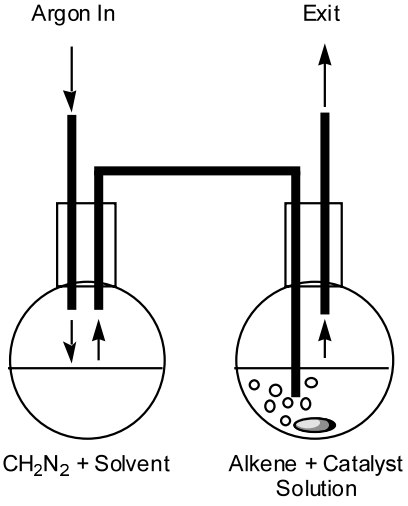
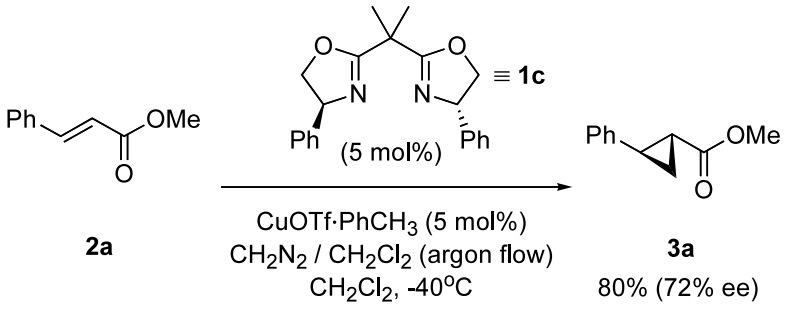


Figure 1. Scheme of experimental apparatus.



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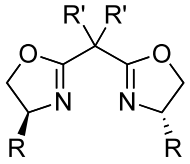

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Figure 2. Chiral bis(oxazoline) ligand scaffold.

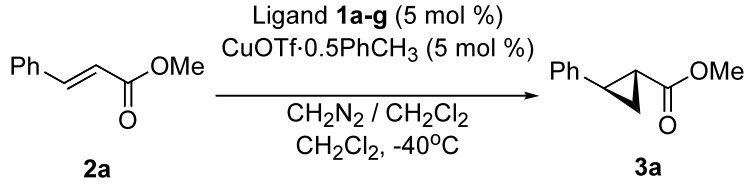
2.2. Variations of the chiral ligand

We then investigated various chiral complexes in the cyclopropanation reaction. Among those tested, chiral bis(oxazoline) ligands (Fig. 2) proved to be the most promising candidates exhibiting good levels of reactivity and enantioselectivity.

Chiral bis(oxazoline) **1a**–**g**[16] ligands were reacted with $CuOTf{\cdot}0.5PhCH_3$ to form bis(oxazoline)–copper complexes that were used directly as catalysts for the cyclopropanation of cinnamate esters. Methyl *trans*-cinnamate was used as a test substrate for this study because it exhibited good reactivity under our reaction conditions. The ligand optimization involving the modification of R and R′ groups is summarized in Table 1. For the ligand optimization study, 5 mol% of a 1:1 ratio of bis(oxazoline)–copper(I) triflate complex was treated with a dichloromethane solution of diazomethane via a flow of argon in the presence of methyl *trans*-cinnamate in dichloromethane at −40°C. The reaction mixture was filtered through a short pad of silica gel using dichloromethane and directly treated with ozone at −78°C and then with methyl sulfide prior to column chromatography to remove the unreacted alkene. The optimal R group was found to be phenyl (entry 3), whereas a methyl group or an ethylene bridge were the optimal R′ groups (entries 3 and 6, respectively).[17] The reactivities and the enantioselectivities were lower when the R substituents were either alkyl (entries 1, 4 and 5) or benzyl groups (entry 2).[18]

Although we used CuOTf, we observed that $Cu(Otf)_2$ was equally effective. It is well known that the active catalyst in the cyclopropanation reaction with diazo compounds is a copper(I) species and that copper(II) species can be reduced to copper(I) during the course of the reaction by the diazo reagent.[19,20]

Table 1. Ligand structure effect on the reactivity and enantioselectivity of the cyclopropanation of methyl *trans*-cinnamate

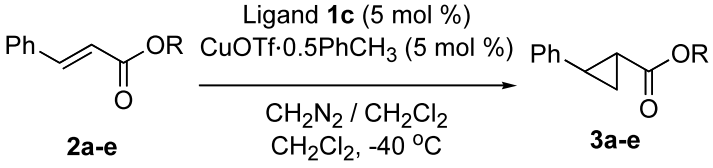


2a 3a

Entry	Ligand	R	R′	Yield (%)[a]	E.e. (%)[b]
1	**1a**	Me	Me	40	50
2	**1b**	Bn	Me	20	53
3	**1c**	Ph	Me	80	72
4	**1d**	*i*-Pr	Me	35	48
5	**1e**	*t*-Bu	Me	30	24
6	**1f**	Ph	$-CH_2CH_2-$	71	77
7	**1g**	Ph	Bn	49	60

[a] Isolated yield.
[b] Determined by SFC or GC using a chiral stationary phase.

Table 2. Alkene structure effect on the reactivity and the enantioselectivity of the cyclopropanation reaction



2a-e 3a-e

Entry	Alkene	R	Yield (%)[a]	E.e. (%)[b]
1	**2a**	Me	80	72
2	**2b**	Et	80	73
3	**2c**	Bn	79	75
4	**2d**	Ph	49	74
5	**2e**	*i*-Pr	43	69

[a] Isolated yield.
[b] Determined by SFC or GC using a chiral stationary phase.

2.3. Substrate variations

In a second set of experiments, the nature of the ester moiety was modified. Using the previously described reaction conditions with catalyst **1c**, we studied the cyclopropanation of alkenes **2a**–**e**.[21] The results are summarized in Table 2 and indicate that non-sterically encumbered alkyl esters gave similar results (entries 1 and 2) as the benzyl ester (entry 3). The phenyl ester is surprisingly less reactive than the alkyl esters, providing the desired cyclopropane in only 49% yield with similar enantioselectivity (74% e.e.) (entry 4). In addition, the more sterically hindered isopropyl ester led to a further decrease in reactivity (43% yield) and enantioselectivity (69% e.e., entry 5).

We also examined the effect of changing the *para*-substituent on the phenyl ring of methyl *trans*-cinnamate with regards to the enantioselectivity and reactivity of the cyclopropanation.[22] Using the previously described reaction conditions, alkenes **2a**,**f**–**h**[23] were submitted to the cyclopranation conditions and the alkene:cyclopropane ratio determined by ^{1}H NMR after a standardized reaction time of 5 h. The cyclopropanation with substrates containing electron donating *para*-groups such as methoxy or methyl was faster but the product was obtained in lower enantiomeric excess (entries 1 and 2) than the parent alkene where R = H (entry 3). In contrast, when the *para*-substituent of the aromatic moiety of the substrate was an electron-withdrawing group, the cyclopropanation reaction was slower while the enantioselectivity increased to 80% (entry 4).

A Hammet-type plot (Fig. 3) shows a linear correlation between the enantioselectivity and the σ^+ value of the *para*-substituent, indicating that the variation in enantioselectivity is due to the electronic character of the alkene.[24] It seems unlikely that the steric perturbation imposed by the variation of the *para*-substituent on the alkene aromatic ring plays a significant role.

It was suggested that the reaction between copper salts and diazomethane leads to the formation of a metal carbene intermediate.[5,25] A possible explanation to account for the observed results could be that the carbene is electrophilic and that electron-rich alkenes react faster through an early transition state which displays less enantiocontrol. According to the Hammond postulate, a later transition state is more product-like which generally implies a greater difference in energy between diastereomeric transition states in an enantioselective system. Therefore, an electron-poor alkene would be less reactive and exhibit higher enantioselectivity. For example, alkene **2h** bearing a *para*-nitro substituent on the aromatic ring gave the highest enantioselectivity yet (Table 3, entry 4) and showed reduced reactivity, whereas alkene **2f** (entry 1) showed increased reactivity but gave lower enantioselectivities in agreement with the above postulate.

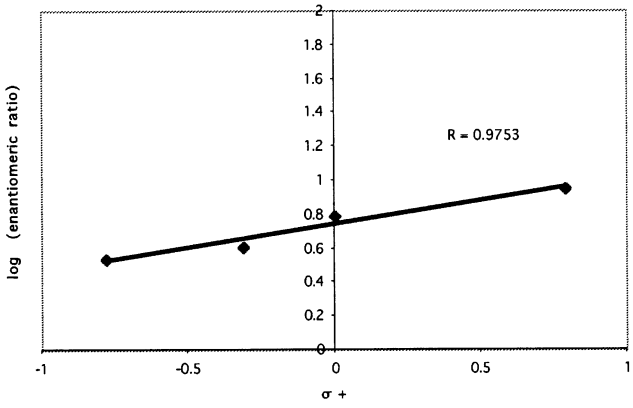
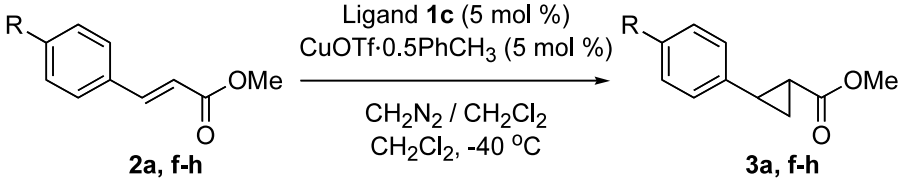


Figure 3. Hammet-type plot correlating the enantioselectivity of the cyclopropanation with the σ^+ values.

3. Conclusion

In conclusion, a methodology has been developed for the catalytic enantioselective cyclopropanation of *trans*-cinnamate esters using an argon flow mediated diazomethane addition method.[26] Our preliminary studies

Table 3. Aromatic ring *para*-substituent effect on the reactivity and the enantioselectivity of the cyclopropanation reaction



Entry	Alkene	R	Ratio (**2n**:**3n**)[a]	Yield (%)[b]	E.e. (%)[c]
1	**2f**	MeO	7:93	81	55
2	**2g**	Me	7:93	79	60
3	**2a**	H	9:91	80	72
4	**2h**	NO_2	23:77	62	80

[a] Determined by ^{1}H NMR analysis of the crude product.
[b] Isolated yield.
[c] Determined by SFC or GC using a chiral stationary phase.

indicate that 5 mol% of a 1:1 ratio of bis(oxazoline)–Cu(I) complex is sufficient for good reactivity. Good yields and enantioselectivities were observed for unhindered cinnamate esters, with electron-poor alkenes giving the highest enantioselectivities. The above described methodology induces the highest reported level of enantioselectivity ever obtained for a cyclopropanation using diazomethane (80% e.e.) with good yields (up to 80%). Further studies are currently in progress to develop a more effective catalyst and expand the scope of the reaction.

Acknowledgements

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10. Properties or references for compounds **3a**–**h**: (1*R*,2*R*)-**3a** $[\alpha]_D^{20}=-238.1$ (*c* 1.24, $CHCl_3$); literature value for enantiopure (1*S*,2*S*)-**3a**: $[\alpha]_D^{20}=324.7$ (*c* 1.24, $CHCl_3$); Krieger, P. E.; Landgrebe, J. A. *J. Org. Chem.* **1978**, *43*, 4447–4452; (1*R*,2*R*)-**3b**: $[\alpha]_D^{20}=-227.5$ (*c* 2.7, $CHCl_3$); literature value for enantiopure (1*S*,2*S*)-**3b**: $[\alpha]_D^{20}=311.7$ (*c* 2.7, $CHCl_3$); Scholl, B.; Hansen, H.-J. *Helv. Chim. Acta* **1986**, *69*, 1936–1958; **3c**: $[\alpha]_D^{20}=-146.5$ (*c* 1.14, $CHCl_3$); IR (neat) *v* 3064, 3032, 2954, 1722, 1605, 1497, 1456, 1406, 1324, 1264, 1166, 753, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.25 (m, 7H), 7.23–7.19 (m, 1H), 7.13–7.07 (m, 2H), 5.17 (d, 1.7 Hz, 2H), 2.61–2.53 (m, 1H), 2.02–1.94 (m, 1H), 1.69–1.61 (m, 1H), 1.39–1.31 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.7, 140.3, 136.3, 129.0, 128.9, 128.7, 128.6, 126.9, 126.6, 67.0, 26.8, 24.5, 17.7. Anal. calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.72; H, 6.78%; **3d**: $[\alpha]_D^{20}=-240.0$ (*c* 0.74, $CHCl_3$); IR (neat) *v* 3062, 3030, 1742, 1592, 1493, 1457, 1400, 1339, 1196, 1161, 1137, 934, 751, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.09 (m, 10H), 2.75–2.66 (m, 1H), 2.21–2.13 (m, 1H), 1.82–1.73 (m, 1H), 1.53–1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 151.2, 140.1, 129.8, 129.0, 127.1, 126.7, 126.2, 121.9, 27.5, 24.5, 18.2; HRMS (MAB) calcd for $C_{16}H_{14}O_2$ $[M]^+$: 238.0994, found 238.1006; **3e**: $[\alpha]_D^{20}=-175.1$ (*c* 1.32, $CHCl_3$); IR (neat) *v* 2980, 2938, 1720, 1606, 1458, 1407, 1321, 1269, 1189, 1108, 755, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.26 (m, 2H), 7.24–7.18 (m, 1H), 7.14–7.08 (m, 2H), 5.06 (h, $J=6.27$ Hz, 1H), 2.55–2.48 (m, 1H), 1.93–1.86 (m, 1H), 1.65–1.56 (m, 1H), 1.34–1.29 (m, 1H), 1.29–1.24 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 140.7, 128.9, 126.8, 126.53, 126.52, 68.4, 26.4, 24.9, 22.3, 17.6; HRMS (MAB) calcd for $C_{13}H_{16}O_2$ $[M]^+$: 204.1150, found 204.1151; **3f** and **3g**: Beres, J. A.; Crouch, R. D., Jr. *Org. Prep. Proced. Int.* **1988**, 187–191; **3h**: Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssié, P. *J. Org. Chem.* **1980**, *45*, 695–702.
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^{13}C NMR (75 MHz, $CDCl_3$) δ 166.8, 142.2, 128.5, 127.4, 126.5, 75.3, 69.3, 18.3, 15.7; LRMS (APCI, Pos) calcd for $C_{21}H_{20}N_2O_2$: 332.15, found 333.2; **1g**: Burgette, M. I.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Herrerias, C. I.; Luis, S. V.; Mayoral, J. A. *J. Org. Chem.* **2001**, *66*, 8893–8901. **1b**, **1c** and **1e** are commercially available.

17. Since catalysts **1c** and **1f** exhibited similar reactivity and enantioselectivity, **1c** was chosen as the optimal catalyst because it is commercially available.
18. Chiral 1-aminoindan-2-ol derived bis(oxazolines) were also tested and exhibited very low reactivity.
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20. Other copper salts were tested and found to be inactive under our reaction conditions: $CuSO_4$, $Cu(BF_4)_2{\cdot}xH_2O$, $Cu(OAc)_2$, $CuCl_2$, CuF_2, CuCN, CuI and CuBr.
21. **2d**: IR (neat) ν 3060, 1723, 1635, 1484, 1305, 1140, 971, 761, 679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J=16.0 Hz, 1H), 7.66–7.58 (m, 2H), 7.49–7.39 (m, 5H), 7.32–7.25 (m, 1H), 7.23–7.17 (m, 2H), 6.67 (d, J=16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 151.2, 147.0, 134.6, 131.1, 129.9, 129.4, 128.7, 126.2, 122.1, 117.7. Anal. calcd for $C_{15}H_{12}O_2$: C, 80.34; H, 5.39. Found: C, 80.63; H, 5.57%; **2a**, **2b**, **2c** and **2e** are commercially available.
22. For an example of electronic effects in catalytic asymmetric reactions, see: Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948–954.
23. **2f** is commercially available; **2g**: IR (neat) ν 3060, 3027, 2919, 2840, 1703, 1631, 1605, 1434, 1316, 1190, 1167, 998, 815 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J=16.0 Hz, 1H), 7.43 (d, J=8.1 Hz, 2H), 7.20 (d, J=8.1 Hz, 2H), 6.41 (d, J=16.0 Hz, 1H), 3.81 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 145.3, 141.1, 132.0, 130.0, 128.5, 117.1, 52.1, 21.9. Anal. calcd for $C_{11}H_{12}O_2$: C, 74.98; H, 6.86. Found: C, 75.36; H, 7.27%; **2h**: IR (neat) ν 3036, 3002, 2951, 2835, 1703, 1633, 1590, 1566, 1489, 1431, 1313, 1191, 1167, 1003, 830, 818 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J=16.0 Hz, 1H), 7.49–7.43 (m, 2H), 7.39–7.33 (m, 2H), 6.42 (d, J=16.0 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 143.2, 136.0, 132.7, 129.1, 129.0, 118.2, 51.6; Anal. calcd for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.91; H, 4.33; N, 6.59%.
24. The best correlation is obtained when the σ+ set of values is used (over σ- and σ_p) since the reaction center is electron rich and directly conjugated with the *para*-substituent imparting the electronic characteristics of the alkene.
25. Other possible mechanistic pathways include: diazomethane attack onto the complexed alkene or [2+2] cycloaddition of copper carbene and the alkene.[1,5] The diastereoselective [3+2] cycloaddition of diazomethane to alkenes is also known, forming pyrazolines which can be decomposed to cyclopropanes with heat or irradiation. For recent examples, see: (a) Rife, J.; Ortuno, R. M. *Tetrahedron: Asymmetry* **1999**, *10*, 4245–4260; (b) Muray, E.; Alvarez-Larena, A.; Piniella, J. F.; Branchadell, V.; Ortuno, R. M. *J. Org. Chem.* **2000**, *65*, 388–396. Under our reaction conditions, without catalyst, formation of pyrazolines does not occur and the starting alkene is recuperated quantitatively. Formation of the pyrazoline and subsequent cyclopropane under lewis acidic conditions cannot be excluded as mechanistic possibilities although no enantioselective examples have been reported.
26. Under a dry argon atmosphere, $CuOTf{\cdot}0.5PhCH_3$ (14 mg, 0.055 mmol) and ligand **1c** (19 mg, 0.056 mmol) are weighed in the reaction flask which was then fitted with a septum. Dichloromethane (5 mL) was added forming a brown suspension that was magnetically stirred at room temperature for 60 min at which point the reaction mixture was a clear green solution. Alkene **2a** (178 mg, 1.098 mmol) was then added as a solution in dichloromethane (5 mL) and the solution was cooled to −40°C (bath temp.). An argon flow was then passed over a cooled (0°C, bath temp.) diazomethane (CAUTION)[12] solution in dichloromethane ($\approx$0.4 M) and directed into the reaction mixture via a Teflon canula (if the yellow coloration of the diazomethane solution subdues, more should be added). After 5–15 min, the reaction mixture became clear pale yellow and diazomethane bubbling was continued for 5 h. The reaction mixture was filtered through a pad of silica gel that was subsequently rinsed with ethyl acetate (50 mL) and volatiles were removed under reduced pressure. The crude product was dissolved in dichloromethane (30 mL) and cooled to −78°C (bath temp.) upon which it is treated with ozone until the solution was blue. Oxygen was then bubbled into the solution until the blue color had subdued (5 min) then methyl sulfide (1 mL) was added at −78°C (bath temp.) and left to warm to room temperature. Volatiles were removed under reduced pressure and the residue was purified by column chromatography using silica gel and 10% ethyl acetate/hexanes as eluent. Compound **3a** was obtained (155 mg) as a clear oil (80% yield, 72% e.e.). E.e.s were determined using GC (cyclodex G, H_2 26 psi, 120°C isotherm, enantiomers: 14.20 and 14.43 min); $[\alpha]_D^{20}=-238.1$ (*c* 1.24, $CHCl_3$).