# Bis(oxazoline)–Copper Complexes as Chiral Catalysts for the Enantioselective Aziridination of Olefins

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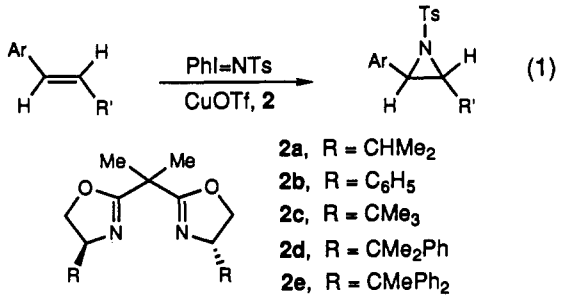
A recent study from this laboratory suggests that soluble copper complexes are the metal catalysts of choice[2] in the aziridination of olefins with (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane, PhI=NTs (**1**).[3] Preliminary evidence also indicates that chiral 4,4′-disubstituted bis(oxazolines), which are excellent ligands for the copper-catalyzed cyclopropanation of olefins, might also be effective in enantioselective aziridination reactions.[4,5] The purpose of this communication is to report our interim studies directed toward the development of this enantioselective process.

Our initial results demonstrate that copper complexes of bis(oxazolines) **2a–e** are efficient catalysts for the asymmetric aziridination of olefins (eq 1). We report here our evaluation of




ligand architecture, medium effects, and metal sources that has led to the development of an efficient enantioselective copper-catalyzed aziridination reaction. Aryl-substituted olefins have been found to be particularly suitable substrates which can be efficiently transformed to *N*-tosylaziridines with enantioselectivities up to 97% ee. Optimized reaction conditions are summarized in Table I for representative substrates. Reactions were carried out employing the alkene as the limiting reagent (2.5 mmol) in the presence of 2 equiv of PhI=NTs[6] **1** and 5 mol % of the catalyst derived from Cu(I) triflate (CuOTf) and the indicated bis(oxazoline) ligand **2**.

Cinnamate esters have been the most synthetically useful substrate class investigated to date. With this family of substrates, the phenyl-substituted ligand **2b** proved to be superior to the more sterically demanding *tert*-butyl analog **2c** (entries 1 and 2). As we have previously noted,[2] there are substantial solvent effects in these reactions, and for the cinnamate esters, reactions carried out in benzene are significantly more enantioselective than those conducted in polar and Lewis basic media (entry 3 vs 2). The low yields that were initially obtained in benzene (~25%) increase markedly when reactions are conducted in the presence of 4-Å molecular sieves.[7] The steric requirements of the cinnamate ester moiety (R″) appear to exert little influence on either the yield or the selectivity of the reaction (entries 3–5). In addition, aryl substituents other than the phenyl group may be employed without alteration of reaction selectivity. For example, highly enantioselective aziridination of both α- and β-3-(naphthyl)acrylate methyl ester derivatives may be realized (entries 6 and 7).

*The optimal conditions identified for the aziridination of the cinnamate esters cannot be reliably extrapolated to other olefinic substrates.* For example, in the aziridination of *trans*-β-methylstyrene, reaction enantioselectivity was found to increase with increasing solvent polarity and donor strength. Reactions carried out with the Cu–**2c** catalyst in MeCN (53% ee, 23 °C) afforded higher enantioselectivity than those carried out in $CH_2Cl_2$ (33% ee, 0 °C) or benzene (15% ee, 23 °C). Furthermore, with solvent and temperature held constant (MeCN, 0 °C), a nearly linear correlation between the enantioselectivity and the *A* value of ligand substituent (R) was observed (**2a**, 21% ee; **2b**, 36% ee; and **2c**, 54% ee). The beneficial effect of increased steric bulk is limited, however, and reaction enantioselectivity decreases when ligand **2d** is employed (38% ee, entry 9). Stereocontrol may be further improved for cases using ligand **2c** by reducing the reaction temperature (–20 °C, 70% ee, entry 8) although rates are significantly retarded.

In the case of styrene,[8] reaction enantioselectivity was also found to be directly related to the steric bulk of the ligand substituent (R) but inversely dependent on solvent polarity and donicity. When carried out in styrene as solvent, reaction enantioselectivity increased as the ligand was varied from **2a** (26% ee) to **2c** (63% ee, entry 10). Further increases in the steric requirements of the ligand substituent (R) diminished enantioselectivity (**2e**, 0 °C, 30% ee, 89% yield). These results are to be contrasted with a recent report with a related catalyst.[9] Stereocontrol increased with other reaction parameters held constant as the solvent was varied from MeCN (6% ee) to $CH_2Cl_2$ (36% ee) and benzene (57% ee). When the reaction was run in neat styrene, the highest enantioselectivity was observed (63% ee, entry 10). It is noteworthy that the absolute configuration of the phenyl-bearing carbon in **8**(*R*) was opposite to those derived from the *trans*-disubstituted olefins with the same catalyst configuration.

Both CuOTf and $Cu(OTf)_2$ can be employed in the formation of competent catalysts, and similar enantioselectivities were observed for reactions involving the illustrated substrates when the two copper triflate complexes were compared. At the present time we speculate that copper is functioning as a catalyst in the 2+ oxidation state.[10] These observations stand in contrast to the asymmetric cyclopropanation reaction in which Cu(II)–bis(oxazoline) complexes are catalytically inactive.[4a] Finally,

(1) (a) Eli Lilly predoctoral fellow. (b) NIH postdoctoral fellow. (c) NSF Predoctoral Fellow.

(2) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744–6746.

(3) For related catalytic aziridination reactions, see: (a) Kwart, H.; Khan, A. A. *J. Am. Chem. Soc.* **1967**, *89*, 1951–1953. (b) Mansuy, D.; Mahy, J-P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161–1163. (c) Mahy, J-P.; Bedi, G.; Battioni, P.; Mansuy, D. *Tetrahedron Lett.* **1988**, *29*, 1927–1930. (d) Mahy, J-P.; Bedi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc., Perkin Trans. II* **1988**, 1517–1524.

(4) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726–728. (b) Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005–6008.

(5) For catalysis with chiral Mn(salen) complexes, see: O'Connor, K. J.; Wey, S.-J.; Burrows, C. J. *Tetrahedron Lett.* **1992**, *33*, 1001–1004.

(6) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361–362.

(7) For the impact of molecular sieves on other catalytic processes see: Tottie, L.; Baeckström, P.; Moberg, C.; Tegenfeldt, J.; Heumann, A. *J. Org. Chem.* **1992**, *57*, 6579–6587.

(8) Unless otherwise indicated, excess styrene was employed (5 equiv) and **1** served as the limiting reagent. The absolute configuration of **8**(*R*) was secured by independent synthesis from 2-(R)-phenylglycinol.

(9) Lowenthal, R. E.; Masamune, S. *Tetrahedron Lett.* **1991**, *32*, 7373–7376. This study includes a footnote stating that the complex derived from *ent*-**3** and CuOTf affords the styrene-derived aziridine **8** in 88% ee (91% yield). We have been unable to reproduce these results. For example, under the following conditions (5 mol % **3**, 5 mol % CuOTf, $CH_2Cl_2$, 0 °C, 24 h), aziridine **8**(*R*) was obtained in 35% ee and 71% yield.

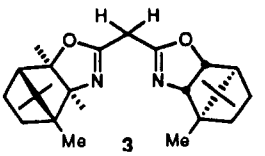



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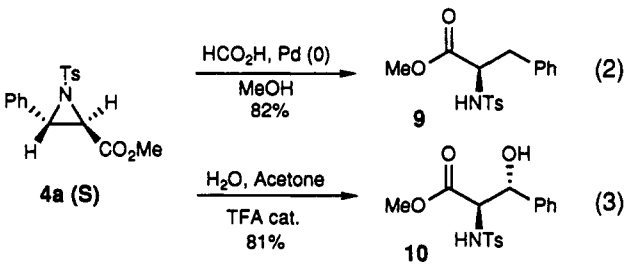
**Table I.** Enantioselective Aziridination of Representative Olefins (eq 1)

| entry | olefin | catalyst[a] | solvent | time (temp) | Yield, %[b] | ee, %[c] | Product[d] |
|---|---|---|---|---|---|---|---|
| 1 | Ph, $CO_2R''$ | **2c** (R = $CMe_3$) | MeCN | 24 h (21 °C) | 16 | 19 | **4a** (S) |
| 2 | R'' = Me | **2b** (R = Ph) | MeCN | 24 h (21 °C) | 21 | 70 | **4a** (S) |
| 3 | | **2b** (R = Ph) | $C_6H_6$[e] | 24 h (21 °C) | 63 | 94 | **4a** (S) |
| 4 | R'' = Ph | **2b** (R = Ph) | $C_6H_6$[e] | 24 h (21 °C) | 64 | 97 | **4b** (S) |
| 5 | R'' = $CMe_3$ | **2b** (R = Ph) | $C_6H_6$[e] | 24 h (21 °C) | 60 | 96 | **4c** (S) |
| 6 | (β)Nap, $CO_2Me$ | **2b** (R = Ph) | $C_6H_6$[e] | 24 h (18 °C) | 73 | 96 | **5** (S) |
| 7 | (α)Nap, $CO_2Me$ | **2b** (R = Ph) | $C_6H_6$[e] | 24 h (21 °C) | 76 | 95 | **6** (S) |
| 8 | Ph, Me | **2c** (R = $CMe_3$) | MeCN | 3d (-20 °C) | 62 | 70 | **7** (S) |
| 9 | | **2d** (R = $CMe_2Ph$) | MeCN | 24 h (0 °C) | 56 | 38 | **7** (S) |
| 10 | Ph, H | **2c** (R = $CMe_3$) | styrene | 2.5 h (0 °C) | 89 | 63 | **8** (R) |

[a] Reactions were performed in the indicated solvent (~0.2 M) with 6 mol % ligand and 5 mol % CuOTf. In entries 1–8, the olefin was selected as the limiting reactant wherein 2.0 equiv of **1** was employed. In entries 9–10, reactions were run in excess olefin with **1** as the limiting reactant.[b] Values represent isolated yields of aziridine based on the defined limiting reagent. [c] Enantiomeric excesses of **4–7** determined by $^1$H-NMR chiral shift reagents, while **8** was determined by chiral HPLC. [d] Absolute configurations of the products are as illustrated. The descriptors (*S*)/(*R*) denote the configuration at the phenyl-bearing stereocenters in **4–8**. [e] 4-Å molecular sieves were employed in each of the indicated experiments.

reactions mediated by bis(oxazoline) complexes of CuCl and CuBr are prohibitively slow and poorly enantioselective. It thus appears that highly electronegative counterions are a design prerequisite for efficient asymmetric catalysis. We have noted similar counterion effects in copper-catalyzed cyclopropanation.[4a]

A concurrent investigation has examined the utility of *N*-tosylaziridines. Accordingly, reductive ring opening of **4a** by transfer hydrogenation[11] (eq 2) afforded the corresponding 2-(*R*)-phenylalanine derivative **9** which was employed to establish the absolute stereochemical assignment of its aziridine precursor. The production of phenylalanine derivatives made available in this study complements existing catalytic methods[12] since the aziridines are generally useful carbon electrophiles which may be employed for further functionalization.[13] This is demonstrated by the acid-catalyzed hydrolysis of **4a** (eq 3) to yield the β-hydroxy-α-amino ester **10** as an 88:12 mixture of diastereomers.




Efforts to extend the scope of this process to other synthetically useful substrates are currently underway.

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**Supplementary Material Available:** Experimental procedures and spectral data for all compounds (6 pages). Ordering information is given on any current masthead page.

(10) Treatment of an acetonitrile solution of CuOTf in the presence of **2c** (1.1 equiv) with **1** (2 equiv) generates a copper species that is spectroscopically indistinguishable (UV–vis) from one which is generated by an identical protocol from $Cu(OTf)_2$. It thus appears that a similar catalytically effective metal complex is accessible from either oxidation state. We speculate that **1** is functioning as an oxidant.

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(12) Other methods include asymmetric hydrogenation, see: (a) Ikariya, T.; Ishii, Y.; Kawano, H.; Arai, T.; Saburi, M.; Yoshikawa, S.; Akutagawa, S. *J. Chem. Soc., Chem. Commun.* **1985**, 922–924. (b) James, B. R.; Pacheco, A.; Rettig, S. J.; Thorburn, I. S.; Ball, R. G.; Ibers, J. A. *J. Mol. Catal.* **1987**, *41*, 147–161.

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