Communications

The Unique Behavior of a Chiral Binaphthyl Oxazoline in the Presence of Cu(I) and Its Role as a Chiral Catalyst

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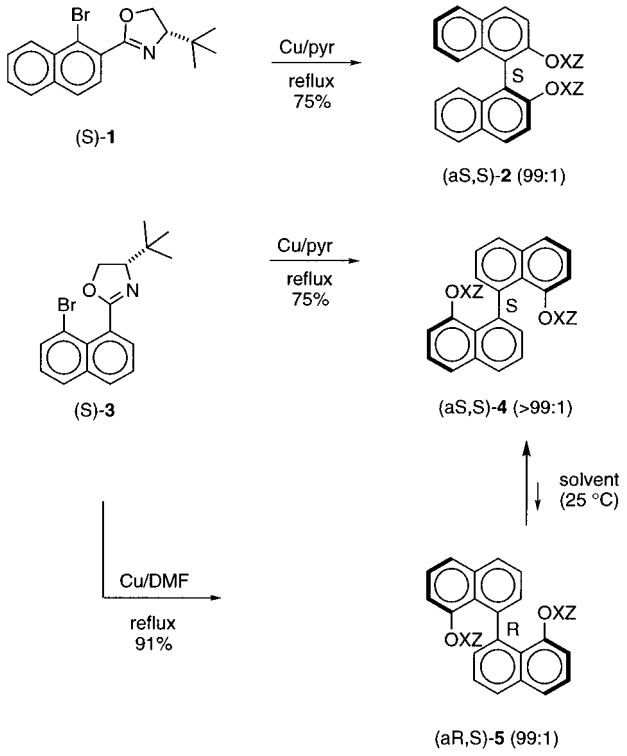
We have been engaged for several years in the acquisition of chiral binaphthyls from the Ullmann coupling of 1-bromo-2-oxazolinylnaphthalenes **1**[1] and 8-bromo-1-oxazolinylnaphthalenes **3**.[2] In both cases, the binaphthyl coupling products **2** and **4**, respectively, were obtained in high diastereoselectivity (>99%).[1,2] In view of the large effort expended by a



number of laboratories to utilize chiral binaphthyls, mainly of the type depicted by **2**, as chiral catalysts, we have focused our recent attention on the more rarely studied[4] 1,1′,8,8′-systems, **4**. In our recent preliminary report,[2] we showed that the chiral bromo derivative **3** gave, upon heating in refluxing pyridine containing activated copper powder, the single diastereomer (a*S*,*S*)-**4** which was quite stable to atropisomerism, even after heating for prolonged periods. Surprisingly, heating **4** for 24 h at 145 °C gave a mixture of **4** and **5** in a 75:25 ratio, only to return to **4** upon standing at room temperature. An X-ray structure[2] of **4** showed that configuration (Scheme 1, **4A**) preferred to have both naphthalene rings at 68° and the oxazolines almost orthoganol to the naphthalenes. The oxazoline rings did not appear to show any rotation about the connecting C−C bond (Scheme 1A, bond a), for this would place the *tert*-butyl groups into the π-face of the naphthalene rings. Since the 3:1 mixture of **4**:**5** returns to >98% **4** at room temperature, this supports the earlier report[5] that the activation barrier to atropisomerization of many 1,1′,8,8′-binaphthyls is rather low. This is especially so when sp^2 substituents are present at the 8,8′ position. The barrier is much higher with sp^3 substituents OH and OMe, since they present greater volume during the rotation, and these derivatives have indeed been resolved into enantiomers.[6−8] Fuji[4] also reported facile atropisomerization in similar systems containing phosphorus substituents and attributes the behavior to distortion from planarity in the naphthalene rings, which was confirmed by X-ray data. Careful examination of the X-ray structure of **4**[2] showed no such distortion in the naphthalene rings so the stability of **4** as the only atropisomer at room temperature must be due to other factors (vide supra).

Although the low barrier to rotation in **4** to **5** may preclude its use as a chiral catalyst, we still felt further study was necessary. We were surprised to learn that when the Ullmann coupling was performed in DMF in place of pyridine, **the sole product** obtained was the a*R*-atropisomer **5**, with none of the a*S*-derivative detectable by NMR.[2] When the copper salts were removed on workup, the a*R*-atropisomer was stable as a crystalline solid at room temperature for several hours and indefinitely at −20 °C. However, when dissolved in various solvents at room temperature, it was rapidly and completely transformed back to the a*S*-isomer **4**. Of most interest was the ability to transform **4** back to **5** only after heating a DMF solution to 90−100 °C containing 1.0 equiv of CuBr. A solution of the copper complex of **5** in $CDCl_3$ at room temperature was also found to be stable to atropisomerization indefinitely.

The reasons for this behavior are now more clearly revealed in light of these data. For example, when **1** was transformed into **2**, only the a*S*-atropisomer was formed, and this was explained earlier[1] by assuming the Cu was holding the two ligands (oxazoline nitrogen) in a manner that minimized all nonbonded interactions. Furthermore, the barrier for aryl−aryl rotation in **2** is very high so the kinetically controlled product was the only one formed and isolated. In the present case of naphthyloxazoline **3**, when the coupling is carried out in pyridine, we were surprised to find that **4** and not **5** was the product, even though the latter is capable of readily forming a bidentate oxazoline complex to copper. We, therefore, attributed the formation of **4** to buttressing of the *tert*-butyl groups.[1] In light of the present results, pyridine may compete with the oxazolines for the copper ion (*R*-configuration). In the absence of copper ion, **5** can suffer lone-pair repulsion from both oxazoline nitrogens, resulting in atropisomerization to **4A**. On the other hand, using DMF to couple **3**, the kinetically formed

(1) Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2655.
(2) Meyers, A. I.; McKennon, M. J. *Tetrahedron Lett.* **1995**, *36*, 5869.
(3) For recent reviews see: (a) Rossini, C.; Fannzini, L.; Raffaelli, A.; Salvadori, P. *Synthesis* **1992**, 503. (b) Narasaka, K. *Synthesis* **1991**, 1. (c) Tomioka, K. *Synthesis* **1990**, 541.
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(5) Harris, M. M.; Patel, P. K.; Korp, J. D.; Bernal, I. *J. Chem. Soc., Perkin Trans. 2* **1981**, *12*, 1621 and earlier references cited.
(6) Fabbri, D.; Delogu, G.; DeLucchi, O. *J. Org. Chem.* **1995**, *60*, 6599.
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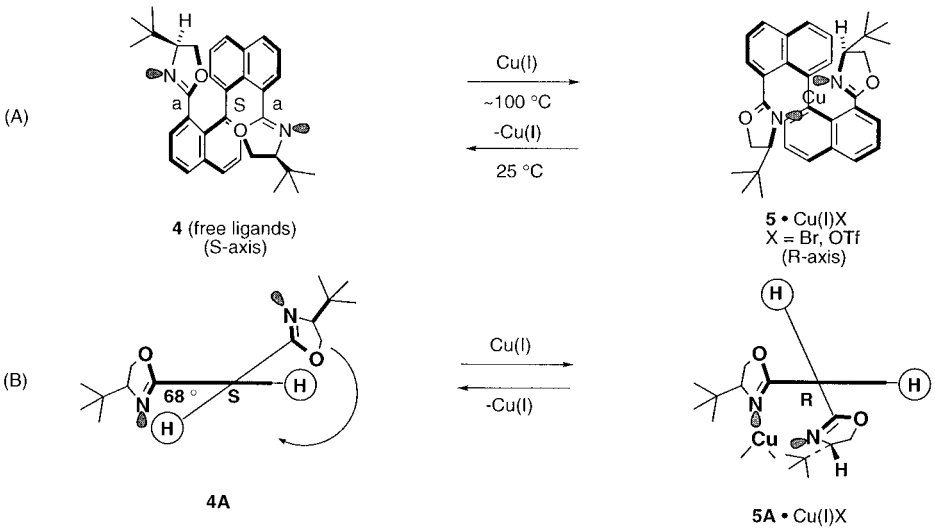
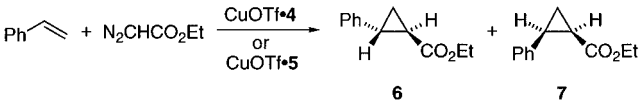
Scheme 1. (A) a*S*-Binaphthyloxazoline without Cu Complex (4) and a*R*-"Configuration" with Cu-Inserted (5). (B) Same, but Simplified Line Schematic



5A is stable as a copper complex since the DMF cannot compete as a ligand with the oxazolines for the copper ion (Scheme 1). In summary, the atropisomerization of **4** to **5** and its reverse is not due to any specific steric buttressing by the *tert*-butyl groups, but purely to a stereoelectronic effect, namely the lone-pair repulsions in **5** that drive the molecule back to **4** or the copper complexation, which drives **4** to **5**. Therefore, one may safely assume that the metal-free thermodynamic product in this process is **4**, but in DMF solvent, the kinetic product, due to Cu-complexation, is actually **5**.

The question was next posed to determine whether either or both binaphthyl bis-oxazolines would serve as a chiral catalyst. Thus, **4** and **5** were employed as chiral ligands for the well-known[9,10] copper-catalyzed cyclopropanation of styrene using ethyl diazoacetate. The cyclopropanation was carried out in CH_2Cl_2 in the presence of 2 mol % copper(I) catalyst formed at room temperature by in situ mixing of CuOTf·$^1/_2C_6H_6$ and either **4** or **5**. The ratio of trans:cis products where monitored by ^{1}H NMR and the enantiomeric excess of **6** and **7**, were determined by chiral HPLC (Chiracel OB). The complex of **4** and CuOTf gave a 21% yield of



cyclopropane products as a 1:1 mixture of **6** and **7** both showing virtually no enantiomeric excess. However, when **5** was complexed[11] with CuOTf, an unoptimized yield of 76% of cyclopropane products (**6**, **7**) was obtained in a 2:1 ratio. In this instance, (1*R*,2*S*)-**7** was formed in 90% ee and (1*R*,2*R*)-**6** in 67% ee. This result suggests that **5** may form a complex that may be more organized (e.g., bidentate) to enter into the transition state of the cyclopropanation than the copper complex of **4**. Clearly, a 1:1 complex of **4** with Cu(I) would be highly unlikely due to a severe *tert*-butyl-naphthalene interaction. In fact, any attempt to complex the Cu(I) to the two oxazolines in **4** would drive the *tert*-butyl group directly into the face of the naphthalene rings. Because of this, the copper complex of **4** is probably oligomeric or exists as nonspecific aggregates.[11,12]

In summary, this difference in behavior is undoubtedly due to the low barrier to rotation, which will allow a single diastereomer (**4**) to be transformed by heating into an alternate configuration by simple metal coordination. The fact that the two copper forms are separated by a significant energy barrier, such that no interconversion occurs at room temperature, also adds to their utility. Further studies and use of other metals are under investigation, as well as structural information on the copper complexes.

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(9) (a) Ojima, I. *Catalytic Asymmetric Synthesis*; VCH: New York, 1993. (b) Pfaltz, A. *Acc. Chem. Res.* **1993**, *26*, 339. See also: Uozumi, Y.; Kyota, H.; Kishi, E.; Kitayama, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1603.

(10) A recent report (Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745) described the use of chiral biphenyloxazolines as effective Cu-ligands for cyclopropanation.

(11) It is important to recall, as mentioned earlier, that **4** cannot be transformed into **5** unless it is heated to 90−100 °C in the presence of CuBr in DMF. Thus, at room temperature, only a "vague complex" or aggregate is formed between Cu(I) and **4**.

(12) Aggregations of Cu(I)·oxazoline complexes have been reported (Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430).