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The Asymmetric Ullmann Reaction III.[1] Application of a First-Order Asymmetric Transformation to the Synthesis of C_2-Symmetric, Chiral, Non-Racemic Biaryls

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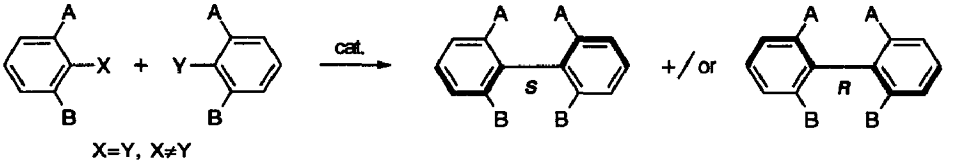
Summary: *Heating a diastereomeric mix of (62:38) chiral biaryls with Cu-ion resulted in a (93:7) mix of diastereomers.*

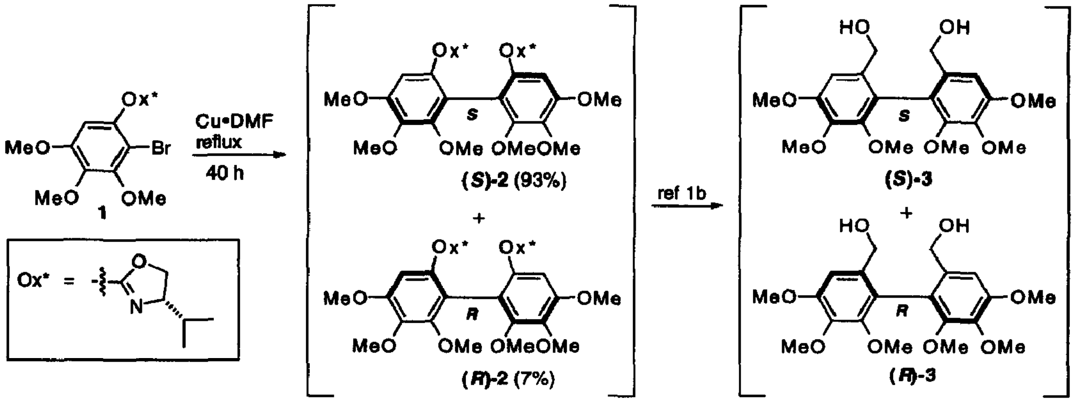
Although considerable effort has been devoted in recent years to the synthesis of chiral, non-racemic, C_2-symmetric biaryls and binaphthyls,[2] the number of general methods that exist to reach them still remain sparse. Enantiomerically pure biaryls and binaphthyls are commonly obtained by some type of aryl-aryl coupling followed by a classical resolution of the resulting atropisomer.[3] In such a process (eq. 1), either A or B must be of suitable functionality so as to allow attachment of a resolving agent. Then, the newly created biaryl diastereomers can be separated by the usual physical means. However, the theoretical yield of the desired homogeneous atropisomer is at best 50 %.



(1)

In general, this limitation also exists for kinetic resolutions, which rely on the specificity and rate of reaction between the two antipodes of the racemate and a chiral, non-racemic reactant. Regardless of how well the resolution proceeds, the maximum yield of enantiomer is still only 50% and ee's of less than 100% are not uncommon. Even in enzymatic resolutions, where the reactant (enzyme) is chemospecific, it is common to obtain less than enantiomerically pure products. The current need for many medicinally important compounds as a single enantiomer has resulted in considerable effort by many laboratories to reach this goal by some process deemed more desirable. This would involve establishing an equilibrium between the two diastereomers such that the undesired one would be converted to the other under the reaction conditions. In this manner, instead of a theoretical yield of 50% of a diastereomerically pure compound, the theoretical yield would be increased two-fold. In other words, a 1:1 mixture would be converted to a diastereomerically enriched or pure product under equilibrating conditions. This process has been referred to as a first-order asymmetric transformation.[4] Stereochemical interconversion of the diastereomeric species, under thermodynamic equilibrating conditions, is necessary to effect such a diastereomeric enhancement. There have only been a few examples of first-order asymmetric transformations reported in the literature in recent years,[5] and we wish to describe another, which has potential to produce a variety of biaryls in a synthetically useful process.

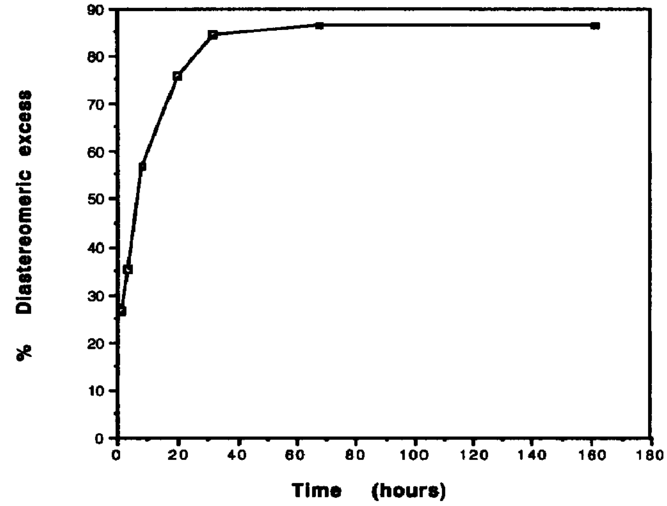
We have recently reported that a chiral oxazoline-mediated Ullmann coupling affords C_2-symmetric biaryls; however, at the time of disclosure it was unclear as to how the asymmetry was induced in this process.[1b] We can now report that a thermodynamically controlled resolution appears to be operative under the reaction conditions so that diastereomerically enriched biaryls are formed (93:7, ***S*:*R*-2**), and may be readily purified to 100% diastereomeric purity. This is the first report of such a protocol affecting "deracemization"[6] of chiral biaryls.



In order to demonstrate that a thermodynamically controlled resolution was responsible for the observed final diastereoselectivity of the intermolecular Ullmann coupling, the diastereomeric ratio of the two atropisomers was monitored over 160 h (Fig. 1). Thus, a flask containing 1.0 g (2.8 mmol) of bromo oxazoline **1**, 10 mL of dry DMF, and 1.7 g of copper powder[7] was heated at reflux and aliquots of the mixture were examined at different time periods. After cooling each aliquot, the mixture was diluted with CH_2Cl_2, washed with aqueous ammonia to remove the copper, dried (Na_2SO_4), filtered, and the solvent removed. Integration of the appropriate portions of the diastereomeric *iso*-propyl resonances in **2** (300 MHz ^1H NMR) afforded a measure (± 5%) of the diastereoselectivity for the process. For a more accurate measure of diasteroselectivity, the crude bis(oxazoline) mixtures were transformed in a three step process to the dicarbinol, **3**, which was assayed by chiral HPLC analysis.[8] Using this technique, the observed enantiomeric ratio of dicarbinol **3** correlated well to the diastereomeric ratio of bis(oxazoline) **2**.

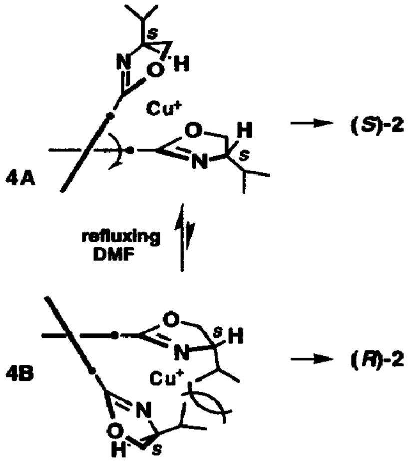
While monitoring the Ullmann coupling, it was found that all of the starting material had been consumed after 1 h and the diastereomeric ratio of the atropisomers **(*S*:*R*)-2** was 62:38. This ratio indicated that there was a stereochemical preference even at the early stages of the coupling. Continuing to heat the mixture at reflux afforded higher ratios (*S*:*R*) of atropisomers with increasing time, until after 40 hours, the diastereomeric mixture of 93:7 (*S*:*R*) remained constant.

Fig. 1 Thermodynamic Equilibrium of Bis(oxazoline) 2



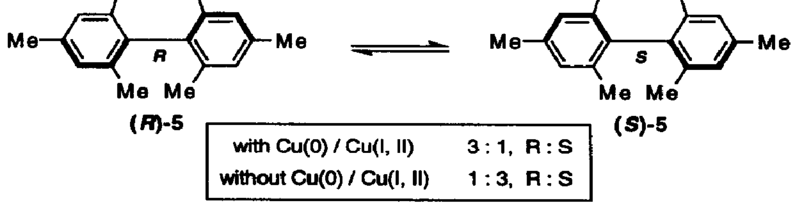
4A

4B



The factors responsible for this reasonably effective first order asymmetric synthesis can be presented with some degree of confidence. First, although the biaryl is tetrasubstituted about the chiral axis, under the reaction conditions (refluxing DMF) rotation is still possible about the biaryl axis. Second, the final diastereomeric ratio may be the result of chelation control utilizing a Cu(I)[9a] and/or Cu(II)[9b] species **4A, 4B** under equilibrating conditions. Thus, although only a small diastereomeric excess was initially observed, the ratio increased steadily until equilibrium for this process was established. The diastereomeric Cu complexes **4A, 4B** indicate how the copper might be complexed between the two oxazoline moieties. Severe non-bonded interactions between the isopropyl groups in **4B** results in the equilibrium being favored to lie towards **4A**, which then led to **(*S*)-2**.

In an attempt to assess the role of the Cu ion, a 3:1 (*R*:*S*) mixture[10] of bis(oxazolines) **(*R*)-5, (*S*)-5**[11] *was heated at reflux (DMF) for 2 d in the absence of any copper catalyst and slowly changed to a 3:1 (S:R) mixture.* Thus, the major atropisomer was now the S-diastereomer, which also appears to confirm that copper was critical to the equilibration leading to the *R*-atropisomer (equivalent to **(*S*)-2** due to a change in priority of the absolute assignment). When



with Cu(0) / Cu(I, II)	3 : 1, R : S
without Cu(0) / Cu(I, II)	1 : 3, R : S

Cu was employed in the mixture of **(*R*)-5**, **(*S*)-5**, no change in ratio was observed, thus suggesting that the chelated species (**4A, 4B**) was involved. Also, the copper species may bring the two oxazoline rings in much closer proximity than they would otherwise be in the absence of copper ion, thus enhancing the severity of the non-bonded interactions seen in **4B**.

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References and Notes

(1) (a) Part 2 "The Asymmetric Ullmann Reaction II. The Synthesis of Enantiomerically Pure C_2-Symmetric Binaphthyls" see: Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994** submitted. (b) For part 1 see: Nelson, T. D.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 3061; (c) another example: "A Rapid Total Synthesis of an Ellagitannin Utilizing an Asymmetric Ullmann Coupling" Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, submitted.

(2) Only a few different methods exist by which to synthesize (save classical resolutions, ref 3) chiral, non-racemic, C_2-symmetric biaryls and binaphthyls. Some reports include: (a) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6989; (b) Moorlag, H.; Meyers, A. I. *Tetrahedron Lett.* **1993**, *34*, 6993; (c) Meyers, A. I.; Meier, A.; Rawson, D. J. *Tetrahedron Lett.* **1992**, *33*, 853; (d) Warshawsky, A. M.; Meyers, A. I. *J. Am. Chem. Soc.* **1990**, *112*, 8090; (e) Smrcina, M.; Poláková, J.; Vyskocil, S.; Kocovsky, P. *J. Org. Chem.* **1993**, *58*, 4534; (f) Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc.* **1988**, *110*, 8153; (g) Brussee, J.; Groeneddijk, J. L. G.; te Koppele, J. M.; Jansen, A. C. A. *Tetrahedron*, **1985**, *41*, 3313; (h) Miyano, S.; Handa, S.; Shimizu, K.; Tagami, K.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1943; (i) Brussee, J.; Jansen, A. C. A. *Tetrahedron Lett.* **1983**, *24*, 3261; (j) Feringa, B.; Wynberg, H. *J. Org. Chem.* **1981**, *46*, 2547; (k) Miyano, S.; Tobita, M.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3522; (l) Bobbitt, J. M.; Noguchi, I.; Yagi, H.; Weisgraber, K. H. *J. Org. Chem.* **1976**, *41*, 845; (m) Feringa, B.; Wynberg, H. *J. Am. Chem. Soc.* **1976**, *98*, 3372; (n) Bobbitt, J. M.; Noguchi, I.; Yagi, H.; Weisgraber, K. H. *J. Am. Chem. Soc.* **1971**, *93*, 3551; For reviews on chiral biaryl synthesis see (o) Bringmann, G.; Walter, R.; Weirich, R. Angew. Chem., Int. Ed. Engl. 1990, 29, 977; (p)Bringmann, G.; Walter, R.; Weirich, R. in *Houben Weyl*, E22, C2; in press.

(3) For example: (a) Takaya, H.; Akutagawa, S.; Noyori, R. *Org. Synth. Coll. Vol. 8*, **1993**, 57; (b) Jacques, J.; Fouquey, C. *Org. Synth. Coll. Vol. 8*, **1993**, 50; (c) Truesdale, L. K. *Org. Synth. Coll. Vol. 8*, **1993**, 57; (d) Kanoh, S.; Hongoh, Y.; Motoi, M.; Suda, H. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1032; (e) Maigrot, N.; Mazaleyrat, J.P. *Synthesis* **1985**, 317; (f) Brown, K. J.; Berry, M. S.; Murdoch, J. R. *J. Org. Chem.* **1985**, *50*, 4345.

(4) Izumi, Y.; Tai, A. *Stereo-differentiating reactions. The Nature of Asymmetric Reactions*; Academic Press: New York, 1977.

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(8) Chiralcel OD column, hexane/2-propanol (85:15), 1.0 mL/min; λ=254 nm, R_t **(*R*)-2** = 13 min; R_t **(*S*)-2** = 18 min.

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(10) Obtained via Cu-mediated Ullmann coupling of the corresponding bromide, which led to an equilibrated final mixture of 75:25.

(11) Only the stereochemical configuration at the biaryl axis is given [i.e. **(*R*)-5**, **(*S*)-5**], omitting stereocenters in the oxazoline moiety.

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