Structural Origins of a Dramatic Variation in Catalyst Efficiency in Enantioselective Alkene Aziridination: Implications for Design of Ligands Based on Chiral Biaryldiamines

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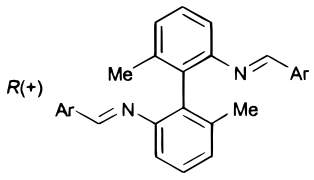
C_2-symmetric biaryl ligands, such as BINAP and its analogues, have found application in many highly enantioselective metal-catalyzed reactions, such as hydrogenation,[1] Diels−Alder addition,[2] and cyclopropanation.[3] The success of these ligands is due not least to the fact that the axial chirality of the ligand is very well expressed in the steric environment of the active site and also that the biaryl unit provides structural rigidity; substrate and reagent are thus brought together at the metal center in highly ordered circumstances. We were thus somewhat surprised at Itoh's observation[4] that diiminobiaryl ligand L^1 in conjunction with Cu^{II} salts gave essentially no enantioselectivity in the catalytic aziridination of alkenes: a reaction which has been moderated by bis(oxazoline)[5] and diiminocyclohexane[6] complexes of the same metal to ee >90%. In this paper we describe the structural basis for this anomalous behavior and the subsequent design of greatly improved catalysts.

A range of ligands L^2−L^7 were synthesized in a straightforward manner by condensation of 2,2′-diamino-6,6′-dimethylbiphenyl[7] and aromatic aldehydes. Reactions of racemic L^2 and L^3 with



L^1 Ar = 2,4-$C_6H_3Cl_2$
L^2 Ar = 4-$C_6H_4Bu^t$
L^3 Ar = 2-naphthyl
L^4 Ar = 2,6-$C_6H_3Cl_2$
L^5 Ar = 2,4,6-$C_6H_2Me_3$
L^6 Ar = 10-anthryl
L^7 Ar = 4-$C_6H_4NO_2$

$[Cu^I(CH_3CN)_4]BF_4$ or with $[\{Cu^IOTf\}_2(C_6H_6)]$ followed by recrystallization from dichloromethane unexpectedly gave complexes containing the ions $[Cu_2L_2]^{2+}$, for example, $[Cu_2(L^2)_2][OTf]_2$ **1** and $[Cu_2(L^3)_2][OTf]_2$ **2**. X-ray crystal structures of both complexes were determined,[8] and the molecular structure of **1** is shown in Figure 1. The two ligands L^2 in each molecular unit have the same relative configuration and form a double-helical array about two linear 2-coordinate Cu^+ centers. Despite this low coordination number[5c] it is clear from space-filling models that the approach of a further ligand would be severely sterically hindered. One of the most striking features of the structure is the presence of close edge−face interactions of the *tert*-butyl phenyl rings, which make a contribution to the stability of the supramolecular structure. The phenomenon of non-covalent interactions between arene rings is well documented,[9] and for edge−face interactions the distances between the two ring centroids are found in the range 4.5−7.0 Å,[10] with a theoretical optimum distance of ∼5.2 Å.[11] In **1** the centroid-centroid distances are .∼4.99 Å. The structure of **2** is similar to that of **1** with the exception that in this case the 2-naphthyl rings are aligned face−face with centroid−centroid distances of ∼3.7−3.8 Å. Again, this appears to be optimum.[11] FAB mass spectra of dichloromethane solutions of these complexes show strong *m*/*z* peaks for the species $[Cu_2L_2][OTf]^+$ and $[Cu_2L_2]^+$, but interestingly no peaks appearing to arise from a species $[CuL]^+$. This suggests very strongly that the major species in solution are the same as those in the solid state, that is, the bimetallics.

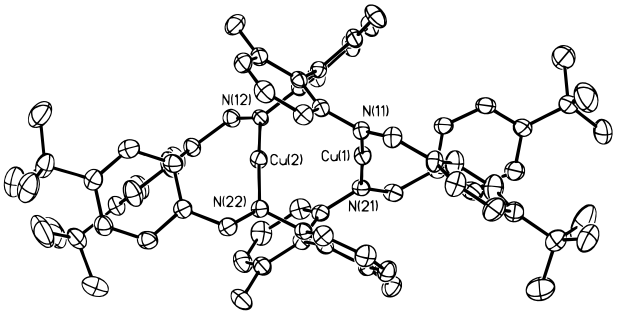


Figure 1. Molecular structure of **1** (hydrogen atoms and triflate counterions omitted). The structure of **2** is closely related (see text).

To reduce the possibility of non-covalent arene−arene interactions and thus promote formation of monomeric complexes,[3a,5,6] proligands with 2,6-disubstituted iminoarene groups were investigated, for example, L^4 and L.[5] The reactions of these compounds with $[Cu(CH_3CN)_4]BF_4$ followed by recrystallization from dichloromethane gave $[Cu(L^4)(CH_3CN)_2]BF_4$ **3** and $[Cu(L^5)(CH_3CN)_2]BF_4$ **4** respectively. X-ray crystal structures of both complexes (e.g., **3**, Figure 2) showed that they adopt monometallic C_2-symmetric structures in the solid state. FAB mass spectra of dichloromethane solutions of these compounds gave no peaks of higher mass than the monometallic molecular ion $[CuL(CH_3CN)_2]^+$. Complexes of L^4 and L^5 derived from $[\{CuOTf\}_2(C_6H_6)]$, that is, $[CuL^4(OTf)]$ and $[CuL^5(OTf)_2]$, behave similarly.

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(1) (a) Takaya, H.; Ohta, T.; Noyori, R. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; VCH: Weinheim, 1993. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley and Sons: New York, 1994.
(2) (a) Corey, E. J.; Imwikelreid, R.; Pikul, S.; Xiang Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493. (b) Chapuis, C.; Jurczak, *Helv. Chim. Acta* **1987**, *70*, 437. (c) Narasaka, K. *Synthesis* **1991**, *1*, 1. (d) Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
(3) (a) Gant, T. G.; Noe, M. C.; Corey, E. J. *Tetrahedron Lett.* **1995**, *36*, 8745. (b) Uozomi, Y.; Kyota, H.; Kishi, E.; Kitayama, K.; Hayashi, T. *Tetrahedron*:*Asymm.* **1996**, *8*, 1603. (c) Suga. H.; Fudo, T.; Ibata, T. *Synlett* **1998**, 933.
(4) Shi, M.; Itoh, N.; Masaki, Y. *J. Chem. Res. M* **1996**, 1946.
(5) (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726. (b) Evans, D. A.; Faul, M. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (c) Evans, D. A.; Woerpel, K. A.; Scott, M. J. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 430. (d) Evans, D. A.; Faul, M. M.; Biodeau, M. T.; Anderson, B. J.; Barnes, D. M. *J. Am. Chem. Soc* **1993**, *115*, 5328.
(6) (a) Li, Z.; Conser, K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1993**, *115*, 5326. (b) Li, Z.; Quan, R. W.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5889. (c) Quan, R. W.; Li, Z.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1996**, *118*, 8156.
(7) Meisenheimer, J.; Horing, M. *Berichte* **1927**, *60*, 1425.
(8) Crystal data for **1**: $C_{75}H_{82}Cl_2Cu_2F_6N_4O_6S_2$, triclinic, *P*1, *a* = 11.4466(6) Å, *b* = 18.1140(9) Å, *c* = 19.5085(6) Å, α = 69.3870(10)°, *β* = 78.2460(10)°, *γ* = 82.4430(10)°, *U* = 3698.7(3) Å^3, *Z* = 2, D_c = 1.357 g cm^{-3}, *T* = 180(2) K, *λ*(M*o* Kα) = 0.71073 Å. Final *R* indices [for 16082 reflections with $I > 2\sigma(I)$]: $R_1 = 0.0536$, $wR_2 = 0.1247$. GOOF on F^2 = 1.070. Crystal data for **3**: $C_{34}H_{26}BCl_8CuF_4N_4$, orthorhombic, *Pbca*, *a* = 13.2095(5) Å, *b* = 23.9347(5) Å, *c* = 25.5398(10) Å, *U* = 8074(5) Å^3, *Z* = 8, D_c = 1.521 g cm^{-3}, *T* = 183(2) K, *λ*(M*o* Kα) = 0.71073 Å. Final *R* indices [for 5276 reflections with $I > 2\sigma(I)$]: $R_1 = 0.0895$, $wR_2 = 0.2640$. GOOF on F^2 = 2.131. Data were collected on a Siemens SMART CCD. The structures were solved by direct methods with additional light atoms found by Fourier methods.
(9) Nishio, M.; Umezawa, Y.; Hirota, M.; Takeuchi, Y. *Tetrahedron* **1995**, *51*, 8665.
(10) Burley, S. K.; Petsko, G. A. *Science* **1985**, *229*, 23.
(11) Jorgenson, W.; Severance, D. L. *J. Am. Chem. Soc.* **1990**, *112*, 4768.

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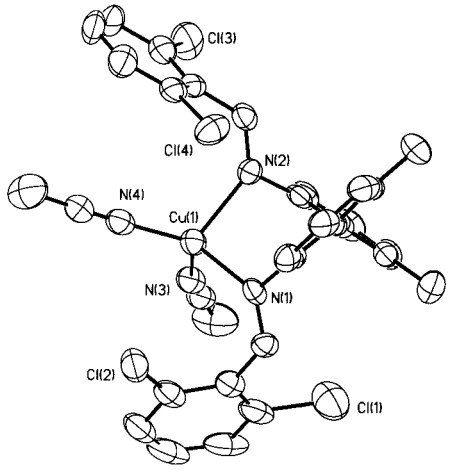

Figure 2. Molecular structure of **3** (hydrogen atoms and triflate counterion omitted). The structure of **4** is very similar.

Scheme 1. Catalytic Enantioselective Synthesis of Aziridine **6**

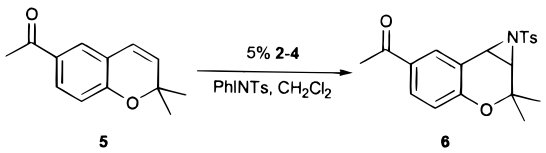

Table 1. Enantioselective Aziridination of Chromene **5**

entry	ligand	Cu source[a]	temp	isolated yield of **6** (%)	time (min)[b]	ee (%)
1	L^2	$[Cu^I(CH_3CN)_4]BF_4$	rt	53	900	13
2	L^3	$[Cu^I(CH_3CN)_4]BF_4$	rt	75	900	16[c]
3	L^4	$[Cu^I(CH_3CN)_4]BF_4$	rt	83	< 10	86
4	L^5	$[Cu^I(CH_3CN)_4]BF_4$	rt	79	< 10	55
5	L^6	$[Cu^I(CH_3CN)_4]BF_4$	rt	56	< 10	65
6	L^7	$[Cu^I(CH_3CN)_4]BF_4$	rt	0	900	-
7	L^4	$[Cu^{II}(CH_3CN)_4][BF_4]_2$	rt	85	<10	85
8	L^4	$[Cu^I(CH_3CN)_4]BF_4$	−40 °C	80	300[d]	94
9	L^4	$[Cu^{II}(CH_3CN)_4][BF_4]_2$	−40 °C	87	300[d]	99

[a] Use of $[(Cu^I_2(OTf)_2].(C_6H_6)$ in place of $[Cu^I(CH_3CN)_4]BF_4$ did not affect the results significantly. [b] Time until all PhINTs had dissolved [c] Opposite enantiomer to other ligand systems [d] The rate of the low temperature reactions is probably limited by the rate of dissolution of PhINTs at −40 °C.

The complexes of chiral non-racemic L^2−L^5 (ee 99.8%) were tested as catalysts for aziridination of the chromene **5** under standard[5d] conditions (Scheme 1, Table 1).[12] In the case of the bimetallic precatalysts **1** and **2**, dissolution of the sparingly soluble trivalent iodinane nitrene source PhINTs[13] was not complete after 900 min, and the enantiomeric excess of the product was, in accordance with Itoh,[4] very poor (entries 1, 2). The monometallic precatalysts **3** and **4** were strikingly more efficient. Dissolution of PhINTs was complete in minutes, isolated yields were good, and the product ee was dramatically improved (entries 3, 4).[14] The ligands L^6 and L^7 are expected on the basis of steric effects to form monometallic and bimetallic complexes, respectively. The corresponding high and low efficiencies were obtained in aziridination (entries 5, 6).[15]

Essentially linear plots were obtained for ee_{ligand} versus $ee_{product}$ for L^2 and L,[4] thus excluding the possibility that some extreme non-linear effect might be responsible for the dramatic variation in catalyst performance.[16] We have also found that the enantiomeric excess of the product obtained does not vary significantly with % conversion. These results are consistent with the presence of a catalyst which contains one ligand only and whose nature does not change during the course of the reaction. In the case of the predominantly bimetallic precatalysts, the low turnover number is probably associated with the fact that the corresponding active monometallic species $[LCu]^+$ is in low concentration.[17]

It remains however that the catalysts giving low rates also give low enantioselectivities. The 2,6-substituents in the most successful ligands (L^3 to L^5) thus appear to have a dual role. First, they discourage the formation of catalytically inactive L_2M_2 bimetallics; an observation that has implications for the design of other ligand systems based on biaryldiamines. Second, they are critically important in determining the steric and electronic profile of the active site and thus the enantioselectivity, perhaps via modulation of substrate−ligand arene−arene interactions.[6c] We note in this context that the most successful ligands in Jacobsen's diiminocyclohexane[6a] and Suga and co-workers' binaphthyldiimine catalysts for cyclopropanation[3c] incorporate 2,6-disubstituted arene groups.

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Supporting Information Available: Complete experimental procedures and characterizing data for all ligands and complexes, chiral HPLC traces for **6**, plots of ee_{ligand} vs $ee_{product}$ for L^2 and L^4 and crystal data for **1**−**4** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) *Typical procedure*: $[Cu(CH_3CN)_4]BF_4$ (0.05 mmol) or $[Cu_2(C_6H_6)][OTf]_2$ (0.025 mmol) were placed in a 25 mL round-bottom flask with proligand (0.055 mmol) and dichloromethane (10 mL) was added under an atmosphere of argon. The mixture was stirred for 10 min before chromene **5** (5.0 mmol) was added. The solution was stirred for a further 20 min before PhINTs (1.0 mmol) was added in one batch. After the specified interval the solution was filtered through a plug of silica gel, and the product was separated from excess chromene using flash chromatography on silica gel using hexane: ethyl acetate (6:1). Enantiomeric excess was readily determined using chiral HPLC (Chiralcel OD).

(13) Södergren, M. J.; Alonso, D. A.; Bedekar, A. V.; Andersson, P. G. *Tettrahedron Lett.* **1997**, *38*, 6897.

(14) Similar variations in efficiency were observed for other alkenes including styrenes and cinnamate esters. For example, L^4/Cu(I) catalyzed the aziridination of *trans*-ethyl cinnamate to *N*-*p*-toluenesulphonyl-2-carboethoxy-3-phenylaziridine in 75% ee and 63% yield (unoptimised) within minutes at room temperature, while L^3/Cu(I) gave 40% ee and 45% yield overnight.

(15) Rates and enantioselectivities in this reaction are not significantly affected by substitution of the Cu(I) sources for Cu(II) e.g., $[Cu^{II}(CH_3CN)_4][BF_4]_2$ (entry 7). See refs 5, 6. Lowering the temperature to −40 °C led to a further improvement in enantioselectivity (entries 8, 9).

(16) Kitamura, M.; Suga, S.; Oka, H.; Noyori, R. *J. Am. Chem. Soc*. **1998**, *120*, 9800.

(17) If a significant proportion of the turnover in the bimetallic systems was being mediated by achiral catalysts arising directly from $[Cu^I(CH_3CN)_4]BF_4$ or $[\{Cu^IOTf\}_2(C_6H_6)]$, we would expect, on the basis of control experiments, the turnover rates to be very much lower. The recent synthesis of soluble PhINTs analogues will allow us to make direct kinetic investigations in this system: Macikenas, D.; Skrzypczak-Jankun, E.; Protasiewicz, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 7164.