Asymmetric Alkene Aziridination with Readily Available Chiral Diimine-Based Catalysts†

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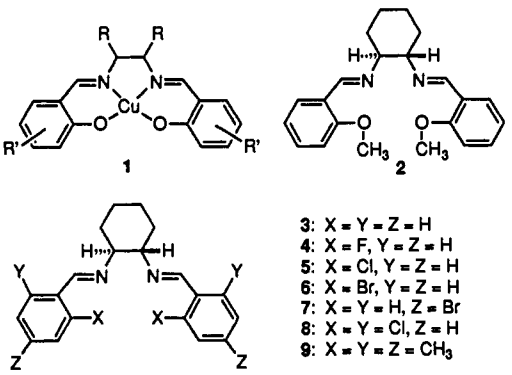
Extensive research in enantioselective atom or group transfer to unfunctionalized alkenes has led to the recent discovery of synthetically useful catalysts for asymmetric dihydroxylation,[1] epoxidation,[2] cyclopropanation,[3] hydrovinylation,[4] hydrosilylation,[5] and hydroboration,[6] as well as the development of promising systems for several other important transformations of alkenes.[7] However, progress in the development of catalysts for enantioselective nitrogen-group transfer to alkenes has been slow, despite the significant utility that such processes would enjoy in organic synthesis.[8] In principle, nitrene-group transfer bears several features in common with oxygen-atom transfer,[9] yet porphyrin- and salen-based systems that are effective for alkene epoxidation have proven to have limited utility as aziridination catalysts, and no enantioselective systems have been uncovered that employ these classes of metal complexes.[10] In this context, it may be significant that, in contrast to epoxidation, there is no known biological model for alkene aziridination. Very recently, Evans and co-workers made the crucial discovery that low-valent copper complexes catalyze the aziridination of various types of olefins by (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs),[11] a result that suggests that an analogy between metal-mediated aziridination and cyclopropanation may be drawn. Indeed, a single observation of enantioselective aziridination of styrene with a chiral bis-oxazoline-based cyclopropanation catalyst was also disclosed by the Evans group,[3d] and Masamune and co-workers subsequently noted a similar result.[3e] We report herein the first full disclosure of a method for enantioselective alkene aziridination, with the discovery that simple benzylidene derivatives of 1,2-diaminocyclohexane serve as excellent ligands for the Cu(I)-catalyzed asymmetric aziridination of olefins by PhI=NTs.

Chart I



Given that complexes of both Cu(I) and Cu(II) are capable of mediating alkene aziridination,[11] and given the recent fruitful application of chiral salen complexes to other types of enantioselective oxidation processes,[2,12] we initially screened a series of (salen)Cu(II) complexes **1** for catalysis of alkene aziridination by PhI=NTs (Chart I). Although copper Schiff base complexes have a venerable history as cyclopropanation catalysts,[13] such systems proved to be uniformly ineffective for mediation of aziridination. Instead, promising results were obtained with *O*-alkylated salen ligands such as **2** in the presence of Cu(I)OTf, with aziridination of 6-cyano-2,2-dimethylchromene (**10**) taking place with enantioselectivities as high as 90%. However, substrate conversion was extremely low, and in no cases could catalyst turnover be induced in the presence of such potentially tetradentate ligands. The failure of (salen)Cu complexes and the preclusion of catalysis with tetradentate neutral ligands indicated that existence of multiple open coordination sites on the copper may be crucial to catalysis of aziridination.

Indeed, catalysis of alkene aziridination was achieved instead with benzylidene derivatives of 1,2-diaminocyclohexane capable only of bidentate chelation to copper (e.g., **3**–**9**). The parent bis-(benzylidenediamino)cyclohexane (**3**), in association with CuOTf, exhibited moderate catalytic activity and enantioselectivity in the aziridination of **10** (8 turnovers, 50% ee) (Table I).[14] Significant improvement in selectivity was observed with substituted bis-benzylidene derivatives, with bis-((2,6-dichlorobenzylidene)diamino)cyclohexane **8** affording best results with regard to both catalysis and enantioselectivity. Comparison of ligands **8** and **9** suggests that for sterically similar substituents, electronic properties have an effect on both catalyst lifetime and selectivity. Derivatives of acyclic diamines such as 1,2-diphenyldiaminoethane were ineffective for enantioselective aziridination, presumably due to the poorer chelating ability of such conformationally

† This paper is respectfully dedicated to our friend and colleague, Professor Peter Beak.

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(14) The procedure for aziridination of **10** with CuOTf·**8** is representative. Under a nitrogen atmosphere, **8** (0.054 mmol, 11 mol %) was added as a solid to a stirred suspension of CuOTf (0.05 mmol, 10 mol %) in CH_2Cl_2 (3 mL) at room temperature. After 1 h, the nearly homogeneous solution was filtered, and the filtrate was transferred to a round-bottom flask and diluted with additional CH_2Cl_2 back to a total volume of 3 mL. Solid olefin **10** (0.5 mmol) was added, and the solution was cooled to −78 °C. Solid PhI=NTs (0.75 mmol, 1.5 equiv) was added against a positive nitrogen counterflow, and the heterogeneous mixture was stirred at −78 °C as the reaction progress was monitored by GC and HPLC. After the reaction progress had ceased, the mixture was filtered through a 2-cm pad of silica with EtOAc, the filtrate was concentrated in vacuo, and the residue was purified by flash chromatography (EtOAc/hexane) to afford pure aziridine as a pale solid (75% yield).

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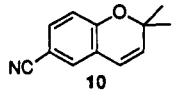
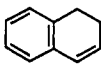
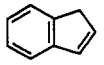
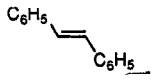
Table I. Asymmetric Aziridination of 6-Cyano-2,2-dimethylchromene Catalyzed by CuOTf in the Presence of Ligands **3–9**[a]

	ligand						
	3	**4**	**5**	**6**	**7**	**8**	**9**
ee (%)[b]	50	64	72	81	42	>98	92
total catalysts turnovers[c]	10	3.6	3.6	8.2	3.6	16	6.1

[a] Reactions were carried out at −78 °C with 5 mol % catalyst following the procedure described in note 14. [b] Determined by HPLC analysis of crude reaction mixtures using a commercial Whelk-O column (Regis). [c] Determined by HPLC analysis of crude reaction mixtures after reaction progress had ceased. In all cases, no significant products other than aziridine were detected.

Table II. Asymmetric Aziridination of Alkenes Catalyzed by (*S,S*)-**8**/CuOTf

substrate	aziridine yield (%)[a]	ee (%)[b]	aziridine config[c]
 **10**	75	>98	(3*R*,4*R*)-(+)
	70	87	(1*R*,2*S*)-(+)
	50	58	(1*R*,2*S*)-(−)
	79	67 (cis)	(1*R*,2*S*)-(−)
	(cis = trans, 3:1) 79	81 (trans) 66	(1*S*,2*S*)-(−) (*R*)-(−)[d]
	nd[e]	30	nd[e]

[a] Reactions were carried out on 0.5 mmol scale of substrate with 10 mol % catalyst; yields are based on alkene and correspond to pure products isolated by flash chromatography (see note 14). [b] All ees were determined by HPLC on a commercial Whelk-O column (Regis). [c] The sign corresponds to that of $[\alpha]_D$. Absolute configurations were established by correlation to the corresponding epoxides, unless otherwise noted. [d] Correlated with (*R*)-(−)-2-phenylglycinol. [e] Not determined.

unrestricted ligands. Ligand **8** was accordingly selected for study with other alkenes, and representative results are summarized in Table II.

Remarkably, the olefins that may be aziridinated with good enantioselectivity fall within the successful substrate pool that has been elucidated for the (salen)Mn-catalyzed epoxidation reaction.[2] In both processes, trans olefins such as stilbene are poor substrates with regard to both selectivity and rate, whereas 2,2-dimethylchromene derivatives undergo oxidation with spectacular levels of selectivity.[15] In addition, oxidation is nonstereospecific in both reactions, with acyclic cis olefins affording mixtures of cis and trans ring products. This nonstereospecificity is certainly partially responsible for the diminished enantioselectivity obtained in the aziridination of styrene, since the trans pathway with such terminal olefins constitutes a mechanism for enantiomeric leakage.[10d]

Beyond these qualitative observations, the mechanism of aziridination by low-valent copper complexes such as those employed in this study remains an open issue. However, the high levels of stereoselectivity achieved with systems such as **8**·CuOTf may provide a powerful new handle for mechanistic analysis. In that context, it was determined that aziridination of **10** with ligand **8** of 50% ee afforded aziridine in 50% ee. Such a linear correlation between ligand ee and product ee indicates that the active oxidant species is a monomer bearing a single chiral ligand.[16]

Chiral diimine ligands such as **3–9** represent previously unstudied yet remarkably simple and potentially versatile templates for asymmetric catalysis. They are less rigid than bisoxazoline or salen ligands, yet they are clearly capable of highly effective stereochemical communication in a metal-mediated process. Their synthetic accessibility renders them amenable to systematic variation of both steric and electronic properties, and our current efforts are directed toward refinement of the aziridination process and application of these ligands to other metal-catalyzed enantioselective processes.

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Supplementary Material Available: Experimental procedure and physical data for **8** and chromatographic analyses of all racemic and enantiomerically enriched aziridines (7 pages). Ordering information is given on any current masthead page.

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