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Ligand-assisted, copper-catalyzed enantioselective benzylic amination

Dipti N. Barman, Kenneth M. Nicholas *

Department of Chemistry and Biochemistry, University of Oklahoma, Norman, OK 73019, USA

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ABSTRACT

Several classes of ligands, including α-amino acids, diamines, diphosphines, bis-oxazolines, and diimines, support efficient copper-catalyzed amination of benzylic hydrocarbons by anhydrous chloramine-T. Catalysts derived from homochiral ligands, particularly chiral diimines, effect aminosulfonation with low to moderate enantioselectivity.

The synthetic potential of the direct N-functionalization of hydrocarbons has stimulated intense interest in the discovery of transition metal-promoted C–H insertion reactions of nitrenoid precursors with hydrocarbons.[1] Many of the recent developments in this area have focused on benzylic substrates, employing imido-iodinanes (ArI = NTs), chloramine-T (TsNNaCl), or aryl azides as aminating agents in conjunction with various metal catalysts, including those of rhodium,[2] ruthenium,[3] cobalt,[4] manganese,[5] silver,[6] gold,[7] palladium,[8] iron,[9] copper,[10] and zinc.[11] Among these, the reactions catalyzed by dinuclear Rh-complexes are the most developed and can effect intra- and some intermolecular aminations of a variety of activated and non-activated C–H bonds.[2] Progress toward the challenging goal of enantioselective C–H amination has been limited, with the most notable success coming in intramolecular $L^*_2Rh_2$- and Ru(pybox*)-catalyzed reactions,[2c,3c] reagent-based [ArS*(O)(NSO_2Ar)NH_2] Rh-catalyzed intermolecular reactions,[2d] and (salen*)Mn-catalyzed intermolecular reactions of benzylic substrates.[5]

Our group has sought the development of new catalytic amination reactions that employ inexpensive and convenient N-reagents and catalysts.[12] We reported recently that benzylic substrates could be efficiently amidated by inexpensive anhydrous chloramine-T with commercial [$Cu(CH_3CN)_4$]Z as the catalyst.[10d] In order to control catalyst activity and selectivity, for example, to achieve enantioselective C–H aminations, it is necessary to identify ligand partners for the metal center that will support catalysis. Although a number of ligated copper catalysts have been reported for enantioselective olefin aziridination,[13] examples of ligand-assisted catalytic C–H aminations are rare[10b,f] and untested for stereoselectivity. We report herein our findings of L-assisted, Cu-catalyzed oxidative amination reactions and efforts to effect enantioselective variants.

To screen ligands for their effect on the activity of Cu-catalyzed amination, 4-ethylanisole was selected as a test substrate since its amination by chloramine-T (TsNNaCl) catalyzed by 'ligandless' $Cu(CH_3CN)_4PF_6$ (10 mol %) is slow at 20 °C (12 h, CH_3CN, <5% yield of 4-$MeOC_6H_4CH(NHTs)CH_3$ (**1**)). Corresponding reactions were conducted in the presence of representative ligand types under

Table 1
Effect of ligands on the amination of 4-ethylanisole[a]

Ligand	Rxn time (h)	Yield of 1[b] (%)
None	12	5
$P(OMe)_3$	16	68
PPh_3	16	62
$Ph_2PCH_2CH_2PPh_2$	16	66
$Me_2N(CH_2)_2NMe_2$	12	52
Phenanthroline	12	77
S-Proline	12	45
S-Lysine	12	67
S-Histidine	12	67
A1	12	20
A2	12	56
A3	6	74
A4	6	81
A5	6	88

[a] See Ref. 14 for procedure.
[b] Yield determined by NMR integration of reaction mixture; $TsNH_2$ is the only detected by-product.

* Corresponding author. Tel.: +1 405 325 3696; fax: +1 405 325 6511.
E-mail address: knicholas@ou.edu (K.M. Nicholas).

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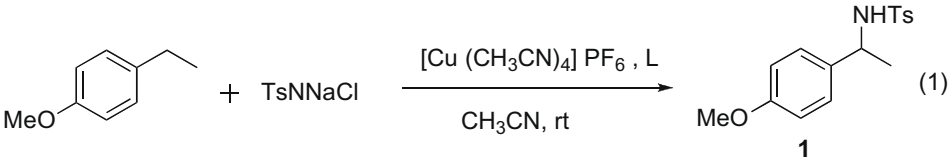
the same conditions (1:1, Eq. 1), including α-amino acids, phosphines, phosphites, diamines, and diimines, and the yield of sulfonamide **1** determined by NMR and/or isolation. The results are summarized in Table 1. Moderate to excellent yields are obtained with several of these ligands, demonstrating ligand-assisted catalysis.[14] The accessibility of diverse diimine ligands from primary diamines and aldehyde building blocks[15] facilitated an assessment of the electronic effects of the ligand on the catalytic activity. Interestingly, the more electron poor the diimine, the higher the reaction rate and yield of **1** (cf. Table 1, **A1–A5**).

Having established the ability of several ligated-Cu systems to effectively catalyze benzylic amination by chloramine-T, homochiral ligands were selected and tested for their ability to effect enantioselective aminations of prochiral benzylic substrates. All reactions were conducted under the previously established conditions with 1:1 L*/Cu. The optical purity of the isolated amination products was assayed polarimetrically and/or by chiral HPLC and the results are shown in Table 3. With 4-ethylanisole as substrate negligible enantioselectivities were observed with the α-amino acid ligands, histidine and proline, however, a low but significant

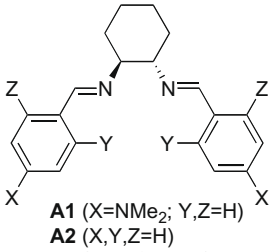


(1)

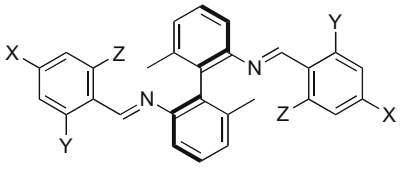
To assess the ligand-assisted reaction's scope a survey of the catalytic amination of a set of representative benzylic substrates was carried out using complexes derived from the nitro-substituted diimine ligands **A5** and **A6**. The reactions were conducted under the same conditions as established for 4-ethylanisole (CH_3CN, rt, 6–12 h, 0.1 equiv $Cu(CH_3CN)_4PF_6$/0.1 equiv L). The results are summarized in Table 2. Several secondary and tertiary benzylic hydrocarbons were thus aminated with moderate efficiency and good regioselectivity, with $TsNH_2$ as the only detected by-product. Catalysts derived from either the mononitro- or dinitro-ligands were comparably effective. The enhanced activity of the diimine-based catalysts was again indicated by the room temperature conversions of the starting material with the former catalysts versus the 60–70 °C required for reactions with $Cu(CH_3CN)_4Z$. More impressively, the saturated substrate adamantane, unreactive to chloramine-T/$[Cu(CH_3CN)_4]Z$ even at 70 °C,[10d] was aminated albeit in modest (unoptimized) yield by the (**A6**)–copper complex.

enantioselectivity was achieved with the chiral phenanthroline **E**.[16] Negligible to low stereoinduction was also found in the reactions employing the diimine ligands derived from 1,2-cyclohexyldiamine (**A5** and **A6**) and from binaphthyldiamine (**C1**). More substantial enantioselectivities were found employing the catalyst derived from the biphenyldiamine ligand **B2**, with 4-ethylanisole, ethylbenzene and indane.

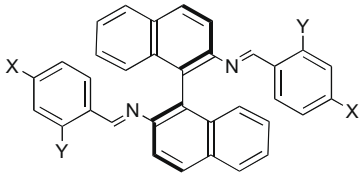
Although the enantioselectivities achieved in the Cu-catalyzed, L-assisted reactions are not synthetically useful, they strongly suggest that a chiral-Cu complex of a –NTs species, at least in part is responsible for the C–H insertion and thus may be improved with more sterically demanding ligands. The modest enantioselectivities observed may reflect ineffective chirality transfer from the ternary LCu–NTs complex and/or a stepwise process for C–H cleavage and C–N bond formation. Preliminary results from a mechanistic study, that is, underway suggest a contribution from the latter. A full report on this study will be forthcoming.



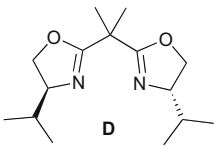
A1 (X=NMe_2; Y,Z=H)
A2 (X,Y,Z=H)
A3 (X,Y=Cl; Z=H)
A4 (X=CF_3; Y,Z=H)
A5 (X=NO_2; Y,Z=H)
A6 (X,Y=NO_2; Z=H)



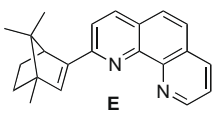
B1 (X=H; Y,Z=NO_2)
B2 (X,Y=NO_2; Y=H)



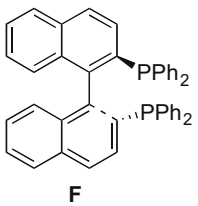
C1 (X,Y=NO_2; Z=H)



D

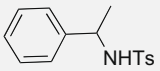
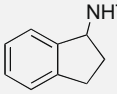
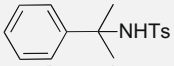
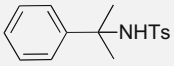
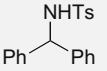
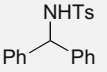
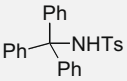
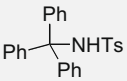
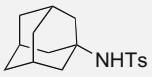


E



F

Table 2
Substrate scope of L-assisted, Cu-catalyzed amination[a]

Substrate	Ligand	Product	Yield[b] (%)
Ethylbenzene	**A6**		68
Indane	**A6**		66
Cumene	**A5**		62
Cumene	**A6**		67
Diphenylmethane	**A5**		64
Diphenylmethane	**A6**		65
Triphenylmethane	**A5**		59
Triphenylmethane	**A6**		62
Adamantane	**A6**		19

[a] See Ref. 14 for procedure.
[b] Isolated yield; by-product is $TsNH_2$.

Table 3
Copper-catalyzed enantioselective amination[a]

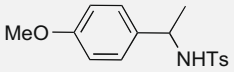
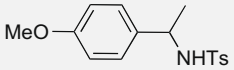
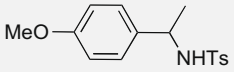
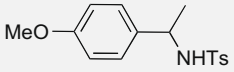
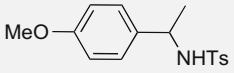
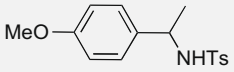
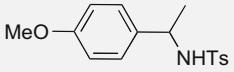
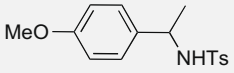
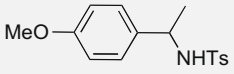
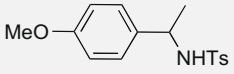
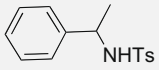
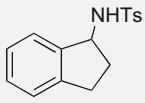
Substrate	Ligand	Product	Yield[b] (%)	ee (%)
4-Ethylanisole	*S*-Histidine		67	3[c]
4-Ethylanisole	*S*-Proline		45	4[c]
4-Ethylanisole	**E**		68	12[c]
4-Ethylanisole	**D**[d]		65	5[c]
4-Ethylanisole	**A5**		88	7[c]
4-Ethylanisole	**A6**		85	4[c]
4-Ethylanisole	**B1**		48	4[c]
4-Ethylanisole	**B1**		84	6[c]
4-Ethylanisole	**B2**		81	39[c], 16[d]
4-Ethylanisole	**C1**		71	5[c]
Ethylbenzene	**B2**		68	22[d]

Table 3 (*continued*)

Substrate	Ligand	Product	Yield[b] (%)	ee (%)
Indane	**F**		55	7[d]
	B2		66	28[d]

[a] See Ref. 14 for procedure.
[b] Isolated yield; by-product is $TsNH_2$.
[c] Determined polarimetrically.
[d] Reaction in 1,2-dichloroethane showed that same yield and enantioselectivity.
[e] Determined by HPLC on Chiralcel OJ column; 15% *i*-PrOH/85% hexane eluant.

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Supplementary data

Supplementary data (procedures and characterizational data for ligands and products) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.118.

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14. *Typical procedure:* Commercial $Cu(CH_3CN)_4PF_6$ (28 mg, 0.073 mmol), the ligand (0.073 mmol), and 5 mL of dry CH_3CN were added to a round-bottomed flask containing dry molecular sieves (4 Å, ca. 200 mg) under argon. To the

well-stirred suspension 4-ethyl anisole (0.10 mL, 0.73 mmol) was added. Anhydrous chloramine-T (vacuum-dried over refluxing toluene; 218 mg, 0.95 mmol) was added after one hour and the mixture was stirred at room temperature overnight. The mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (4:1 hexane/ethyl acetate).

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