

Angular Ligand Constraint Yields an Improved Olefin Aziridination Catalyst

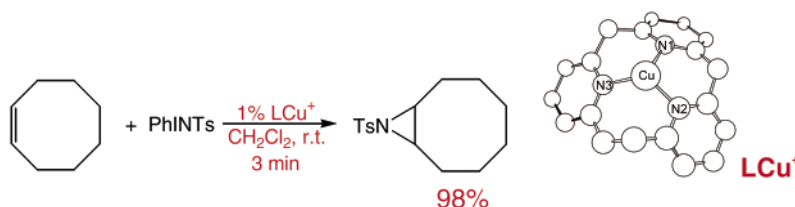
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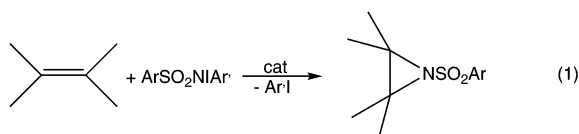
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ABSTRACT



The use of a pyridinophane, a macrocycle composed of three pyridines linked, via all ortho positions through CH₂ or CH₂CH₂ groups, bound to copper, gives good performance (rate and yield) catalyzing the conversion of substituted aliphatic olefins and PhINTs to aziridines. Advantages also derive from using CH₂Cl₂ solvent and the weakly coordinating anions BAR₄[−] (Ar = C₆H₅ or 3,5-C₆H₃(CF₃)₂). Reactions are complete in minutes at 20 °C, and yields are almost quantitative for olefins not bearing secondary allylic CH bonds; however, *cis*-cyclooctene gives only the aziridine despite the allylic hydrogens.

Aziridines serve a significant role as reactive precursors in the synthesis of a variety of polyfunctional compounds with C–N bonds.¹ One of the important routes to aziridines is transition-metal-catalyzed transfer of the nitrene moiety to olefin from a suitable source like ArSO₂NIAr, ArN₃, ArSO₂–NNa(Cl), etc. eq 1:

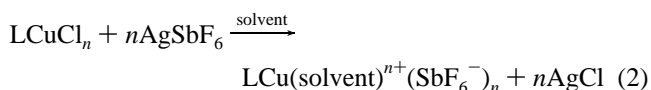


Synthetic interest in aziridines increased after the discovery of simple and inexpensive copper catalysts.^{2–4} Nevertheless copper catalysts have many important limitations such as high catalyst loading (>5%) and poor yields in the case of simple aliphatic olefins.⁵ Limited knowledge of the mech-

anism of the copper-catalyzed aziridination, eq 1, remains a problem that affects the development of better catalytic systems.^{3,6}

In this communication we report a new copper catalyst for olefin aziridination with TsNIPh that allows very fast (2–10 min at 0–20 °C) and often quantitative conversion of simple mono-, di-, tri-, and tetrasubstituted olefins including those with electron-withdrawing groups attached to the C=C bond, together with an examination of the scope and limitations of the catalyst.

Faster ligand substitution is important if catalysis involves coordination of reactants to a metal center. It can be generally achieved by “preparing” the catalytic metal center with only weakly binding ligands, whose role is to be displaced by certain of the reactants in eq 1. One example of this is the removal of halide ligands with a silver salt of a weakly coordinating anion (eq 2):



In the work described here, this will be accomplished by

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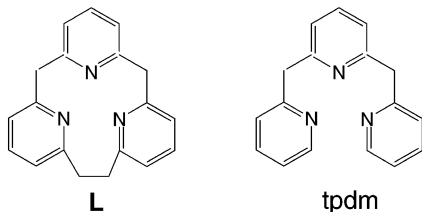
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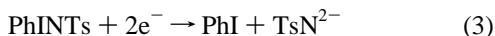
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using less ligating anions BAR_4^- ($\text{Ar} = \text{C}_6\text{H}_5$ or 3,5-bis(CF_3)- C_6H_3). The polar or ionic catalysts employed demand a polar solvent. The commonly employed acetonitrile certainly is a ligand competitive for a metal center with the reactants (eq 1), and so catalysis in the less coordinating dichloromethane is, in principle, anticipated to be preferable.⁷

The work described here tests the above hypothesis but introduces a new potentially facial tridentate ligand, which has been shown to be advantageous for other reactivity objectives^{8–10} based on the fact that the ligand has a constrained distorted 3-fold symmetric character. Thus, the new macrocyclic tripyridine ligand, [2.1.1]-(2,6)-pyridinophane (L), which is readily available from commercial



pyridines,¹¹ has steric and electronic characteristics significantly different from those of “pybox” pincer ligands,⁴ α -diimines,^{12–14} triazacyclononane,^{15–17} and even tris-pyrazolylborates,¹⁸ all of which have been tested for aziridination catalysis on copper. The macrocycle-constrained deviation from 3-fold symmetry makes L poorly suitable for the near-tetrahedral or trigonal planar geometry preferred by d^{10} Cu(I) in the catalyst precursor. The reagent PhINTs commonly employed in aziridination is a two-electron oxidant (eq 3)



and $(\eta^3\text{-L})\text{Cu}^{\text{I}}$ species can be potentially oxidized to Cu(III). Therefore, a constrained ligand, destabilizing the reagent $(\eta^3\text{-L})\text{Cu}^{\text{I}}$, will help in producing $(\text{L})\text{Cu}^{\text{III}}(\text{NTs})^+$ and thus enhances reactivity of $(\eta^3\text{-L})\text{Cu}^{\text{I}}$ toward PhINTs. This destabilization translates hopefully into enhanced catalytic

performance for aziridination.¹⁹ We report here a test of these ideas, including the question of precursor metal oxidation state.

Dichloro (Cu^{II}) and monochloro (Cu^{I}) pyridinophane copper complexes were synthesized in almost quantitative yield by stirring the corresponding anhydrous CuCl_n with equimolar L in benzene. When slurried with NaBAR_4 in $\text{CH}_2\text{-Cl}_2$ at 20 °C, the chloro complexes dissolved to produce the corresponding cationic species, stable for days ($n = 1$, copper(I) complex) or for a few minutes ($n = 2$, copper(II) complex) in the *absence* of substrate. The catalytic activity of both catalysts is shown in Table 1. The enhanced solubility of these catalysts in a weakly coordinating solvent is one of their advantages.

Initial catalytic studies involved 5% catalyst loading (vs PhINTs) and an olefin:PhINTs mole ratio of 3–10 and gave turnover numbers up to 20. Ethylene (entries 1 and 2) reacted slowly and in poor yield, while propylene (entries 3 and 4) and *cis*-2-butene (entries 5 and 6) were much more reactive and converted into the corresponding aziridines in very high yields. Partial loss of stereochemistry (entries 5 and 6) suggests the involvement of an intermediate where the carbon–carbon π -bond is broken. In contrast, substrates with *secondary* allylic CH bonds such as 1-butene, cyclopentene, and cyclohexene (entries 7–12) produced significant amounts of products of α -amination in addition to aziridines. Nevertheless, *cis*-cyclooctene, possessing a weaker and more reactive C=C bond, can be transformed into the corresponding aziridine almost quantitatively (entries 13 and 14). Anticipating that substrates with less reactive primary or no allylic CH bonds might react cleanly, we tried *tert*-butyl-ethylene and tri- and tetramethyl-ethylene (entries 19–24). In all of these cases aziridines were rapidly and quantitatively obtained. Remarkably, electron-poor substrates such as methyl acrylate and methyl methacrylate (entries 25–28) also reacted quantitatively and rapidly.

Using *cis*-cyclooctene as a test substrate, we explored the effect of some variation in catalyst loading and composition on the aziridine yield (entries 13–18). It was found that

(a) Both mono- and dichloro copper-derived catalysts (entries 13 and 14) showed almost indistinguishably high activity. The same result was observed for other substrates listed in Table 1 (compare even and odd entries 1–14, 19–28). This result is consistent with our observation of quantitative stoichiometric oxidation of yellow $(\text{LCu}^{\text{I}})^+$ tetraarylborate by PhINTs into PhI and a deep purple dinuclear copper(II) complex $[(\text{LCu}^{\text{II}})_2\text{NTs}]^{2+}$. The latter is stable in CH_2Cl_2 solution and diamagnetic, so allowing its characterization by ^1H and ^{13}C NMR techniques. Thus, easy oxidation of a Cu^{I} precatalyst to a Cu^{II} compound proves that the catalytic environment is sufficiently oxidizing that no Cu^{I} persists.

(b) We tried 1% catalyst loading and found almost the same performance (entry 15 vs 14). Significant catalyst degradation (evident by color change from reddish to green) prevented further reduction of the amount of catalyst.

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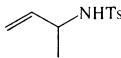
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Table 1. Olefin Aziridination Catalysis with PhINTs, LCuCl_n , and $n\text{NaBAR}_4$ in CH_2Cl_2

entry	substrate (equiv.)	precatalyst: n, amount, mol %	aziridine, % on PhINTs ^a	byproducts, %	t°C / time, min
1	$\text{CH}_2=\text{CH}_2$ (1-10)	I, 1	27		r.t. / 180
2		II, 10	28		r.t. / 5
3	$\text{MeCH}=\text{CH}_2$ (10)	I, 10	90		r.t. / 10
4		II, 10	95		r.t. / 10
5	<i>cis</i> - $\text{MeCH}=\text{CHMe}$ (7)	I, 10	90 (5:1, <i>cis/tr</i>)		r.t. / 10
6		II, 10	93 (5.5:1, <i>cis/tr</i>)		r.t. / 5
7	$\text{CH}_2=\text{CHC}_2\text{H}_5$ (10)	II, 10	64		16 r.t. / 5
8		I, 10	51		16 r.t. / 10
9	Cyclopentene (5)	I, 10	66	α -tosylaminocyclopentene	13 0 / 2
10		II, 10	65		12 0 / 2
11	Cyclohexene (5)	I, 2.5	40	α -tosylaminocyclohexene	28 0 / 2
12		II, 10	32		20 0 / 2
13	<i>cis</i> -Cyclooctene (3)	I, 5	98		r.t. / 5
14		II, 5	98		r.t. / < 1
15		II, 1	98		r.t. / 3
16		II, 5 ^b	80		r.t. / 1
17	<i>cis</i> -Cyclooctene (1)	I, 5	87 ^c		r.t. / < 1
18		I, 1	56 ^c		r.t. / 30
19	<i>t</i> - $\text{BuCH}=\text{CH}_2$ (3)	II, 5	90		0 / 2
20		I, 5	85		0 / 5
21	$\text{MeCH}=\text{CMe}_2$ (3)	I, 5	98		0 / 1
22		II, 5	93		0 / 1
23	$\text{Me}_2\text{C}=\text{CMe}_2$ (3)	I, 5	98		0 / 1
24		II, 5	98		0 / 0.5
25	$\text{CH}_2=\text{CHCO}_2\text{Me}$ (5)	II, 5	98		0 / 1
26		I, 5	96		0 / 5
27	$\text{CH}_2=\text{CMeCO}_2\text{Me}$ (5)	II, 5	98		0 / 1
28		I, 5	98		0 / 1
29	Cyclopentene (5)	II, 5 ^d	25		0 / 5
30		II, 5 ^e	14		0 / 10
31		I, 5 ^f	5		0 / 10

^a NMR yield; integration relative to signals of unreacted olefin and/or PhI liberated. ^b BPh_4^- derivative. ^c Yield on olefin. ^d $\text{LCu}(\text{OTf})_2$, no NaBAR_4 . ^e no NaBAR_4 ; ^f $(\text{tpdm})\text{CuCl} + \text{NaBAR}_4$.

(c) The much less expensive BPh_4^- salt in place of the BAR_4^- analogue showed very fast catalysis, but accompanied by competitively rapid and complete (color change) catalyst degradation, resulting in poorer (but still high) yield of the aziridine (entry 16 vs 14).

(d) Aziridinations have traditionally been carried out with excess olefin, a situation seldom tolerable when a complicated olefinic intermediate is the more valuable reagent. We therefore tested our reagent at a 1:1 reagent mole ratio. Stoichiometric (equimolar) substrate loading turned out to be also a satisfactory condition for fast and high yield aziridination (entry 17 vs 13).

(e) Finally, the combination of low catalyst loading (1%) and stoichiometric amount of olefin leads to increased reaction time and decrease of the yield to 56% (entry 18 vs 17).

The importance of preactivation of the LCuX_n complex, to produce a highly unsaturated catalyst, was illustrated by experiments with $\text{LCu}(\text{OTf})_2$, containing weakly coordinating triflate (entry 29) and LCuCl_2 with strongly copper-bound chloride (entry 30). In this series, catalytic activity dropped

significantly. Finally, the importance of the macrocyclic feature of the tripyridine ligand attached to copper was shown by an experiment with $(\text{tpdm})\text{CuBAR}_4$ catalyst derived from tripyridinedimethane (tpdm), a nonmacrocyclic analogue of **L**.²⁰ In this case (entry 31) only a very low noncatalytic yield of aziridine was obtained. Thus a nonmacrocyclic “pincer” ligand shows diminished performance.

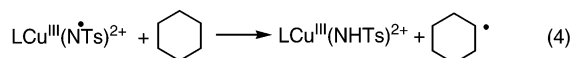
The facts reported here are consistent with hypothesis of a homolytic mechanism of aziridination with transient radical species capable of cleaving not only carbon–carbon π -bonds, which is easier for substituted ethylene as compared with ethylene itself, but also secondary allylic CH bonds of olefins.

Free radical reactivity of the $\text{LCu}^{\text{II}}/\text{PhINTs}$ system is implicated by the results of DFT calculations.²¹ According to these results, $\text{LCu}^{\text{II}}(\text{PhINTs})^{2+}$ readily loses PhI to produce a ligand-centered radical, $\text{LCu}^{\text{III}}(\text{N-Ts})^{2+}$, with most of its spin density localized on the nitrene nitrogen. The species

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(21) See Supporting Information for details.

should be able to attack either a C=C or an allylic C–H bond. Indeed, calculations show that, even in the case of alkane secondary CH bonds, hydrogen atom abstraction, eq 4, is just (barely) feasible; $\Delta G_{298}^{\circ} = 1$ kcal/mol for eq 4.



It is currently premature to assert that we know whether the active catalyst is *this* mono-copper species or the Cu^I-derived dicopper, imide-bridged species discussed above. However, the oxidizing radical character of the metal complexes produced by the catalyst recipe seems clearly demonstrated and should figure in future mechanistic analyses.

The rapid rate shown here yields identifiable benefits. For example, imino reagents are subject to competitive degradation by reaction with solvent or with adventitious nucleophiles, including water. Such side reactions are less important for a catalyzed reaction that is complete in minutes. Imino

reagents also undergo slow (~12 h) uncatalyzed reaction with olefins, which can competitively degrade regio- and stereoselectivity only for a slow-acting catalyst.

Taken together, the observations reported show attractive performance (low catalyst loading, rate, yield) of new cationic copper–pyridinophane complexes prepared in low coordinating solvent, allowing quantitative conversion of simple (poly)substituted olefins without reactive CH bonds into corresponding aziridines.

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Supporting Information Available: Computational and synthetic protocols and results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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