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# Facile alkane functionalization in copper-[2.1.1]-(2,6)-pyridinophane-PhINTs systems†

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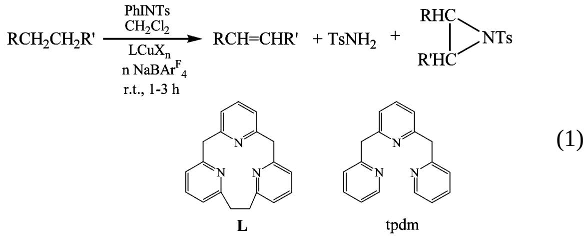
**Mild catalytic dehydrogenation of cycloalkanes (cyclo-$C_5H_{10}$, cyclo-$C_6H_{12}$, cyclo-$C_8H_{16}$) and aziridination of resulting olefins is reported with PhINTs and copper-[2.1.1]-(2,6)-pyridinophane (L) complexes $\mathrm{LCuX}_n$ ($n$ = 1, 2; X = Cl, OTf) "activated" with $\mathrm{NaBAr^F_4}$ in dichloromethane solution.**

Mild transition metal catalyzed alkane *functionalization* remains challenging for today's chemists.[1,2] Known examples of thermal (non-photochemical) transformations include alkane conversion to oxygenation products,[3–6] nitrene[7] and carbene CH insertion products,[8,9] dehydrogenation,[10,11] and borylation,[12,13] among others.[1,4] We report here preliminary observations on a new room-temperature alkane dehydrogenation and aziridination using PhINTs-copper-[2.1.1]-(2,6)-pyridinophane (L) systems, eqn. (1).



(1)

Copper(I) and copper(II) pyridinophane complexes $\mathrm{LCuX}_n$ (X = Cl, OTf; $n$ = 1, 2) were prepared in benzene in almost quantitative yield from the corresponding anhydrous copper salts and L, readily available from commercial pyridines.[14,15] Pyridinophane, L, has a steric constraint that prevents it from being coplanar and $\eta^3$ to a metal at the same time (hence no *mer*-geometry), even if this is not ideal for three coordinated $\mathrm{Cu^{I}}$ or $\mathrm{Cu^{II}}$. This "unhappy" geometry of copper complexes makes a proposed reactive transient $\mathrm{Cu^{III}}$ species[16] more accessible, and that is the basis of the exceptional reactivity of the system "$\mathrm{LCu}^{n+}$"/ PhINTs towards alkanes shown here. This coordination geometry control idea has been independently developed for a $d^8$ $\mathrm{Pt^{II}}$ system,[17–19] but this report represents a significant advance in showing its applicability to a 3d metal.

$\mathrm{LCuX}_n$ complexes undergo $\mathrm{Cl}^-$ removal in dichloromethane by the "naked" $\mathrm{Na}^+$ in stoichiometric $\mathrm{NaBAr^F_4}$, eqn. (2) ($m \leq n$). Both the copper(I) chloride and the triflate give pale yellow solutions stable for several days.

Two major peaks with $m/z$ ratio of 350.0 and 352.0 in 2 : 1 ratio were observed in the ESI-mass-spectrum of this solution confirming presence of isotopomeric $\mathrm{L^{63}Cu^+}$ and $\mathrm{L^{65}Cu^+}$ species. In the case of copper(II) compounds, the color of the catalyst solution was dependent on ligand X, being bluish-green (X = Cl) or yellow (X = OTf); this indicates incomplete ligand X abstraction by the cation in $\mathrm{NaBAr^F_4}$ for at least X = Cl (*i.e.* the different precursors do not give the same $\mathrm{Cu^{II}}$ product, $m$ values, in eqn. (2)). For $n$ = 2, the resulting solutions (both X = Cl and OTf) lost their activity in approximately 30 min.

$$\mathrm{LCuX}_n + (n-m)\mathrm{NaBAr}^{\mathrm{F}}_4 \xrightarrow[\mathrm{CH_2Cl_2}]{\text{1 min}} [\mathrm{LCuX}_m](\mathrm{BAr}^{\mathrm{F}}_4)_{n\text{-}m} + (n-m)\mathrm{NaX} \qquad (2)$$

Exploratory studies with cyclooctane, cyclohexane or cyclopentane, introduced at 25 vol% concentration to the dichloromethane solution derived from $\mathrm{LCu(OTf)_2}$, showed C–H bond cleavage chemistry with PhINTs (eqn. (1), Table 1, entries 1–3). The reaction solutions turned reddish in the presence of PhINTs; all three substrates produced the corresponding olefin, in yields that indicate mildly catalytic turnover of copper. Also produced are the aziridines, presumably by a secondary conversion of the primary olefinic product, as has been established independently.[15] A control experiment with cyclopentane and PhINTs but without any copper reagent showed no alkane dehydrogenation even after 12 h. under the conditions of Table 1. No tosylamides, the products of nitrene insertion into a substrate C–H bond,[7] were observed. The copper(II) reagent derived from the triflato complex showed distinctly higher activity than that produced by incomplete chloride abstraction from $\mathrm{LCuCl_2}$ (entry 4). Both copper(II) and copper(I) cationic complexes exhibited almost equal activity (entry 4 and 5). Triflato and chloro complexes, without the $\mathrm{NaBAr^F_4}$ "activation," showed reduced activity (entries 6–7). Addition of 30 vol% acetonitrile to the catalyst solution showed a sharp decrease of the rate of the cyclopentane dehydrogenation and aziridination (entry 9). Thus, the macrocyclic structure of the tripyridine ligand and a low coordinating environment (solvent, counterion) are equally important in developing the new systems for alkane functionalization.

The main limitation to catalyst efficiency is catalyst lifetime; judging by the color change observed in the presence of PhINTs from reddish to green, the copper complex decomposes in 2–3 h at rt. Despite that limitation, the reactivity of some other alkanes was studied. Isobutane introduced at low concentration (10 equiv.) produced isobutylene and its aziridine, 2,2-dimethyl-*N*-tosylaziridine, in less than catalytic yields (entry 10). n-Butane taken under similar conditions produced exclusively a 3 : 1 mixture of *trans*- and *cis*-2-butenes and a 1 : 1 mixture of diastereomeric *cis*- and

**Table 1** Alkane dehydrogenation and aziridination with PhINTs in the presence of $\mathrm{LCu(OTf)_2}$ + 2 $\mathrm{NaBAr^F_4}$. Dichloromethane solution, 25 vol% of alkane, rt, 1–3 h

| # | Substrate (amount) | Amount of LCu/mol %[a] | Alkene yield (%)[a] | Aziridine yield (%)[a] |
|---|---|---|---|---|
| 1 | Cyclooctane | 5 | 15 | 5 |
| 2 | Cyclohexane | 6 | 9 | 8 |
| 3 | Cyclopentane | 5 | 26 | 18 |
| 4 | " | 5[b] | 16 | 10 |
| 5 | " | 5[c] | 16 | 10 |
| 6 | " | 5[d] | 8 | 1 |
| 7 | " | 5[e] | 8 | 1 |
| 8 | " | 5[f] | 1 | 3 |
| 9 | " | 5[g] | 4 | 3 |
| 10 | Isobutane[h] | 10 | 4 | 0.3 |
| 11 | n-Butane[h] | 10 | 4 (3 : 1, *trans*-/*cis*-2-butene) | 5 (1 : 1, *cis*/*trans*) |
| 12 | Cyclopropane[h] | 10 | — | 7[i] |

[a] Based on the available limiting reagent PhINTs (200 μmol per 0.6 ml of reaction solution); [b] $\mathrm{LCuCl_2}$ + 2 $\mathrm{NaBAr^F_4}$; [c] LCuCl + $\mathrm{NaBAr^F_4}$; [d] LCuCl; [e] LCu(OTf); [f] (tpdm)CuCl + $\mathrm{NaBAr^F_4}$; [g] 30 vol% of acetonitrile as a co-solvent, 24 h; [h] 10 equiv.; [i] 2-Methyl-*N*-tosylaziridine.

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† Electronic supplementary information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b3/b309519c/

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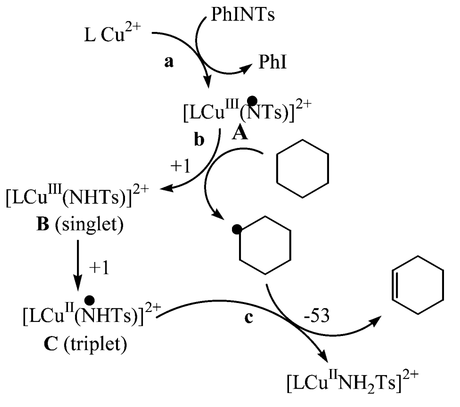
*trans*-2,3-dimethyl-*N*-tosylaziridines, also in non-catalytic yield (entry 11), thus showing selectivity for 2° *vs*. 1° alkane CH bonds. Cyclopropane produced no cyclopropene, but instead an aziridine. The aziridine formed was that derived from propene (entry 12), so cyclopropane functionalization occurred with C–C and C–H bond cleavage. Precedents of cyclopropane ring opening are well-known to occur *via* both homolytic and heterolytic mechanisms.[20]

While future work must focus on copper/*N*-tosylate complex identity, a few preliminary results are relevant. In the absence of substrate, the $LCu^+$ complex reacted cleanly with PhINTs in *2 : 1 ratio* to produce diamagnetic, presumably dinuclear, deep-purple imido complex $[(LCu^{II})_2NTs]^{2+}$ ( > 90% yield based on integration relative to $BAr^F_4$ signals), stable for at least several days in dichloromethane solution at room temperature in the absence of moisture, but alone it is completely inert towards both alkanes and olefins.[21] The same solution showed the presence of $[(LCu)_2NTs](BAr^F_4)^+$ and $LCu(NHTs)^+$ species in the ESI-mass-spectrum with expected isotopic pattern, *m*/*z* of 1732, 1734 and 1736 for the former and 520.0 and 522.0 for the latter. The latter species could result from $LCu^{II}(N{\cdot}Ts)^+$, (from $LCu^+$ and PhINTs) *via* hydrogen atom abstraction from the solvent. Trapping of this intermediate, $LCu^{II}(N{\cdot}Ts)^+$, by $LCu^+$ could produce $[(LCu^{II})_2NTs]^{2+}$.

Based on these observations, DFT calculations support a mechanism for alkane dehydrogenation involving $Cu^{II}$ as a viable catalyst precursor (Scheme 1). The main hypothesis of the Scheme suggests a ligand-centered radical $[LCu^{III}(N{\cdot}Ts)]^{2+}$, **A,** as a reactive transient.[21,22]

DFT(PBE) calculation shows 76 % spin density localized on the NTs nitrogen of **A** and a viable free energy (eqn. **b**) to abstract a hydrogen atom from cyclohexane. Abstraction of the *second* hydrogen atom can result from subsequent essentially thermoneutral $Cu^{III} \rightarrow Cu^{II}$ intramolecular redox isomerization, converting singlet $[LCu^{III}NHTs]^{2+}$, **B**, into the triplet $[LCu^{II}(NH{\cdot}Ts)]^{2+}$, (**C**, with 25% calculated spin density on amide nitrogen), followed (eqn. **c**) by reaction of **C** with the cyclohexyl radical. An olefin formed this way could then compete with alkane for reactive Cu/NTs species, producing the corresponding aziridine. The very high alkane : olefin ratio in the reaction mixtures makes this competition difficult for the latter, thus explaining why not all olefin formed was converted into aziridine.

Indeed, a separate competition experiment on dehydrogenation *vs*. olefin aziridination of a mixture containing 25 vol% of *cyclopentane* and 0.3 equivalents of *cyclohexene* ($10^3$ : 1 alkane : olefin ratio), with "$LCu^{2+}$" catalyst under the standard conditions of Table 1 showed formation of cyclopentene (8%) along with the remaining unreacted cyclohexene and aziridines derived from both olefins (4 and 6% respectively). Thus, the reactive species responsible for the observed hydrocarbon transformations, eqn. (1), shows only limited selectivity towards olefins *vs*. alkanes, consistent with the proposed radical reaction mechanism.



**Scheme 1** ($\Delta G^o_{298}$, kcal mol$^{-1}$; DFT(PBE)-calculations)

In the absence of alkane substrate but in the presence of *excess* PhINTs, both $[(LCu^{II})_2NTs]^{2+}$ and $LCu^{2+}$ species transform PhINTs to $TsNH_2$ and PhI concomitant with rapid (few minutes at rt) complex degradation, as evidenced by complete disappearance of the initial reddish color as well as NMR signals associated with L and growth of $CHDCl_2$ (yield up to 80% on PhINTs). The latter is consistent with radical D/H exchange between the solvent and benzylic hydrogens of L.

Only low non-catalytic yields of olefins and aziridines were formed using $(tpdm)CuBAr^F_4$ (entry 8), which employs a *non-macrocyclic* (hence less strained) analog of the pyridinophane.[22] The much lower stability of $(tpdm)Cu^+$ species toward oxidative degradation in the presence of PhINTs is also consistent with the hypothesis of a homolytic mechanism of alkane CH bond cleavage. Faster copper complex degradation here is attributed to facilitated radical attack at the benzylic hydrogen in the (tpdm)Cu species, which can achieve a (resonance-stabilized) planar benzyl radical geometry. The inability of the analogous radical to achieve a planar geometry at carbon in the *coordinated macrocycle* makes the pyridinophane/copper reagent detectably longer-lived.

In summary, we report a copper-pyridinophane-based system allowing the first observation of an unprecedented mild catalytic alkane dehydrogenation and one-pot aziridination where both low coordinating environment (*i.e.* anions and solvent) and macrocyclic ligand structure play important roles in determining the system reactivity.

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