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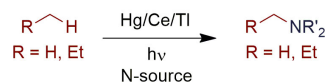**Homogeneous Catalysis** | Hot Paper

Copper-Catalyzed Dehydrogenative Amidation of Light Alkanes

M. Ángeles Fuentes, Riccardo Gava, Noam I. Saper, Erik A. Romero, Ana Caballero,* John F. Hartwig,* and Pedro J. Pérez*
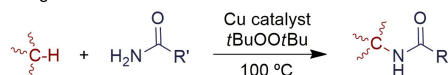
Abstract: *The functionalization of C−H bonds in light alkanes, particularly to form C−N bonds, remains a challenge. We report the dehydrogenative coupling of amides with C1–C4 hydrocarbons to form N-alkyl amide products with tBuOOtBu as oxidant, and a copper complex of a phenanthroline-type ligand as catalyst. The reactions occurred in good yields in benzene or supercritical carbon dioxide as solvents. This strategy allowed for the determination of the relative reactivity of these alkane C−H bonds toward this amination process and showed, in contrast to prior work with larger alkanes, that the reactivity correlated with bond dissociation energies.*

The catalytic formation of carbon–nitrogen bonds from C−H bonds has been a major target of catalysis during the past several decades.[1] While many advances have been made, aminations of light alkanes, which lack any activating group and cannot be present in solvent quantities,[2] are rare.[3,4] These hydrocarbons are resistant to the formation of C−N bonds, owing to the high bond dissociation energies (BDE) and low polarity of their C−H bonds, and scarcity of nitrogen-based reagents that readily form intermediates that cleave the strong C−H bonds of light alkanes.[5] The amination of light alkanes has been limited to just a few examples. Crabtree reported the formation of imines from ammonia and methane or ethane by photo-activated mercury,[6] Guo and Zuo reported the formation of hydrazides by addition of alkyl radicals, formed photochemically by Ce halides, to the N−N bonds of azo compounds,[7] and Ess and Periana reported stoichiometric reactions of organomercury compounds in triflimide solvents (Scheme 1a).[8] Most recently, Chang reported the insertion of a nitrene unit, predominantly into
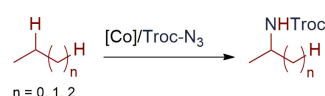
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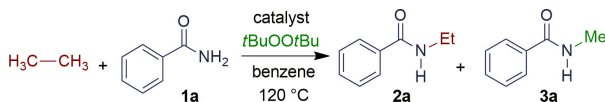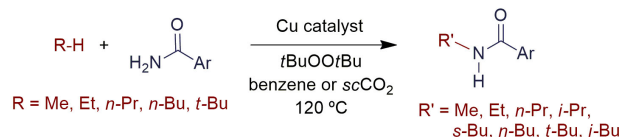**Scheme 1.** a) Previous reports of metal-mediated or metal-catalyzed amination of light alkanes. b) Nitrene insertions into light alkane C−H bonds. c) Prior work on copper-catalyzed dehydrogenative amidation of alkanes. d) Dehydrogenative amidation of C1-C4 light alkanes described in this work.

the methylene units of alkanes, catalyzed by cobalt complexes.[9] Reaction with the primary C−H bonds of ethane was observed, but the yields were modest, and no reactivity with methane was described (Scheme 1b).

A few years ago, one of our groups reported the catalytic amidation of the C−H bonds of liquid cyclic and acyclic alkanes with a copper-based catalyst, tBuOOtBu as oxidant and amides as the nitrogen-based reagent (Scheme 1c).[10] Since this publication, several additional aminations have been reported,[11] but the applicability of this reaction to the functionalization of strong C−H bonds in light alkanes was unclear. Previous studies[10] showed that the combination of benzamide, alkane and di-*tert*-butyl peroxide with a copper catalyst led to functionalization of secondary and primary positions, but the reactions occurred in low yields at unactivated tertiary and primary C−H bonds. On this basis, we sought to 1) determine whether reactions would occur with the light alkanes ethane and methane, which contain solely primary C−H bonds and 2) determine the selectivity for the copper-catalyzed amination of primary, secondary, and tertiary C−H bonds in light alkanes, which possess less hindered C−H bonds than those in the prior work on heavier alkanes.

Here, we report the high-yield dehydrogenative amidations of the primary C−H bonds in ethane and the observation

of analogous reactions with the even stronger C−H bond in methane, as well as dehydrogenative amidations of the weaker secondary and tertiary bonds of propane and butanes (Scheme 1d). The reaction with ethane is an unusual, high-yield C−N bond formation with an unactivated primary C−H bond, and the amidation of methane has not been observed previously. The selectivities of these aminations of light alkanes differ from the analogous reactions of higher alkanes.

To assess the potential of conducting the dehydrogenative amidation of the unhindered, but strong, primary C−H bonds in light alkanes, we initiated our studies with the reaction between ethane and benzamide (**1a**) in the presence of an array of copper catalysts (5 mol%) at 120°C with benzene as the solvent and di-*t*-butyl peroxide as oxidant. As shown in Table 1, ethane reacted with benzamide to form *N*-ethyl benzamide (**2a**) in yields that depended on the copper source.

**Table 1:** Catalyst screening for ethane amidation.[a]

Entry	Catalyst	% **2a**	% **3a**
1	CuI	0	0
2	CuI-phen	41	49
3	CuI-bipy	12	5
4	Cu(acac)$_2$	26	40
5	Cu(OAc)$_2$ H$_2$O	10	12
6	Cu(HCOO)$_2$	<2	0
7	(IPr)CuCl	5	<2

[a] Catalyst (0.05 mmol), benzamide (1 mmol), *t*BuOO*t*Bu (6 mmol), ethane (35 bar), benzene (20 mL), 120°C, 24 h. Yields were determined by GC analysis using calibration curves and referred to initial benzamide. phen = 1,10-phenanthroline, bipy = 2,2′-bipyridine, acac = acetylacetonate, OAc = acetate, (IPr) = [1,3-bis(2,6-diisopropylphenyl) imidazole-2-ylidene]. Mass balance completed with unreacted amide and minor unidentified products.

No product was obtained without added ligand, but 41% yield was observed with CuI-phen (phen = 1,10-phenantroline). In addition to *N*-ethyl **2a**, *N*-methyl benzamide **3a** formed as a result of the generation of Me radicals from peroxide decomposition, as previously reported.[10] Reactions catalyzed by the related CuI-bipy occurred in lower yield, whereas those catalyzed by (IPr)CuCl proceeded to low conversions. Copper(II) sources displayed moderate to low catalytic activity that was well below that observed for CuI-phen. Control experiments in the absence of ethane formed only *N*-methyl amide **3a**, which was detected in 54% yield with CuI-phen as the catalyst.
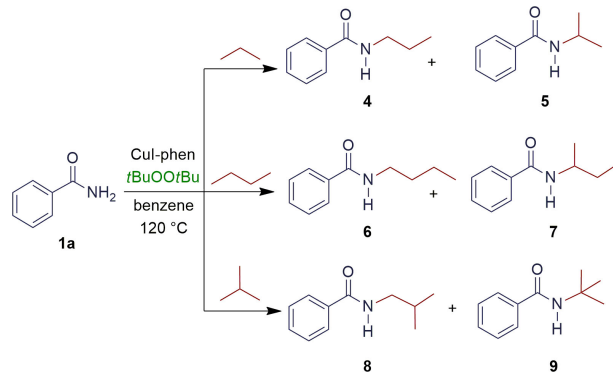
Variation of the amide led to the dehydrogenative amidation of ethane in remarkably high yield. The effect of the identity of the amide group on the reaction outcome is shown by the data in Scheme 2. The reaction with amide **1b** bearing trifluoromethyl groups at the meta positions of the aryl ring formed the *N*-ethyl product **2b** in 94% yield, based on the amide. This yield of the product from functionalization of ethane is more than double that of prior catalytic aminations of ethane.[6–9]
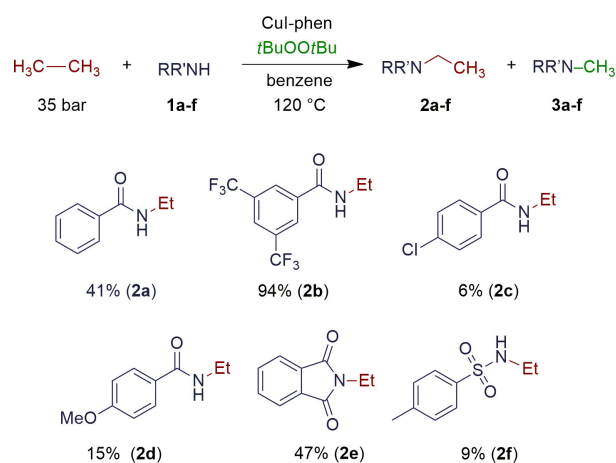
Scheme 2. Effect of the amide on yield of Cu-catalyzed amidation of ethane. Conditions correspond to those described in Table 1 (see the Supporting Information for a full description).

With a high yield obtained for reaction of ethane,[12] we determined the reactivity and selectivity of the amidation of light alkanes containing weaker C−H bonds. Propane, *n*-butane and isobutane were allowed to react with a benzene solution of amide **1a**, *t*BuOO*t*Bu as oxidant, and CuI-phen as the catalyst. The data in Table 2 show that these three light alkanes, which contain two distinct types of C−H bonds, reacted at either of these C−H bonds to form a mixture of two *N*-alkyl amide products. Propane and n-butane reacted at their primary and secondary C−H bonds, whereas *iso*-butane underwent amidation at primary and tertiary sites. The solubility of these gases in benzene is low,[13] but reactions occurred with only 1–8 bar of the alkane, at values for the

**Table 2:** Amidation of C3–C4 alkanes with benzamide catalyzed by CuI-phen.[a]

Alkane[b]	% Products	% **3a**	Relative Reactivity[c]
propane	13:53 (4:5)	16	1:12 (1°:2°)
n-butane	7:32 (6:7)	47	1:6.8 (1°:2°)
iso-butane	27:13 (8:9)	58	1:4.3 (1°:3°)

[a] Corresponding alkane, catalyst (0.05 mmol), benzamide (1 mmol), *t*BuOO*t*Bu (6 mmol), benzene (20 mL), 120°C, 24 h. [b] Pressures employed for each alkane: ethane (35 bar), propane (8 bar), n-butane (1 bar), iso-butane (2.5 bar). [c] Corrected for the number of hydrogens of each type. Yields were determined by GC analysis using calibration curves and refer to initial benzamide.

individual reactions that equalize the amounts of the alkanes in the reaction solutions. In all cases, the *N*-alkylation of benzamide was achieved with moderate to high yields: 66% (13%, 1°: 53%, 2°) for propane, 40% (27%, 1°:13%, 3°) for isobutane, and 39% (7%, 1°: 32%, 2°) for n-butane. *N*-Methyl-benzamide **3a** accounted for the remainder of the mass balance; only 2–7% of the amide **2a** remained unreacted.

After achieving the amidation of the primary, secondary, and tertiary C−H bonds of the C2–C4 alkanes, we tested the reaction of methane. As shown in Scheme 3a, the mechanism proposed for the amidation[10] is based on the generation of *t*BuO radicals that abstract the C−H bond of the alkane to form an alkyl radical. The alkyl radical, then, reacts with an NHR′ ligand at the copper center, leading to products **2** and **4–9**. However, decomposition of the *tert*-butoxy radical forms methyl radicals, which produce the *N*-methyl amide product. Thus, the product from this decomposition and the product from reaction of methane would be the same.
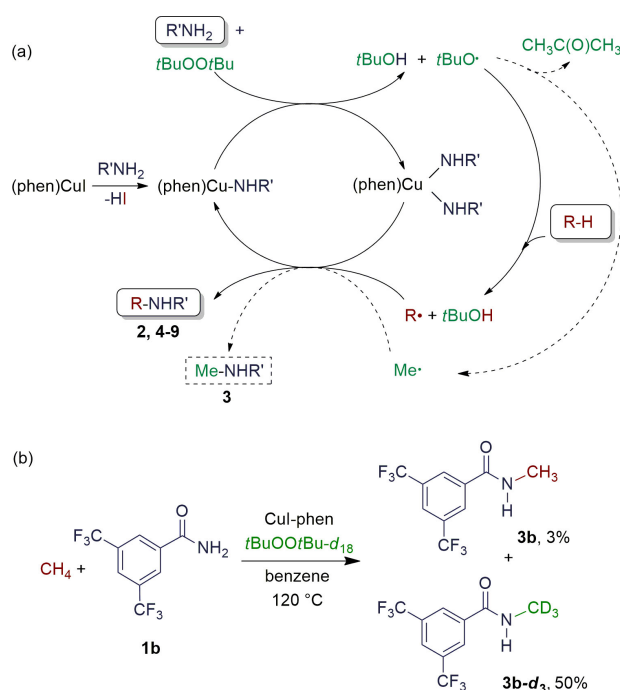

Scheme 3. a) Previous mechanistic proposal for Cu-catalyzed amidations of liquid alkanes. b) Amidation of methane using perdeuterated peroxide (see Supporting Information for full description).

To avoid the identity of these two products, we conducted reactions of methane with the perdeuterated oxidant $(CD_3)_3CO-OC(CD_3)_3$. With the exception of using the labeled oxidant and 200 bar of methane as alkane, we conducted the amidation reaction identically to those previously described with ethane and the fluorinated amide **1b** (Scheme 3b). Under these conditions a mixture of **3b** (3%) and **3b-d_3** (50%) was observed. The observation of protiated **3b** indicates that the system cleaves the C−H bond of methane and transfers the NHR′ group to methyl radicals. Although the majority of the amide couples with the methyl-

d_3 radical generated from *t*BuO-d_9, these results do reveal that the dehydrogenative amidation of methane occurs from reaction of the methyl radical derived from methane.

To increase the concentration of the gaseous alkane at the catalytic center, we tested whether supercritical carbon dioxide could be used as the reaction medium. This strategy was previously described for catalytic insertion of a carbene unit into methane catalyzed by a silver carbene complex.[14] This method relies on the formation of one single phase consisting of *sc*CO₂ and methane. For the catalyst to be soluble in this medium, it must contain a high level of fluorination. Thus, we conducted reactions of ethane and methane in *sc*CO₂ catalyzed by several copper catalysts containing fluorinated alkyl groups on the ligand (Table 3).

Table 3: Copper-catalyzed amidation of ethane with 3,5-bis(trifluoromethyl)benzamide in *sc*CO₂ as solvent.[a]
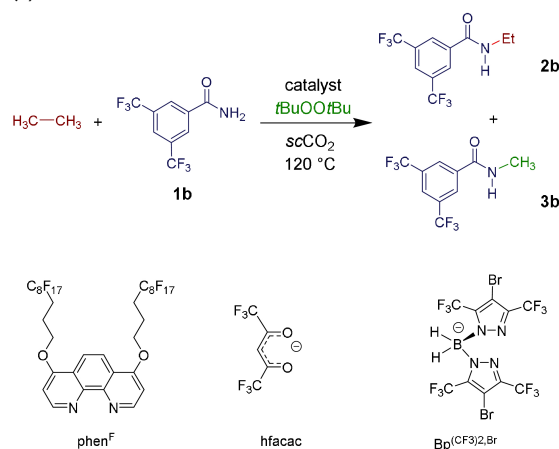
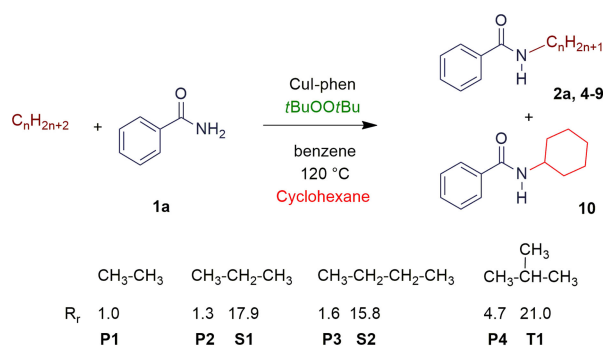| Entry	Catalyst (loading)	% **2b**	% **3b**
1	Bp$^{(CF3)2,Br}$Cu (NCMe) (1.5%)	12	5
2	Cu(hfacac)₂ (1.5%)	21	49
3	CuI-phen^F (1.5%)	39	10
4	Cu(hfacac)₂ (5%)	49	33
5	CuI-phen^F (5%)	80	7
6[b]	CuI-phen^F (5%)	66	33

[a] Catalyst (1.5–5%), 3,5-bis(trifluoromethyl)benzamide (1 mmol), *t*BuOO*t*Bu (6 mmol), ethane (35 bar at rt), *sc*CO₂ (165 bar at rt), 120°C (final pressure 410 bar), 24 h. Yields were determined by GC analysis using calibration curves and referred to initial amide. [b] Experiment carried out in benzene as solvent, no CO₂ used.

Although this medium did not promote reactions of methane, likely due to low solubility of the catalyst,[15] reactions of ethane did occur in good yield. Three fluorine-containing copper complexes were tested, Bp$^{(CF3)2,Br}$Cu-(NCMe), Cu(hfacac)₂ and CuI-phen^F (phen^F = phenanthroline-based ligand with two fluorinated ponytails in the backbone). All of the complexes gave functionalized product, and CuI-phen^F led to functionalization in the highest yield. (Table 3, entries 1–3). The reaction of ethane with benzamide **1b** in *sc*CO₂ with 5 mol% CuI-phen^F gave the product in 80% yield (entry 5). In benzene, CuI-phen^F gave less product than CuI-phen (entry 6), showing that the *sc*CO₂ medium increases the yield of product over the analogous reaction in benzene.

Because the reaction mechanism previously proposed (Scheme 3a) involves the generation of alkyl radicals, one would expect the yields of the various *N*-alkyl amides to follow the trends in bond dissociation energy and give rise to the relative amounts of *N*-alkyl products, tertiary > secondary > primary. However, the previous study on the functionalization of heavier alkanes[10] did not lead to functionalization of tertiary sites, presumably because reaction of the hindered radical with the copper complex was slower than other reactions of this radical.

To determine if this steric effect is equally pronounced for reactions of the less hindered light alkanes, we conducted a series of experiments to measure the relative reactivities of the seven different C−H bonds in the four C2–C4 alkanes. The reactions were conducted in the presence of cyclohexane, in benzene, with CuI-phen as the catalyst and **1a** as the amide (Scheme 4). The relative amounts of the amides generated from each alkane versus cyclohexane, corrected for the number of C−H bonds, reveal the relative reactivity of the different types of C−H bonds. For the sake of simplicity, values are reported relative to the reactivity of the ethane C−H bond ($R_r(P1) = 1.0$, see Supporting Information for details).

Figure 1 shows a plot of the R_r values versus the corresponding BDEs[5] for each bond. Literature data on H•

abstraction by *t*BuO radical[16] reveal the relative reactivities of primary vs. secondary vs. tertiary to be ca. 1:14:40. Our data follow a clear parallel reactivity trend of primary < secondary < tertiary, which tracks with relative BDE values, but the relative ratios of products are lower than would be expected solely from the rates of H• abstraction by the *t*BuO radical. In contrast to reactions of the heavier alkanes, the reaction with isobutane reported here includes product from reaction at the tertiary C−H bonds, but the amount of product from reaction at this tertiary site remains less than would be expected from C−H BDE values alone. Of course, the correlation observed between R_r and BDE in this system is distinct from the lack of correlation observed for the non-radical, heterolytic, silver-catalyzed functionalization of gaseous alkanes by carbene insertion, one of the few other homogeneous, catalytic functionalization of light alkanes.[17]

In conclusion, we achieved the dehydrogenative amidation of light alkanes (methane, ethane, propane, isobutane and n-butane) catalyzed by phenanthroline-ligated copper with di-*tert*-butyl peroxide as oxidant. Reactions in super-critical carbon dioxide, as an alternative reaction medium to benzene, formed the product from amidation of ethane in higher yield than that from reaction with the same catalyst in benzene. Finally, the relative reactivity of the C−H bonds of C2–C4 alkanes showed a closer correlation with the values of the corresponding bond dissociation energies than those of higher alkanes. We hope these findings open avenues to more efficient systems that generate C−N bonds at non-activated alkyl C−H bonds.

R_r = relative reactivities for amination at primary, secondary, and tertiary positions with cyclohexane as a reference

Scheme 4. Competition experiments leading to the relative reactivity values for alkanes C2–C4, referred to ethane (P1).
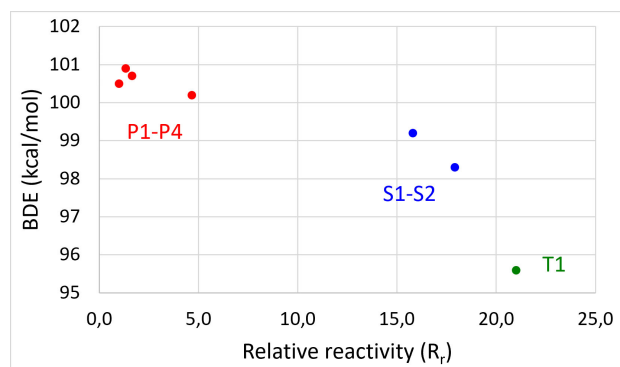

Figure 1. Plot of the relative reactivity (R_r) values for the C−H bonds of alkanes C2–C4 (referred to ethane) vs. bond dissociation energies.

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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[12] A reviewer raised the possibility that methyl radicals from ˙O*t*Bu couple in our reactions to form ethane. We have no experimental data to address this proposal. However, ethane from coupling of methyl radicals would not be detectable in reactions with ethane as the substrate, and we have not observed the formation of *N*-ethyl amide **2a** derived from ethane potentially generated by coupling of methyl radicals during reactions with the other alkanes as substrate.

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