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O-Methyl-*N*-Nitroisourea as a NCO Surrogate in Cu-Catalyzed Alkane C–H Amidination. A Masked Isocyanate Strategy.

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ABSTRACT: The Cu-catalyzed C–H activation of alkanes in the presence of *O*-methyl-*N*-nitroisourea allows a facile entry to *O*-methyl-*N*-alkylnitroisoureas, shelf stable isocyanate precursors. The latter are then readily converted into carbamates and ureas via an uncommon chloride-mediated demethylation process. *O*-methyl-*N*-nitroisourea is available in two steps and large-scale from urea and constitutes an easy to handle NCO surrogate. The methodology has also been applied to the synthesis of a methylisocyanate (MIC) precursor, a valuable synthon for pharmaceutical and agrochemical purposes and for the post-functionalization of polyolefins.

1. INTRODUCTION

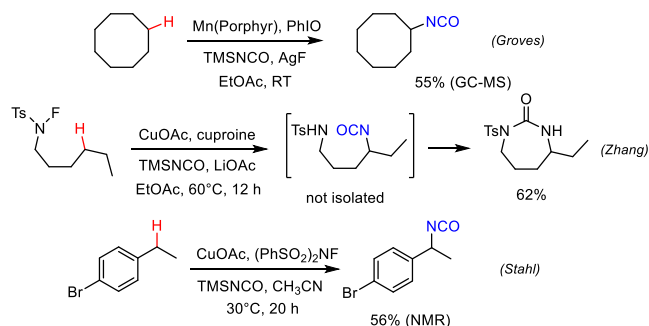
The direct functionalization of the C(sp³)-H bond represents one of the most efficient, atom and step economic strategy to introduce functional groups on a hydrocarbon chain.¹ Late stage C(sp³)-H functionalization on highly functionalized molecules, is also of definite interest, allowing the conversion of known bioactive targets into new molecules with potentially increased biological activity.² The selective C–H activation, however still remains an important challenge to synthetic organic chemists, due to the high energy of the C–H bond (BDE ~ 98-100 kcal/mol).¹ Over the past two decades, organic synthesis has made remarkable advances in this field and achieved direct functionalization of C(sp³)-H bonds of alkanes to forge C–C and C–X bonds (X = N, O, S, etc.).³ In this context, several intermolecular amination processes of simple unfunctionalized and functionalized hydrocarbons **1** have been reported (Figure 1A).⁴ In contrast, the direct incorporation of an isocyanate (NCO) moiety is a challenging process, which has received so far little attention, despite its high potential. The preparation of alkyl isocyanates via Mn-porphyrin catalyzed C–H activation of alkanes was reported in 2017 by Groves *et al.* using Mn-porphyrin complexes originally isolated by Hill *et al.* (Figure 1B).⁵ A remote Cu-catalyzed C–H abstraction then isocyanation using TMSNCO proceeding through a sulfonamidyl radical was described by Zhang.⁶ A recent work by Stahl and co-workers⁷ described the direct isocyanation of benzylic substrates using a copper catalyst and NFSI as the hydrogen atom transfer (HAT) agent. Beside hydrocarbon precursors, isocyanates may also be accessed from alkyl halides through alkylation, using nitrocyanamide silver salts as reported earlier by Boyer *et al.* (Figure 1C).⁸ This overlooked approach relies on a silver nitrocyanamide salt available through a basic treatment of *S*-alkyl-*N*-nitroisourea **2**. Thermal rearrangement of the resulting *N*-alkylnitrocyanamide **3** is believed to occur through *N*-nitrocarbodiimide **I**, finally decomposing into the isocyanate **4** and N₂O. Recent studies by Churakov and co-workers clearly established the thermal decomposition of **I** into isocyanates.⁹ Based on these premises, it was anticipated that the basic treatment of an *O*-alkyl-*N*-nitroisourea such as **6** would generate *N*-nitrocarbodiimide intermediate **I**, through elimination of MeOH (Figure 1D). In turn, **6** might be available through a metal-catalyzed C–H amidination of hydrocarbons using simple *O*-methyl-*N*-nitroisourea **5a**, available on gram scale in

only two-steps from urea (ESI). This sequence would thus offer a rapid entry toward isocyanates from shelf-stables, easy to handle and safe *O*-methyl-*N*-alkylnitroisoureas **6**, avoiding the manipulation of the known carcinogenic isocyanates and the recourse to toxic phosgene or TMSNCO.

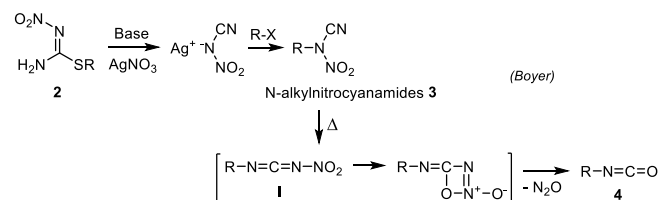
A. C–H amination



B. C–H isocyanation



C. Preparation of isocyanates from nitrocyanamides



D. C–H amidination through *O*-methyl-*N*-alkylnitroisoureas (This work)

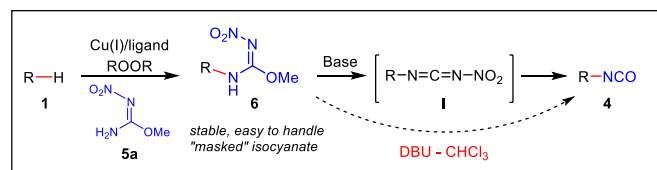


Figure 1. Literature precedent on C–H amination (A), C–H isocyanation (B) and preparation of isocyanates from *N*-alkylnitrocyanamides (C). Present work on the C–H amidination using *O*-methyl-*N*-nitroisourea **5a** (D).

We describe below the synthesis of **6**, through a Cu(I)-catalyzed C–H functionalization of alkanes using *O*-methyl-*N*-nitroisourea **5a** as a masked NCO (Figure 1, D). During the studies on the base-mediated conversion of **6** into **I** we also uncovered an

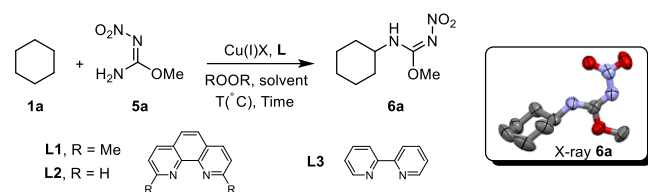
efficient entry to isocyanates **4** from **6** through an unprecedented Krapcho-type process using DBU in CHCl₃.¹⁰ This methodology thus gives rise to a range of aminated products from simple hydrocarbons, including polyolefin waste, using *N*-alkylnitrosoareas **6** as non-toxic isocyanate surrogates.

2. RESULTS AND DISCUSSION

2.1. Alkane C–H amidination

The first part of the study was devoted to the development of the C–H amidination of alkanes using *O*-methyl-*N*-nitrosoareas **5a** as the aminating agent under Cu(I) catalysis.⁴ Optimization of the C–H amidination reaction was performed using cyclohexane **1a** as the model alkane, varying the nature of the copper salt, ligands as well as oxidants and solvents, as summarized in Table 1. After extensive studies (ESI), the soluble [Cu(MeCN)₄]PF₆ salt was found to be the most active copper salt for the reaction, leading to the desired product **6a** with 79% NMR yield (Table 1, entry 1). The structure of **6a** was unambiguously assigned through X-ray diffraction studies (XDRS, ESI) indicating that the reaction occurred on the NH₂ nitrogen of **5a** and not at the N–NO₂ nitrogen. A unique isomer of the nitrosoareas was obtained, the stereochemistry of which was assigned based on XRDS, showing hydrogen bonding between the NH and one of the NO₂ oxygen. The counter-anion of the copper salt had no effect on the yield (Entry 2). In contrast, other Cu(I) salts led to very low conversion (entries 3–5). Copper(II) salt provided **6a**, albeit with reduced yield (entry 6). When the copper catalyst was omitted, no trace of **6a** could be observed (entry 7). The choice of the solvent proved also to be crucial, with the “greener” acetone leading consistently to higher yields (entries 8–13). The nature of the ligands was also studied with the 2,9-dimethyl-1,10-phenanthroline (neocuproine) **L1**, leading to higher conversion (entry 1 vs entries 14–15), while the absence of ligand led to low efficiency (entry 16). Di-*tert*-butyl peroxide was found to be the most efficient oxidant, which contrasts with the very low conversion using AcOO*t*-Bu for instance (entry 17). It is worthy of note that at this temperature, the *t*-BuO radical fragments into acetone and the highly reactive methyl radical, which can also act as a hydrogen atom transfer (HAT) agent (*vide infra*).¹¹ In the last part of the study, quantities of starting material **1a** and **5a**, as well as reagents in entry 1 were varied. For instance, reducing the amount of oxidant led to a slight decrease in yield (entry 18), so that 2.5 equivalent was kept as optimal conditions. Decreasing the amount of cyclohexane did not affect the isolated yield (entry 19), while simultaneously increasing the amount of **5a** slightly improved the yield (entry 20). The efficiency of the process using only 1 equivalent of alkane (ESI) is however noteworthy considering reported literature where hydrocarbons are usually used in excess.^{4d} Finally, decreasing the amount of copper catalyst led to reduced yield (entry 21). Up-scaling of the process was also performed starting from 250 mmol of **5a** and cyclohexane (5 equiv.), which led to the isolation of 3.31 grams of **6a** (66% yield).

Table 1. Optimization of the C–H amidination of **1a with *O*-methyl-*N*-nitrosoareas **5a****



entry ^a	L	ROOR	Cu(I)X	Solvent	Yield (%) ^b
1	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	79
2	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]BF ₄	Acetone	78
3	L1	<i>t</i> -BuOO <i>t</i> -Bu	CuCl	Acetone	5
4	L1	<i>t</i> -BuOO <i>t</i> -Bu	CuI	Acetone	4
5	L1	<i>t</i> -BuOO <i>t</i> -Bu	CuOAc	Acetone	8
6	L1	<i>t</i> -BuOO <i>t</i> -Bu	Cu(TFA) ₂	Acetone	15
7	L1	<i>t</i> -BuOO <i>t</i> -Bu	-	Acetone	0
8	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	CH ₃ CN	11
9	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	PhCF ₃	15
10	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	benzene	7
11	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	CH ₃ NO ₂	58
12	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	CH ₂ Cl ₂	25
13	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	PhCl	56
14	L2	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	32
15	L3	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	28
16	-	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	7
17	L1	AcOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	1
18 ^c	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	66
19 ^d	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	80
20 ^e	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	85
21 ^f	L1	<i>t</i> -BuOO <i>t</i> -Bu	[Cu(MeCN) ₄]PF ₆	Acetone	60

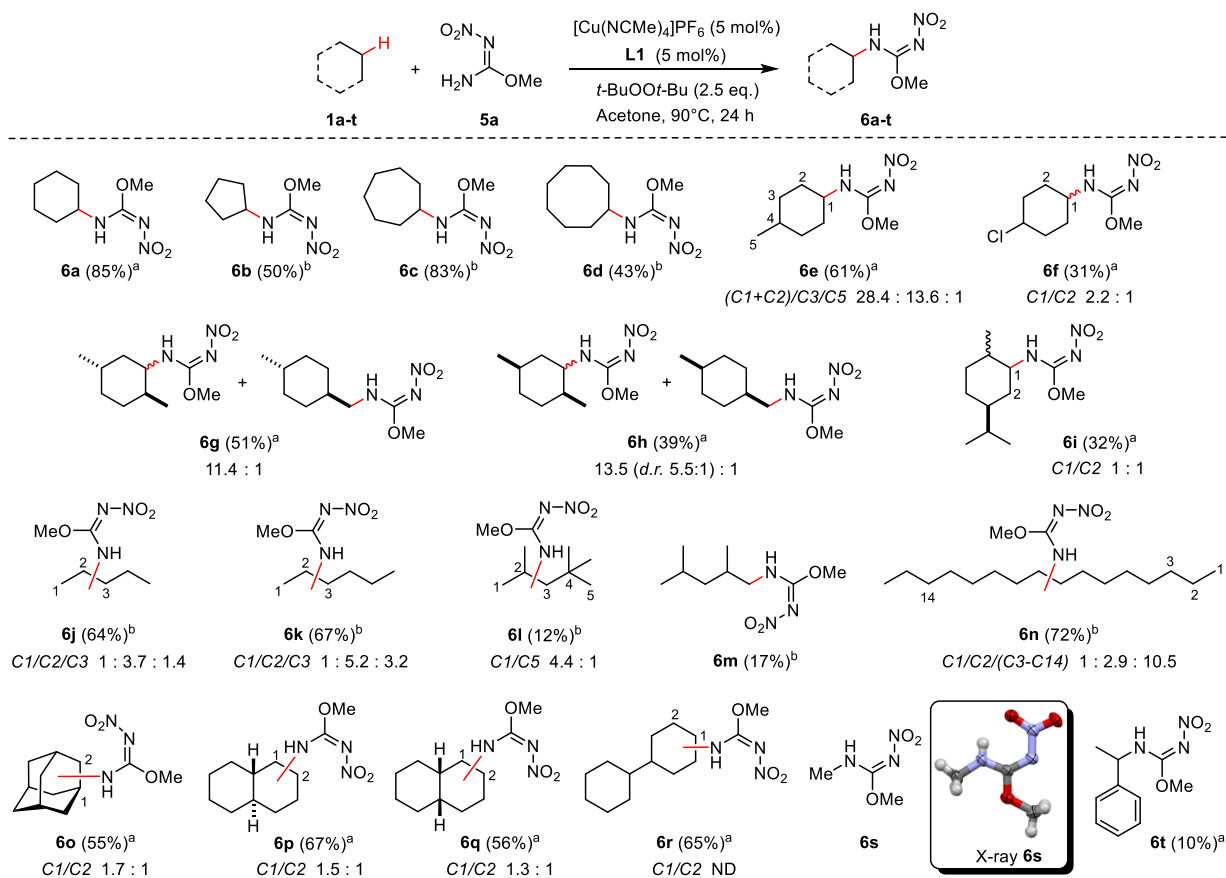
^aUnless otherwise mentioned, all reactions were performed with **1a** (10 eq.), **5a** (0.5 mmol), oxidant (2.5 eq.) Cu(I)X (0.05 eq.), **L1** (0.05 eq.) in solvent (1.0 mL) under argon at 90°C for 12 h. ^bYield was determined by ¹H NMR spectrum using 1,2,4,5-tetramethylbenzene as an internal standard. ^c *t*-BuOO*t*-Bu (1.5 eq.) instead of 2.5 eq. ^d **1a** (5 eq.) and **5a** (0.5 mmol). ^e **1a** (5 eq.) and **5a** (1 mmol). ^f[Cu(MeCN)₄]PF₆ (0.02 eq.), **L1** (0.02 eq.).

The scope and limitation of the C–H amidination was then established using **5a** and varying the nature of the alkanes **1a–t** (Scheme 1). Overall, nitrosoareas **6b–t** were obtained with yields ranging between modest and good using **5** and up to 20 equivalents of alkanes relative to **5a**, depending on the nature of the alkane. Volatile alkanes for instance generally led to improved yields when used in larger excess. An excess of the alkane is required to favor the bimolecular HAT process between the alkoxy radical and the alkane relative to the unimolecular β-scission of the *t*-BuO radical.^{11b} Mass balance contained unreacted alkanes which could easily be separated from the product by distillation. With poorly reactive alkanes, variable amount of *O*-methyl-*N*-methyl-nitrosoareas **6s** was also isolated as a by-product, resulting from the coupling between methyl radical, issued from the decomposition of the *t*-BuO radical,¹¹ and the Cu-amine complex (*vide infra*).^{4d} As discussed below, **6s** may find interesting applications as methylisocyanate (MIC) surrogate. Unsubstituted cyclic alkanes reacted smoothly to provide the desired nitrosoareas **6a–6d** in satisfying yields. Monosubstituted methylcyclohexane led to **6e** as a mixture of inseparable regioisomers, indicating again a higher reactivity of the methylene C–H bonds. Reaction at the C5 methyl

substituent was however observed in small amount. The reaction was also moderately efficient on chlorocyclohexane as shown with the isolation of **6f** as a 2.2:1 mixture of regioisomers and diastereomers, in which the C–H bond away from the chlorine atom appears as the more reactive. *Cis*- and *trans*-1,4-dimethylcyclohexanes led to CH₂/CH₃ activation (*i.e.* **6g-h**) and no reaction at the tertiary site. The methodology was successfully extended to acyclic systems. Similar to their cyclic analogues, methylene C–H were also more reactive than primary and tertiary C–H.¹² This is illustrated with regioisomers ratio in **6j**, **6k** and hexadecane **6n**. When steric effects become significant and CH₂ less accessible, then functionalization at CH₃ is favoured, as in **6l** and **6m**, albeit obtained in poor yields. Polycyclic substrates were also reacted under the same conditions producing the expected regioisomers

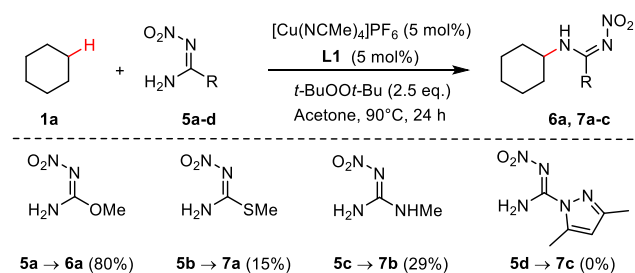
6p-r as mixtures of regio and diastereomers, which structure could not be determined. Adamantane led to nitroisourea **6o** as a mixture of C1/C2 regioisomers where the tertiary C–H was the most reactive in good agreement with previous literature reports.^{4d} Site-selectivities observed here thus indicate a pro-emergence for the methylene hydrogen abstraction as compared to the CH₃, and amidination at the usually more reactive tertiary C–Hs is not observed likely for steric reasons, in good agreement with related C–H functionalizations using Cu/DTBP processes (*vide infra*).^{4d,12} Efforts to extend this C–H activation process to functionalized substrates led to poor conversion whatever the functional group present on the substrate (*i.e.* **6t**). Further studies will be required to find alternative conditions to overcome this problem.

Scheme 1. Scope of the Cu(I)-catalyzed C–H amidination of alkanes 1a-t with O-methyl-N-nitroisourea 5a.



The optimized conditions above (Table 1, entry 19) were extended to other nitroisoureas **5b-d**, possessing a different leaving group (R) on the central carbon center (*vide infra*). **5b-d** are readily available from the corresponding urea or thiourea (ESI). *S*-methyl-*N*-nitroisothiourea **5b** and nitroguanidine **5c** provided the desired C–H amidination product **7a-b**, albeit in low yields (Scheme 2). In contrast,azole **5d** led only to recovered starting material.

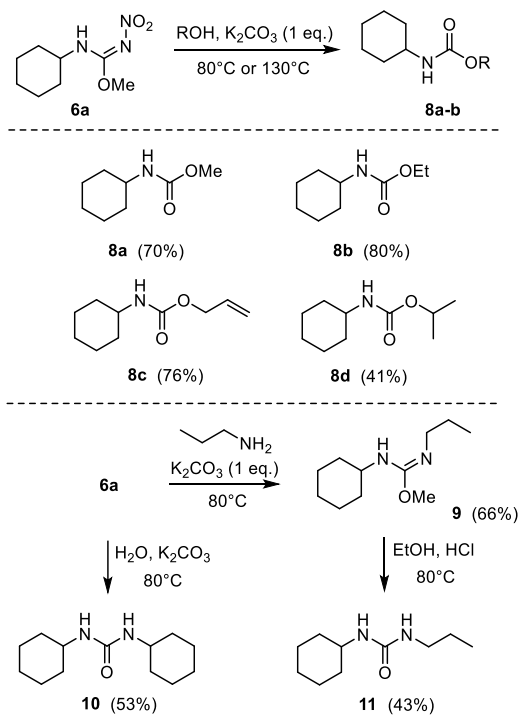
Scheme 2. C–H amidination using various nitroisoureas 5a-d.



2.2. Conversion of *O*-methyl-*N*-alkylnitrosoisourea into isocyanate, urethanes and ureas

The treatment of *O*-methyl-*N*-alkylnitrosoisoureas **6** under basic conditions was then studied to generate the *N*-nitrocarbodiimide intermediate **I**, precursor of isocyanates **4** (Figure 1C). Elimination of MeOH from **6a** was thus investigated varying the nature of the base. Carbonates, NaOH, KOH, K₃PO₄ or NaOEt in alcohols as solvents were thus tested (ESI), K₂CO₃ invariably leading to the best yields in urethanes **8a-d** (Scheme 3). As expected, higher conversion in urethanes were obtained using primary alcohols at 80°C, although secondary alcohols were also shown to react, but at higher temperature (130°C).¹³ Amines also added to **6a** at 80°C under these conditions, but surprisingly, the elimination of MeOH did not take place, but instead *N*-cyclohexyl-*N*-alkylnitrosoisourea **9** was isolated in good yield. Treatment of the latter under acidic conditions finally afforded urea **11**. The conversion of **6a** into **9** suggests that more nucleophilic reagents such as amines preferentially adds onto the isourea carbon center, prior to elimination. Finally treatment of **6a** under basic conditions in water led to the symmetrical urea **10**.

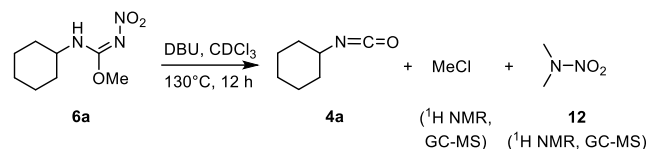
Scheme 3. Base-catalyzed decomposition of *O*-methyl-*N*-alkylnitrosoisoureas **6a into urethanes **8** and urea **10-11**.**



Although the treatment of *O*-methylnitrosoisoureas **6** under basic conditions provides urethanes and urea using simple and reproducible conditions, the access to unsymmetrical ureas such as **11** in 3 steps from cyclohexane is not satisfying. In the course of our studies, we eventually discovered an unusual and more general pathway to urethanes and urea starting from **6**. During ¹H NMR studies on the base-catalysed elimination reaction of **6a** in CDCl₃ using DBU as a base, we not only observed the formation of the isocyanate **4a** (Scheme 4), but the ¹H NMR of the crude reaction

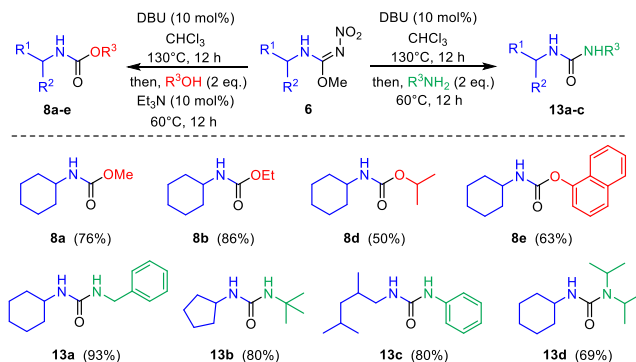
mixture (Figure S1-S3) also showed the formation of a compound presenting a singlet at 3.05 ppm attributed to MeCl, which was confirmed through GC-MS (Figure S4 and S7). *N,N*-Dimethylnitroamine **12** was also generated after 3 h as shown by ¹H NMR (Figure S1-S2) and GC-MS (Figure S5 and S7), but progressively disappeared due to its known instability at this temperature.¹⁴

Scheme 4. Conversion of *O*-methyl-*N*-alkylnitrosoisourea **6a into isocyanate **4a**.**



4a could be isolated in nearly quantitative yield, and could be more conveniently reacted *in situ* with a suitable nucleophile. As summarized in Scheme 5, the scope of these new conditions was established and showed that urethanes and ureas could be prepared in generally high yield, using a two-steps one pot procedure, including the generation of the isocyanate, which was directly treated with a given alcohol or amine using Et₃N as a catalyst. The reaction was shown to proceed in excellent yield, whatever the alkane precursor, alcohol or amine. For instance, less nucleophilic naphthol and aniline led to urethane **8e** and urea **13c** in good yields. Secondary amines also proved reactive under these conditions as shown with the synthesis of **13d**.

Scheme 5. Conversion of *O*-methyl-*N*-alkylnitrosoisoureas **6 into urethanes **8a-e** and ureas **13a-d**.**



A tentative mechanism to rationalize the quantitative formation of isocyanate **4** from **6** in the presence of a catalytic amount of DBU in CHCl₃ is depicted in Figure 2. Formation of both MeCl and **12** as by-products strongly supports the displacement of the methyl substituent in **6** by a chloride anion as for instance in Krapcho decarboxylation.¹⁰ The formation of Cl⁻ likely results from the deprotonation of CHCl₃ by DBU to produce a dichlorocarbene and DBU-HCl, although our efforts to trap Cl₂C; through cyclopropanation of styrene or C-H insertion in adamantane, met with failure.¹⁵ This demethylation would thus form intermediate **i**, in equilibrium with nitrosoisourea anion **ii**, the decomposition of which leading to isocyanate **4** and nitroamine anion **iii**. The latter would then be methylated by MeCl to form a *N*-methylnitroamine **iv** and regenerate DBU-HCl, the true catalyst of the process.

iv which was not detected in GC-MS may be further alkylated *in situ* with MeCl to form **12**. An alternative pathway proceeding through a demethylation reaction of **6** by **iii** could also generate **iv** and **i**. However, the monitoring of the reaction indicates a continuous formation of MeCl during the reaction (Figure S1), supporting the demethylation of **6** by the chloride anion as shown in Figure 2.

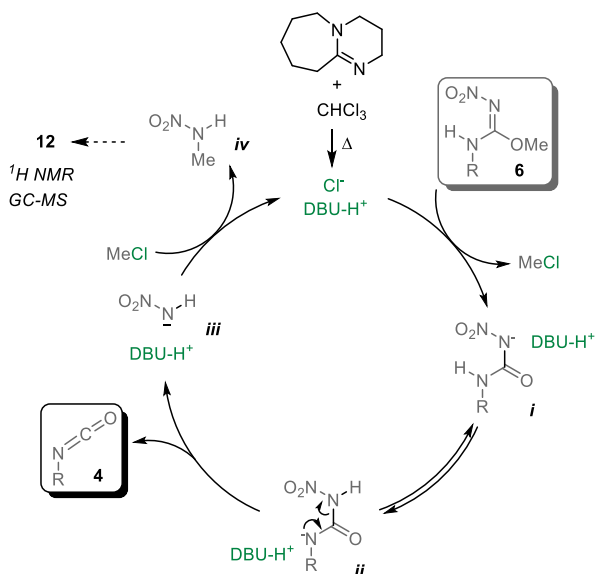
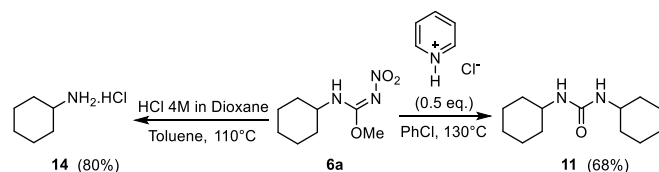


Figure 2. Putative catalytic cycle for the conversion of *O*-methyl-*N*-alkylnitroisoureas **6** into isocyanates **4**.

Our efforts to substitute the DBU-CHCl₃ medium by other sources of chloride anion (as LiCl in DMSO, DBU-HCl or pyridinium hydrochloride) led to the formation of the desired isocyanate albeit in lower yields due to the unavoidable presence of traces of water in these salts. For instance, treatment of **6a** with pyridinium hydrochloride in chlorobenzene led to urea **11** (Scheme 6), supporting the role of Cl⁻ as a catalyst and the presence of water in this hydrochloride salt. Similarly, reaction of **6a** with HCl in dioxane led to the amine as its hydrochloride salt **14** in excellent yield, demonstrating that the nitroisourea route may also constitute an attractive method to prepare free amines from alkanes.

Scheme 6. Treatment of *O*-methyl-*N*-alkylnitroisoureas **6a** under acidic conditions.

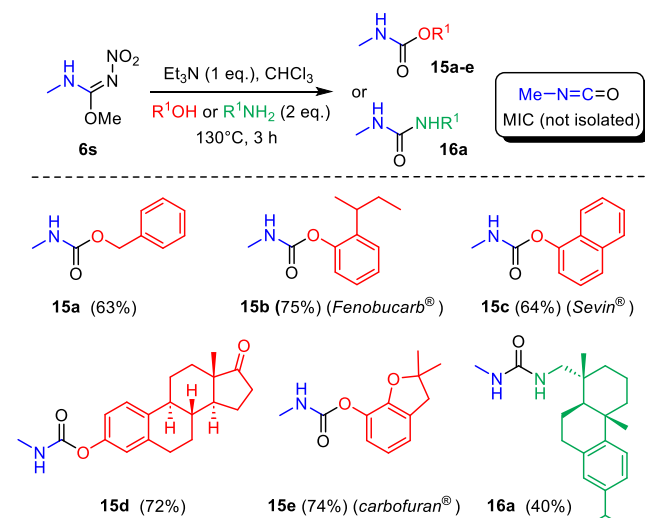


2.3. *O*-methyl-*N*-methylnitroisourea, a masked Methylisocyanate (MIC)

As discussed before, the C–H amidination of less reactive alkanes with *O*-methyl-*N*-alkylnitroisourea **6a** led to variable amount of *O*-methyl-*N*-methylnitroisourea **6s**. It is worthy of note

that **6s** may also be prepared, by a simple heating of **5a**, *t*-BuOOt-Bu, [Cu(MeCN)₄]PF₆ and **L1** at 90°C for 12h (75% yield, ESI). Application of the above demethylation protocol to **6s** would thus produce the methylisocyanate (MIC) a key component in the elaboration of the important family of carbamate pesticides (carbaryl, aldicarb, metolcarb, ...).¹⁶ MIC is a volatile and flammable colorless liquid, potentially explosive when mixed with air. It is highly toxic and was responsible for thousands of deaths in Bhopal disaster in 1984.¹⁷ It is prepared industrially by the reaction of methylamine with poisonous phosgene, leading to the *N*-methylcarbamoyl chloride, the reaction of which with Et₃N providing MIC. The development of **6s** as a safe precursor of MIC, generated *in situ*, would avoid the dangerous handling of the isocyanate.¹⁸ The above protocol was thus applied to the preparation of some methylcarbamates exploiting the high reactivity of both **6s** and MIC under these conditions. Previous conditions in Scheme 5 were slightly modified to avoid the accumulation of MIC at the end of the reaction. A one-pot process mixing an equimolar amount of NEt₃ and the reacting alcohol or amine with **6s** was thus found to lead to reaction completion in less than 3h (as compared to 24h for other isoureas) and slightly higher yields than the two-steps one pot procedure based on catalytic DBU (Scheme 5). Fenobucarb® **15b** used for the control of hemipteran pests on rice and cotton was thus prepared in this way in 75% yield, while Sevin® **15c**, a broad-spectrum systemic insecticide, was obtained in a 64% overall yield (Scheme 7). Carbamoylation of oestrone was also efficiently performed, leading to **15d** in excellent yield. Finally, urea **16a** could also be prepared following this method.¹⁹

Scheme 7. Nitroisourea **6s** as a masked “MIC”. Synthesis of carbamate insecticides.



2.4. Upcycling of polyethylenes through C–H isocyanation using *O*-methyl-*N*-nitroisourea **5a**

The efficacy of the strategy was ultimately illustrated by the functionalization of polyolefins including polyethylenes (PEs). PEs are amongst the most widely used and least expensive classes of polymers currently on the market. Their usefulness, especially in packaging, stems from their high ductility, thermal stability and

high chemical resistance. However, these attractive properties have a counterpart with the accumulation of these plastic wastes in landfills causing major environmental issues.²⁰ Recycling of polyolefins through their post-functionalization has recently emerged as a solution to the problem, offering an access to new thermoplastic materials not accessible by copolymerisation and exhibiting unique properties.²¹ The incorporation of polar functional groups on the PE polymer chains might also allow their subsequent degradation into useful chemicals, waxes and fuels.²² Functionalization of PEs is however challenging, considering the inertness of apolar C–H and C–C bonds, and the insoluble nature of these materials in organic solvents. Several studies have however been reported recently²¹ that prompt us to describe our own investigations in the field.

The above C–H amidination conditions was first applied to a linear low density polyethylene (LLDPE) (Scheme 8 and Table 2). The reaction was performed in chlorobenzene (0.5 M) as a solvent using 0.1 equivalent of **5a** and the above copper/ligand complex (0.5 mol%) for 1 eq. of LLDPE. The peroxide was added in 4 portions every 2 hours and the reaction mixture heated at 105°C overnight. The resulting polymer **P1** was then recovered through precipitation in acetone and analysed through ¹H NMR, SEC (Figure S8–10), TGA (Figure S11–13) and DSC (Figure S14–16). The presence of ¹H NMR signals at 8.85 (NH), 4.00 (OMe) and 3.84 ppm (CH–N) is diagnostic of the incorporation of the NH(C=NNO₂)OMe functional group on the polymer chain. However, in contrast with C–H amidination of short linear alkane chains **1a–t** (Scheme 1), desaturation and/or C–C cleavage also occurred as shown by multiplets at 5.41–5.47 ppm (CH=CH) and 2.05–2.09 (allylic CH₂). The ratio desaturation/C–H amidination may be estimated around 1.15:1.3 based on the integration of signals in ¹H NMR of the OMe and olefinic protons respectively. SEC analysis at 140°C also revealed that C–C bond cleavage has taken place (entry 1 vs 2, Table 2), which is further confirmed by DSC analysis and TGA, showing a noticeable decrease in melting and decomposition temperature (T_m).^{23,24} The LLDPE functionalization was determined to be 1.3 mol% by ¹H NMR (ESI).^{21f} The NEt₃-CHCl₃ mediated decomposition of the isourea functional group in **P1** led to the -NCO-modified LLDPE (not shown), which was directly treated with an excess of benzylamine to afford **P2** with conversion exceeding 95% (Scheme 8). Multiplets at 7.39–7.60 (ArH), 4.40 (benzylic CH₂N) and 3.66 ppm (CHN) are diagnostic of the formation of the benzylurea in **P2**. SEC analysis showed that the polymer chain in **P2** was not affected by the reaction which occurred selectively on the isourea motif, with no additional C–C bond cleavage (entry 3, Table 2). This was further supported by DSC and thermogravimetric analysis exhibiting similar T_m and T_d for **P1** and **P2** (entry 2 and 3). The same conditions were finally applied to a high density polyethylene (HDPE) (Scheme 8), which provided polymer **P3**, in

which again both desaturation and incorporation of an *O*-methyl-*N*-alkylnitroisourea were observed, as shown by signals in ¹H NMR at 8.85 (NH), 5.41–5.48 (CH=CH), 4.00 (OMe) and 3.84 ppm (CHN) (Figure 3). Additional COSY and HMQC experiments confirmed the structure of **P3**, and in particular the presence of allylic and olefinic protons indicative of the presence of CH=CH fragments in the polymer chain (Figure 3)(ESI). In contrast to polymers **P1** and **P2**, the SEC analysis of **P3** showed that the HDPE polymer chain did not suffer from C–C bond cleavage, the molecular weight remaining nearly constant (entry 4 vs 5)(Figure S10). The functionalization in **P3** (*i.e.* 1.0 mol%) only slightly modified the melting transition temperature of the polymer, but the crystallinity dropped significantly (32% in **P3** vs 68% in HDPE) (Figure S16). Interestingly, when the reaction was repeated using only 0.1 equivalent of *t*-BuOO*t*-Bu (4 x 0.025 eq.), the amount of desaturation also increased (olefin/C–N 2.6:1).

Scheme 8. Cu(I)-catalyzed C–H amidination of LLDPE and HDPE with **5a**.

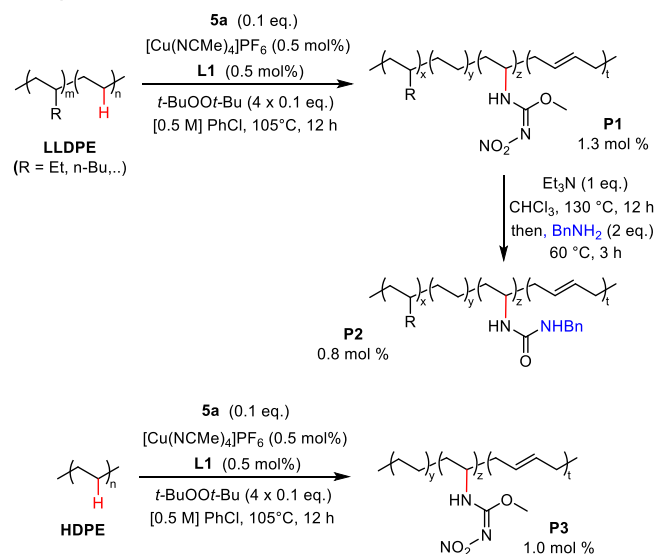


Table 2. Polyolefin analysis

entry	P	DF ^b	Mn ^c	<i>D</i> ^d	Tm ^e	Td ^f
1	LLDPE	-	61000	3.69	122	415
2 ^a	P1	1.3	29000	4.15	94	291
3	P2	0.8	28000	2.87	92	273
4	HDPE	-	21000	11.61	130	441
5 ^a	P3	1.0	18000	5.68	112	265

^a Reactions were performed with LLDPE or HDPE (1 eq.), **5a** (0.1 eq.), *t*-BuOO*t*-Bu (4 x 0.1 eq.), [Cu(MeCN)₄]PF₆ (0.5 mol%), **L1** (0.5 mol%) in chlorobenzene (0.5 M) under argon at 105°C for 12 h. ^b Degree of functionalization (in mol%). ^c Molecular weight estimated using SEC analysis. ^d Polydispersity. ^e Melting temperature measured through Differential Scanning Calorimetry (DSC). Data was taken from the second heating cycle. ^f Decomposition temperature measured through ThermoGravimetric Analysis (TGA). T_d was defined by the temperature at which 5% of total mass was lost.

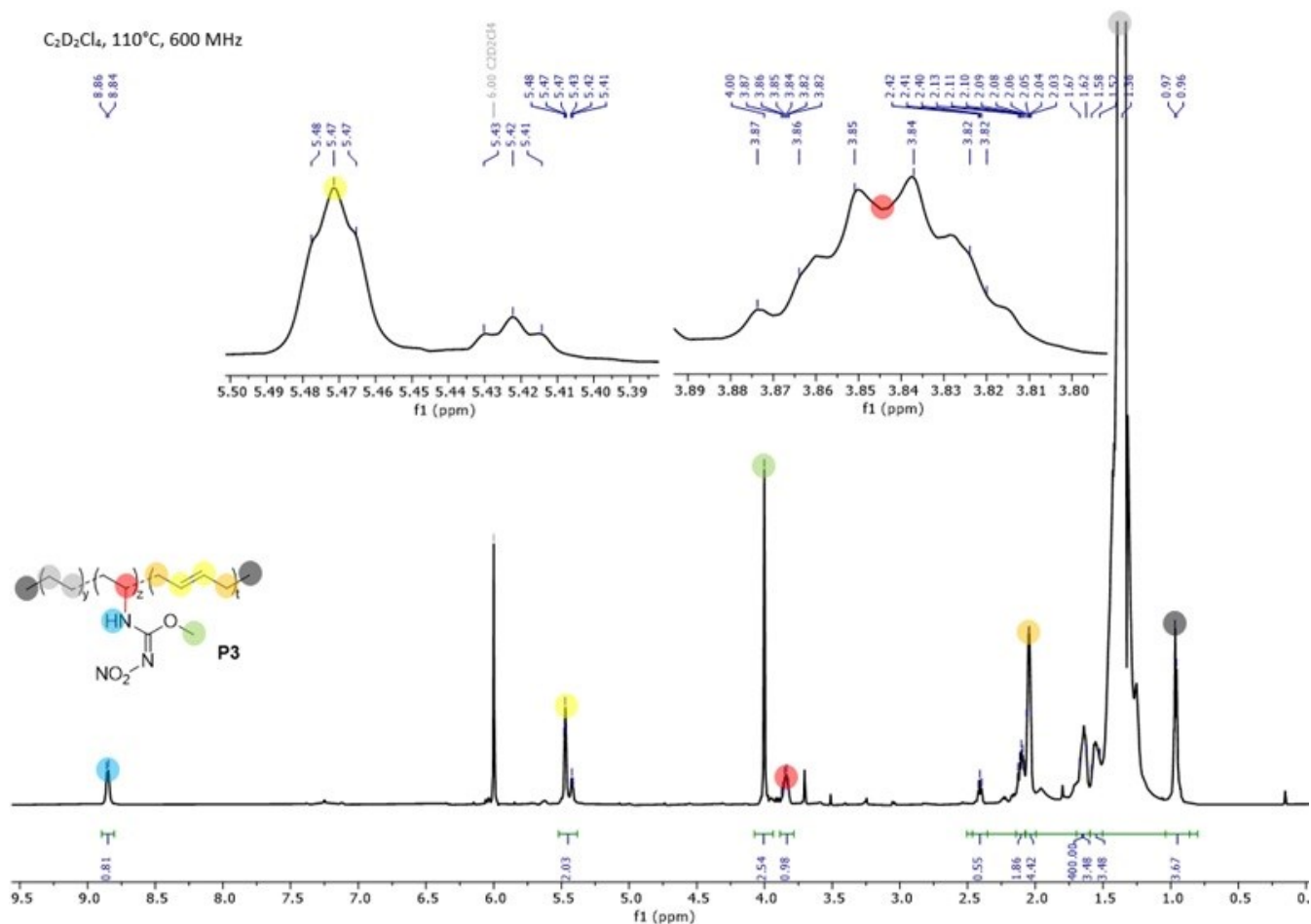


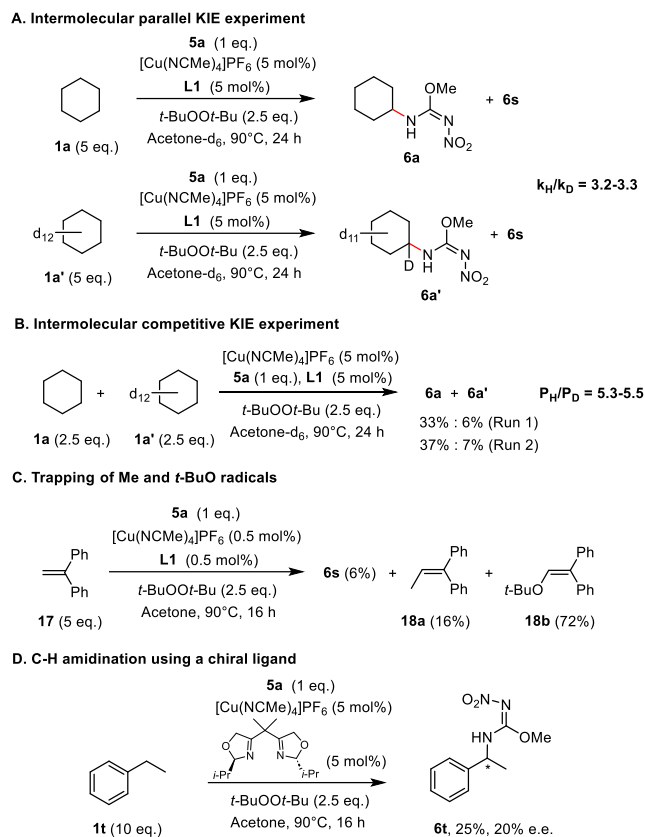
Figure 3. ^1H NMR (600 MHz, $\text{C}_2\text{D}_2\text{Cl}_4$) of a HDPE functionalized under Cu-catalyzed C–H amidination with amine **5a**.

2.5. Mechanistic studies on the C–H amidination of alkanes and polyethylenes with **5a**

To gain insight into the C–H amidination reaction mechanism and to understand the origin of the C–H amidination *versus* desaturation in the polymer series, several experiments were conducted and summarized in Scheme 9. KIE was first determined by measuring independent rate constant for the C–H amidination of cyclohexane and cyclohexane- d_{12} under standard conditions above (ESI), leading to a KIE value of 3.2 (Scheme 9A, Figures S17–S22).^{4d,25} Competition experiments led to higher ratio of products in the range of 5 (Scheme 9B, Figures S23–S24). These KIE experiments therefore suggest that the hydrogen abstraction is the turn-over limiting step of the catalytic cycle.^{4d,26} Next radical trapping experiment was performed to identify the key radical intermediates in the HAT process. When diphenylethylene **17** was added under the standard conditions, addition products **18a** and **18b** were formed in a 18/82 ratio along with **6s**, indicating the formation of methyl and *t*-butoxy radical intermediates, in good agreement with previous studies by Watanabe *et al.*²⁷ This result along with the known higher reactivity of electrophilic alkoxy radicals as compared to alkyl radicals in HAT processes point toward the *t*-BuO radical being the HAT reagent in this C–H amidination.

Recent studies by Doyle and co-workers showed that methyl radical may also act as a HAT reagent,²⁵ but exhibits good reactivity toward benzylic and tertiary C–H bonds and much poorer toward cycloalkanes. KIE value up to 12 in this study was also measured, which contrasts with the lower KIE observed here and in related C–H abstractions using *t*-BuO radicals.^{4d} Finally, ethylbenzene **1t** was treated under standard conditions, using a chiral BOX (2,2-bis((4*S*)-(–)-4-isopropylloxazoline)propane) as a ligand. This led to isourea **6t** in 25% yield and 20% e.e. (Figure S25–S26), suggesting that the C–N bond is formed via a chiral copper complex. This latter observation also indicates that the present reaction has the potential for an application to enantioselective synthesis of chiral isocyanates.

Scheme 9. Mechanistic investigations on the C–H amidination of alkanes.



A tentative catalytic cycle consistent with the above experiments and precedent from literature on the Cu/DTBP C–H amination,^{4d,4l} is depicted in Figure 4A. This includes as key-steps: the formation of the *t*-BuO radical through reduction of DTBP by a Cu(I)-L complex, which is followed by the abstraction of an hydrogen from alkane **1** by the *t*-BuO radical to form the C-centered radical **A**, along with a Cu(II) complex **B**. The latter then combines with **A** to form Cu(III) intermediate **C**, or with the methyl radical issued from the β -scission of *t*-BuO to form **D**. Reductive elimination of **C** and **D** gives rise respectively to **6a-t** and **6s**,²⁸ regenerating the Cu(I) catalyst. As mentioned above, the access to benzylic amidine **6t** with some enantiocontrol, rules out the formation of a carbocation **E** through a radical-polar crossover process. In the polymer series, the C–H amidination was also accompanied by a desaturation of the polymer chain. The presence of unsaturations resulting from chain scission during free-radical oxidation of polyolefins is well documented.^{21,23} Desaturation within the polymer chain is however surprising, notably for HDPE, where C–C bond cleavage is not observed. Noticeably, such desaturation was not observed during the C–H amidination of alkane chains in **1j-n** and formation of **6j-n** (Scheme 1). Conversion of alkyl radicals into olefins in Cu-catalyzed oxidation of alkanes has been thoroughly studied by Kochi *et al.*²⁹ Cu(I)-catalyzed desaturation process may follow a radical polar crossover pathway, through an intermediate such as **E** or a β -elimination from alkyl-Cu(III) intermediate such as **C**. Desaturation through the former pathway may be excluded on the basis of experiment D (Scheme 9). The formation of a Cu(III) complex such as **C** is likely to be sensitive to steric hindrance around the radical center³⁰ as indicated by the preferential and low yielding methyl C–H functionalization in model compounds **6l-m** (Scheme 1). Based on these observations and literature reports,^{4d,29,30} it may be argued that the bulky Cu(II)-NHR complex **A** is experiencing difficulties to access the sterically hindered macroradical

due the long (and probably folded) alkyl chains in LLDPE and HDPE (*path b*, Figure 4B),³¹ slowing down the formation of the intermediate Cu(III) complex **C**. The macroradical, would then follow a less sterically demanding *path a* (Figure 4B), through **C'**, leading to significant amount of desaturation within the polymer chain. The same reasoning may explain the absence of tertiary C–H amidination products observed in Scheme 2, which does not reflect the reported site selectivity during C–H abstraction by *t*-BuO radicals,^{12b} but rather the slow coupling reaction between tertiary C-centered radicals and amino-Cu complex such as **B** (ESI). Finally, the lower amount of **5a** per C–H motif in PE compared to simple alkanes would also support *path a* and the desaturation observed in the former and not the latter.

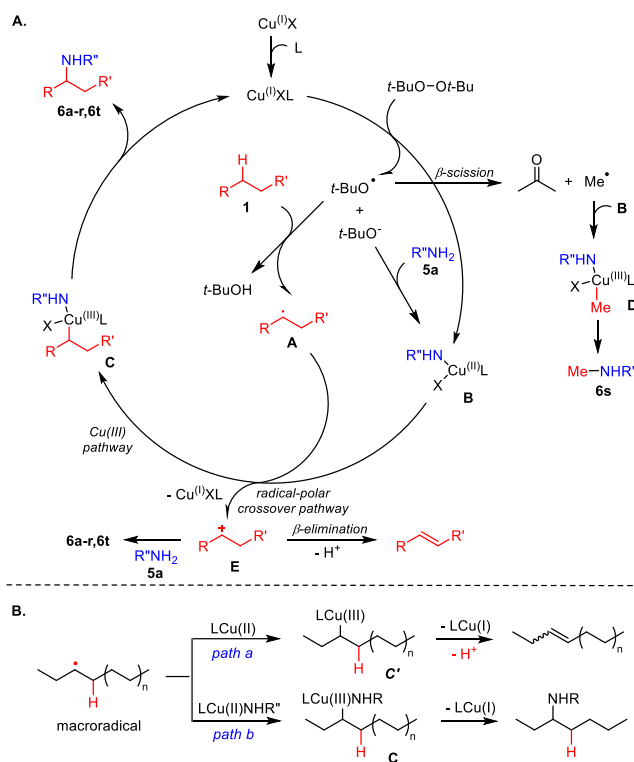


Figure 4. Catalytic cycle of the C–H amidination. Putative mechanism for the C–H amidination *versus* desaturation in polyolefins.

The above experiments thus demonstrate that the Cu-catalyzed C–H amidination of polyolefins using **5a** constitutes a straightforward strategy to incorporate an isocyanate functional group into commodity polymers such as PE's. The particular reactivity of the isocyanate function offers a very attractive gateway to a wide range of functional polymers with new properties starting from post-consumer wastes. The competing desaturation of the polymer chain also offers an additional functional group to anchor useful functional groups thus widening the field of applications of the future material. In addition, the access to shorter NCO-functionalized PE chains through β -scission or C–C bond cleavage in LLDPE may also be of interest, due to their higher solubility and higher bioavailability with potent biological applications.³²

3. CONCLUSION

In summary, we report here an unprecedented C–H amidination of hydrocarbons using readily available *O*-methyl-*N*-nitroisourea **5a** as a masked isocyanate functional group. This strategy allows the incorporation on a carbon backbone of the highly reactive isocyanate function using benign urea as phosgene surrogate. Various linear and cyclic alkanes were thus converted into *O*-methyl-*N*-alkylnitroisoureas **6** in moderate to good yields. The later were then converted through an unusual Krapcho-type demethylation, into the desired isocyanates, which were reacted *in situ* with alcohols and amines to give the corresponding urethanes and ureas in high yields. This simple procedure was extended to the *in situ* generation of poisonous, yet very useful, methylisocyanate (MIC). Finally, the method was applied to the functionalization of commodity polymers such as polyethylenes. The recycling of these plastic wastes under mild conditions is particularly attractive giving access to new materials, which would be difficult to prepare through classical copolymerization methods.^{20,21}

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