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

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The Cu-catalyzed C-H activation of alkanes in the presence of O-methyl-N-nitroisourea affords a facile entry to O-methyl-N-alkylnitroisoureas, shelf stable and benign isocyanate precursors. The latter is 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 a low density polyethylene.

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 process of simple unfunctionalized and functionalized hydrocarbons **1** have been reported (Figure 1, **A**).[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 first reported in 2017 by Groves *et al.* (Scheme 1, **B**).[5] A remote Cu-catalyzed C-H abstraction then isocyanation using TMSNCO proceeding through a sulfonamidyl radical was described by Zhang.[6] A more recent work by Stahl and co-workers[7] described the direct isocyanation of benzylic substrates using a copper catalyst and NFSI as the hydrogen atom transfer agent. Beside hydrocarbon precursors, isocyanates may also be accessed through the alkylation of alkyl halides using nitrocyanamide silver salts as reported earlier by Boyer *et al.* (Scheme 4, **C**).[8] This overlooked approach relies on a silver nitrocyanamide salt available through a basic treatment of *S*-methyl-*N*-nitroisourea **2**. Thermal rearrangement of the resulting *N*-alkylnitrocyanamide **3** was believed to occur through *N*-nitrocarbodiimide **I**, finally decomposing into the isocyanate **4** and N_2O. Recent studies by Churakov and co-workers clearly established the thermal decomposition of **I** into isocyanates.[9]

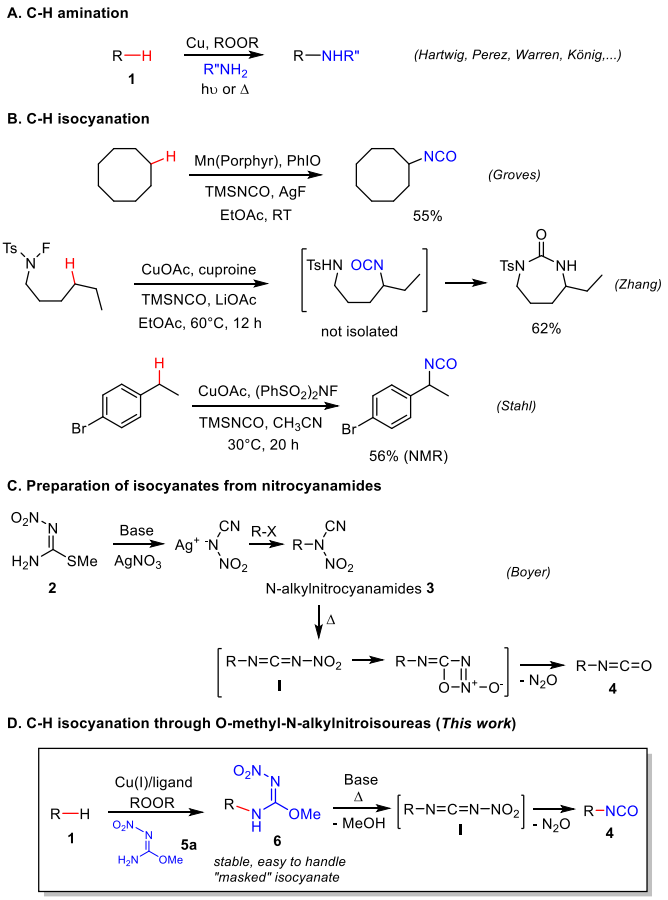

Figure 1. Literature precedent on C-H amination **(A)**, isocyanation **(B)** and preparation of isocyanates from *N*-alkylnitrocyanamides **(C)**. Present work on the C-H isocyanation using *O*-methyl-*N*-nitroisourea **5a (D)**.

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 (Scheme 4, **D**). In turn, **6** might be available through a metal-catalyzed C-H amination of hydrocarbons using simple *O*-methyl-*N*-nitroisourea **5a**, available in only two-steps

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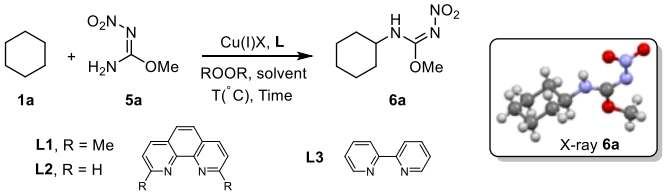
Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data (^{1}H and ^{13}C NMR, HRMS, FTIR) for all new compounds (PDF).

on gram scale from cheap 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. We thus 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 access to intermediate **I** from **6** we also uncovered an efficient entry to isocyanates **4** from **6** through an unprecedented Krapcho-type process.[10] This methodology thus gives rise to a range of aminated products from simple hydrocarbons, including polyolefin waste on demand using *N*-alkylnitroisoureas **6** as non-toxic isocyanate surrogates.

Results and discussion

The first part of the study was devoted to the development of the so far unknown C-H amination of alkanes using *O*-methyl-*N*-nitroisourea **5a** as the aminating agent under Cu(I) catalysis.[4] Optimization of the C-H amination reaction was performed using cyclohexane 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, the soluble $[Cu(MeCN)_4]BF_4$ salt was found to be the most active copper salt for the reaction, leading to the desired product **6a** in 78% isolated yield (Table 1, entry 1). The structure of **6a** was unambiguously attributed through X-ray diffraction studies (XDRS, ESI) indicating that the reaction occurred at the NH_2 moiety of **5a** and not at tautomeric NH-NO_2 center. A unique isomer of the nitrosourea was obtained, the stereochemistry of which was assigned based on XRDS, showing hydrogen bonding between the NH and one of the NO_2 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). The choice of the solvent proved also to be crucial, with the "greener" acetone leading consistently to higher yields (entries 6-10). Polarity of the medium also seems to influence the efficiency of the process as indicated by higher yields observed in both acetone and nitromethane (entry 9). 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 11-12), while the absence of ligand led to low efficiency (entry 13). 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 14). It is worthy of note that at this temperature, the *t*-BuO radical is known to fragment, into acetone and the highly reactive methyl radical which can also act as a hydrogen atom transfer (HAT) agent (*vide infra*).[11] Interestingly, polarity of the solvent is also reported to accelerate this process. 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 15), so that 2.5 equivalent was kept as optimal conditions. Decreasing the amount of cyclohexane did not affect the isolated yield (entry 16), while simultaneously increasing the amount of **5a** slightly improved the yield (entry 17). An excess of alkane is however required as shown in entries 18-20, where satisfying yields are maintained only when increasing in the same time the amount of **5a** (entry 20). The efficiency of the process using only 1 equivalent of alkane is however noteworthy considering reported literature where the hydrocarbons is usually used in excess.[4d] A temperature of 90°C was found to be optimal, as lowering the temperature to 60°C led to lower yield (entry 21) or no conversion at 30°C (entry 22). Finally, decreasing the amount of copper catalyst led to reduced yield (entry 23). Up-scaling of the process was also performed starting from 5 mmol of **5a** and cyclohexane (10 equiv.) which led to the isolation of 3.31 grams of **6a** (66% yield).

Table 1 Optimization of the C-H amination of **1a** with *O*-methyl-*N*-nitroisourea **5a**.

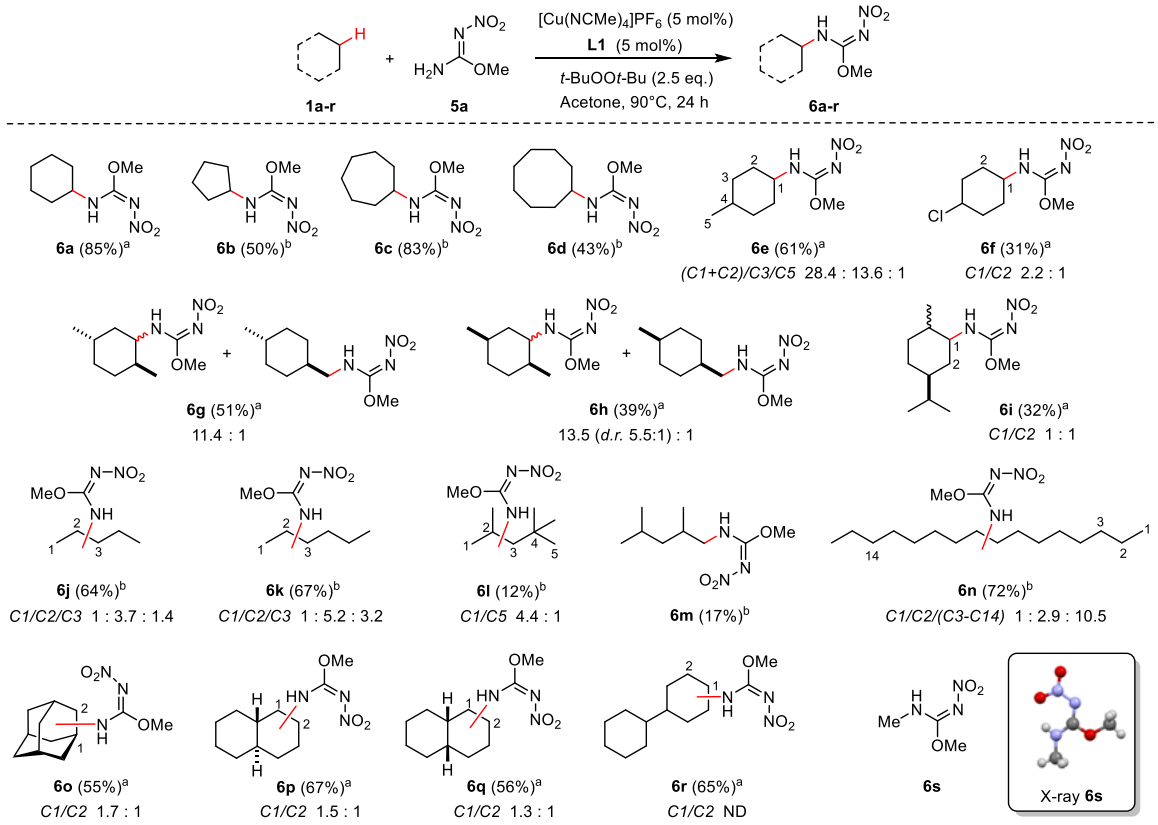


entry[a]	L	ROOR	Cu(I)X	Solvent	Yield (%)[b]
1	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]BF_4$	Acetone	78
2	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	79
3	**L1**	*t*-BuOO*t*-Bu	CuCl	Acetone	5
4	**L1**	*t*-BuOO*t*-Bu	CuI	Acetone	4
5	**L1**	*t*-BuOO*t*-Bu	CuOAc	Acetone	8
6	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	CH_3CN	11
7	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	$PhCF_3$	15
8	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	benzene	7
9	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	CH_3NO_2	58
10	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	CH_2Cl_2	25
11	**L2**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	32
12	**L3**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	28
13	-	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	7
14	**L1**	AcOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	1
15[c]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	66
16[d]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	80
17[e]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	85
18[f]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	59
19[g]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	46
20[h]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	64
21[i]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	16
22[j]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	-
23[k]	**L1**	*t*-BuOO*t*-Bu	$[Cu(MeCN)_4]PF_6$	Acetone	60

[a] Unless 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 acetone (1.0 mL) under argon at 90°C for 24 h. [b] Isolated yields. [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] **1a** (2 eq.) and **5a** (0.5 mmol.). [g] **1a** (1.5 eq.) and **5a** (0.5 mmol.). [h] **1a** (1 eq.) and **5a** (1 mmol.). [i] 60°C instead of 90°C. [j] 30°C instead of 90°C. [k] $[Cu(MeCN)_4]PF_6$ (0.02 eq.), **L1** (0.02 eq.).

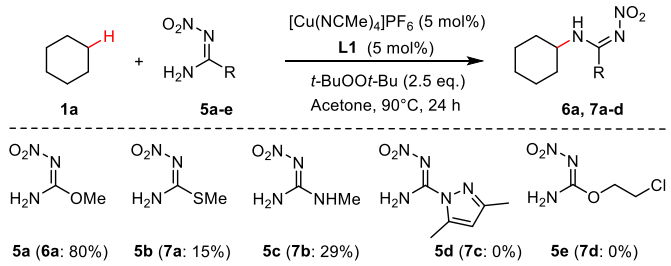
The scope and limitation of the C-H amidination was then established using amidine **5a** and varying the nature of the alkanes **1a-r** (Scheme 2). Overall, nitroisoureas **6b-r** were obtained with yields ranging between modest and good using 5 and up to 20 equivalents of alkanes relative to **5a**, depending on the nature of the alkane. Volatile alkanes for instance generally led to improved yields when used in larger excess. Regioselectivities indicate a pro-eminence for the CH_2 abstraction as compared to the CH_3, in good agreement with

studies of Hartwig *et al.*[4d] Interestingly amination at the usually more reactive tertiary C-Hs are not observed likely for steric reasons.[12] Unsubstituted cyclic alkanes reacted smoothly to provide the desired nitroisoureas **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 in which the C-H bond away from the chlorine atom appears as the more reactive. *Cis*- and *trans*-1,4-dimethylcyclohexanes led to CH_2/CH_3 activation (*i.e.* **6g-h**) and no reaction at the tertiary site, with site-selectivities in good agreement with reports on related amidation.[4d] The methodology was successfully extended to aliphatic systems. Similarly to their cyclic analogues, methylene C-H were also more reactive than primary and tertiary C-H. This is illustrated with regioisomers ratio in **6j**, **6k** and hexadecane **6n**. When steric effects become significant and CH_2 less accessible, then functionalization at CH_3 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] Finally, it is worth mentioning that with poorly reactive alkanes, variable amount of O-methyl-N-methylnitroisourea **6s** was also isolated, as a result of the coupling between methyl radical, issued from the decomposition of the *t*-BuO radical,[11] and the Cu-amine complex.[4d] As discussed below, **6s** may find interesting applications as methylisocyanate (MIC) surrogate.



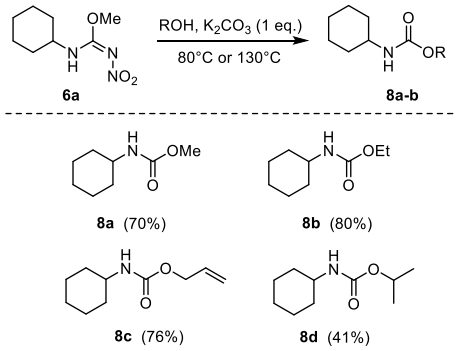
Scheme 2. Scope of the Cu(I)-catalyzed C-H amination of alkanes **1a-r** with *O*-methyl-*N*-nitroisourea **5a**. [a] 5 eq. of alkane is used. [b] 20 eq. of alkane is used.

The optimized conditions above (Table 1, entry 16) were extended to other nitroisoureas **5b-e**, possessing a different leaving group (R) on the central carbon center (*vide infra*). **5b-e** were readily available from the corresponding urea or thiourea (ESI). *S*-methyl-*N*-nitroisothiourea **5b** and nitroguanidine **5c** provided the desired C-H amination product **7a-b**, albeit in low yields (Scheme 3). In contrast, azole **5d** led only to recovered starting material, while **5e** suffered from the nucleophilic displacement of the chlorine atom by the NH_2 group, thus preventing the formation of the desired **7d**.

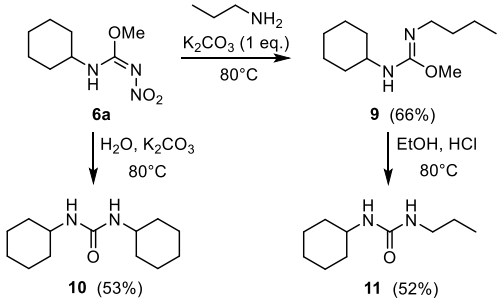


Scheme 3. C-H amination using various nitro-isoureas **5a-e**.

The conversion of *O*-methyl-*N*-alkylnitroisoureas **6** into isocyanates **4** has not been reported to date (Scheme 4).[9] However, it was anticipated that treatment of **6** under appropriate basic conditions would generate the *N*-nitrocarbodiimide intermediate **I**, discussed above, through elimination of MeOH (Figure 1, D). The methanol elimination from *O*-methyl-*N*-cyclohexylnitroisourea **6a** was thus investigated varying the nature of the base. Carbonates, NaOH, KOH, K_3PO_4 or NaOEt in alcohols as solvents were thus tested (ESI), K_2CO_3 invariably leading to the best yields in urethanes **8a-d** (Scheme 4). As expected, higher conversion in urethanes were obtained using primary alcohols at 80°C, although secondary alcohols were also shown to react, but a 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*-alkylisourea **9** was isolated in good yield (Scheme 5). 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**.

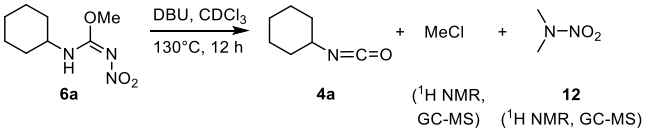


Scheme 4. Base-catalyzed decomposition of *O*-methyl-*N*-alkylnitroisoureas **6a** into urethanes **8**.



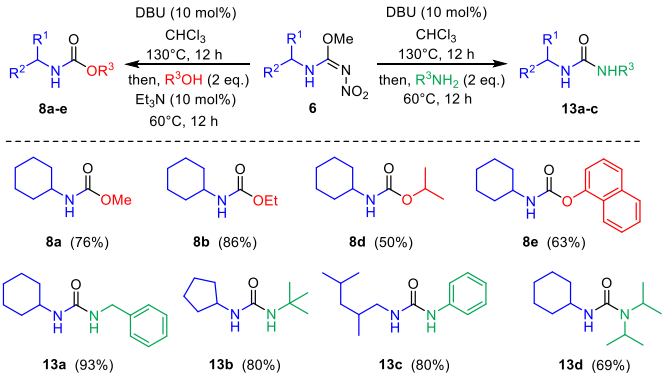
Scheme 5. Addition of amines to *O*-methyl-*N*-alkylnitroisoureas **6a**.

Although the treatment of *O*-methylnitroisoureas **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 ^{1}H NMR studies on the base-catalysed elimination reaction of **6a** in $CDCl_3$ using DBU as a base, we observed the unexpected formation of the isocyanate **4a** after heating the reaction mixture at 130°C for 12h (Scheme 6). The ^{1}H NMR of the crude reaction mixture showed the formation of **4a** along with a compound presenting a singlet at 3.05 ppm attributed to MeCl, which was confirmed through GC-MS (ESI). *N*,*N*-Dimethylnitroamine **12** was also formed after 3 h as shown by ^{1}H NMR and GC-MS (ESI), but progressively disappeared due to its known instability at this temperature.[14]



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

4a could be isolated in high yield, but was more conveniently reacted *in situ* with a suitable nucleophile. As summarized in Scheme 7, 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 Et_3N 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 excellent yields. Secondary amines also proved reactive under these conditions as shown with the synthesis of **13d**.



Scheme 7. Conversion of *O*-methyl-*N*-alkylnitroisoureas **6** into urethanes **8** and ureas **13**.

A tentative mechanism to rationalize the quantitative formation of isocyanate **4** from **6** in the presence of a catalytic amount of DBU in $CHCl_3$ is depicted in Figure 2. Formation of both MeCl and **12** as by-products strongly support the displacement of the methyl substituent in **6** by a chloride anion as for instance in Krapcho decarboxylation.[10] The formation of Cl^- might result from the deprotonation of chloroform by DBU to produce a dichlorocarbene and DBU-H^+Cl^-, although our efforts to trap Cl_2C:, through cyclopropanation of styrene or C-H insertion in adamantane, met with failure. Nucleophilic substitution of a chlorine atom from $CHCl_3$ by DBU constitutes another option. This demethylation would thus form intermediate ***i***, the protonation of which with DBU-H^+ ($pka_{(DMSO)}$ = 12) leading to the nitroisourea ***ii*** (estimated pK ~ 20), which could then react with the free DBU to form the isocyanate **4**, along with a nitroamine anion ***iii***. The latter would then be methylated by MeCl to form a *N*-methylnitroamine ***iv*** and regenerate DBU-H^+Cl^-, the true catalyst of the process. ***iv*** which was not detected in GC-MS may be further alkylated 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, supporting the demethylation of **6** by the chloride anion as shown in Figure 2.

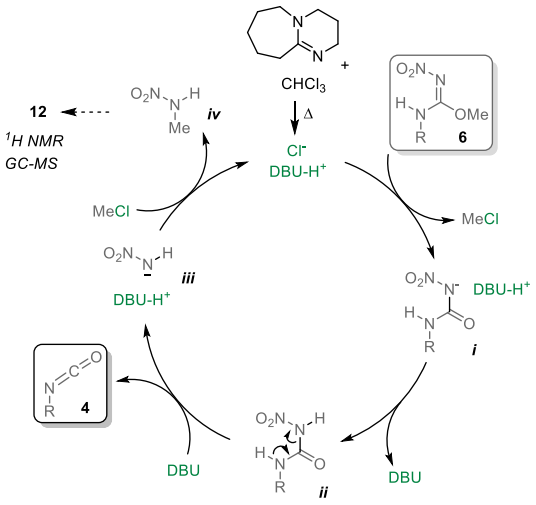
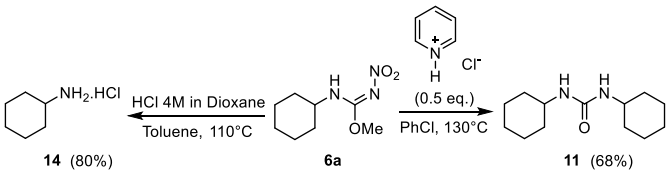


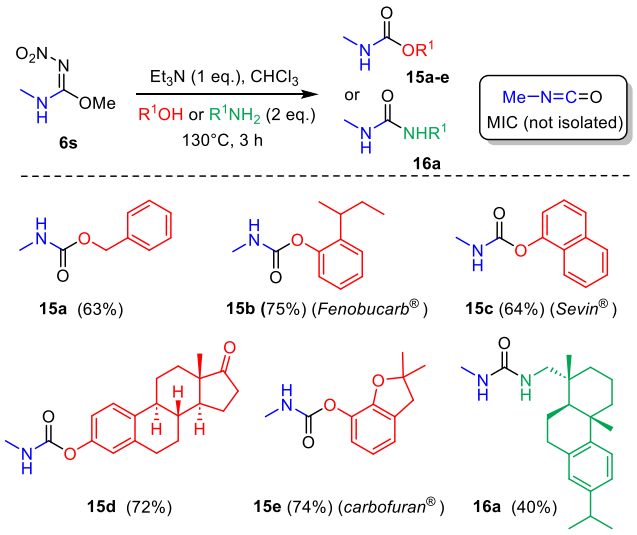
Figure 2. Putative mechanism for the conversion of *O*-methyl-*N*-alkylnitroisoureas **6** into isocyanates **4**.

Our efforts to substitute the DBU-$CHCl_3$ medium by other sources of chloride anion (as LiCl in DMSO, DBU-H^+Cl^- 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 8) in 68% yield 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 it hydrochloride salt **14** in excellent yield, demonstrating that the nitroisourea route may also constitute an attractive method to prepare free amines from alkanes.



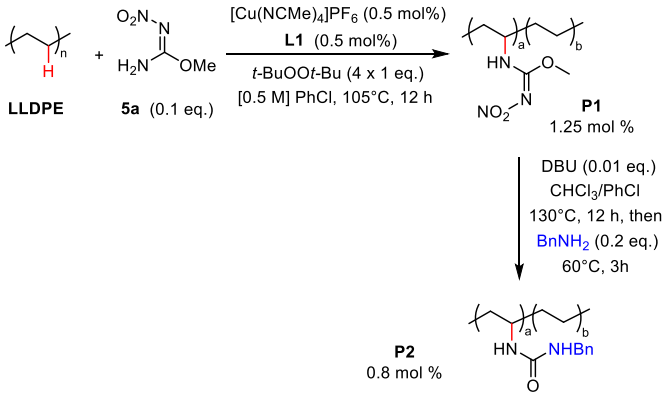
Scheme 8. Treatment of *O*-methyl-*N*-alkylnitroisoureas **6a** under acidic conditions.

As mentioned before, when the C-H amination of alkanes with *O*-methyl-*N*-alkylnitroisourea **6a** was less efficient, variable amount of *O*-methyl-*N*-methylnitroisourea **6s** accompanied the desired product.[4d] Application of the above protocol to **6s** would produce the methylisocyanate (MIC) a key component in the elaboration of the important family of carbamate pesticides (carbaryl, aldicarb, metolcarb,….).[15] 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.[16] It is prepared industrially by the reaction of methylamine with poisonous phosgene leading to the *N*-methylcarbamoyl chloride, the reaction of which with Et_3N providing MIC. Among the measures taken by the chemical industry to avoid the dangerous handling of MIC, one was to develop a less hazardous alternative to MIC production that would consume the MIC immediately upon its generation.[17] 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 7 were slightly modified to avoid the accumulation of MIC at the end of the process. The alcohol was directly mixed at the start of the process with an equimolar amount of base (Et_3N) in $CHCl_3$ as a solvent, leading to reaction completion in less than 3h (as compared to 24h for other isoureas). 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 9). Carbamoylation of oestrone was also efficiently performed, leading to **15d** in excellent yield. Finally, urea **16a** could also be prepared following this method. It is worthy of note that **6s** may also be prepared, by a simple heating of **5a**, *t*-BuOO*t*-Bu, $Cu(CH_3CN)_4]PF_6$ and **L1** at 90°C for 12h (75% yield, ESI).



Scheme 9. Nitroisourea **6s** as a masked "MIC". Synthesis of carbamate insecticides.

Finally, the strategy was extended to the functionalization of a linear polyolefin such as polyethylene. 35% of the polymers produced in the world are polyolefins, of which an estimated 95% are single-use and account for plastic wastes.[18] Therefore, in the same way that it is particularly attractive to functionalise bioactive molecules at a late stage in order to access new drug-like molecule platforms, the functionalization of branched polyolefins would allow the recycling of these plastic wastes in order to produce new high-performance thermoplastic materials. The functionalization of these aliphatic chains in a controlled manner under mild conditions is however challenging, considering the strength of the C-H bonds, but also the insoluble nature of these materials in organic solvents. Several studies have however recently emerged in this context[19] that prompt us to describe our own investigations. The C-H amination sequence devised above was thus applied to a linear low density polyethylene (LLDPE). Solubilization of the LLDPE was achieved in chlorobenzene at 105°C, using 0.1 eq. of **5a** as aminating agent. After heating overnight at this temperature, the polymer **P1** was precipitated in acetone. The LLDPE functionalization was determined to be 1.25 mol% by ^{1}H NMR (relative to repeat unit).[19f] DBU-catalyzed decomposition of the isourea functional group led to the -NCO-modified LLDPE, which was directly treated with an excess of benzylamine to afford **P2**, showing urea fragment incorporated along the carbon chain. The above experiment thus demonstrates that upcycling of post-consumer waste offers an opportunity to create new materials, with novel mechanical properties, which would be difficult to elaborate for instance through co-polymerization.



Scheme 10. Cu(I)-catalyzed C-H nitroamination of low density polyethylene (LLDPE).

Conclusions

In summary, we report here an unprecedented C-H amination 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 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). This safe method should find applications for late stage derivatization of biological active alcohols and amines. Finally, the method was applied to the functionalization of commodity polymers such as polyethylene. The recycling of these plastic wastes under mild conditions is particularly attractive giving access to new materials inaccessible by traditional polymerization methods.[19]

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1. *(a)* M. C. White, *Science*, 2012, **335**, 807-809; *(b)* C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi and A. Lei, *Chem. Rev.*, 2015, **115**, 12138-12204; *(c)* J. F. Hartwig and M. A. Larsen, *ACS Cent. Sci.*, 2016, **2**, 281-292; *(d)* J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754-8786; *(e)* J. C. K. Chu and T. Rovis, *Angew. Chem. Int. Ed.*, 2018, **57**, 62-101; *(f)* T. W. Lyons, M. S. Sanford, *Chem. Rev.*, 2010, **110**, 1147-1169; *(g)* O.

Daugulis, J. Roane and L. D. Tran, *Acc. Chem. Res.*, 2015, **48**, 1053-1064; (h) D. Dailler, G. Danoun, O. Baudoin *Top. Organomet. Chem.* Eds.: Dixneuf, P. H., Doucet, H., C–H bond activation and catalytic functionalization II, 2016, 133-154.

2. *(a)* M. Huang, J. Ma, Z. Zou, H. Li, J. Liu, L. Kong, Y. Pan, W. Zhang, Y. Liang and Y. A Wang, *Chem. Sci.*, 2022, 10.1039.D2SC03989C. https://doi.org/10.1039/D2SC03989C. *(b)* W. L. Czaplyski, C. G. Na and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 13854–13857. *(c)* R. K. Quinn, Z. A. Könst, S. E. Michalak, Y. Schmidt, A. R. Szklarski, A. R. Flores, S. Nam, D. A. Horne, C. D. Vanderwal and E. J. Alexanian, *J. Am. Chem. Soc.*, 2016, **138**, 696-702. *(d)* Q. Michaudel, D. Thevenet and P. S. Baran, *J. Am. Chem. Soc.*, 2012, **134**, 2547-2550.
3. *(a)* R. A. Johnson and F. D. Greene, *J. Org. Chem.,* 1975, **40**, 2186-2192. *(b)* R. A. Johnson and F. D. Greene, *J. Org. Chem.,* 1975*,* **40***, 2192-2196 (c)* D. Ravelli, S. Protti and M. Fagnoni, *Acc. Chem. Res.*, 2016, **49**, 2232–224. *(d)* G.-X. Li, C. A. Morales-Rivera, F. Gao, Y. Wang, G. He, P. Liu and G. Chen, *Chem. Sci.*, 2017, **8**, 7180–7185. *(e)* H. Yue, C. Zhu, L. Huang, A. Dewanji and M. Rueping, *Chem. Commun.*, 2022, **58**, 171–184. *(e)* C. L. Hill, J. A. Smegal and T. J. Henly, *J. Org. Chem.*, 1983, **48**, 3277–3281. *(f)* Y. Jin, Q. Zhang, L. Wang, X. Wang, C. Meng and C. Duan, *Green Chem*., 2021, **23**, 6984-6989 *(g)* S. M. Treacy and T. Rovis, *J. Am. Chem. Soc.*, 2021, **143**, 2729–2735. *(h)* R. Mao, S. Bera, A. C. Turla and X. Hu, *J. Am. Chem. Soc.*, 2021, **143**, 14667–14675. *(i)* Z. Zhang, P. Chen and G. Liu, *Chem Soc Rev*, 2022, **51**, 1640-1658. *(j)* L. Capaldo, D. Ravelli and M. Fagnoni, *Chem. Rev.*, 2022, **122**, 1875–1924. *(k)* M. Galeotti, M. Salamone and M. Bietti, *Chem. Soc. Rev.*, 2022, **51**, 2171–2223. *(l)* Q. Zhang, S. Liu, J. Lei, Y. Zhang, C. Meng, C. Duan and Y. Jin, *Org. Lett.*, 2022, **24**, 1901–1906. *(m)* Y. Qiu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2020, **142**, 19239–19248. *(n)* K. Ohkubo, A. Fujimoto and S. Fukuzumi, *Chem. Commun.*, 2011, **47**, 8515. *(o)* L. Capaldo, S. Bonciolini, A. Pulcinella, M. Nuño and T. Noël, *Chem. Sci.*, 2022, **13**, 7325–7331. *(p)* R. Zhang, W. Zhou and J. J. Warren, *Chem. Commun.*, 2021, **57**, 4007–4010. *(q)* M. Oliva, G. A. Coppola, E. V. Van der Eycken and U. K. Sharma, *Adv. Synth. Catal.*, 2021, **363**, 1810–1834. *(r)* N. Holmberg-Douglas and D. A. Nicewicz, *Chem. Rev.*, 2022, **122**, 1925–2016. *(s)* A. J. McMillan, M. Sieńkowska, P. Di Lorenzo, G. K. Gransbury, N. F. Chilton, M. Salamone, A. Ruffoni, M. Bietti and D. Leonori, *Angew. Chem. Int. Ed.*, 2021, **60**, 7132–7139. *(t)* A. M. Carestia, D. Ravelli and E. J. Alexanian, *Chem. Sci.*, 2018, **9**, 5360–5365. *(u)* Y. Yang, W. Gao, Y. Wang, X. Wang, F. Cao, T. Shi and Z. Wang, *ACS Catal.*, 2021, **11**, 967–984. *(v)* H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016–9085. *(w)* A. Fawcett, M. J. Keller, Z. Herrera and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2021, **60**, 8276–8283. *(x)* M. Borrell, S. Gil-Caballero, M. Bietti and M. Costas, *ACS Catal.*, 2020, **10**, 4702–4709. *(y)* S. A. Moteki, A. Usui, T. Zhang, C. R. Solorio Alvarado and K. Maruoka, *Angew. Chem. Int. Ed.*, 2013, **52**, 8657–8660. *(z)* Z. Ye, Y. Lin and L. Gong, *Eur. J. Org. Chem.*, 2021, **2021**, 5545–5556.
4. *(a)* G. Pelletier, D. A. Powell, *Org. Lett.*, 2006, **8**, 6031-6034. *(b)* S. Wiese, Y. M. Badici, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari, T. H. Warren, *Angew. Chem. Int. Ed.*, 2010, **49**, 8850-8855. *(c)* R. T. Gephart III, D. L. Huang, M. J. B. Aguila, G. Schmidt, A. Shahu, T. H. Warren, *Angew. Chem. Int. Ed.,* 2012, **51**, 6488-6492. *(d)* B. L. Tran, B. Li, M. Driess, J. F. Hartwig, *J. Am. Chem. Soc.*, 2014, **136**, 2555-2563. *(e)* M. A. Fuentes, R. Gava, N. I. Saper, E. A. Romerro, A. Caballero, J. F. Hartwig, P. J. Pèrez, *Angew. Chem. Int. Ed.*, 2021, **60**, 18467-18471. *(f)* G. Deng, W. Chen and C.-J. Li, *Adv. Synth. Catal.*, 2009, **351**, 353–356. *(g)* G. Laudadio, Y. Deng, K. van der Wal, D. Ravelli, M. Nuño, M. Fagnoni, D. Guthrie, Y. Sun and T. Noël, *Science*, 2020, **369**, 92–96. *(h)* R. Narobe, K. Murugesan, C. Haag, T. E. Schirmer and B. Konig, *Chem. Commun.*, 2022, **58**, 8778-8781. *(i)* S. Wiese, Y. M. Badiei, R. T. Gephart, S. Mossin, M. S. Varonka, M. M. Melzer, K. Meyer, T. R. Cundari and T. H. Warren, *Angew. Chem., Int. Ed.*, 2010, **49**, 8850–8855. *(j)* X. Wu, K. Yang, Y. Zhao, H. Sun, G. Li and H. Ge, Nat Commun, 2015, 6, 6462. *(k)* P. K. Chikkade, Y. Kuninobu and M. Kanai, *Chem. Sci.*, 2015, **6**, 3195–3200. *(l)* F. Teng, S. Sun, Y. Jiang, J.-T. Yu and J. Cheng, *Chem. Commun.*, 2015, **51**, 5902–5905. *(m)* C.-S. Wang, X.-F. Wu, P. H. Dixneuf and J.-F. Soulé, *ChemSusChem*, 2017, **10**, 3075–3082. *(n)* W. S. Ham, J. Hillenbrand, J. Jacq, C. Genicot and T. Ritter, *Angew. Chem. Int. Ed.*, 2019, **58**, 532–536. *(o)* Y.-W. Zheng, R. Narobe, K. Donabauer, S. Yakubov, B. König, *ACS Catal.*, 2020, **10**, 8582-8589.
5. X. Huang, P. A. Kates, H. Gao, X. Chen and J. T. Groves *J. Am. Chem. Soc.,* 2017, **139**, 15407-15413.
6. H. Zhang, P. Tian, L. Ma, Y. Zhou, C. Jiang, X. Lin and X. Xiao, *Org. Lett.*, 2020, **22***,* 997-1002.
7. S.-E. Suh, L. E. Nkulu, S. Lin, S. W. Krska and S. S. Stahl, *Chem. Sci.*, 2021, **12**, 10380-10387.
8. J. H. Boyer, T. Manimaran and L. T. Wolford, *J. Chem. Soc.*, *Perkin Trans I* 1988, 2137-2140.
9. *(a)* A. M. Churakov, S. L. Ioffe, A. A. Voronin, and V. A. Tartakovsky, *Russ. Chem. Bull., Int. Ed.* 2017, **66**, 991-994. *(b)* A. M. Churakov, S. L. Ioffe, A. A. Voronin, and V. A. Tartakovsky, *Russ. Chem. Bull., Int. Ed.* 2018, **67**, 56-60.
10. A. P. Krapcho and A. J. Lovey, *Tetrahedron Lett.*, 1973, **14**, 957-960.
11. T. Nakamura, W. K. Busfield, I. D. Jenkins, E. Rizzardo, S. H. Thang, S. Suyama, *J. Org. Chem.*, 2000, **65**, 16-23.
12. *(a)* V. A. Schmidt, R. K. Quinn, A. T. Brusoe, and E. J. Alexanian, *J. Am. Chem. Soc.,* 2014, **136**, 14389-14392. *(b)* M. S. Chen, M. C. White, *Science*, 2010, **327**, 566-571. *(c)* P. E. Gormisky, M. C. White, *J. Am. Chem. Soc.*, 2013, **135**, 14052-14055; *(d)* S. A. Moteki, A. Usui, T. Zhang, C. R. Solorio Alvarado, K. Maruoka, *Angew. Chem., Int. Ed.*, 2013, **52**, 8657-8660. *(e)* I. Prat, L. Gomez, M. Canta, X. Ribas, M. Costas, *Chem. Eur. J.*, 2012, **19**, 1908-1913.
13. *(a)* J. Alsarraf, Y. Ait Ammar, F. Robert, E. Cloutet, H. Cramail and Y. Landais, *Macromolecules*, 2012, **45**, 2249; *(b)* H. Sardon, A. C. Engler, J. M. W. Chan, J. M. García, D. J. Coady, A. Pascual, D. Mecerreyes, G. O. Jones, J. E. Rice, H.S W. Horn, and J.S L. Hedrick, *J. Am. Chem. Soc.*, 2013, **135**, 16235.
14. *(a)* John M. Flournoy, *J. Chem. Phys.* 1962*,* **36***,* 1106; (b) A. Bhattacharya, Y. Q. Guo and E. R. Bernstein, *J. Phys. Chem. A* 2009, **113**, 811; (c) I. V. Kuchurov, I. V. Fomenkov and S. G. Zlotin, *Russ. Chem. Bull., Int. Ed.* 2010, **59**, 2147.
15. *(a)* J. J. D'Amico, F. G. Bollinger, ACS Symposium Series Vol. 443, 1991, Chapter 25, pp 300-320. (b) O. Lopez, J. G. Fernandez-Bolanos and M. V. Gil, *RSC Green Chem. Series*, 2011, **11**, 53-93.
16. P. Limaye, *Encyclop. Tox.*, 2014, **3**, 306-309.
17. National Research Council 2012. The Use and Storage of Methyl Isocyanate (MIC) at Bayer CropScience. Washington, DC: The National Academies Press. https://doi.org/10.17226/13385.
18. *(a)* R. Geyer, J. R. Jambeck and K. L. Law, *Sci. Adv.* 2017, **3**, e1700782. *(b)* J. M. Garcia, M. L. Robertson, *Science*, 2017, **358**, 870–872.
19. *(a)* Z. Huang, C. Feng, H. Guob and X. Huang, *Polym. Chem.*, 2016, **7**, 3034-3045. *(b)* S. E. Lewis, B. E. Wilhelmy and F. A. Leibfarth, *Chem. Sci.*, 2019, **10**, 6270–6277. *(c)* J. B. Williamson, C. G. Na, R. R. Johnson, W. F. M. Daniel, E. J. Alexanian, F. A. Leibfarth, *J. Am. Chem. Soc.,* 2019, **141**, 12815–12823. *(d)* W. Liu, Y. Dong, S. Zhang, Z. Wu and H. Chen, *Chem. Commun.*, 2019, **55**, 858-861. *(e)* J. Y. Q. Teo, C. W. S Yeung, T. T. Y. Tan, W. W. Loh, X. J. Loha, and J. Y.C. Lim, *Green Chem.*, 2022, **24**, 6287-6294. *(f)* T. J. Fazekas, J. W. Alty, E. K. Neidhart, A. S. Miller, F. A. Leibfarth and E. J. Alexanian, *Science*, 2022, **375**, 545–550. *(g)* M. L. Lepage, C. Simhadri, C. Liu, , M. Takaffoli, L. Bi, B. Crawford, A. S. Milani, and J. E. Wulff, *Science*, 2019, **366**, 875–878. *(h)* S. Oh and E. E. Stache, *J. Am. Chem. Soc.*, 2022, **144**, 5745–5749. *(i)* M. Valle, M.

Ximenis, X. Lopez de Pariza, J. M. W. Chan and H. Sardon, *Angew. Chem. Int. Ed.*, 2022, **61**, e202203043.