C(sp³)–H Bromination

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Copper-Catalyzed Bromination of C(sp³)–H Bonds Distal to Functional Groups

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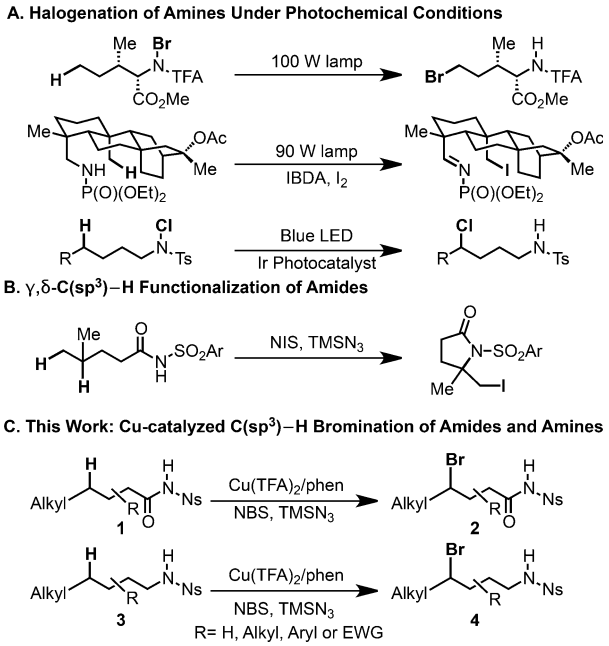
Abstract: *Selective bromination of γ-methylene C(sp³)–H bonds of aliphatic amides and δ-methylene C(sp³)–H bonds of nosyl-protected alkyl amines are developed using NBS as the brominating reagent and catalytic amount of Cu^{II}/phenanthroline complexes as the catalyst. Aryl and benzylic C–H bonds at other locations remain intact during this directed radical abstraction reaction.*

Transition metal-catalyzed functionalizations of C(sp³)–H bonds that are β to carbonyl and carboxyl groups or γ to amino groups have the potential to provide new synthetic disconnections, largely owing to the predictable and commonly encountered structural patterns generated by these transformations.[1] Following the same considerations, functionalizations of C(sp³)–H bonds that are further away will afford new sets of strategic tools for organic synthesis. To date, Pd-catalyzed functionalizations of distal C–H bonds are generally rare[2] due to the predominant five-membered cyclometallation reactions. In light of this limitation, we initiated efforts to exploit the possibility of combining directed radical 1,5 and 1,6-H-abstraction[3–5] with metal catalysis to achieve diverse C–H functionalizations. The interception of the remote carbon radical center by suitable metal catalysts to mediate the subsequent carbon–carbon and carbon–heteroatom bond formation has proved challenging. Early investigations demonstrated the potential of metal-free 1,5-H-abstraction reactions for functionalizations of remote C–H bonds (Scheme 1 B).[6]

Herein we report Cu^{II}/phenanthroline-catalyzed bromination of γ-C–H bonds of aliphatic amides and δ-C–H bonds of alkyl amines (Scheme 1 C). Both Cu^{II} catalyst and phenanthroline ligands are essential for the observed reactivity. Although photo-induced chlorination and bromination of C–H bonds by using preformed stoichiometric N–Cl or N–Br precursors have been reported with alkyl amine substrates (Scheme 1 A),[7] analogous γ-C–H halogenation of amide substrates have not been demonstrated.

1,5-H-abstraction has been successfully utilized for remote C–H nitration by Barton.[3d,f] Extending this approach to other intermolecular C–H functionalizations has met with limited success due to the predominant cyclization pathway. Important examples of photochemical halogenation of remote C(sp³)–H bonds of amine substrates have been achieved by preforming N–Cl or N–Br precursors (Scheme 1 A).[7] Non-directed radical halogenation of C(sp³)–H bonds has also been developed with synthetically useful site selectivity.[8] Guided by our previous work on H-abstraction and subsequent cyclization of amides (Scheme 1 B) and other reports,[3–6] we began to develop a catalytic system to intercept the carbon radical of both amine and amide substrates thereby achieving intermolecular C–H functionalization.



Scheme 1. Remote C(sp³)–H functionalization. IBDA = iodobenzene diacetate, TFA = trifluoroacetic acid, NIS = *N*-iodosuccinimide, NBS = *N*-bromosuccinimide, phen = phenanthrolin, $TMSN_3$ = trimethylsilyl azide, EWG = electron-withdrawing group.

Our experimental efforts began with finding conditions for C(sp³)–H bromination of readily prepared electron deficient *N*-nosyl pentanamide **1a**. We found that the reaction of amide **1a** with 3.0 equivalent of NBS in the presence of 10 mol % of $CuBr_2$, 10 mol % of 2,2′-bipyridine, and 3.0 equivalent of NaN_3 (in DCE at 60 °C under air for 18 h) gave exclusively the γ-bromo pentanamide **2a** in 7% yield (Table 1, entry 4). Replacing NaN_3 with $TMSN_3$ improved the yield to 11% (entry 5). In the absence of azide additives, no desired product was detected. The use of catalytic amounts of 1,10-phenanthroline afforded the brominated product **2a**

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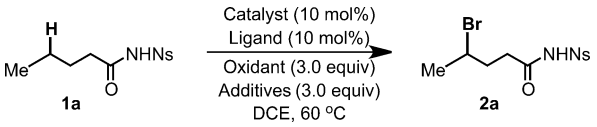
Table 1: Development of Cu^{II}-catalyzed C(sp^3)–H bromination of aliphatic amides.[a,b]



Entry	Catalyst	Ligand	Oxidant	Additives	Yield [%]
1	$CuBr_2$	bipy	Br_2	–	< 5
2	$CuBr_2$	bipy	Br_2	$PhI(OAc)_2$	< 5
3	$CuBr_2$	bipy	NBS	–	< 5
4	$CuBr_2$	bipy	NBS	NaN_3	7
5	$CuBr_2$	bipy	NBS	$TMSN_3$	11
6	$CuBr_2$	bipy	NBS	TMSBr	< 5
7	$CuBr_2$	phen	NBS	$TMSN_3$	35
8	$CuBr_2$	phen	NBS	$TMSN_3$	25
9	$Cu(TFA)_2$	phen	NBS	$TMSN_3$	52
10[c]	$Cu(TFA)_2$	phen	NBS	$TMSN_3$	27
11	$Cu(TFA)_2$	–	NBS	$TMSN_3$	< 5
12	–	phen	NBS	$TMSN_3$	< 5
13	–	–	NBS	$TMSN_3$	< 5

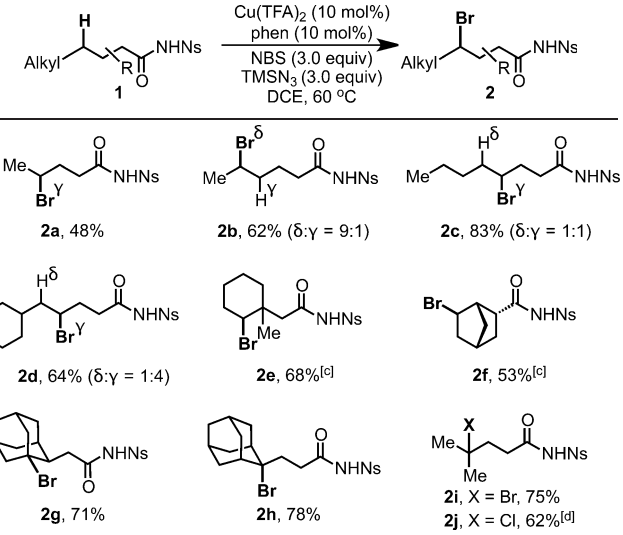
[a] Conditions: catalyst (10 mol%), ligand (10 mol%), oxidant (3.0 equiv), additive (3.0 equiv), DCE (0.1 M), 60 °C, air, 18 h. [b] Yields determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as internal standard. [c] phen (20 mol%) was used.

in 35% yield (entry 7, see the Supporting Information for systematic screening of additives and ligands). The yield was further increased to 52% when using a catalytic amount of $Cu(TFA)_2$. Control experiments showed that both copper catalyst and appropriate bisdentate ligand are essential for the desired bromination reaction to proceed.

To examine the scope of this protocol, aliphatic amides bearing various substitutions are subjected to the standard conditions (Table 2). Selective γ-bromination of pentanamide **1a** gave **2a** in 48% isolated yield. While the exclusive γ-selectivity observed with **1a** bearing α-, β- and γ-methylene C–H bonds is anticipated based on the radical abstraction pathway, the selectivity observed with **1b–d** provides detailed mechanistic information. Bromination of **1b** containing both γ- and δ-methylene C–H bonds afforded the δ-bromo-amide **2b** as the main product in 62% yield. With longer side chain in **1c**, however, γ- and δ-C–H bonds are equally reactive, giving a mixture of **2c** in 1:1 ratio. These combined results suggests that the difference of electron-richness between γ- and δ-C–H bonds is not sufficient for differentiation by radical abstraction. Instead, the steric effects play a predominant role in determining the regio-selectivity. Consistent with this hypothesis, the presence of a more sterically hindered cyclohexyl group in **1d** at the ε-position retarded δ-C–H activation further, favoring γ-C–H bromination product **2d**. The exclusive formation of **2e** suggests that the radical H-abstraction of methylene C–H bonds is favored over primary C–H bonds due to significant electronic effects. Bromination of γ-C–H bonds on a bicyclic ring occurred to give **2f** in 53% yield. Bromination of the γ-methine C–H were highly selective affording **2g** and **2h** in good yields. γ-Chlorination was also realized by replacing NBS with NCS to give **2j** in 62% yield.

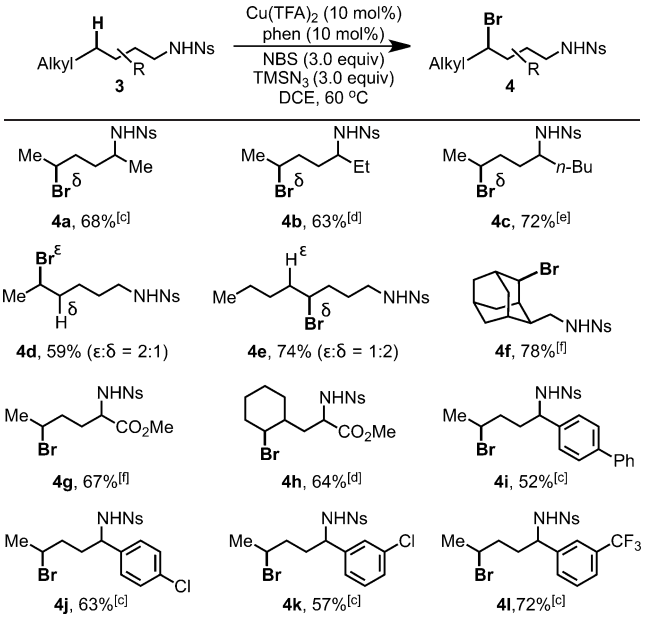
The applicability of this copper-catalyzed bromination protocol to *N*-nosyl amine substrates was also examined (Table 3). Bromination of *N*-nosyl aliphatic amines **3a–c** proceeded highly selectively to afford δ-bromo-amines in good yields (**4a–4c**). In the presence of both δ- and ε-methylene C–H bonds, a mixture of bromination products **4d** in the ratio of 2:1 favoring the bromination of the less hindered ε-C–H bonds were obtained. When the steric

Table 2: γ,δ-C(sp^3)–H bromination of aliphatic amides.[a,b]



[a] Conditions: $Cu(TFA)_2$ (10 mol%), phenanthroline (10 mol%), NBS (3.0 equiv), $TMSN_3$ (3 equiv), DCE (0.1 M), 60 °C, air, 18 h. [b] Isolated yields. [c] Obtained as a mixture of diastereomers (3:1). [d] Use of NCS (*N*-chlorosuccinimide) (3.0 equiv) instead of NBS.

Table 3: δ,ε-C(sp^3)–H bromination of aliphatic amines.[a,b]



[a] Conditions: $Cu(TFA)_2$ (10 mol%), phenanthroline (10 mol%), NBS (3.0 equiv), $TMSN_3$ (3 equiv), DCE (0.1 M), 60 °C, air, 18 h. [b] Isolated yields. [c] Obtained as a mixture of diastereomers (2:1). [d] Obtained as a mixture of diastereomers (3:1). [e] Obtained as a mixture of diastereomers (4:1). [f] Obtained as a mixture of diastereomers (1:1).

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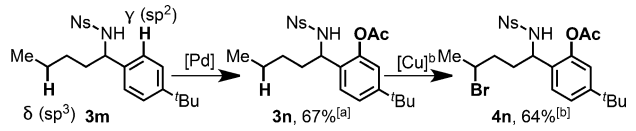
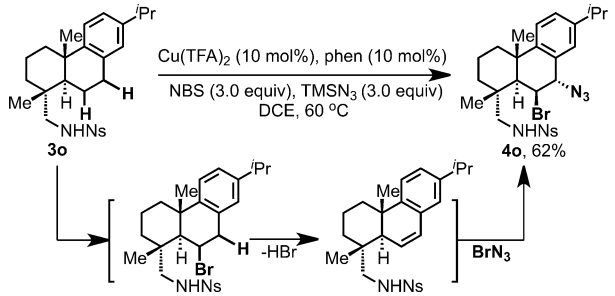
environments of δ- and ε-C–H bonds are similar, the bromination of δ-C–H bonds was the major pathway (**4e**), indicating that 1,5-H-abstraction is slightly favored over the 1,6-H-abstraction. δ-Bromination of *N*-nosyl adamantanyl methanamine afforded **4f** in 78% yield. Remote functionalizations of amino acids using this protocol is also demonstrated. δ-Bromo norleucine **4g** was obtained in 67% yield. Bromination of the cyclohexyl C–H bond afforded δ-bromo cyclohexylalanine **4h** in 64% yield. It is noteworthy that this newly established δ-bromination conditions are also applicable to benzylamines. Substrates containing *para*-phenyl, *para*-chloro, *meta*-chloro and *meta*-trifluoromethyl gave the desired δ-bromination products selectively (**4i**–**4l**). Both the potentially reactive arenes and benzylic C–H bonds remained intact.

The tolerance of arene and benzylic C–H bonds prompted us to perform a sequential Pd-catalyzed *ortho*-C–H acetoxylation[9] and Cu-catalyzed δ-C(sp^3)–H bromination to give an advanced synthetic intermediate **4n** (Scheme 2).



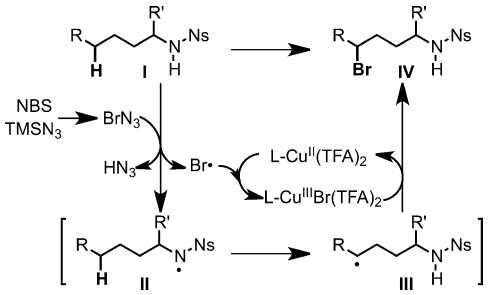
Scheme 2. Selective C–H functionalization by palladium and copper catalysts. a) Conditions: $Pd(OAc)_2$ (10 mol%), Ac-Ala-OH (20 mol%), $PhI(OAc)_2$ (2.0 equiv), HFIP/Ac_2O (4:1, 0.2 M), 60 °C, air. Isolated yield: 67% (mono) and 10% (di). b) Conditions: $Cu(TFA)_2$ (10 mol%), phen (10 mol%), NBS (3.0 equiv), $TMSN_3$ (3 equiv), DCE (0.1 M), 60 °C, air. Obtained as a mixture of diastereomers (3:1). Isolated yield: 64%. HFIP = hexafluoroisopropanol.

Subjecting *N*-nosyl dehydroabietylamine **3o** in Scheme 3 to standard conditions gave a *trans*-1,2-bromo azidyl product **4o**. This unexpected result also lends evidence to the formation of the bromo azide BrN_3. Apparently, the initial δ-bromination product was converted to an olefin intermediate via the elimination of HBr. It is known that halogen azidation of the corresponding olefin[10] will give **4o**.



Scheme 3. Regio- and stereoselective difunctionalization of dehydroabietylamine.

While the directed radical abstraction by the nitrogen radical and subsequent C–N bond forming cyclization is well established, the interception by these new conditions to achieve intermolecular bromination is not well understood at this stage. Although the oxidation of the carbon radical intermediate **III** to carbon cation by Cu^{III} is proposed by Kochi,[11] our radical clock experiment indicate that such oxidation process is not sufficiently fast under these conditions (see the Supporting Information for details). We have also subjected the preformed stoichiometric N–Br precursor[7] to the reaction conditions and found that the yield of the desired product is low (15%). Based on these experimental observations, a plausible mechanism for this copper-catalyzed C–H bromination reaction is proposed in Scheme 4. In situ generated azidyl radical[10] from BrN_3 (see evidence from Scheme 3) initiates reaction process by abstracting hydrogen of N–H on substrate **I** to form intermediate **II**. Intermediate **III** is formed via hydrogen abstraction from intermediate **II**. The key carbon centered radical **III** is not oxidized to a cation intermediate under these conditions so that the cyclization pathway is prevented. Instead, **III** reacts with high valent $CuBr(TFA)_2$ to give the brominated product **IV**.



Scheme 4. Proposed mechanism.

In conclusion, we have developed a copper-catalyzed methodology to achieve remote C(sp^3)–H bromination of aliphatic amines and amides through directed radical H-abstraction. The facile deprotection of *N*-nosyl protection groups in both amide and amine products was also demonstrated (see the Supporting Information). While the 1,5-H-abstraction is generally favored reaction pathway, steric effects can have significant impact leading to 1,6-H-abstraction as the major pathway.

Acknowledgements

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Keywords: bromination · C–H functionalization · copper · radical H-abstraction · synthetic methods

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Communications

C(sp³)–H Bromination

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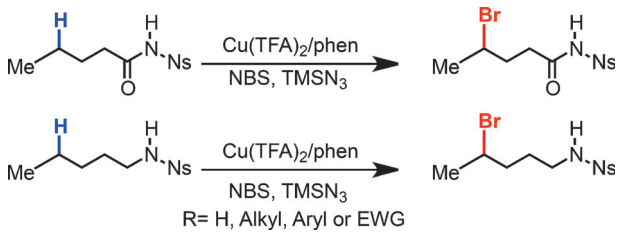

Selective bromination of γ-methylene C(sp³)–H bonds of aliphatic amides and δ-methylene C(sp³)–H bonds of nosyl-protected alkyl amines are achieved by using *N*-bromosuccinimide as the brominating reagent and catalytic amounts of Cu^{II}/phenanthroline complexes. Aryl and benzylic C–H bonds at other locations remain intact during this directed radical abstraction reaction.

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