Copper-Catalyzed Bromination of C(sp^3)-H Bonds Distal to Functional Groups

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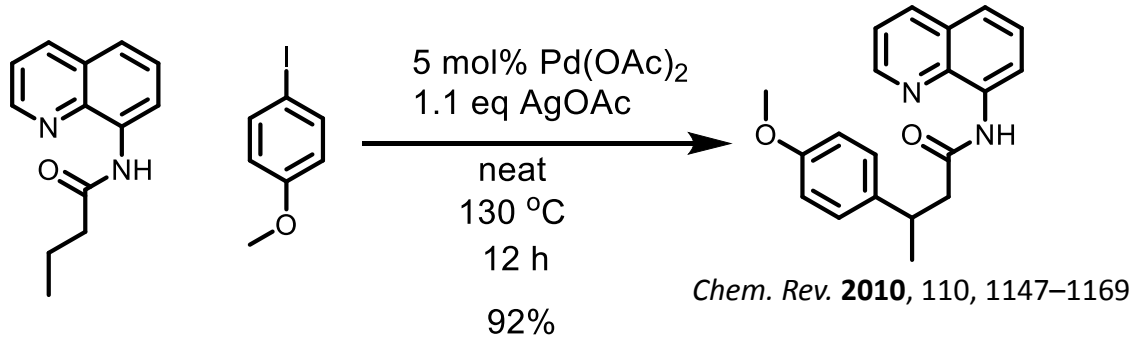
Wipf Group
01/21/2017

C(sp^3)-H Functionalizations

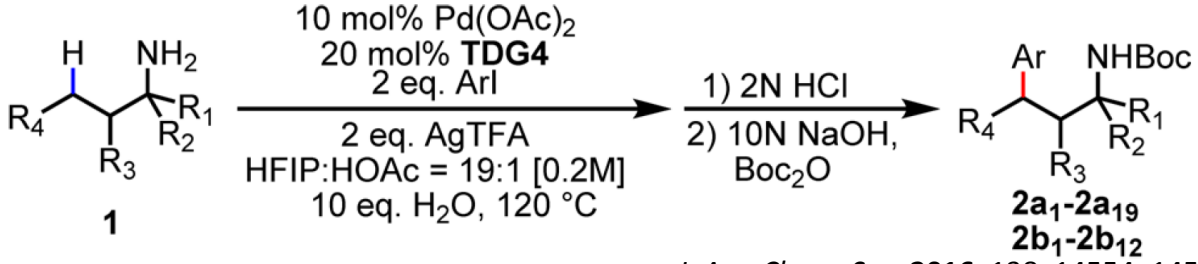
Common C-H functionalizations:

β to carbonyl groups



Chem. Rev. **2010**, 110, 1147–1169

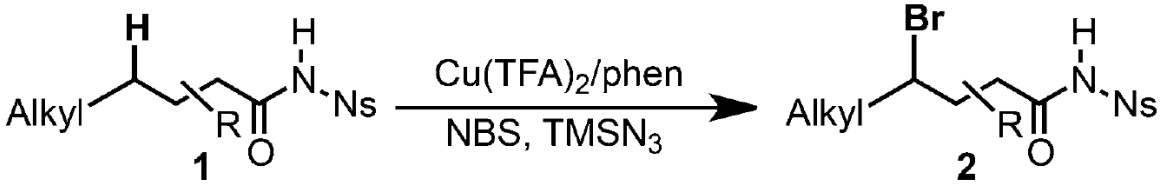
γ to amino groups



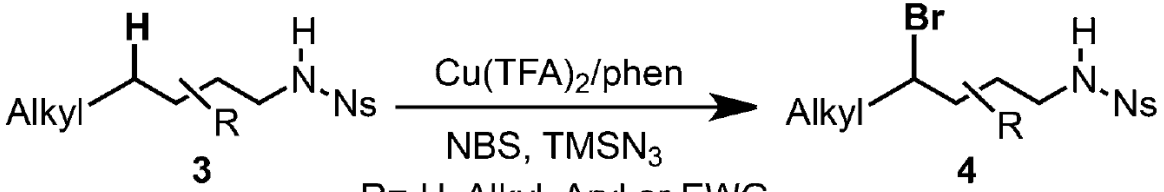
J. Am. Chem. Soc. **2016**, 138, 14554–14557

This work: C-H functionalization via directed radical 1,5 and 1,6 -H abstraction

γ to carbonyl groups



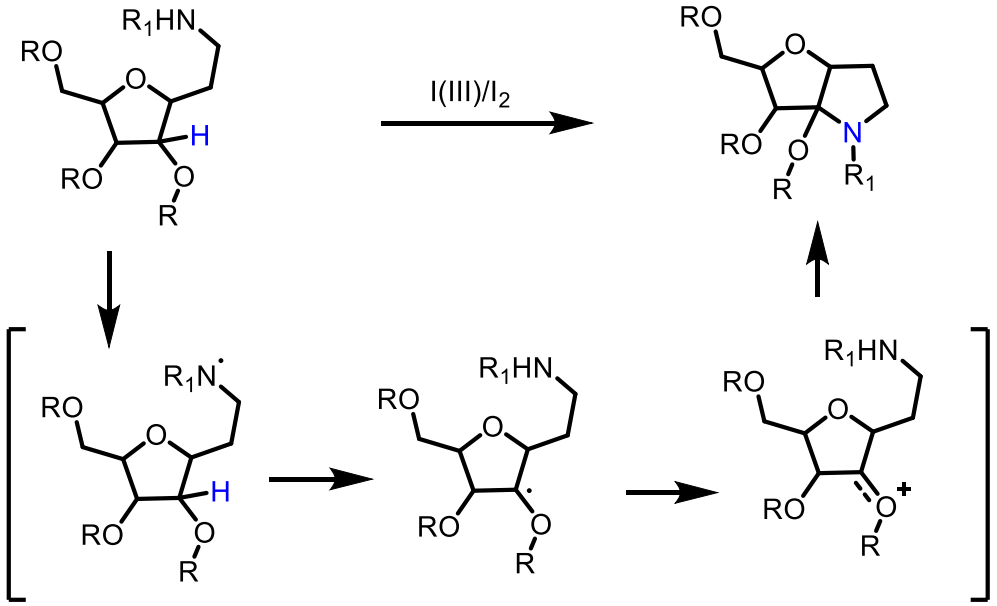
δ to amino groups



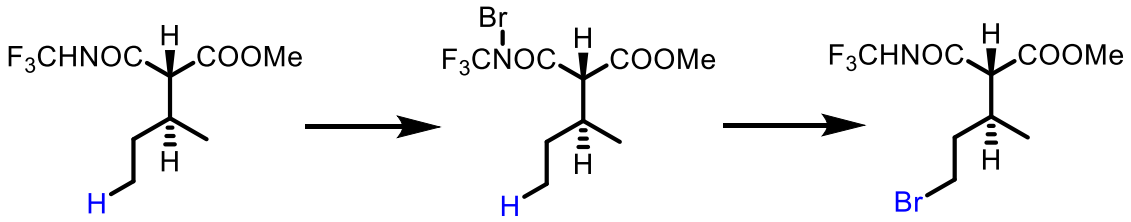
R= H, Alkyl, Aryl or EWG

Angew. Chem. Int. Ed. **2017**, 56, 306 –309

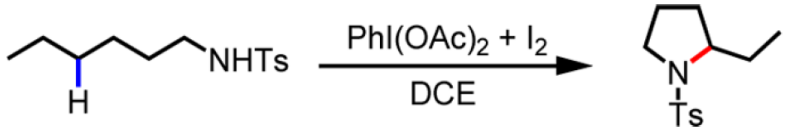
Remote C(sp^3)-H Functionalizations



Tetrahedron Letters ***2007***, 48, 6384–6388

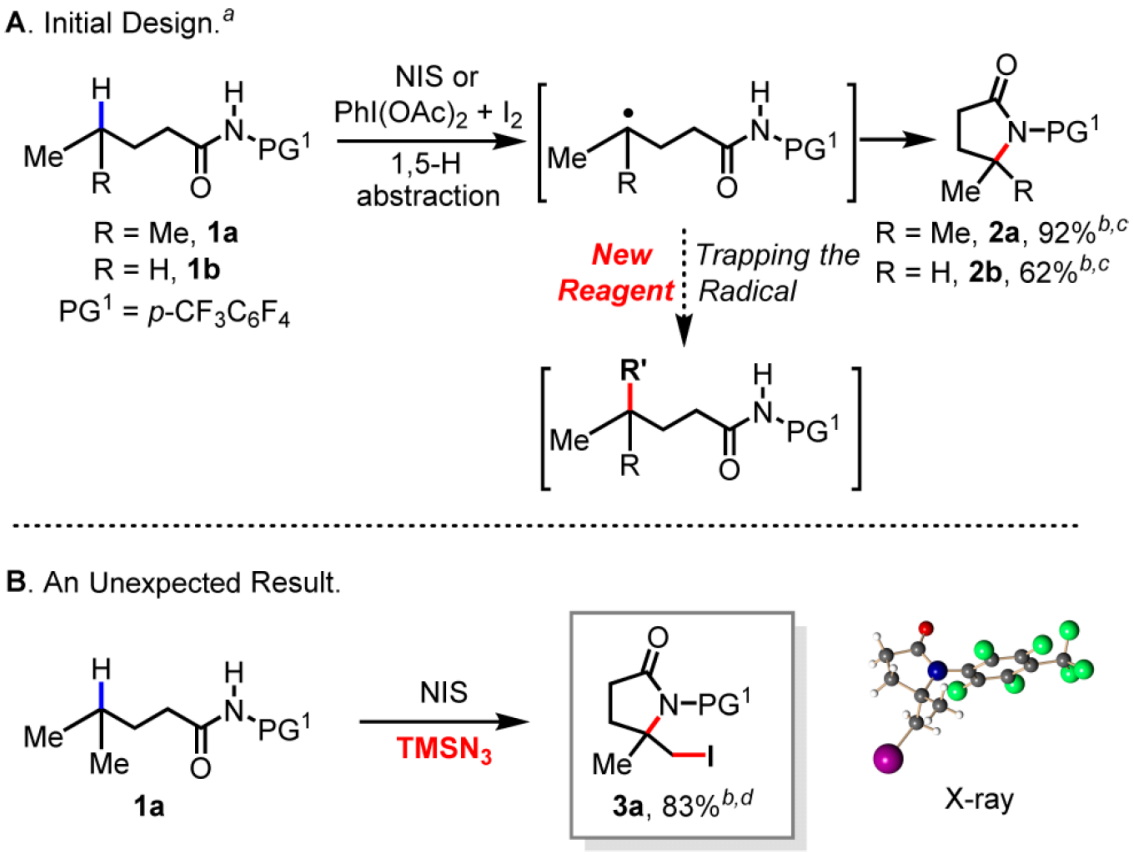


Org. Lett. **2006**, 8, 2819-2821



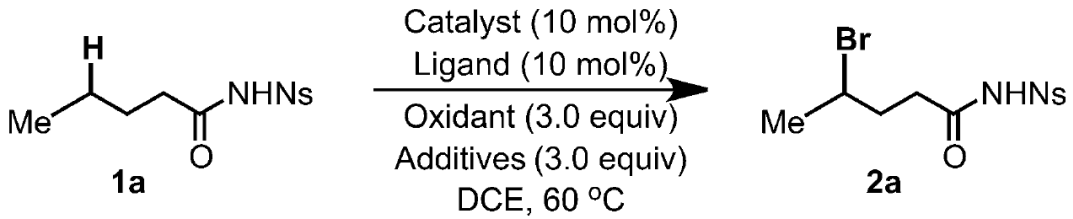
J. Am. Chem. Soc. **2015**, 137, 5871−5874

Previous work



J. Am. Chem. Soc. **2015**, 137, 5871−5874

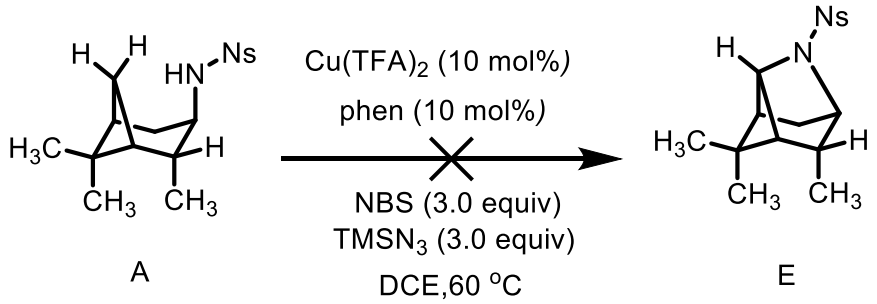
Reaction Conditions

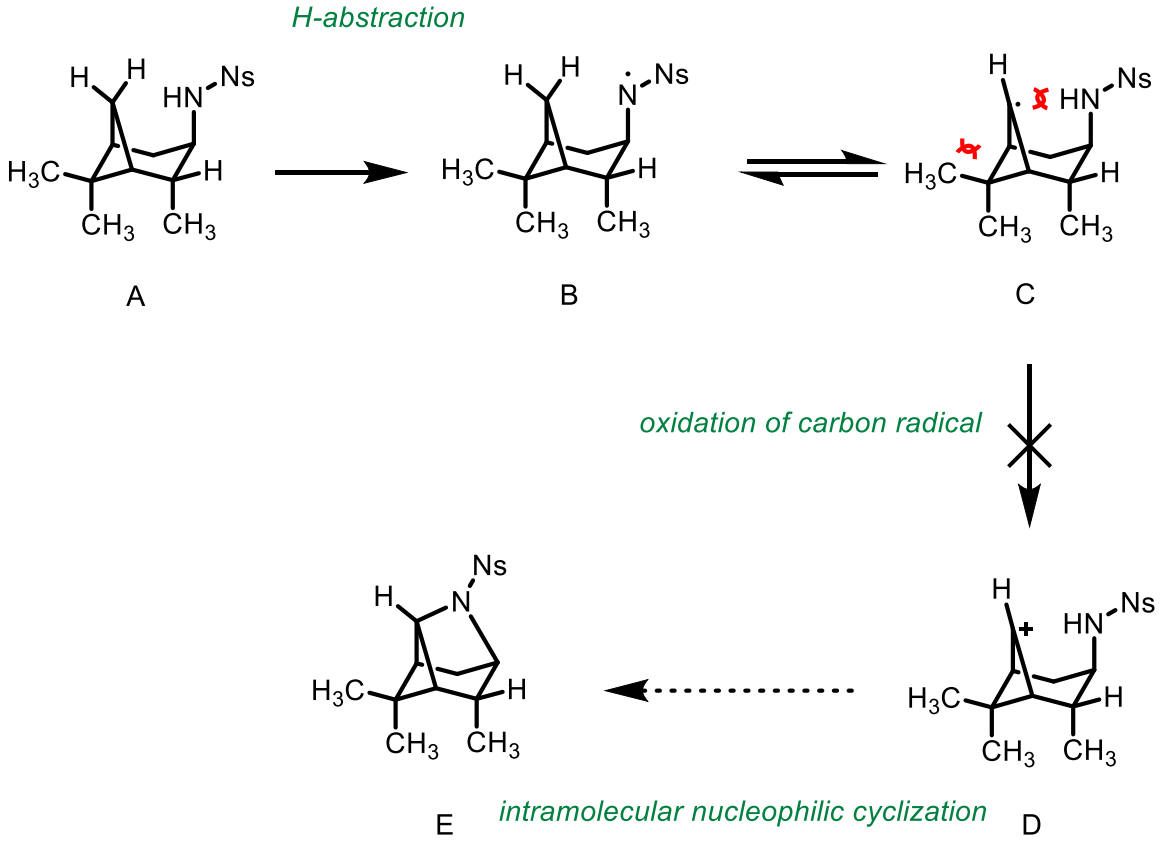


Entry	Catalyst	Ligand	Oxidant	Additives	Yield [%]
1	$CuBr_2$	bipy	Br_2	–	< 5
2	$CuBr_2$	bipy	Br_2	$PhI(OAc)_2$	< 5
3	$CuBr_2$	bipy	NBS	–	< 5
4	$CuBr_2$	bipy	NBS	NaN_3	7
5	$CuBr_2$	bipy	NBS	$TMSN_3$	11
6	$CuBr_2$	bipy	NBS	TMSBr	< 5
7	$CuBr_2$	phen	NBS	$TMSN_3$	35
8	$CuBr_2$	phen	NBS	$TMSN_3$	25
9	$Cu(TFA)_2$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

Angew. Chem. Int. Ed. **2017**, 56, 306 –309

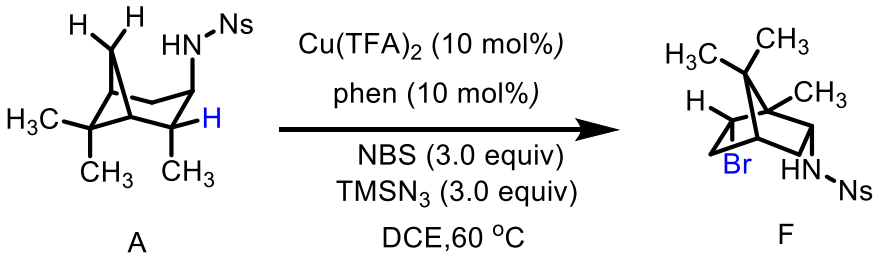
Cyclized product- not observed

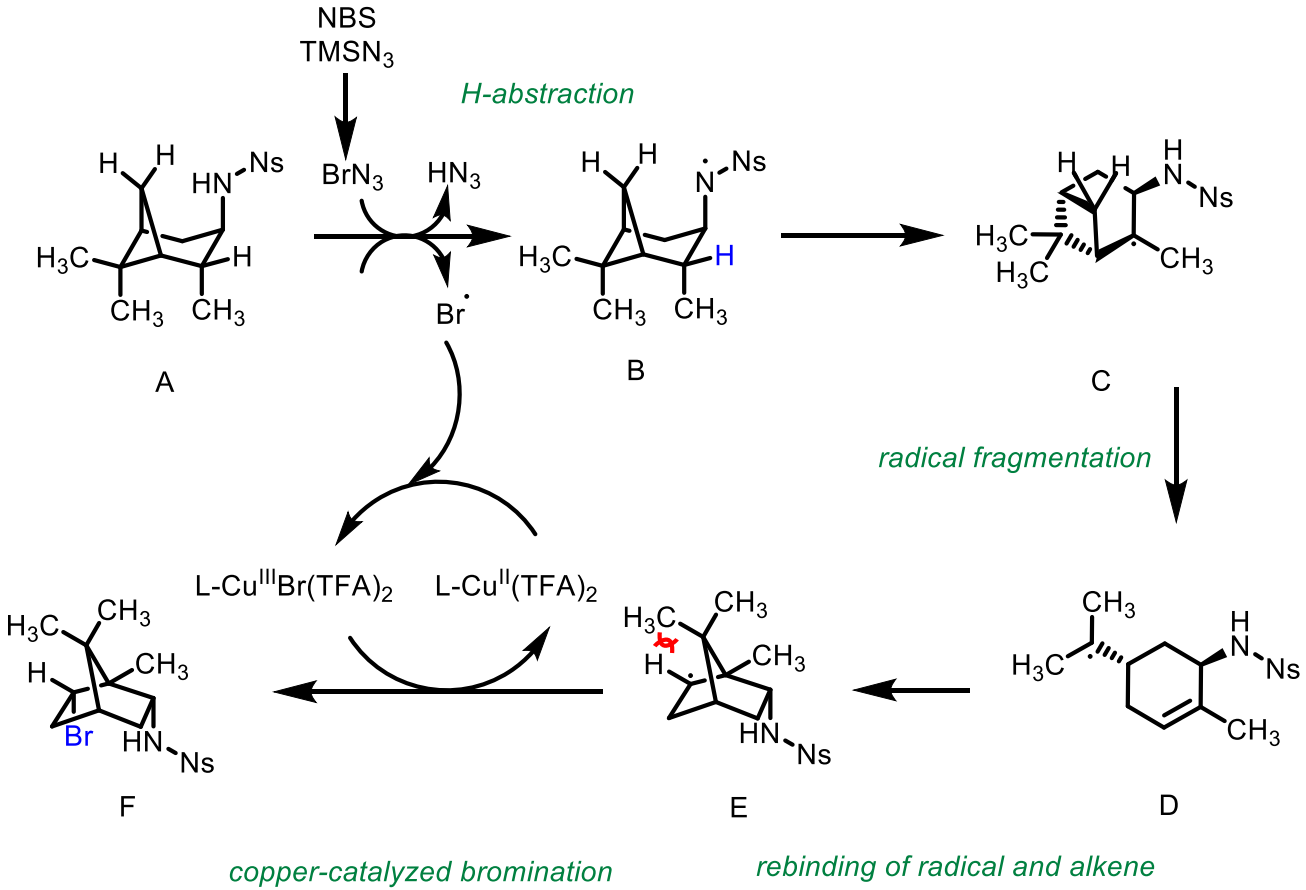




Angew. Chem. Int. Ed. **2017**, 56, 306 –309

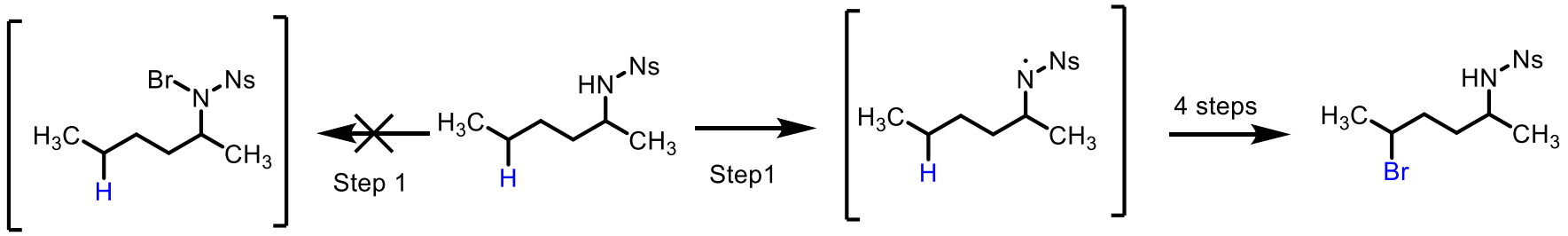
Proposed Mechanism

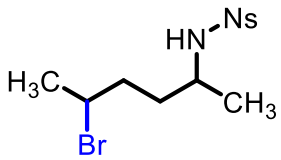


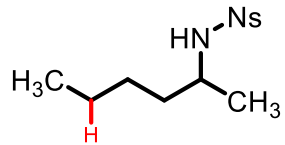


Angew. Chem. Int. Ed. **2017**, 56, 306 –309

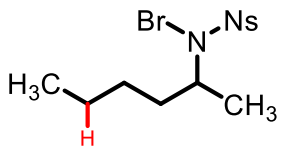
Requirement of Free N-H



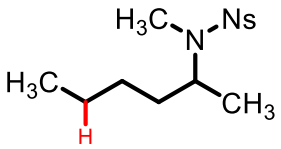




conditions → **68 %**



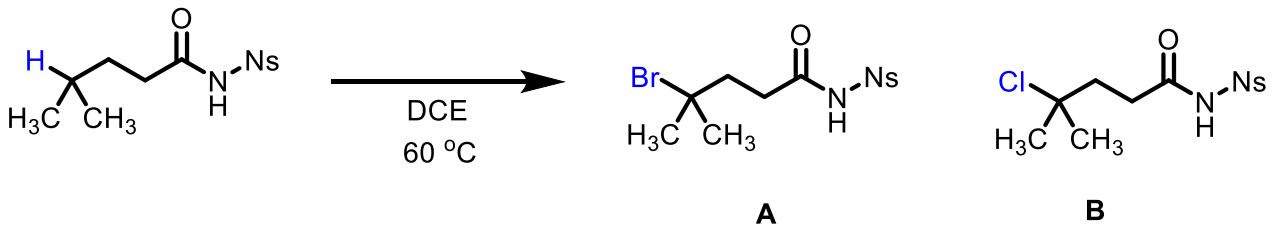
conditions → **15 %**



conditions → **0%**

Angew. Chem. Int. Ed. **2017**, 56, 306 –309

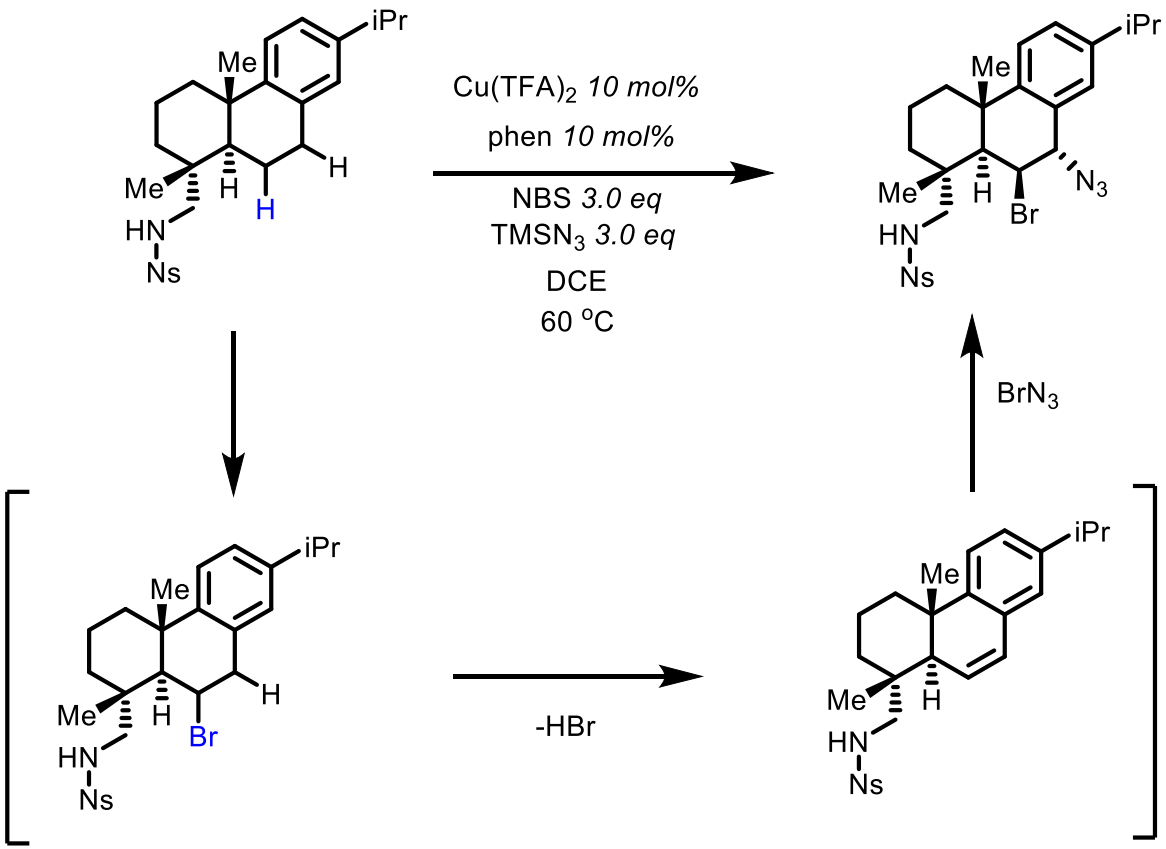
Origin of the Halogen Atom



Catalyst	Ligand	Oxidant	Additive	A	B
$CuBr_2$	phen	NCS	$TMSN_3$	11%	13%
$CuCl_2$	phen	NBS	$TMSN_3$	14%	5%

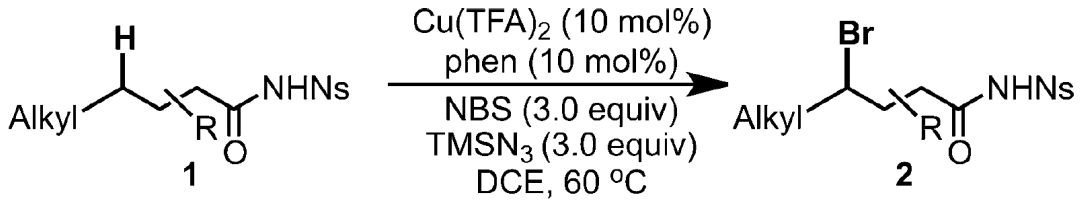
Angew. Chem. Int. Ed. **2017**, 56, 306 –309

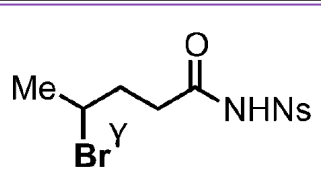
Side Reaction



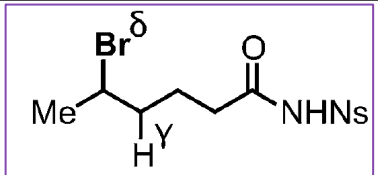
Angew. Chem. Int. Ed. **2017**, 56, 306 –309

Scope for amides

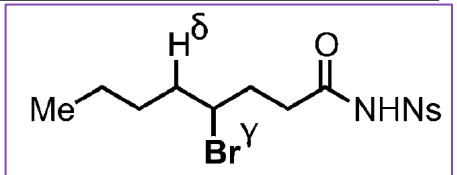




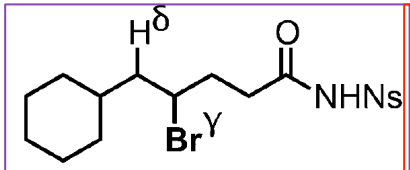
2a, 48%



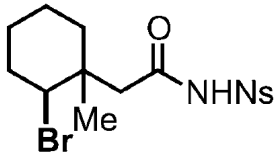
2b, 62% (δ:γ = 9:1)



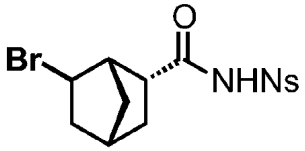
2c, 83% (δ:γ = 1:1)



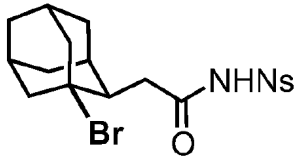
2d, 64% (δ:γ = 1:4)



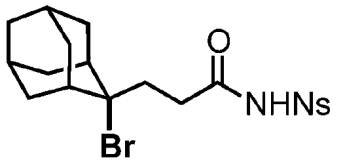
2e, 68%[c]



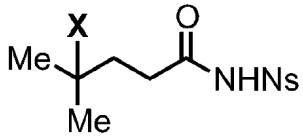
2f, 53%[c]



2g, 71%



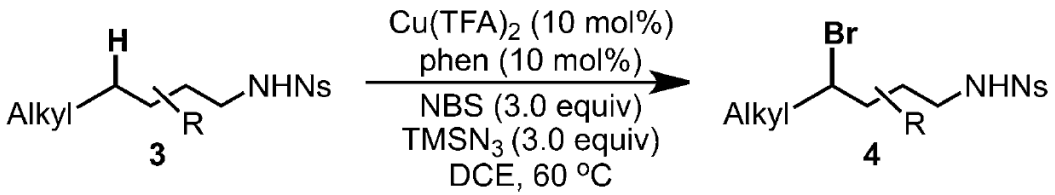
2h, 78%

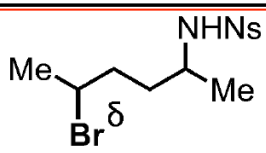


2i, X = Br, 75%
2j, X = Cl, 62%[d]

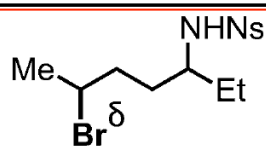
Angew. Chem. Int. Ed. **2017**, 56, 306 –309

Scope for aliphatic amines

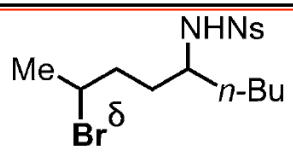




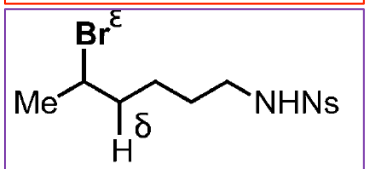
4a, 68%[c]



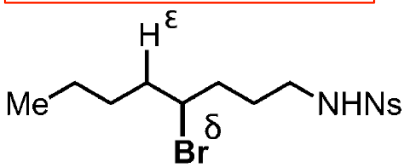
4b, 63%[d]



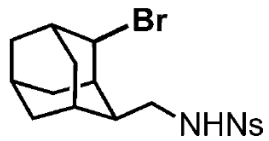
4c, 72%[e]



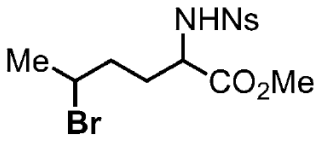
4d, 59% (ε:δ = 2:1)



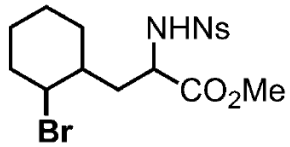
4e, 74% (ε:δ = 1:2)



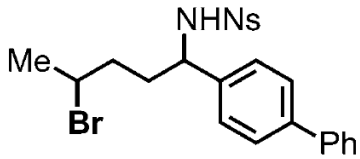
4f, 78%[f]



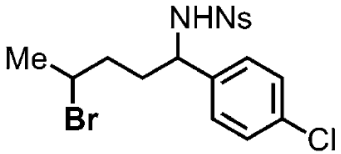
4g, 67%[f]



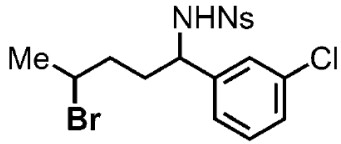
4h, 64%[d]



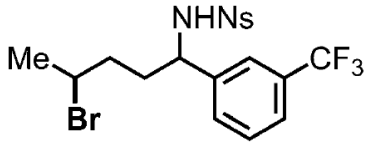
4i, 52%[c]



4j, 63%[c]



4k, 57%[c]



4l,72%[c]

Angew. Chem. Int. Ed. **2017**, 56, 306 –309

Conclusion

Directed radical 1,5-H abstraction to obtain remote C(sp^3)-H bromination of aliphatic amines and amides.

1,6-H abstraction when there are significant steric effects

Removal of Protecting groups as advanced intermediates: