

# Intermolecular Ritter-Type C–H Amination of Unactivated $sp^3$ Carbons

Quentin Michaudel,<sup>†</sup> Damien Thevenet,<sup>†</sup> and Phil S. Baran\*

Department of Chemistry, The Scripps Research Institute, 10550 North Torrey Pines Road, La Jolla, California 92037, United States

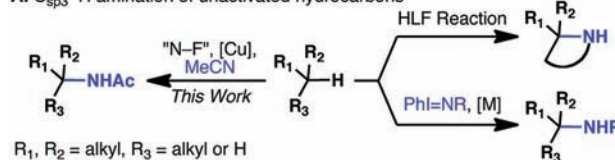
**S** Supporting Information

**ABSTRACT:** Intermolecular Ritter-type C–H amination of unactivated  $sp^3$  carbons has been developed. This new reaction proceeds under mild conditions using readily available reagents and an inexpensive source of nitrogen (acetonitrile). A broad scope of substrates can be aminated with this method since many functional groups are tolerated. This reaction also allows for the direct, innate C–H amination of a variety of hydrocarbons such as cyclohexane without the need of prefunctionalization or installation of a directing group.

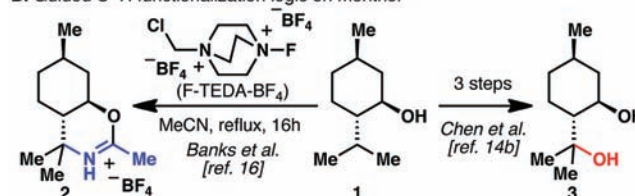
The pioneering studies of Barton,<sup>1</sup> Breslow,<sup>2</sup> and Corey<sup>3</sup> on the functionalization of C–H bonds in terpenoid skeletons have contributed to the recent resurgence of interest in this area. The direct conversion of C–H bonds to C–N bonds is of particular importance in the area of alkaloid and heterocycle synthesis.<sup>4</sup> Historically, the venerable Hofmann–Löffler–Freitag (HLF) reaction (Figure 1A)<sup>5</sup> has served as a practical and reliable method in intramolecular settings. With the notable exception of some radical-based functionalizations,<sup>6</sup> state-of-the-art developments are dominated by nitrene chemistry. Free nitrenes had been mostly generated *in situ* by thermolysis or photolysis of azides, and those rather harsh conditions often resulted in both low selectivities and safety concerns.<sup>7</sup> Thus, metallonitrenes, also prepared *in situ* from azides,<sup>8</sup> haloamines,<sup>9</sup> *N*-arenesulfonyloxycarbamates,<sup>10</sup> or iminodanes,<sup>11</sup> are preferred for intramolecular  $C_{sp^3}$ –H amination. However, due to the instability of metallonitrene intermediates, early intermolecular versions of these reactions generally have not led to high yields and have mostly allowed for the functionalization of benzylic or allylic positions. To circumvent these problems, elegant methods that enhance the reactivity of the metal catalyst have been reported by Müller,<sup>12a</sup> Che,<sup>12b</sup> Du Bois,<sup>12c</sup> Dauban,<sup>12d</sup> Lebel,<sup>12e</sup> Pérez,<sup>12f</sup> He,<sup>12g</sup> and Warren.<sup>12h</sup> Metal-free organonitrenoid reagents have recently been discovered by Bettinger<sup>13a</sup> and Ochiai,<sup>13b</sup> enabling the functionalization of alkanes when used as solvent. Herein, we report the invention of a copper-catalyzed intermolecular  $C_{sp^3}$ –H amination of both unactivated (non-benzylic and allylic) hydrocarbons and functionally rich molecules (see Figure 1A). This reaction proceeds at room temperature or 50 °C, is operationally simple, and is scalable. Moreover, the substrate can be used as the limiting reagent, and the catalyst and nitrogen source are readily available.

In the course of a research program geared toward the synthesis of terpenes, a guided C–H oxidation was invented to

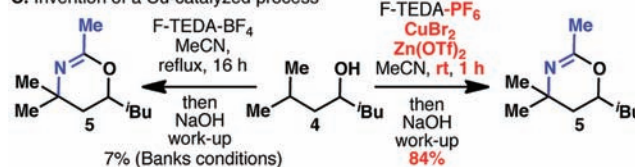
A.  $C_{sp^3}$ –H amination of unactivated hydrocarbons



B. Guided C–H functionalization logic on menthol



C. Invention of a Cu-catalyzed process



Entry	F-TEDA <sup>a</sup>	CuBr <sub>2</sub> <sup>a</sup>	Zn(OTf) <sub>2</sub> <sup>a</sup>	Temperature	Time	Yield <sup>b</sup> (%)
1	BF <sub>4</sub> ; 2.2	—	—	90°C	16 h	7
2	BF <sub>4</sub> ; 2.2	0.25	—	rt	1 h	37
3	BF <sub>4</sub> ; 2.2	—	—	rt	1 h	0
4	—	0.25	—	rt	1 h	0
5 <sup>c</sup>	BF <sub>4</sub> ; 1.5	0.25	—	rt	1 h	24
6	BF <sub>4</sub> ; 2.2	0.25	0.5	rt	1 h	51
7	PF <sub>6</sub> ; 2.2	0.25	0.5	rt	1 h	84

**Figure 1.** (A) Overview of  $C_{sp^3}$ –H amination methods. (B) Reported synthesis of dihydrooxazinium salt **2** derived from (–)-menthol (**1**) by Banks et al. and synthesis of hydroxymethyl menthol **3** by Chen et al. (C) Reaction optimization with 2,6-dimethylheptan-4-ol (**4**) (1.0 equiv, 0.13 mmol). <sup>a</sup>Number of equivalents. <sup>b</sup>Yields determined by <sup>1</sup>H NMR with an internal standard. <sup>c</sup>16% of recovered starting material **4**.

achieve the direct oxidation of (–)-menthol (**1**) to hydroxymethyl menthol **3**, as well as the synthesis of more complex natural products of the eudesmane family.<sup>14</sup> In a continuing effort to use such logic for the synthesis of terpenoid alkaloids,<sup>15</sup> a  $C_{sp^3}$ –H amination was pursued, inspired by the unexpected finding by Banks et al. of the formation of dihydrooxazinium salt **2** derived from **1** (Figure 1B).<sup>16</sup> Those authors serendipitously found that treatment of **1** with 2.0 equiv of F-TEDA-BF<sub>4</sub> (Selectfluor<sup>®</sup> reagent, Air Products and Chemicals, Inc.) in

Received: December 23, 2011

Published: January 24, 2012

refluxing acetonitrile gave heterocycle **2** instead of the expected oxidation product (–)-menthone. Although the relatively harsh reaction conditions and the very limited substrate scope (three substrates reported) were obvious limitations, those findings represented a useful starting point for optimization (see selected examples shown in Figure 1C and Supporting Information (SI) for more details). For instance, the conditions of Banks et al. afforded 7% yield of dihydrooxazine **5** from alcohol **4** after workup with 10% aq NaOH to neutralize the dihydrooxazinium salt (entry 1). Since a radical-based mechanism for the conversion of **1** to **2** was originally put forth, it was reasoned that a metal such as Cu(I) or Cu(II) could facilitate C–H abstraction, based on the pioneering studies of Kochi.<sup>17</sup> After extensive screening, a few commercial Cu salts were found to dramatically affect the rate of the reaction. In particular, the use of 25 mol% of CuBr<sub>2</sub> with 2.2 equiv of F-TEDA-BF<sub>4</sub> led to 37% yield of **5** in only 1 h at room temperature (entry 2). As a control, the same reaction was performed without either copper or F-TEDA-BF<sub>4</sub> and in both cases failed to generate product (entries 3 and 4). At least 2.0 equiv of F-TEDA-BF<sub>4</sub> is needed to obtain full conversion (entry 5). Fortunately, the addition of 50 mol% of a Lewis acid such as Zn(OTf)<sub>2</sub> allowed for a notable improvement in yield (entry 6). Next, solubility issues of F-TEDA-BF<sub>4</sub> at room temperature were addressed by using a related fluorinating agent, F-TEDA-PF<sub>6</sub>, which can be prepared in quantitative yield from F-TEDA-BF<sub>4</sub> by a simple anion exchange with NH<sub>4</sub>PF<sub>6</sub>, according to Ritter's procedure.<sup>18</sup> Using this reagent, the reaction became homogeneous, and the yield notably improved (entry 7). Interestingly, no other fluorinating agents or common oxidants that were tested enabled the reaction to proceed. Hydrolysis of the dihydrooxazine moiety to the hydroxyacetamide product was performed at 80 °C with 1.0 equiv of NaOH in a 1:1 mixture of acetonitrile and water. Although a one-pot process is feasible, an intermediate workup allowed for the use of only 1.0 equiv of NaOH in the subsequent hydrolysis, resulting in a slightly higher yield.

With this simple procedure in hand, a range of saturated alcohols were employed as limiting reagents (Table 1). C<sub>sp<sup>3</sup></sub>-H amination of alcohols **1**, **4**, and **6** proceeded with isolated yields ranging from 53 to 91%. Although Banks et al. specifically reported that **7** is unreactive under their reaction conditions,<sup>16</sup> the reaction presented herein led to amination of **7** in 42% isolated yield. Moreover, this demonstrates that phenyl groups are tolerated, since fluorination of the arene was not observed. Interestingly, hydroxyl groups are not necessary for the reaction, since ketones **8** and **9** were transformed in 1 step into β-amidoketones in good yields. In the case of **9**, a mixture of mono- (**16**) and bisamidation (**17**) products was observed when only 1.0 equiv of **9** was used. When an excess of **9** (8.0 equiv) was used, monoadduct **16** was the exclusive product (89% yield). Lastly, this process can be used to functionalize fairly complex substrates in good yield, as exemplified by 6-*epi*-dihydrojunenol (**10**), which could provide an important functional handle for the synthesis of related natural products.<sup>19</sup>

Encouraged by these results, we attempted this C<sub>sp<sup>3</sup></sub>-H amination reaction on hydrocarbon substrates bearing no directing functional groups (Table 2). Gratifyingly, the transformation of adamantane (**19**) proceeded at room temperature in 90% yield with only 1.0 equiv of **19**. The reaction with 5.0 equiv of **19** and 1.0 equiv of F-TEDA-PF<sub>6</sub> afforded only 0.44 equiv of acetamide **27** along with 4.2 equiv of unreacted **19** (see Table 2), which supports the postulation

Table 1. Scope of the C<sub>sp<sup>3</sup></sub>-H Amination for Alcohol and Ketone Substrates

Substrate	Product	Yield <sup>a</sup> (%)
		91 81 [gram-scale]
		84
		53
		42 (dr 2:1)
		61 <sup>b</sup> [X-ray]
		19 <sup>b</sup> , 89 <sup>b,c</sup>
		23 <sup>b</sup> , 0 <sup>b,c</sup> [X-ray]
		65 <sup>d</sup>

<sup>a</sup>Isolated yields. <sup>b</sup>Hydrolysis (step 2) was not necessary. <sup>c</sup>8.0 equiv of **9** was used, and yield was based on 2.0 equiv of F-TEDA-PF<sub>6</sub> as the limiting reagent. <sup>d</sup>Hydrolysis conditions were modified: Ba(OH)<sub>2</sub> (5.0 equiv), 2:1 dioxane:H<sub>2</sub>O, 110 °C, 3 h.

that 2.0 equiv of F-TEDA-PF<sub>6</sub> is required to transform 1.0 equiv of substrate, in accord with our initial observations (see Figure 1C). When the temperature of the reaction was increased to 50 °C, hydrocarbons **20–26** were amidated with isolated yields ranging from 21 to 62%, whereas the use of 5.0 equiv of substrate gave yields of up to 90%. Interestingly, the regioselectivity observed on *trans*-decalin (**25**) suggests that sterics can favor the reaction of methylene over methine positions. In the case of *cis*-decalin (**26**), formation of **34** is probably due to the fact that the tertiary C–H bonds in this molecule are more accessible. Moreover, isomerization of the *cis*-junction to a *trans*-junction for **34** is consistent with a radical or a carbocation involved in the reaction mechanism.<sup>20</sup> Although many functional groups are tolerated, free amines and olefins are currently not compatible with the reaction conditions.

Removal of the protecting group on the amine (e.g., sulfonimidoyl, alkoxy-sulfonamide, or trifluoromethanesulfonamide) introduced at the C–H amination step in other methods is often not trivial.<sup>12–14</sup> In comparison, an acetamide can be cleaved in many ways,<sup>21</sup> and acid hydrolysis has shown to

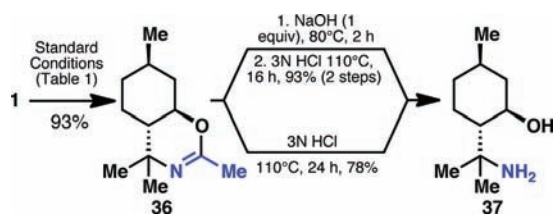
Table 2. Scope of the C<sub>sp</sub><sup>3</sup>-H Amination for Hydrocarbon Substrates

Substrate	Product	Yield <sup>a</sup>	Yield <sup>b</sup>
		90 <sup>c</sup>	88 <sup>c</sup>
		39	63
		51	72
		41	62
		62	90
		25 <sup>d</sup>	28 <sup>d</sup>
		36 <sup>e</sup>	55 <sup>e</sup>
		5	15
		16 <sup>f</sup>	31 <sup>f</sup>

<sup>a</sup>Isolated yields (%) starting from 1.0 equiv of substrate. <sup>b</sup>Isolated yields (%) starting from 5.0 equiv of substrate and based on 2.0 equiv of F-TEDA-PF<sub>6</sub> as the limiting reagent. <sup>c</sup>Reaction performed at rt. <sup>d</sup>Reaction performed at 95 °C. <sup>e</sup>Inseparable mixture of three unassigned regio- and stereoisomers at C1 and C2. <sup>f</sup>Inseparable mixture of two unassigned regio- and/or stereoisomers.

efficiently remove the acetamide moiety. For instance, enantiopure aminomenthol 37 can be synthesized from inexpensive (–)-menthol (1) in 3 steps and 87% yield (or in 2 steps and 73% yield) with only one chromatographic separation (Scheme 1). The only other reported synthesis of

Scheme 1. Hydrolysis of Acetamide Products: Synthesis of Aminomenthol 37



37 required 3 steps for an overall yield of 34% from (+)-pulegone, a starting material that is considerably more expensive than (–)-menthol.<sup>22</sup>

A postulated mechanistic scenario that is consistent with experimental data and literature precedent is summarized in Figure 2A, with cyclohexane as a model. The role of the Lewis

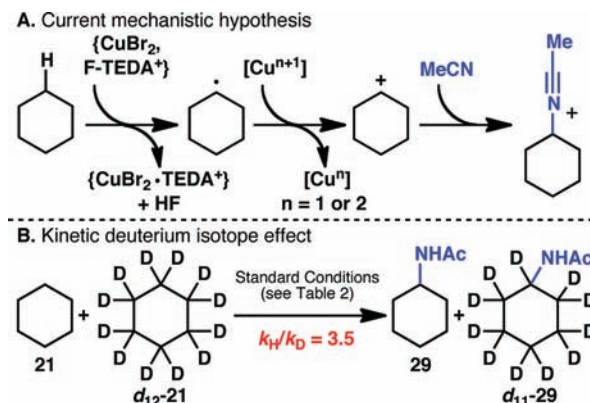


Figure 2. (A) Postulated mechanism for the reaction. (B) Kinetic isotope effect with cyclohexane and cyclohexane-*d*<sub>12</sub>.

acid was neglected here, since it is not necessary for the reaction to proceed; F-TEDA<sup>+</sup> is shown without a counteranion, since the counterion is not believed to affect the mechanism of the reaction. Copper(II) is likely to be oxidized to copper(III) using F-TEDA<sup>+</sup> through a single-electron transfer (SET) mechanism, since it is known that N–F fluorinating agents such as F-TEDA<sup>+</sup> can react through a SET pathway<sup>23</sup> as a bystander oxidant.<sup>24</sup> In the present reaction, the addition of 1.0 equiv of 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) decreased the yield; 5.0 equiv inhibited the C–H amination completely, which is consistent with a radical-based mechanism.<sup>25</sup> A premixed solution of CuBr<sub>2</sub> and F-TEDA-BF<sub>4</sub> remains active but affords lower yields if the substrate is added 1 h later (see SI). This suggests the formation of a rather unstable copper(III) species, which has been previously reported for the reaction of copper(II) with F-TEDA-BF<sub>4</sub>.<sup>6c,26</sup> The structure of a complex obtained by mixing copper(II) trifluoroacetylacetonate and F-TEDA-BF<sub>4</sub> has been previously characterized by X-ray crystallography,<sup>27</sup> but all attempts to identify a similar structure starting with CuBr<sub>2</sub> failed. However, crystalline H-TEDA-BF<sub>4</sub> was isolated after mixing F-TEDA-BF<sub>4</sub> and CuBr<sub>2</sub> in MeCN, and the resulting salt was characterized by X-ray crystallography (see SI for details), suggesting that hydrogen abstraction occurred on the solvent. A similar abstraction is proposed to occur when an electron-rich hydrocarbon substrate is present, with the resulting carbocation trapped by a molecule of acetonitrile to form a Ritter nitrilium intermediate. In the case of the alcohol substrates (1, 4, 6, 7, or 10), this nitrilium is then trapped by the hydroxyl moiety, leading to dihydrooxazine derivatives. Other examples of Ritter-type reactions that occur via two SETs have been reported.<sup>6b</sup> A significant isotope effect was observed (*k*<sub>H</sub>/*k*<sub>D</sub> = 3.5, Figure 2B), consistent with the fact that C–H bond cleavage takes place during the rate-limiting step of the reaction.

In summary, C–H amination of unactivated sp<sup>3</sup> centers (non-benzylic and allylic) using readily available reagents and an inexpensive source of nitrogen has been disclosed. This reaction proceeds under mild conditions for a broad scope of

substrates used in limiting amounts. It displays a high functional group tolerance, is operationally trivial to execute, is scalable, and can be used to directly functionalize natural product derivatives such as 6-*epi*-dihydrojunenol. The mechanism of this intriguing transformation and the nature of the interaction between copper salts and TEDA-based reagents are clear areas for further study. We expect this new protocol to complement existing amination methods and serve as a potential lead for the design of future C–H functionalization methods.<sup>28</sup>

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Experimental procedures and characterization data for all reaction and products, including <sup>1</sup>H and <sup>13</sup>C NMR spectra and CIF files. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## ■ AUTHOR INFORMATION

### Corresponding Author

pbaran@scripps.edu

### Author Contributions

<sup>†</sup>These authors contributed equally to this paper.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Prof. A. Rheingold and Dr. Curtis E. Moore for X-ray crystallographic analysis. Financial support for this work was provided by the NIH/NIGMS (GM-097444) and the Swiss National Science Foundation (postdoctoral fellowship to D.T.).

## ■ REFERENCES

- (1) Barton, D. H. R., Ed. *Reason and Imagination: Reflections on Research in Organic Chemistry: Selected Papers of Derek H. R. Barton*; World Scientific: River Edge, NJ, 1996.
- (2) Breslow, R.; Baldwin, S. W. *J. Am. Chem. Soc.* **1970**, *92*, 732–734.
- (3) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1958**, *80*, 2903–2904.
- (4) For selected recent reviews, see: (a) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926–1936. (b) Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347–378. (c) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061–5074. (d) Diaz-Requejo, M. M.; Pérez, P. *J. Chem. Rev.* **2008**, *108*, 3379–3394.
- (5) (a) Hofmann, A. W. *Ber.* **1883**, *16*, 558–560. (b) Hofmann, A. W. *Ber.* **1885**, *18*, 5–23.
- (6) (a) Zhdankin, V. V.; Krasutsky, A. P.; Kuehl, C. J.; Simonsen, A. J.; Woodward, J. K.; Mismash, B.; Bolz, J. T. *J. Am. Chem. Soc.* **1996**, *118*, 5192–5197. (b) Sakagushi, S.; Hirabayashi, T.; Ishii, Y. *Chem. Commun.* **2002**, 516–517. (c) Xiong, T.; Li, Y.; Bi, X.; Lv, Y.; Zhang, Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 7140–7143. (d) Ni, Z.; Zhang, Q.; Xiong, T.; Zheng, Y.; Li, Y.; Zhang, H.; Zhang, J.; Liu, Q. *Angew. Chem., Int. Ed.* **2011**, *51*, 1244–1247.
- (7) (a) Moody, C. J. In *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 7, p 21. (b) Breslow, D. S.; Edwards, E. I.; Linsay, E. C.; Omura, H. *J. Am. Chem. Soc.* **1976**, *98*, 4268–4275.
- (8) (a) Ragaini, F.; Penoni, A.; Gallo, E.; Tollari, S.; Li Gotti, C.; Lapadula, M.; Mangioni, E.; Cenini, S. *Chem. Eur. J.* **2003**, *9*, 249–259. (b) Omura, K.; Murakami, M.; Uchida, T.; Irie, R.; Katsuki, T. *Chem. Lett.* **2003**, 32, 354–355. (c) Lu, H.; Subbarayan, V.; Tao, J.; Zhang, X. *P. Organometallics* **2010**, *29*, 389–393.
- (9) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30–34.

(10) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198–14199.

(11) (a) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361–362. (b) Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1983**, *105*, 6728–6729. (c) Mansuy, D.; Mahy, J.-P.; Dureault, A.; Bedi, G.; Battioni, P. *J. Chem. Soc., Chem. Commun.* **1984**, 1161–1163.

(12) (a) Nägeli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Müller, P. *Helv. Chim. Acta* **1997**, *80*, 1087–1105. (b) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233–2236. (c) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379. (d) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641–4644. (e) Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639–642. (f) Fructos, M. R.; Trofimenko, S.; Mar Díaz-Requejo, M.; Pérez, P. *J. Am. Chem. Soc.* **2006**, *128*, 11784–11791. (g) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184–5186. (h) Badiei, Y. M.; Dinescu, A.; Dai, X.; Palomino, R. M.; Heinemann, F. W.; Cundari, T. R.; Warren, T. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9961–9964.

(13) (a) Bettinger, H. F.; Filthaus, M.; Bornemann, H.; Oppel, I. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 4744–4747. (b) Ochiai, M.; Miyamoto, K.; Kaneaki, T.; Hayashi, S.; Nakanishi, W. *Science* **2011**, *332*, 448–451.

(14) (a) Brückl, T.; Baxter, R. D.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2012**, No. DOI: 10.1021/ar200194b. (b) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247–7249. (c) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824–828.

(15) Cherney, E. C.; Baran, P. S. *Isr. J. Chem.* **2011**, *51*, 391–405.

(16) Banks, R. E.; Lawrence, N. J.; Besheesh, M. K.; Popplewell, A. L.; Pritchard, R. G. *Chem. Commun.* **1996**, 1629–1630.

(17) Kochi, J. K. *Science* **1967**, *155*, 415–424.

(18) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662–1663.

(19) Ciminiello, P.; Fattorusso, E.; Magno, S.; Mayol, L. *Can. J. Chem.* **1987**, *65*, 518–522.

(20) Hill, R. K.; Conley, R. T.; Chortyk, O. T. *J. Am. Chem. Soc.* **1965**, *87*, 5646–5651.

(21) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999; p 779.

(22) (a) He, X.-C.; Eliel, E. L. *Tetrahedron* **1987**, *43*, 4979–4987. (b) (–)-Menthol (99% purity) costs \$0.39/g, and (+)-pulegone (97%) costs \$2.95/g (Sigma-Aldrich, 2011).

(23) (a) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192–212. (b) Stavber, S.; Zupan, M. *Acta Chim. Slov.* **2005**, *52*, 13–26. (c) Stavber, S.; Jereb, M.; Zupan, M. *J. Phys. Org. Chem.* **2002**, *15*, 56–61.

(24) Engle, K. M.; Mei, T.-S.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 1478–1491.

(25) Vincent, S. P.; Burkart, M. D.; Tsai, C.; Zhang, Z.; Wong, C.-H. *J. Org. Chem.* **1999**, *64*, 5264–5279.

(26) Jin, Z.; Xu, B.; Hammond, G. B. *Tetrahedron Lett.* **2011**, *52*, 1956–1959.

(27) Twamley, B.; Gupta, O. D.; Shreeve, J. M. *Acta Crystallogr.* **2002**, *E58*, 663–665.

(28) While this manuscript was in preparation, two elegant Pd-catalyzed intramolecular C<sub>sp</sub><sup>3</sup>–N bond formations were reported: (a) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3–6. (b) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7–10. For related studies, see: (c) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058–14059. (d) Pan, J.; Su, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8647–8651.