JOC Article

Intermolecular Hydroaminations via Strained (*E*)-Cycloalkenes

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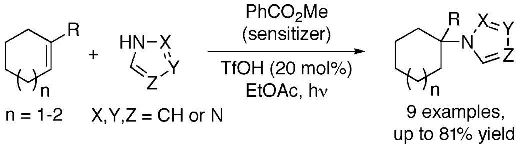

A photoinduced procedure for the intermolecular hydroamination of alkenes using azoles is described. This reaction occurs in modest to good yield for 6- and 7-membered cyclic alkenes. Upon irradiation at 254 nm in the presence of methyl benzoate and a small amount of triflic acid as an additive (20 mol %), imidazoles, pyrazoles, triazoles, and tetrazole can react with the alkene to afford complex Markovnikov adducts. The proposed mechanism involves photoisomerization to generate highly strained (*E*)-cycloalkene intermediates and (*E*)-cycloalkene protonation followed by reaction with the azole nucleophile. Alkene isomerization was found to be a competing side reaction under these conditions.

Introduction

Nitrogen-containing motifs are ubiquitous in natural products and drug discovery. Given the widespread availability of nitrogen nucleophiles and alkenes, there is substantial interest in developing efficient C–N bond-forming reactions from these simple starting materials. Considerable efforts have notably been directed at hydroamination of electron-rich alkenes, both in intra- and intermolecular systems.[1] Various strategies are used to overcome the high activation energy associated with combining two electron-rich reactants, notably transition-metal and Brønsted acid catalysis.[2] While considerable progress has been made, intermolecular reactions remain limited, notably with respect to substrate scope and functional group compatibility. For example, various functionalities are not compatible with the strength of the Brønsted acids required to protonate the double bond. On the other hand, various nitrogen nucleophiles do not lead to hydroamination products due to an acid–base reaction with the Brønsted acid. This buffering effect results in both inefficient alkene protonation and in the deactivation of the nucleophile by the formation of the conjugate acid. As such, most Brønsted acid-based approaches are related to the Ritter reaction,[3] in which nitriles are used as the nitrogen nucleophiles (eq 1). Other weakly basic reagents such as anilines,[4] azoles,[5] hydrazines,[6] sulfonamides,[7] and amides[7c] can also add efficiently under strongly acidic conditions. It was recently reported that the nature of the counterion has a profound impact on the efficiency of these reactions (eq 2).[4a]

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[1] For selected reviews, see: (a) Matsunaga, S. *J. Synth. Org. Chem. Jpn.* **2006**, *64*, 778. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (c) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (d) Roesky, P. W.; Müller, T. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 2708. (e) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (f) Nobis, M.; Driessen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (g) Brunet, J.-J.; Neibecker, D. In *Catalytic Heterofunctionalization*; Togni, A., Grützmacher, H., Eds.; VCH: Weinheim, 2001; pp 91–141. (h) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

[2] For selected alternatives, see: (radicals) (a) Guin, J.; Mück-Lichtenfeld, C.; Grimme, S.; Studer, A. *J. Am. Chem. Soc.* **2007**, *129*, 4498–4503. For a review on base-catalyzed hydroaminations, see: (b) Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795–813.

[3] (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. For a review of the Ritter reaction, see: (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.

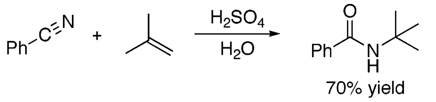
[4] (a) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542. (b) Lapis, A. A. M.; DaSilveira Neto, B. A.; Scholten, J. D.; Nachtigall, F. M.; Eberlinb, M. N.; Duponta, J. *Tetrahedron Lett.* **2006**, *47*, 6775.

[5] (a) Katritzky, A. R.; Puschmann, I. B.; Stevens, C. V.; Wells, A. P. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1645. (b) Katritzky, A. R.; Qi, M.; Wells, A. P. *Geterotsikl. Soedin.* **1996**, 1520. (c) Ostrovskii, V. A.; Koren, A. O. *Heterocycles* **2000**, *53*, 1421 (and references cited therein). (d) Gaponik, P. N.; Voitekhovich, S. V.; Klyaus, B. G. *Zh. Org. Khim.* **2004**, *40*, 624.

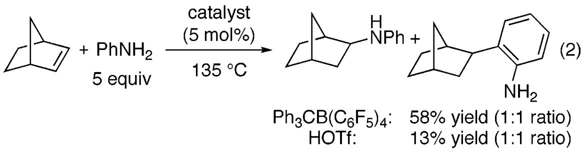
[6] (a) Kelly US Patent 4,954,655, filed 03/1989. (b) Eichinger; Fiege US Patent 5,585,521, filed 09/1995.

[7] (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, *8*, 4179. (c) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617.

10.1021/jo701985w CCC: $40.75

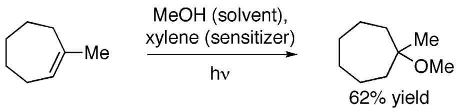


(1)

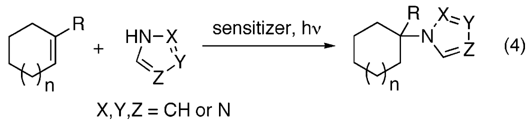


(2)

As highlighted in the example shown in eq 2, strained organic molecules are typically more reactive due to a higher ground-state energy.[8] In hydroamination reactions, strained alkenes could potentially allow reactions with more basic nitrogen nucleophiles due to the increased ability of the olefin to undergo protonation. In this context, we were inspired by the seminal work of Kropp[9] and Marshall,[10] and recent contributions by Inoue,[11] who showed that intermolecular hydroetherification of strained (*E*)-cycloalkenes occurs under acid-free conditions (eq 3).[12] Under their conditions, sensitized photoisomerization leads to the formation of short-lived, ground-state (*E*)-cycloalkenes possessing approximately 30 kcal/mol of ring strain. These highly strained intermediates react with the alcohol, typically used as solvent, under acid-free conditions.[13] Herein, we report that this reactivity can be used to perform intermolecular hydroaminations using azole nucleophiles (eq 4).

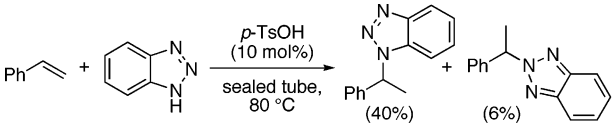


(3)

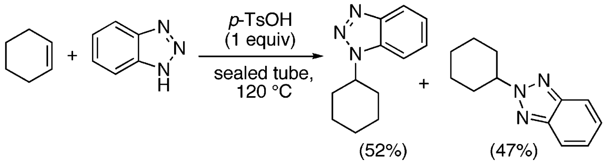


(4)

Reported additions of azoles to electron-rich alkenes are scarce.[5] A representative, well-studied system involves the acid-catalyzed addition of benzotriazole to various alkenes. Katritzky and co-workers have shown that benzotriazole will form a mixture of hydroamination products in the presence of a strong acid additive and excess alkene.[5a] While styrene affords the desired hydroamination products in the presence of catalytic amounts of *p*-TsOH at 80 °C (eq 5), cyclohexene requires the use of a stoichiometric amount of *p*-TsOH at 120 °C (eq 6). Typically, alkene isomerization (if possible) also occurs under the latter conditions.



(5)



(6)

Results and Discussion

We embarked on our search for conditions to perform intermolecular hydroaminations drawing precedence from the work of Kropp and Marshall,[9,10] in which xylenes (or *p*-xylene) are used as a triplet sensitizer and the nucleophile, MeOH, is used as a solvent (see eq 3). Our initial goal was to identify conditions in which the nucleophile could be used in near stoichiometric quantities. For these studies, 1-methyl-1-cyclohexene was used and imidazole was selected as the azole nucleophile; selected results from the initial screening are presented in Table 1.

The data presented in Table 1 highlight the key findings of our initial search for hydroamination reactivity. Initial attempts to perform photoinduced, direct hydroamination in a variety of solvents failed, as illustrated in entry 1. The addition of 20 mol % of an acid additive (leading to the in situ formation of the imidazolium conjugate acid) to facilitate protonation of the putative (*E*)-cycloalkene intermediate provided our initial leads (entries 2 and 3), and our results are consistent with the counterion effects documented by Anderson, Arnold, and Bergman (entry 3).[4a] While encouraging reactivity was observed in various solvents (entries 3 and 4 are representative examples), multiple products could be seen in the unpurified reaction mixture. Inspired by the elegant work of Inoue using benzoates as singlet sensitizers,[11] methyl benzoate-sensitized photoisomerization was explored and led to a similar conversion (entry 5) but minimized the side reactions associated with the use of *p*-xylene as triplet sensitizer. Importantly, irradiation of an equimolar mixture of 1-methylcyclohexene and imidazole using $PhCO_2Me$ as sensitizer led to a 26% conversion to the desired product (entry 6) and served as the starting point for the reaction optimization presented in Table 2. Control experiments were routinely performed during this investigation, and *in all cases, no hydroamination could be observed in the absence of UV irradiation*, which is consistent with the buffering effect of azoles (illustrated by Table 1, entry 7).

Solvent and counterion effects were briefly reinvestigated using methyl benzoate as sensitizer, and both the use of imidazolium *trifluoromethanesulfonate* as a conjugate acid and EtOAc as solvent were found to be optimal (Table 2, entry 2). Surprisingly, increasing the ratio in favor of one of the reactants had only a minimal impact on the reaction outcome (entries 5 and 6). Stimulated by a recent publication by Squillacote and co-workers suggesting that the (*E*)-cycloalkene "thermal" isomerization (i.e., their lability) arises from a bimolecular pathway involving alkenes,[14] we performed the reaction by adding the excess alkene in five portions over the course of

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[8] Liebman, J. F.; Greenberg, A. *Chem. Rev.* **1976**, *76*, 311.

[9] (a) Kropp, P. J. *J. Am. Chem. Soc.* **1966**, *88*, 4091. (b) Kropp, P. J.; Krauss, H. J. *J. Am. Chem. Soc.* **1967**, *89*, 5199. (c) Kropp, P. J. *J. Am. Chem. Soc.* **1969**, *91*, 5783. (d) Tise, F. P.; Kropp, P. J. *Org. Synth.* **1983**, *61*, 112.

[10] (a) Marshall, J. A.; Carroll, R. D. *J. Am. Chem. Soc.* **1966**, *88*, 4092. (b) Marshall, J. A.; Wurth, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 6788.

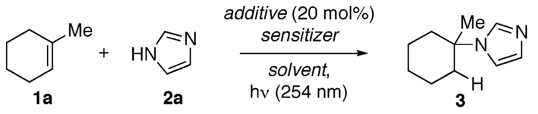
[11] (a) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Chem. Commun.* **1981**, 1031. (b) Inoue, Y.; Ueoka, T.; Kuroda, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1983**, 983. (c) Inoue, Y.; Ueoka, T.; Hakushi, T. *J. Chem. Soc., Perkin Trans. 2* **1984**, 2053. (d) Shim, S. C.; Kim, D. S.; Yoo, D. J.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2002**, *67*, 5718. (e) Hoffmann, R.; Inoue, Y. *J. Am. Chem. Soc.* **1999**, *121*, 10702. (f) Asaoka, S.; Horiguchi, H.; Wada, T.; Inoue, Y. *J. Chem. Soc., Perkin Trans. 2* **2000**, 737.

[12] For reviews, see: (a) Marshall, J. A. *Science* **1970**, *170*, 137. (b) Kropp, P. J. *Mol. Photochem.* **1978**, *9*, 39.

[13] In some cases, trace amounts of acid (not sufficient to promote hydroetherification) were found to be beneficial. See ref 9d.

[14] Squillacote, M. E.; DeFellipis, J.; Shu, Q. *J. Am. Chem. Soc.* **2005**, *127*, 15983.

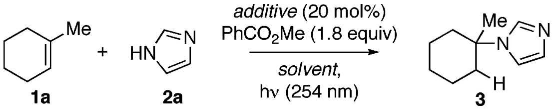
TABLE 1. Selected Optimization Data Highlighting the Importance of Sensitizer and Additives to Achieve Intermolecular Hydroamination[a]



entry	additive	sensitizer	solvent	conversion[b] (%)
1		*p*-xylene	dioxane	0
2	AcOH	*p*-xylene	dioxane	4
3	TfOH	*p*-xylene	dioxane	13
4	TfOH	*p*-xylene	EtOAc	5
5	TfOH	$PhCO_2Me$	dioxane	14
6	TfOH	$PhCO_2Me$	dioxane	26[c]
7 (no *hν*)	TfOH	$PhCO_2Me$	dioxane	0

[a] Conditions: **1a** (1 equiv) was added to a solution of **2a** (7.6 equiv), additive (20 mol %), sensitizer (7% v/v for *p*-xylene or 1.8 equiv of $PhCO_2Me$), and solvent (0.05 M) in a quartz tube under N_2 and then irradiated with UVC lamps (254 nm) for 18 h. [b] Conversions were determined by ^1H NMR based on imidazole resonances. [c] Only 1.0 equiv of imidazole was used.

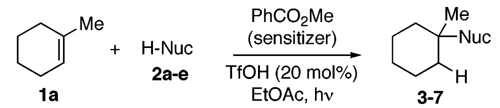
TABLE 2. Optimization Using Methyl Benzoate as Sensitizer[a]

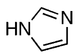
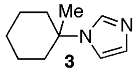
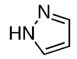
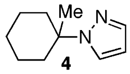
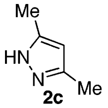
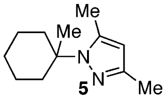
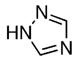
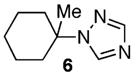
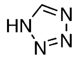
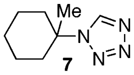


entry	solvent	additive	alkene/azole ratio	conversion[b] (%)
1	dioxane	TfOH	1:1	26
2	EtOAc	TfOH	1:1	22
3	EtOAc	AcOH	1:1	0
4	EtOAc	CF_3CO_2H	1:1	7
5	EtOAc	TfOH	1:2	18
6	EtOAc	TfOH	5:1	23
7	EtOAc	TfOH	5:1 (portionwise addition)	72

[a] Conditions: **1a** was added to a solution of **2a** (molar ratio shown), additive (20 mol %), $PhCO_2Me$ (1.8 equiv), and solvent (0.05 M) in a quartz tube under N_2 and then irradiated with UVC lamps (254 nm) for 18 h. [b] Conversions were determined by ^1H NMR based on imidazole resonances.

TABLE 3. Photoinduced Additions of Azoles to 1-Methyl-1-cyclohexene[a]



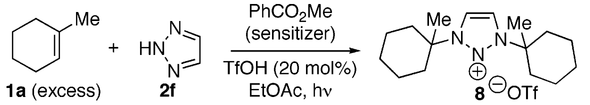
Entry	Azole	Product	Yield(%)[b]
1	 **2a**	 **3**	72
2	 **2b**	 **4**	72
3	 **2c**	 **5**	47
4	 **2d**	 **6**	68
5	 **2e**	 **7**	74

[a] Conditions: **1a** (0.41 mmol) was added to a solution of nitrogen heterocycle (0.41 mmol), TfOH (20 mol %), $PhCO_2Me$ (1.8 equiv), and EtOAc (8 mL) in a quartz tube under N_2 and then irradiated with UVC lamps (254 nm). Additional 1-methyl-1-cyclohexene was added portionwise over time (1 equiv/6−12 h to a total of 5 equiv) with continued irradiation. [b] Isolated yield.

approximately 30 h. This new procedure led to a significant improvement: 72% conversion to the desired hydroamination product was observed (entry 7 vs entry 6).

With optimized conditions in hand, we could examine the reaction scope with respect to the azole reacting partner. These studies were performed using 1-methyl-1-cyclohexene as substrate and are presented in Table 3.

The hydroamination reactivity discovered with imidazole (Table 3, entry 1) extended well to other azole nucleophiles. For example, pyrazoles (entries 2 and 3) led to the formation of the desired adducts, albeit in lower yield with the hindered 2,5-dimethylpyrazole (**2c**, entry 3). 1,2,4-Triazole (entry 4) and tetrazole (entry 5) also afforded the desired products in good yield. An unexpected result was obtained with 1,2,3-triazole, which afforded the nitrenium salt **8** in an unoptimized 20% yield (eq 7). Such nitrenium salts have been shown by Boche to have remarkable properties,[15] as expected based on their isoelectronic nature with the related Arduango carbenes.[16] Therefore, the method provides simple access to hindered nitrenium derivatives such as **8**.



(7)

With the azole scope explored, we turned our attention to the reaction of other cyclic alkenes with imidazole. These results are presented in Table 4.

As shown, the hydroamination reactivity observed with 1-methyl-1-cyclohexene and imidazole (Table 4, entry 1) could also be extended to other alkenes. Variation of the alkene substituent or of the ring size led to somewhat lower yields, as shown by the reaction of 1-ethyl-1-cyclohexene (entry 2) and 1-methyl-1-cycloheptene (entry 3). Encouragingly, (−)-limonene (**1d**) led to selective hydroamination of the cyclic alkene,[17] with a mixture of diastereoisomers isolated in good yield (entry 4). The use of cyclohexene (**1e**) led to the hydroamination product in modest yield (entry 5). In contrast, 1-methylcyclopentene and cyclooctene did not lead to product formation under our reaction conditions. This lack of reactivity suggests that the ring strain present in (*E*)-cyclooctene, which is known to be stable at room temperature, is not sufficient to allow the desired reaction.

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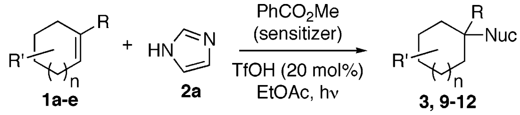
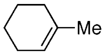
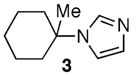
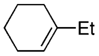
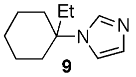
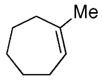
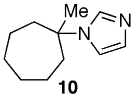
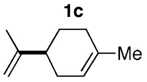
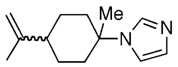
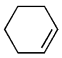
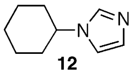
(15) Boche, G.; Andrews, P.; Harms, K.; Marsch, M.; Rangappa, K. S.; Schimeczek, M.; Willeke, C. *J. Am. Chem. Soc.* **1996**, *118*, 4925.

(16) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361.

(17) This selectivity for the cyclic alkene in limonene, as well as the lack of reactivity observed with 1-methylcyclopentene, cyclooctene, and in control experiments performed with other cyclic alkenes (α-pinene and 2-carene, for example) strongly suggest the intermediacy of highly strained (*E*)-cycloalkene intermediates. We also prefer this rationale over other possibilities, including reactivity arising from azole excited states being more acidic, for example.

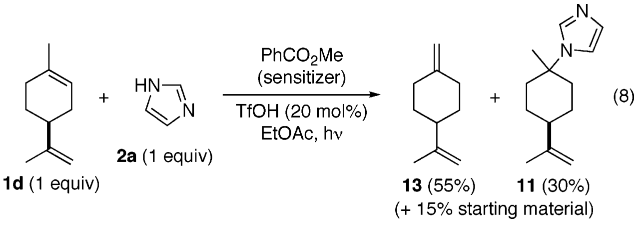
TABLE 4. Photoinduced Additions of Imidazole to Cyclic Alkenes[a]



Entry	Alkene	Product	Yield(%)[b]
1	 **1a**	 **3**	72
2	 **1b**	 **9**	40
3	 **1c**	 **10**	45
4	 **1d**	 **11**	81[c]
5	 **1e**	 **12**	26

[a] Conditions: Cycloalkene (0.41 mmol) was added to a solution of imidazole (0.41 mmol), TfOH (20 mol %), $PhCO_2Me$ (1.8 equiv), and EtOAc (8 mL) in a quartz tube under N_2, then irradiated with UVC lamps (254 nm). Additional cycloalkene was added portion-wise over time (1 equiv/6−12 h to a total of 5 equiv) with continued irradiation. [b] Isolated yield. [c] 1.3:1 mixture of diastereoisomers.

The variability observed with respect to the alkene structure can be explained by looking at the efficiency of the hydroamination step. The reaction conditions require the presence of an excess of alkene to obtain high yields of the hydroamination product. This excess is necessary due to an unproductive isomerization step, which leads to the formation of the exocyclic alkene. For example, if the reaction with (−)-limonene (**1d**) is performed using equimolar amounts of alkene and imidazole, the product distribution favors the isomerization product **13** over the hydroamination product **11** (eq 8). This control experiment suggests the formation of highly strained (*E*)-cycloalkenes under our reaction conditions is efficient as shown by the total conversion to **11** and **13**. However, the tertiary carbocation formed upon alkene protonation can either react with imidazole to provide the desired hydroamination product or undergo deprotonation, which either leads back to the starting material (with erosion of ee)[18] or leads to the formation of an exocyclic alkene. The latter reaction is irreversible as it cannot lead to the formation of hydroamination products; this reactivity of (*E*)-cycloalkenes is well documented.[19]



1d (1 equiv) **2a** (1 equiv) **13** (55%) **11** (30%) (+ 15% starting material)

Conclusion

A photoinduced procedure for intermolecular hydroamination of cyclic alkenes using azoles has been developed. The presence of a mild acid and sequential addition of the alkene over time were found to be crucial to obtain good yields of the complex *N*-alkylazole products. Highly strained *trans*-cycloalkenes, formed in situ via sensitized photoisomerization using methyl benzoate at 254 nm, are likely reaction intermediates.

Experimental Section

General Procedure for Photoinduced Hydroamination of Cycloalkenes (Tables 3 and 4). A 10 mL quartz tube was charged with a stir bar, methyl benzoate (0.10 g, 0.73 mmol), nitrogen heterocycle (0.41 mmol), and 8.0 mL of EtOAc, followed by trifluoromethanesulfonic acid (0.012 g, 0.081 mmol). The mixture was stirred for 10 s. Cycloalkene (0.41 mmol) was added, and the tube was capped with a rubber septum and purged with a nitrogen balloon and an outlet for 5 min while stirring. The tube was then placed between two Luzchem exposure panels, each equipped with four ultraviolet lamps, for 6−12 h while stirring. The reaction was carried out in a well-ventilated hood, and little, if any, sample warming occurred. Irradiation was then stopped, a further equivalent of cycloalkene (0.41 mmol) was added, and the tube was again purged with nitrogen and subjected to irradiation. This was continued until 5 equiv of the cycloalkene had been added. The reaction was monitored by thin layer chromatography. The crude reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography to give the *N*-substituted heterocycle.

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Supporting Information Available: Typical experimental procedures, experimental details, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) In agreement with this rationale, the limonene recovered from the reaction shown in eq 8 was found to be racemic. See the experimental details.

(19) See ref 12 for a discussion. For an example of application in total synthesis, see: Marshall, J. A.; Pike, M. T. *J. Org. Chem.* **1968**, *33*, 435.