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Is an Iodine Atom Almighty as a Leaving Group for Bu_3SnH-Mediated Radical Cyclization? The Effect of a Halogen Atom on the 5-Endo-trig Radical Cyclization of *N*-Vinyl-α-halo Amides

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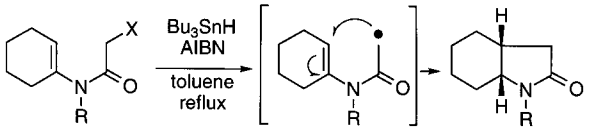
The effect of a halogen atom as a leaving group on Bu_3SnH-mediated 5-endo-trig radical cyclization of *N*-(cyclohex-1-enyl) α-halo amides was examined. The cyclization of α-chloro amides occurred with a high degree of efficiency, whereas the corresponding α-iodo congeners gave only limited quantities of cyclization products. A detailed study revealed that these phenomena could be attributed to the initial conformations of α-halo amides. The cyclizing ability of α-iodo amides can be restored with Bu_3SnCl or Bu_3SnF as an additive. The cyclization of an α-iodo amide in the presence of Bu_3SnF could be applied to a short-step synthesis of lycoranes featuring sequential 5-endo-trig and 6-endo-trig radical cyclizations.

Introduction

γ-Lactam formation using 5-exo or 5-endo cyclization of a carbamoylmethyl radical has attracted considerable attention over the past two decades.[1,2] Since our report on the Bu_3SnH-mediated 5-endo-trig cyclization of *N*-(cyclohex-1-enyl)-*N*-alkyl-α-chloroacetamides (Scheme 1, X = Cl),[3a] 5-endo cyclization of carbamoylmethyl radicals

SCHEME 1



of enamides has been extensively studied and applied to syntheses of several natural products and related compounds.[3−6] This cyclization mode has therefore now become a standard reaction for examining new methods of generating carbamoylmethyl radicals.[4−6]

It is recognized that an iodine atom is a better leaving group for Bu_3SnH-mediated radical cyclizations of ω-halo alkenes than is a bromine or chlorine atom[7] because the bond dissociation energy (BDE) of a carbon−iodine bond is significantly lower than those of a carbon−bromine

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(1) For reviews, see: (a) Giese, B. *Radicals in Organic Synthesis: Formation of Carbon−Carbon Bonds*; Pergamon: New York, 1986. (b) Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons: New York, 1995. (c) Curran, D. P. *Synthesis* **1988**, 417, 489. (d) Jasperse, C. P.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237.

(2) For reviews on synthesis of heterocycles by radical cyclization, see: (a) Bowman, W. R.; Bridge, C. F.; Brookes, P. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1. (b) Bowman, W. R.; Cloonan, M. O.; Krintel, S. L. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2885. For a review on 5-endo radical cyclizations, see: (c) Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* **2002**, 695.

(3) For Bu_3SnH-mediated 5-endo radical cyclization of *N*-vinyl-α-halo amides, see: (a) Ishibashi, H.; Nakamura, N.; Sato, T.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* **1991**, *32*, 1725. (b) Sato, T.; Nakamura, N.; Ikeda, K.; Okada, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2399. (c) Sato, T.; Machigashira, N.; Ishibashi, H.; Ikeda, M. *Heterocycles* **1992**, *33*, 139. (d) Sato, T.; Chono, N.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1115. (e) Ishibashi, H.; Fuke, Y.; Yamashita, T.; Ikeda, M. *Tetrahedron: Asymmetry* **1996**, *7*, 2531. (f) Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* **1998**, *39*, 75. (g) Ikeda, M.; Ohtani, S.; Sato, T.; Ishibashi, H. *Synthesis* **1998**, 1803. (h) Ikeda, M.; Ohtani, S.; Yamamoto, T.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1763. (i) Ikeda, M.; Hamada, M.; Yamashita, T.; Matsui, K.; Sato, T.; Ishibashi, H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1949. (j) Goodall, K.; Parsons, A. F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3257. (k) Goodall, K.; Parsons, A. F. *Tetrahedron* **1996**, *52*, 6739. (l) Goodall, K.; Parsons, A. F. *Tetrahedron Lett.* **1997**, *38*, 491. (m) Baker, S. R.; Parsons, A. F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 2815. (n) Baker, S. R.; Parsons, A. F.; Pons, J.-F.; Wilson, M. *Tetrahedron Lett.* **1998**, *39*, 7197. (o) Baker, S. R.; Burton, K. I.; Parsons, A. F.; Pons, J.-F.; Wilson, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 427.

(4) For nickel-mediated 5-endo radical cyclization of *N*-vinyl-α-halo amides, see: (a) Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1996**, *37*, 1397. (b) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 1029. (c) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron Lett.* **1998**, *39*, 8995. (d) Cassayre, J.; Zard, S. Z. *Synlett* **1999**, 501. (e) Cassayre, J.; Dauge, D.; Zard, S. Z. *Synlett* **2000**, 471.

(5) For Cu(I)-mediated 5-endo radical cyclization of *N*-vinyl-α-halo amides, see: (a) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron Lett.* **1999**, *40*, 8615. (b) Clark, A. J.; Dell, C. P.; Ellard, J. M.; Hunt, N. A.; McDonagh, J. P. *Tetrahedron Lett.* **1999**, *40*, 8619. (c) Clark, A. J.; Filik, R. P.; Haddleton, D. M.; Radigue, A.; Sanders, C. J.; Thomas, G. H.; Smith, M. E. *J. Org. Chem.* **1999**, *64*, 8954. (d) Bryans, J. S.; Chessum, N. E. A.; Parsons, A. F.; Ghelfi, F. *Tetrahedron Lett.* **2001**, *42*, 2901.

(6) For Mn(III)-mediated 5-endo radical cyclization of *N*-vinyl-β-keto or α-methylthio amides, see: (a) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron Lett.* **1998**, *39*, 4397. (b) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941. (c) Ishibashi, H.; Toyao, A.; Takeda, Y. *Synlett* **1999**, 1468. (d) Toyao, A.; Chikaoka, S.; Takeda, Y.; Tamura, O.; Muraoka, O.; Tanabe, G.; Ishibashi, H. *Tetrahedron Lett.* **2001**, *42*, 1729.

(7) See ref 1b, pp 243−255.

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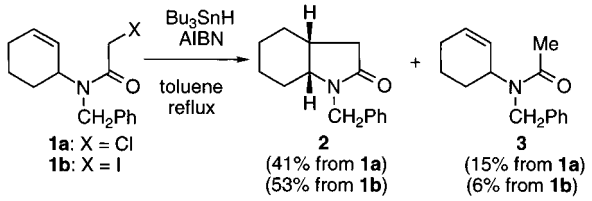
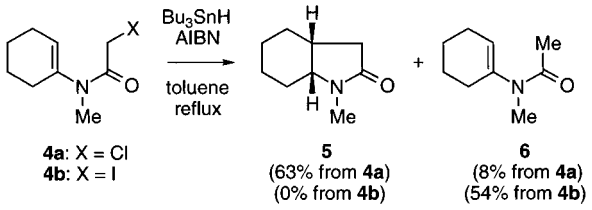
SCHEME 2



SCHEME 3



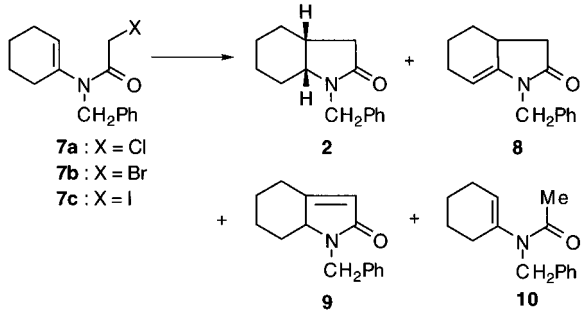
bond and a carbon−chlorine bond (BDE: CH_3−I, 57 kcal/mol; CH_3−Br, 71 kcal/mol; CH_3−Cl, 83 kcal/mol).[8] Therefore, the use of a chlorine atom as a leaving group for the radical cyclizations of *ω*-halo alkenes frequently resulted in an increase in the amount of uncyclized reduction products due to an attack of the accumulated Bu_3SnH on the initially generated radicals. This was also the case for 5-exo radical cyclization of *N*-(cyclohex-2-enyl)-α-haloacetamides **1a**,**b**. Thus, Bu_3SnH-mediated reaction of α-iodo amide **1b** gave a higher yield of cyclization product **2** with a lower amount of simple reduction product **3** than did that of α-chloro amide **1a** (Scheme 2).[9]

Recently, we reinvestigated Bu_3SnH-mediated 5-endo radical cyclization of *N*-(cyclohex-1-enyl)-α-haloacetamides (Scheme 1; X = Cl, Br, and I) and found that, in contrast to the 5-exo cyclization described above, α-chloro amides gave much higher yields of the 5-endo cyclization products than did the corresponding α-iodo congeners and that the cyclization abilities of the iodo congeners could be restored by the use of Bu_3SnCl as an additive.[10] We now give a full account of this work and its application to a short-step synthesis of lycoranes using sequential radical cyclizations.

Results and Discussion

1. Effect of a Halogen Atom. Our studies were begun by comparing the effect of a halogen atom on the radical cyclization of *N*-(cyclohex-1-enyl)-*N*-methyl-α-haloacetamides **4a**,**b** (Scheme 3). In our previous study, on treatment of α-chloro amide **4a** with Bu_3SnH in the presence of AIBN in boiling toluene, 5-endo-trig radical cyclization product **5** and simple reduction product **6** were obtained in 63 and 8% yields, respectively.[3a,b] Treatment of the corresponding iodo congener **4b** under similar conditions, surprisingly, gave only simple reduction product **6** without any cyclization product **5**.

TABLE 1. Radical Cyclization of α-Halo Amides 7a−c



			products (% yield)				
entry	amide **7**	conditions[a]	**2**	**8**	**9**	**2** + **8** + **9**	**10**
1	**7a**	A	92			92	
2	**7b**	A	55	11	11	77	
3	**7c**	A		13	11	24	68
4	**7a**	B	56		12	68	
5	**7c**	B					76

[a] Condition A: Bu_3SnH (1.2 equiv), AIBN (0.1 equiv), toluene, reflux. Condition B: $(TMS)_3SiH$ (1.2 equiv), AIBN (0.1 equiv), toluene, reflux.

We further examined the effect of a halogen atom in 5-endo radical cyclization of α-halo amides by employing *N*-benzyl amides **7a**−**c** in place of *N*-methyl amides **4a**,**b** (Table 1). The cyclization ability, interestingly, decreased in the order of chloro amide **7a**, bromo amide **7b**, and iodo amide **7c**. Thus, treatment of **7a** with Bu_3SnH in the presence of AIBN in boiling toluene gave cyclization product **2** in 92% yield (entry 1). A similar treatment of **7b** gave **2**, enamide **8**, and α,*β*-unsaturated product **9** in 55, 11, and 11% yields, respectively (entry 2). In contrast, reaction of α-iodo amide **7c** gave simple reduction product **10** in 68% yield accompanied by small amounts of cyclization products **8** and **9** (entry 3). This tendency was also observed in $(TMS)_3SiH$-mediated reactions. Reaction of α-chloro amide **7a** with $(TMS)_3SiH$ in the presence of AIBN gave **2** and **9** in 68% combined yield (entry 4), whereas α-iodo amide **7c** gave only simple reduction product **10** in 76% yield (entry 5).

Formation of the cyclization products **2**, **8**, and **9** from α-halo amides **7a**−**c** may be rationalized as depicted in Scheme 4. Carbamoylmethyl radical **11** generated from **7** causes 5-endo-trig cyclization to give α-amidoyl radical **12**, which undergoes an attack of Bu_3SnH or $(TMS)_3SiH$, affording **2**. On the other hand, a single electron transfer (SET) from α-amidoyl radical **12** to the starting α-halo amides **7** generates cation **13** and an anion radical of **7**,[11] which releases a halide anion, giving rise to the required radical **11**. The cation **13** affords amides **8** and **9**.[12] Another possibility for the formation of **8** and **9** involves an atom transfer reaction.[13] Halogen atom transfer takes place from α-halo amide **7** to radical **12** to give radical

(8) See ref 1b, pp 113, 298.

(9) Bu_3SnH-mediated 5-exo-trig radical cyclization of the *N*-methyl congener of **1b** was reported to give a ca. 1:2 mixture of the cyclization product **5** and the reduction product; see: (a) Jolly, R. S.; Livinghouse, T. *J. Am. Chem. Soc.* **1988**, *110*, 7536. (b) Curran, D. P.; Tamine, J. *J. Org. Chem.* **1991**, *56*, 2746.

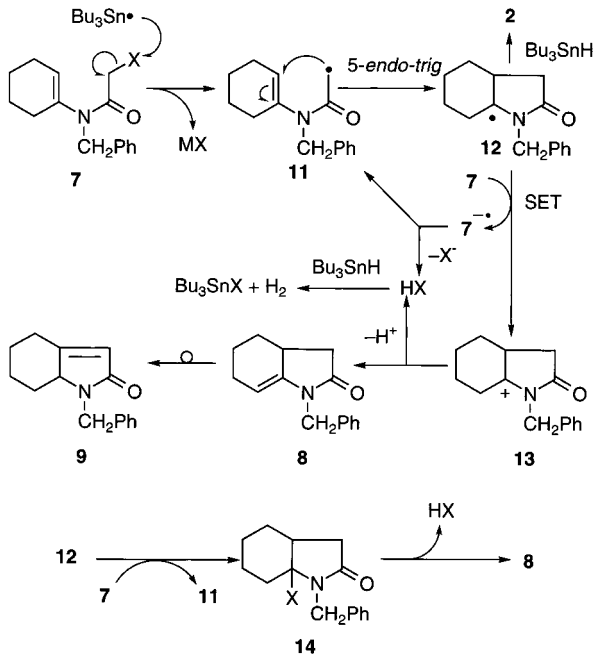
(10) Ishibashi, H.; Matsukida, H.; Toyao, A.; Tamura, O.; Takeda, Y. *Synlett* **2000**, 1497.

(11) For SET reaction from a long-lived radical to a starting halide, see refs 4b and 5c. See also: Marco-Contelles, J.; Rodríguez-Fernández, M. *Tetrahedron Lett.* **2000**, *41*, 381.

(12) Amide **8** appears to be the kinetic product from cation **13**, and α,*β*-unsaturated amide **9** may be the thermodynamic product produced by isomerization of **8**, because amide **8** was selectively obtained in some cases (Table 2, entries 3 and 4, vide infra). Of course, the intermediate for the formation of **9** from **8** might be cation **13**.

(13) For iodine atom transfer reaction, see: Miranda, L. D.; Cruz-Almanza, R.; Pavón, M.; Romero, Y.; Muchowski, J. M. *Tetrahedron Lett.* **2000**, *41*, 10181 and references therein.

SCHEME 4



11 and halide **14**, which affords enamide **8** along with release of hydrogen halide. The present cyclizations involving either the SET or the halogen atom transfer require stoichiometric amounts (not catalytic amounts) of Bu_3SnH or $(TMS)_3SiH$ since the cyclizations are accompanied by loss of hydrogen halides, which consume Bu_3SnH or $(TMS)_3SiH$.[11]

The tendency for reactions of α-chloro amides **4a** and **7a** to give higher yields of cyclization products than those obtained by reactions of α-iodo congeners **4b** and **7c** is thought to be due to the amides themselves, since the reactions of **7a** and **7c** under different conditions showed the same tendency (Table 1; entries 1 and 3 and entries 4 and 5, respectively). One possible explanation for the difference between the modes of cyclization of α-chloro and α-iodo amides may be derived from consideration of the rotamers of the amides (Figure 1).[14] Two conformers anti-**7a** and syn-**7a** are considered for **7a** and anti-**7c** and syn-**7c** for **7c**. The carbamoylmethyl radical **11** from syn-**7a**,**c** can cyclize, whereas that from anti-**7a**,**c** cannot. Taking into account the fact that **7a**,**c**, having bulkier *N*-benzyl groups, afforded higher yields of cyclization products than **4a**,**c**, bearing *N*-methyl groups, one of the factors to determine equilibrium constants ^{Cl}K and ^{I}K may be steric interaction between an *N*-substituent and a halomethyl group.[15] It is well-known that a chlorine−carbon bond is much shorter than an iodine−carbon bond,[16] and hence the internal steric interaction between the chlorine atom and the benzyl group in anti-**7a** may be more severe than that between an iodine atom and benzyl group in anti-**7c**.[17] Therefore, the population of syn-**7a** would be larger than that of syn-**7c** ($^{Cl}K > {}^{I}K$).[18,19]

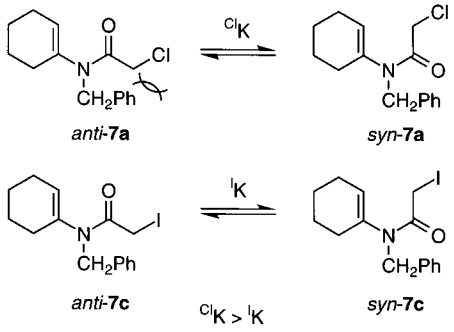


FIGURE 1. Rotamers of α-halo amide **7a** and **7c** due to the amide bonds.

The above consideration appears to be supported by the previous result with the *N*-methyl-substituted α-chloropropionamide **15a**, which has more severe steric interaction between both methyl groups than acetamide derivative **4a** (Scheme 5). Reaction of **15a** with Bu_3SnH

(14) It has been suggested that the geometry of an initial rotamer of a radical precursor plays a crucial role in determining the course of a radical reaction; see: (a) Stork, G.; Mah, R. *Heterocycles* **1989**, *28*, 723. (b) Sato, T.; Wada, Y.; Nishino, M.; Ishibashi, H.; Ikeda, M. *J. Chem. Soc., Perkin Trans. 1* **1989**, 879. (c) Curran, D. P.; DeMello, N. C. *J. Chem. Soc., Chem. Commun.* **1993**, 1314. (d) Curran, D. P.; Liu, W.; Chen, C. H.-T. *J. Am. Chem. Soc.* **1999**, *121*, 11012. (e) Musa, O. M.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 1022. (f) Miyata, O.; Nishiguchi, A.; Ninomiya, I.; Aoe, K.; Okamura, K.; Naito, T. *J. Org. Chem.* **2000**, *65*, 6922. (g) Besev, M.; Engman, L. *Org. Lett.* **2000**, *2*, 1589. (h) Ishibashi, H.; Kato, I.; Takeda, Y.; Kogure, M.; Tamura, O. *Chem. Commun.* **2000**, 1527. (i) Iwamatsu, S.; Matsubara, K.; Nagashima, H. *J. Org. Chem.* **1999**, *64*, 9625. (j) Nagashima, H.; Isono, Y.; Iwamatsu, S. *J. Org. Chem.* **2001**, *66*, 315 and references therein; See also ref 9b.

(15) It was reported that the benzyl-axial conformer of *cis*-1-benzyl-4-methylcyclohexane is slightly predominant over the corresponding benzyl-equatorial one at low temperatures (for example, at −71 °C) and that the benzyl-equatorial conformer becomes the major conformer at room temperature due to the contribution of the entropic factor; see: Juaristi, E.; Labastida, V.; Antúnez, S. *J. Org. Chem.* **1991**, *56*, 4802. This strongly suggests that a benzyl group can be regarded as a bulkier substituent than a methyl group at temperatures greater than room temperature. The present radical reactions were carried out in boiling toluene, and hence the steric interaction of the benzyl group would be important.

(16) Bond lengths of C−X of CH_2X are as follows: C−Cl = 1.78 Å, C−Br = 1.94 Å, and C−I = 2.14 Å. Equatorial−axial free energy differences ($\Delta G°$, kcal/mol) of chloro-, bromo-, and iodocyclohexanes are 0.53, 0.48, and 0.47, respectively; see: Carey, F. A.; Sandberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Publishing: New York, 1990; Part A, pp 133−135.

(17) In sulfonyl radical-mediated cyclization of diallylbenzylamines, the use of the BH_3 as a Lewis acid gave better diastereoselectivity than the use of $AlMe_3$. This result was explained by a conformational analysis of the transition state for the cyclization of the amine−Lewis acid complex. The bond length of N−B is shorter than that of N−Al, so BH_3 can make a more rigid conformation, resulting in a higher degree of diastereoselectivity, than $AlMe_3$. See: Bertrand, M.-P.; Gastaldi, S.; Nouguier, R. *Tetrahedron* **1998**, *54*, 12829.

(18) The rotamers anti-**7** and syn-**7** are not detected in the NMR time scale. The ^{1}H NMR spectrum of **7a** exhibits the signals due to the vinyl proton and the allylic proton at δ 4.99 and 1.60, respectively, whereas that of **7c** exhibits signals at δ 5.20 and 1.75. Since the carbonyl group of an anti conformer of α-halo amide **7** is located closer to the cyclohexene ring than that of the syn conformer, the vinyl proton and the allylic proton of the anti conformer may resonate more downfield due to the anisotropy effect from the carbonyl group than those of the syn conformer. The chemical shifts of the protons of **7a** and **7c** seem to support that **7c** has a higher population of the anti conformer than **7a**.

(19) Another assumption for the lesser cyclization ability of **4b** and **7c** may involve steric interaction between α-halomethyl groups and cyclohexene rings in α-halo acetamides **4** and **7**; that is, steric repulsion between the iodomethyl group and the cyclohexene ring in syn-**7c** might be larger than that between the chloromethyl group and the cyclohexene ring in syn-**7a**, which may result in the larger population of anti-**7c** than that of anti-**7a**. However, this assumption can be ruled out by considering the fact that radical reaction of **15a** gave **16a** in 73% yield without a reduction product (Scheme 5, vide infra) because if the hypothesis was correct, radical reaction of α-chloro propionamide **15a**, having a more sterically demanding haloalkyl group, should give a lower yield of cyclization product **16a** with a higher yield of the reduction product than that of **6** from α-chloroacetamide **4a**.

SCHEME 5

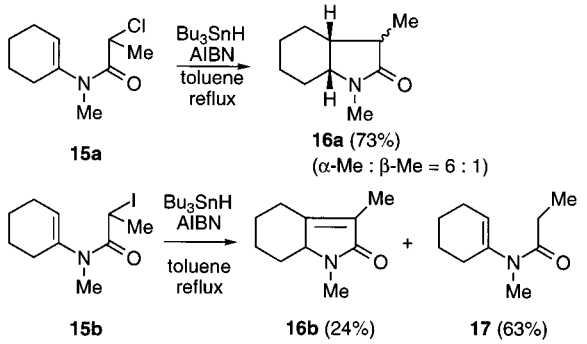
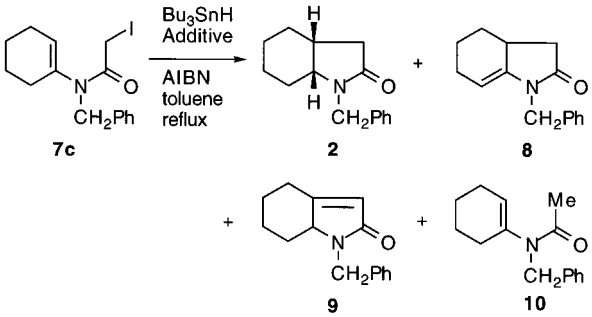


TABLE 2. Radical Cyclization of 7c in the Presence of Additives



		products (% yield)				
entry	additive (equiv)	**2**	**8**	**9**	**2 + 8 + 9**	**10**
1	Bu_3SnCl (1)	11	13	14	38	30
2	Bu_3SnCl (5)	18	20	28	66	9
3	Bu_3SnF (5)	9	54		63	
4	Bu_3SnOAc (5)		52		52	
5	Bu_3SnI (5)		14	12	26	71
6	$(TMS)_3SiCl$ (5)	6		18	24	48

in the presence of AIBN gave no reduction product and afforded 5-endo-trig cyclization product **16a** (a mixture of diastereomers) in 73% yield (compared with the reaction of **4a**).[3a,b] α-Iodo congener **15b** also gave cyclization product **16b**, although the yield was low (24%), together with the reduction product **17**, whereas α-iodo amide **4b** gave no cyclization product.

2. Effect of Bu_3SnCl. Next, we turned our attention to improvement of the reaction of α-iodo amide **7c**. The fact that radical reaction of **7a** using Bu_3SnH gave a better yield of cyclized product than that employing $(TMS)_3SiH$ (Table 1, entry 1 vs 4) led us to consider the influence of Bu_3SnCl generated as the reaction of **7a** with Bu_3SnH proceeds. We therefore examined radical reactions of **7c** in the presence of various types of Bu_3SnX (Table 2). The reaction using 1 equiv of Bu_3SnCl as an additive gave cyclization products **2**, **8**, and **9** in 38% combined yield along with simple reduction product **10** in 30% yield (entry 1). We were delighted to find that use of a large excess of Bu_3SnCl improved the yield of cyclization products to 66% (total yield) (entry 2). When Bu_3SnF or Bu_3SnOAc was employed as an additive, enamide **8** was obtained selectively (entries 3 and 4). In contrast, the addition of Bu_3SnI or $(TMS)_3SiCl$ mainly afforded simple reduction product **10** (entries 5 and 6).[20]

One possible explanation of the role of Bu_3SnCl as an additive may involve consideration of initial conformations of complex **7c**−Sn formed from **7c** and Bu_3SnCl as a Lewis acid (Figure 2).[21] The anti-**7c**−Sn might have severe steric repulsion between the cyclohexene ring and the tin group, and hence the equilibrium might therefore shift to syn-**7c**−Sn ($^{I}K < {}^{Sn-I}K$). Another possibility may be due to the relatively long lifetime of radical **18** generated from **7c**−Sn. Radical anti-**11** generated from anti-**7c** undergoes facile attack of Bu_3SnH to afford simple reduction product **10**, whereas the radical center of anti-**18** derived from anti-**7c**−Sn is efficiently blocked from attack of Bu_3SnH by sterically hindered Bu_3SnCl; thereby, radical anti-**18** gains sufficient lifetime to isomerize to syn-**18**, which is the favored conformation for cyclization.[22] The fact that Bu_3SnI is much less efficient as an additive than Bu_3SnCl or Bu_3SnF may be ascribed to the lack of Lewis acidity.

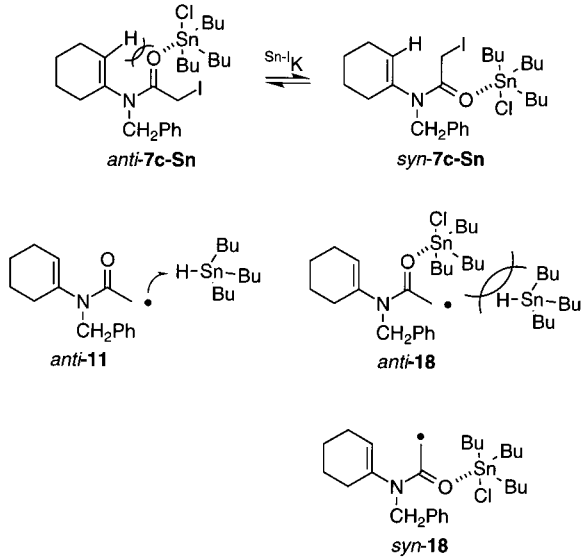


FIGURE 2. Plausible role of Bu_3SnCl on the radical cyclization of **7c**.

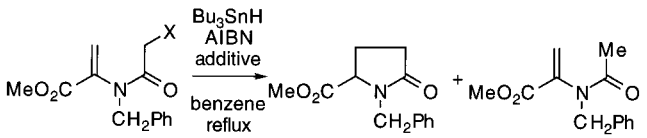
Parsons and co-workers also reported that the cyclization abilities of *N*-(α-haloacetamido)dehydroalanines **19** decreased in the order of the use of Cl, Br, and I as leaving groups (the yields of **20** for chloro amide, bromo amide, and iodo amide are 52, 47, and 38%, respectively), although they gave no explanation for the phenomenon.[3k] Therefore, we reinvestigated Bu_3SnH-mediated radical cyclization of Parsons's substrates **19a**,**b** (Table 3). Treat-

(20) Although there has been no sufficient work on the refinement of Lewis acids, titanium tetraisopropoxide and diethylaluminum chloride gave unsatisfactory results due to decomposition of the starting material **7c**. Ytterbium(III) triflate was not appropriate as the Lewis acid because of its low solubility in toluene.

(21) An example of controlling a rotamer population with Bu_3SnCl has been reported. See: Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063. For a review on the use of Lewis acids in free radical reactions, see: Renaud, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562. Bu_3SnCl acts as a Lewis acid in regioselective reductive cleavage of ketals. See: Srikrishna, A.; Viswajanani, R. *Synlett* **1995**, 95.

(22) This discussion is based on the consideration that complex **7c**−Sn undergoes an attack by Bu_3Sn• more rapidly than **7c**. It was reported that asymmetric radical allylation of an α-methyl-α-iododihydrocoumarin with allyltributyltin in the presence of only 0.2 equiv of a chiral Lewis acid gave the allylation product in 81% yield with 80% ee. This suggests that an α-halo carbonyl compound complexed with a Lewis acid exhibits higher reactivity for Bu_3Sn• than an uncomplexed one; see: Murakata, M.; Jono, T.; Mizuno, Y.; Hoshino, O. *J. Am. Chem. Soc.* **1997**, *119*, 11713.

TABLE 3. Radical Cyclization of α-Halo Amides 19a,b



entry	α-halo amide	additive (5 equiv)	products (% yield) 20	21
1	**19a** (X = Cl)		53	9
2	**19a** (X = Cl)	Bu_3SnCl	61	14
3	**19a** (X = Cl)	Bu_3SnF	59	9
4	**19b** (X = I)		51	7
5	**19b** (X = I)	Bu_3SnCl	65	12

ment of **19a** with Bu_3SnH in the presence of AIBN in boiling benzene gave cyclization product **20** and uncyclized reduction product **21** in 53 and 9% yields, respectively (entry 1). Radical reaction of **19a** with Bu_3SnH in the presence of Bu_3SnCl or Bu_3SnF afforded better yields of **20** (entries 2 and 3). The effect of Bu_3SnCl was also observed in the reaction of **19b**. Thus, the reaction of **19b** in the absence of Bu_3SnCl provided **20** and **21** in 51 and 7% yields, respectively, whereas in the presence of Bu_3SnCl, the yield of **20** was improved to 65%.[23]

3. Formal Syntheses of (±)-α-Lycorane and (±)-γ-Lycorane. [2-Halo-4,5-(methylenedioxy)benzyl]hexa-(or tetra)hydroindones such as **23a** and **23b** are known to be intermediates for syntheses of lycoranes **22** having galanthane ring systems within the *Amaryllidaceae* alkaloid family (Figure 3). Several groups have synthesized lycoranes by employing radical cyclization or Heck reaction of **23a** or **23b**.[3g,4d,24] Therefore, we envisioned a short-step entry to lycoranes using the sequential 5-endo and 6-endo radical cyclizations from radical precursor **26**, on the basis of the aspect that radical reaction of α-iodo amide **7c** in the presence of Bu_3SnF gave hexahydroindolone **8**, closely related to **23a**, as the major product (Table 2, entry 3).[25] Bu_3SnH-Mediated 5-endo radical cyclization of α-iodo amide **26** would first provide enamide **25**, which in turn could undergo 6-endo radical cyclization in situ to afford lycorane framework **24**.

The requisite α-iodo amide **26** was readily prepared from cyclohexanone (Scheme 6). Thus, condensation of cyclohexanone with 2-iodo-(4,5-methylenedioxy)benzylamine[26] followed by treatment of the resulting crude imine **27** with chloroacetyl chloride and triethylamine furnished α-chloro amide, which was treated with sodium iodide to afford **26**.

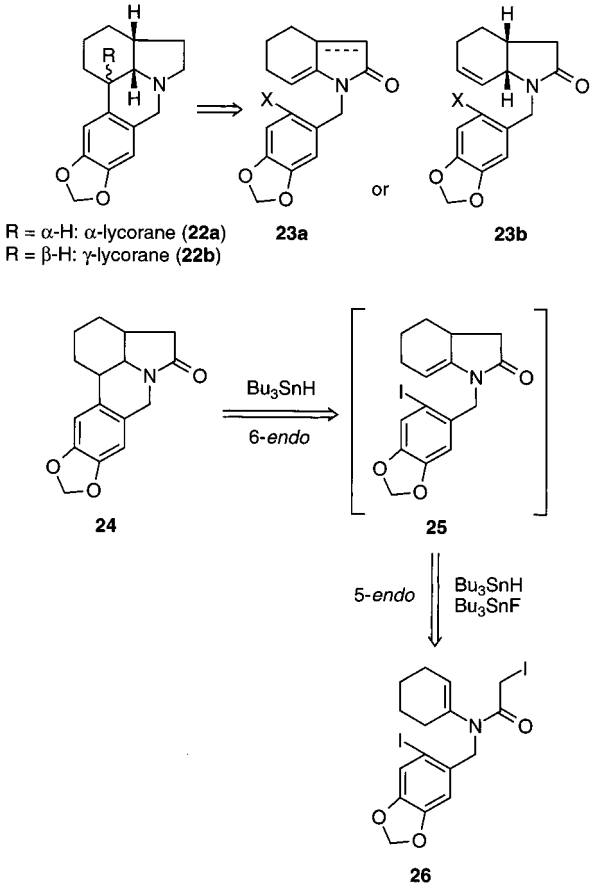
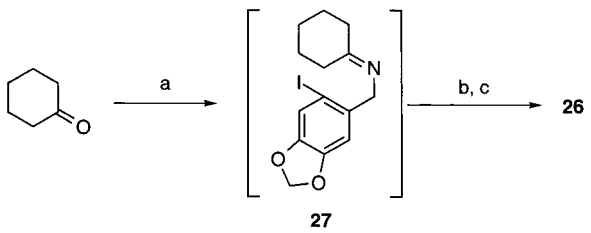


FIGURE 3. Synthetic plan for lycoranes by employing sequential 5-endo and 6-endo radical cyclizations of α-iodo amide **26**.

SCHEME 6[a]



[a] Key: (a) 2-iodo-4,5-(methylenedioxy)benzylamine, toluene, reflux; (b) $ClCOCH_2Cl$, Et_3N, toluene, 0 °C → rt, 51% (two steps); (c) NaI, acetone, rt, 42%.

With α-iodo amide **26** in hand, we examined the sequential radical cyclization of **26** (Table 4). α-Iodo amide **26** was treated with Bu_3SnH (2.4 equiv) and *N*,*N*-azobis(cyclohexanecarbonitrile) (ACN) (0.1 equiv) in the presence of Bu_3SnF (5 equiv) in boiling toluene to give lycorane derivative **24a** (21%) and its dehydro derivative **28** (25%) along with 5-endo cyclization products **29** (13%) and **30** (18%) (entry 1). The structure of **24a** was established by direct comparison of the ^1H NMR spectrum with that reported.[24b] Use of benzene for the reaction slightly increased the total yield of double cyclization products **24a**, **24b**, and **28** (entry 2). Use of xylene as a solvent or Bu_3SnOAc as an additive did not result in any improvement in the reaction (entries 3 and 4). Since the products **24a** and **24b** had already been

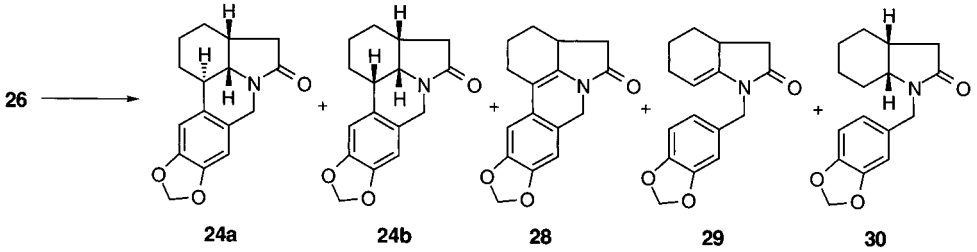
(23) The possibility of coordination of Bu_3SnCl with the ester group of **19** cannot be ruled out, whereas the amide carbonyl group seems to be a stronger Lewis base than the ester carbonyl group. Therefore, it is reasonable to consider that the mechanism of the reaction of **19** in the presence of Bu_3SnX is similar to that of **7**. The reason for the increased yield of the reduction product **21** in the presence of Bu_3SnCl is, however, still obscure at the moment.

(24) (a) Yoshizaki, H.; Satoh, H.; Sato, Y.; Nukui, S.; Shibasaki, M.; Mori, M. *J. Org. Chem.* **1995**, *60*, 2016. (b) Rigby, J. H.; Mateo, M. E. *Tetrahedron* **1996**, *52*, 10569. See also: (c) Cossy, J.; Tresnard, L.; Pard, D. G. *Eur. J. Org. Chem.* **1999**, 1925. (d) Padwa, A.; Brodney, M. A.; Lynch, S. M. *J. Org. Chem.* **2001**, *66*, 1716.

(25) For a synthesis of (±)-γ-lycorane using a cascade reaction initiated by an acylaminyl radical, see: Hoang-Cong, X.; Quiclet-Sire, B.; Zard, S. Z. *Tetrahedron Lett.* **1999**, *40*, 2125.

(26) Beugelmans, R.; Chastanet, J.; Ginsburg, H.; Quintero-Cortes, L.; Roussi, G. *J. Org. Chem.* **1985**, *50*, 4933.

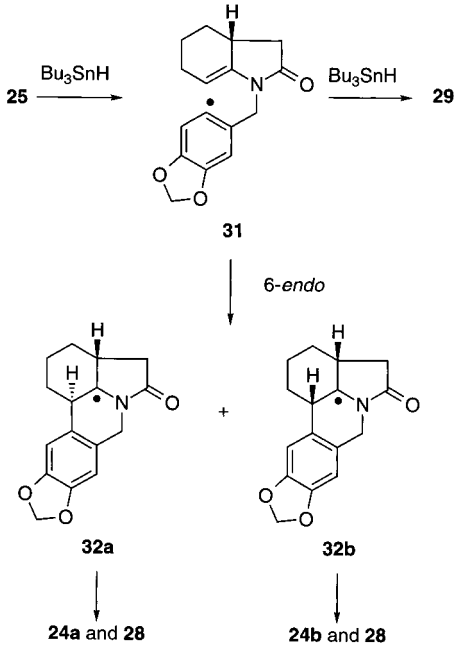
TABLE 4. Radical Cyclization of α-Iodo Amide 26



entry	conditions[a] additive (5 equiv)/solvent	products (% yield) 24a	24b	28	29	30
1	Bu_3SnF/toluene	21		25	13	18
2	Bu_3SnF/benzene	29	5	27		10
3	Bu_3SnF/xylene	16	4	20	15	18
4	Bu_3SnOAc/xylene	18	6	21	17	15

[a] All reactions were carried out by using Bu_3SnH (2.4 equiv) and ACN (0.1 equiv) under refluxing conditions.

SCHEME 7



converted to α-lycorane (**22a**)[24b] and γ-lycorane (**22b**),[3g,4d,24a] respectively, a short-step synthesis of **22a** and **22b** could be realized by the present reaction, although the yields were moderate.

Formation of **24a**,**b** and **28** may involve 6-endo cyclization of aryl radical **31** generated from intermediate **25** (Scheme 7). An attack of aryl radical **31** on the enamide double bond from the less-hindered β-face gives α-amidoyl radical **32a**, and α-face attack gives **32b**. The radicals **32a** and **32b** undergo attacks of Bu_3SnH to afford **24a** and **24b**, respectively, and SET or atom transfer reaction from α-amidoyl radicals **32a**,**b** to starting α-iodo amide **26** in a way similar to that of **8** affords **28**. Simple reduction of the radical **31** furnishes **29**. It is interesting to note that 6-endo cyclization of **31** gives α-lycorane derivative **24a**[27] predominantly, in light of our previous result with the radical from **23b** (X = Br), which undergoes cyclization in a 6-exo manner to afford a γ-lycorane-type product.[3g]

(27) Rigby and co-workers also reported that a 6-endo aryl radical cyclization similar to that of radical **31** affords an α-lycorane-type product. See ref 24b.

Conclusion

We have revealed that the general guideline that "an iodine atom acts as a better leaving group for Bu_3SnH-mediated radical cyclization of ω-halo alkenes" is not applicable to the 5-endo-trig cyclization of α-halo amides having an alkenic sp^2 carbon atom α to the amide nitrogen atom. In addition, we also showed that the cyclization ability of α-iodo amide can be restored by the use of Bu_3SnCl or Bu_3SnF as an additive. Moreover, this cyclization could be applied to a short-step synthesis of (±)-lycoranes.

Experimental Section

Melting points are uncorrected. Column chromatography was performed on silica gel 60 PF_{254} under pressure.

***N*-Benzyl-2-chloro-*N*-(cyclohex-2-enyl)acetamide (1a).** To a stirred solution of 3-bromocyclohex-1-ene (1.79 g, 10 mmol) and benzylamine (3.21 g, 30 mmol) in CH_3CN (30 mL) was added K_2CO_3 (1.3 g, 20 mmol) at room temperature, and the mixture was further stirred for 1 h. The mixture was diluted with water and extracted with AcOEt. The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was chromatographed (1:6 *n*-hexane/AcOEt) to give *N*-benzyl-*N*-(cyclohex-2-enyl)amine (1.13 g, 60%). This material was used in the next step without further purification. To a solution of the amine (935 mg, 5 mmol) and triethylamine (0.83 mL, 6 mmol) in benzene (10 mL) was added a solution of chloroacetyl chloride (678 mg, 6 mmol) in benzene (2 mL) at room temperature, and the mixture was stirred for 2 h. The mixture was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (3:1 *n*-hexane/AcOEt) to afford **1a** (1.30 g, 99%) as an oil. Two rotamers of **1a** (3:2) due to the amide bond were observed by ^1H and ^{13}C NMR: ^1H NMR (270 MHz, $CDCl_3$) δ 1.36−1.99 (m, 6 H), 3.86 (s, 2 H × 3/5), 4.20 (s, 2 H × 2/5), 4.34 (d of a pair of ABq, *J* = 15.6 Hz, 1 H × 2/5), 4.47−4.55 (m, 1 H × 2/5), 4.51 (d of a pair of ABq, *J* = 18.2 Hz, 1 H × 3/5), 4.60 (d of a pair of ABq, *J* = 18.2 Hz, 1 H × 3/5), 4.69 (d of a pair of ABq, *J* = 15.6 Hz, 1 H × 2/5), 5.28−5.33 (m, 1 H × 3/5), 5.47 (t, *J* = 9.4 Hz, 1 H), 5.91 (dt, *J* = 9.4, 2.9 Hz, 1 H), 7.18−7.38 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.2 (major), 21.5 (minor), 24.3 (minor), 24.6 (major), 27.4 (major), 29.0 (minor), 41.6 (minor), 42.1 (major), 46.4 (minor), 47.2 (major),

52.3 (major), 56.1 (minor), 125.5 (major), 126.7 (minor), 126.9 (major), 127.0 (minor), 127.50 (major), 128.3 (minor), 129.0 (major), 132.5 (minor), 132.8 (major), 138.1 (major), 138.5 (minor), 167.2 (minor), 167.6 (major). Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.18; H, 6.95; N 5.35.

***N*-Benzyl-*N*-(cyclohex-2-enyl)-2-iodoacetamide (1b).** To a stirred solution of **1a** (480 mg, 1.8 mmol) in acetone (10 mL) was added NaI (540 mg, 3.6 mmol) at room temperature, and the mixture was further stirred for 15 h. The mixture was diluted with water and extracted with Et_2O. The organic phase was washed successively with a 10% solution of $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (1:5 Et_2O/benzene) to afford **1b** (224 mg, 47%) as a colorless oil. Two rotamers of **1b** (3:2) due to the amide bond were observed by ^{1}H NMR: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25−1.99 (m, 6 H), 3.52 (s, 2 H × 3/5), 3.85 (d of a pair of ABq, J = 9.9 Hz, 1 H × 2/5), 3.90 (d of a pair of ABq, J = 9.9 Hz, 1H × 2/5), 4.33 (d of a pair of ABq, J = 15.8 Hz, 1 H × 2/5), 4.41−4.48 (m, 1 H × 2/5), 4.47 (d of a pair of ABq, J = 18.1 Hz, 1 H × 3/5), 4.57 (d of a pair of ABq, J = 18.1 Hz, 1 H × 3/5), 4.67 (d of a pair of ABq, J = 15.8 Hz, 1 H × 2/5), 5.26−5.32 (m, 1 H × 3/5), 5.45 (dq, J = 10.2, 1.6 Hz, 1 H × 3/5), 5.52 (dq, J = 10.2, 1.6 Hz, 1 H × 2/5), 5.91 (dq, J = 9.9, 3.3 Hz, 1 H), 7.18−7.39 (m, 5H). These spectral data were identical with those reported.[28]

General Procedure for Radical Reactions. To a boiling solution of α-halo amide (0.5 mmol) in toluene (or benzene) (50 mL) was added dropwise a solution of Bu_3SnH (175 mg, 0.60 mmol) [or $(TMS)_3SiH$ (149 mg, 0.60 mmol)] and AIBN (8 mg, 50 μmol) [or ACN (10 mg, 50 μmol)] in toluene (or benzene) (50 mL) over 1−4 h by employing a syringe-pump technique, and the mixture was further heated at reflux for an appropriate period of time. After evaporation of the solvent, Et_2O (20 mL) and an 8% aqueous KF solution (50 mL) were added to the residue, and the mixture was vigorously stirred at room temperature for 16 h. The organic phase was separated, and the aqueous phase was further extracted with Et_2O. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (*n*-hexane/AcOEt) to afford the product(s).

***cis*-1-Benzyl-octahydroindol-2-one (2) and *N*-Benzyl-*N*-(cyclohex-2-enyl)acetamide (3): (a) Radical Reaction of 1a.** According to the general procedure, a boiling solution of chloro amide **1a** (132 mg) in toluene was treated with a solution of Bu_3SnH and AIBN in toluene (4 h for addition; 3 h further for heating). Since **1a** was not consumed, an additional solution of Bu_3SnH (175 mg, 0.60 mmol) and AIBN (8 mg, 0.05 mmol) in toluene was added to the mixture over 3 h, and the mixture was further heated for 7 h. After workup, the crude material was chromatographed on silica gel (3:1 *n*-hexane/AcOEt) to afford **2**[28] (48 mg, 41%) and **3**[29] (17 mg, 15%). **2**: ^{1}H NMR (270 MHz) δ 1.22−1.51 (5 H, m), 1.54−1.70 (3 H, m), 2.17−2.44 (3 H, m), 3.39 (1 H, q, J = 5.6 Hz), 3.97 (1 H, d of a pair of ABq, J = 15.0 Hz), 4.93 (1 H, d of a pair of ABq, J = 15.0 Hz), 7.21−7.33 (5 H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.3, 22.6, 24.7, 27.2, 27.9, 49.9, 127.4, 128.3, 128.7, 129.2, 137.2, 137.8, 166.1. These spectral data were identical with those reported.[28] **3**: two rotamers of **3** (1:1) were observed by the ^{1}H and ^{13}C NMR spectra due to the amide bond; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.26−2.06 (m, 6 H), 2.77 (s, 3 H × 1/2), 2.79 (s, 3 H × 1/2), 3.72 (s, 2 H × 1/2) 3.76 (s, 2 H × 1/2), 4.44 (m, 1 H × 1/2), 5.21−5.46 (m, 1 H + 1 H × 1/2), 5.84−5.92 (m, 1 H), 7.21−7.33 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.3, 21.6, 22.1, 22.4, 24.4, 24.6, 27.7, 28.8, 46.0, 48.1, 51.3, 56.1, 125.6, 126.5, 127.0, 127.1, 128.0, 128.1, 128.2, 128.7, 131.6, 132.0, 138.9, 139.5, 170.9, 171.9; HRMS calcd for $C_{15}H_{19}NO$ 229.1466, found 229.1470. **(b) Radical Reaction of 1b.** According to the general procedure, a boiling solution of **1b** (177 mg) in toluene was treated with a solution of Bu_3SnH and AIBN in toluene (4 h for addition). Workup and chromatography gave **2** (60 mg, 53%) and **3** (7 mg, 6%).

***N*-Cyclohex-1-enyl-*N*-methyl-2-iodoacetamide (4b).** According to a procedure similar to that for the preparation of **1b**, chloro amide **4a**[3b] (225 mg, 1.2 mmol) was treated with NaI (270 mg, 1.8 mmol) in dry acetone (30 mL). After workup, the crude material was chromatographed (2:1 *n*-hexane/AcOEt) to give **4b** (335 mg, quantitative) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.58−1.67 (m, 2 H), 1.74−1.83 (m, 2 H), 2.12−2.19 (m, 2 H), 2.21−2.24 (m, 2 H), 2.98 (s, 3 H), 3.81 (s, 2 H), 5.85 (br s, 1 H); ^{13}CNMR (67.8 MHz, $CDCl_3$) δ −2.6, 24.0, 25.2, 27.2, 37.3, 129.2, 142.8, 169.7; HRMS calcd for $C_9H_{14}NOI$ 279.0220, found 279.0115. Anal. Calcd for $C_9H_{14}NOI$: C, 38.73; H, 5.06; N, 5.02. Found: C, 38.59; H, 5.01; N, 5.06.

***N*-(Cyclohex-1-enyl)-*N*-methylacetamide (6).** According to the general procedure, a boiling solution of **4b** (140 mg) in toluene was treated with a solution of Bu_3SnH and AIBN in toluene for 2 h. Workup and chromatography (8:1 *n*-hexane/AcOEt) gave **6**[3b] (42 mg, 54%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.55−1.64 (m, 2 H), 1.69−1.78 (m, 2 H), 2.01 (s, 3 H), 2.04−2.15 (m, 4 H), 2.97 (s, 3 H), 5.64 (br s, 1 H). This ^{1}H NMR spectrum was identical with that reported for **6**.[3b]

***N*-Benzyl-2-chloro-*N*-(cyclohex-1-enyl)acetamide (7a).** A mixture of cyclohexanone (981 mg, 10 mmol) and benzylamine (1.07 g, 10 mmol) in toluene (50 mL) was heated at reflux with a Dean−Stark trap for 2 h. After cooling, the mixture was concentrated to ca. 25 mL under reduced pressure. The mixture was added dropwise to a stirred solution of chloroacetyl chloride (2.26 g, 20 mmol) in toluene (50 mL) at 0 °C, and the mixture was further stirred under the same temperature for 2 h. To the mixture was added triethylamine (4.1 mL, 30 mmol) at 0 °C, and the mixture was further stirred under the same temperature for 2 h. The mixture was washed successively with a saturated aqueous solution of $NaHCO_3$ and with brine. After drying ($MgSO_4$), the mixture was concentrated and purified by column chromatography on silica gel (5:1 *n*-hexane/AcOEt) to give **7a** (1.22 g, 46%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.52−1.70 (m, 4 H), 2.03 (br s, 4 H), 4.13 (s, 2 H), 4.63 (s, 2 H), 5.47 (br s, 1 H), 7.26−7.30 (m, 5 H); ^{1}H NMR (270 MHz, C_6D_6) δ 1.05−1.20 (m, 2 H), 1.20−1.32 (br s, 2 H), 1.52 (br s, 1 H), 1.60 (br s, 1 H), 3.85 (s, 2 H), 4.49 (s, 2 H), 4.99 (br s, 1 H), 7.00−7.28 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.3, 22.6, 24.7, 27.9, 41.7, 49.9, 127.4, 128.3, 128.7, 129.3, 137.1, 137.4, 165.8. Anal. Calcd for $C_{15}H_{18}ClNO$: C, 68.30; H, 6.88; N, 5.31. Found: C, 68.18; H, 6.92; N, 5.29.

***N*-Benzyl-2-bromo-*N*-(cyclohex-1-enyl)acetamide (7b).** According to a procedure similar to that described for the preparation of **7a**, treatment of cyclohexanone (981 mg, 10 mmol) with benzylamine (1.07 g, 10 mmol) followed by treatment of the resulting imine with bromoacetyl bromide (2.20 g, 11 mmol) and triethylamine (4.1 mL, 30 mmol) gave crude **7b**, which was chromatographed (5:1 *n*-hexane/AcOEt) to afford **7b** (1.22 g, 46%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.52−1.70 (m, 4 H), 2.03−2.07 (m, 4 H), 3.94 (s, 2 H), 4.62 (s, 2 H), 5.52 (br s, 1 H), 7.27−7.30 (m, 5 H); ^{1}H NMR (270 MHz, C_6D_6) δ 1.05−1.20 (m, 2 H), 1.20−1.38 (m, 2 H), 1.55 (br s, 2 H), 1.68 (br s, 2 H), 3.67 (s, 2 H), 4.49 (2 H, s), 5.10 (br s, 1 H), 7.00−7.30 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.3, 22.6, 24.7, 27.2, 27.9, 49.9, 127.4, 128.3, 128.7, 129.1, 137.2, 137.8, 166.1. Anal. Calcd for $C_{15}H_{18}BrNO$: C, 58.45; H, 5.89; N, 4.54. Found: C, 58.17; H, 5.93; N 4.19.

***N*-Benzyl-*N*-(cyclohex-1-enyl)-2-iodoacetamide (7c).** According a procedure similar to that described for the preparation of **1b**, chloro amide **7a** (526 mg, 2 mmol) was treated with

(28) Mori, M.; Kanda, N.; Oda, I.; Ban, Y. *Tetrahedron* **1985**, *41*, 5465.

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NaI (330 mg, 2.2 mmol) in dry acetone (30 mL). After workup, the crude material was chromatographed (5:1 *n*-hexane/AcOEt) to give **7c** (732 mg, quantitative) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.49−1.58 (m, 2 H), 1.64−1.76 (m, 2 H), 2.00−2.04 (m, 2 H), 2.11 (br s, 2 H), 3.85 (s, 2 H), 4.60 (s, 2 H), 5.57 (br s, 1 H), 7.21−7.32 (m, 5 H); ^{1}H NMR (270 MHz, C_6D_6) δ 1.05−1.20 (m, 2 H), 1.20−1.35 (m, 2 H), 1.52−1.67 (m, 2 H), 1.75 (br s, 2 H), 3.56 (s, 2 H), 4.50 (s, 2 H), 5.20 (br s, 1 H), 7.00−7.31 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ −2.3, 21.3, 22.7, 24.6, 27.6, 50.0, 127.3, 128.3, 128.6, 128.9, 137.4, 138.2, 167.3. Anal. Calcd for $C_{15}H_{18}INO$: C, 50.72; H, 5.11; N, 3.94. Found: C, 50.65; H, 5.13; N 3.62.

Compound 2, 1-Benzyl-1,3,3a,4,5,6-hexahydroindol-2-one (8), 1-Benzyl-1,4,5,6,7,7a-hexahydroindol-2-one (9), and *N*-(Cyclohex-1-enyl)-*N*-methylacetamide (10) (Tables 1 and 2): (a) Table 1, Entry 1. According to the general procedure, a solution of **7a** (132 mg) in toluene was treated with a solution of Bu_3SnH and AIBN in toluene for 4.5 h. Workup and chromatography (10:1 *n*-hexane/AcOEt) gave **2** (106 mg, 92%) as a colorless oil. The ^{1}H NMR spectral data were identical with those obtained from radical reaction of **1a**. **(b) Table 1, Entry 2.** According to a procedure similar to that described above in **a**, α-bromo amide **7b** (154 mg) was treated with Bu_3SnH to give **2** (63 mg, 55%), **8** (12 mg, 11%), and **9**[4b] (13 mg, 11%). **8**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25−1.65 (m, 2 H), 1.82−2.14 (m, 4 H), 2.20 (dd, J = 15.4, 9.5 Hz, 1 H), 2.62−2.78 (m, 2 H), 4.47 (d of a pair of ABq, J = 15.5 Hz, 1 H), 4.76 (d of a pair of ABq, J = 15.5 Hz, 1 H), 4.77 (dd, J = 5.6, 3.3, 1 H), 7.21−7.36 (m, 5 H); HRMS calcd for $C_{15}H_{17}NO$ 227.1312, found 227.1308. **9**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92−1.11 (m, 1 H), 1.19−1.43 (m, 2 H), 1.17−2.39 (m, 4 H), 2.72 (br d, J = 11.2 Hz, 1 H), 3.58 (dd, J = 11.2, 5.9 Hz, 1 H), 4.17 (d, J = 15.1 Hz, 1 H), 4.99 (d, J = 15.1 Hz, 1 H), 5.80 (s, 1 H), 7.21−7.37 (m, 5 H). The ^{1}H NMR spectral data were identical with those reported. [4b] **(c) Table 1, Entry 3.** According to a procedure similar to that described above in **a**, α-iodo amide **7c** (178 mg, 0.50 mmol) was treated with Bu_3SnH to give **8** (15 mg, 13%), **9** (12 mg, 11%), and **10**[30] (78 mg, 68%). **10**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.47−1.69 (m, 4 H), 1.97−2.03 (m, 4 H), 2.06 (s, 3 H), 4.61 (s, 2 H), 5.39 (br s, 1 H), 7.22−7.28 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.4, 21.5, 22.7, 24.6, 28.0, 49.4, 127.0, 128.0, 128.1, 128.6, 138.0, 138.8, 169.8; HRMS calcd for $C_{17}H_{19}NO$ 229.1467, found 229.1467. **(d) Table 1, Entry 4.** According to the general procedure, a boiling solution of **7a** (132 mg) in toluene was treated with a solution of $(TMS)_3SiH$ and AIBN in toluene for 8 h. After evaporation, the residue was chromatographed (4:1 *n*-hexane/AcOEt) to afford **2** (65 mg, 56%) and **9** (14 mg, 12%). **(e) Table 1, Entry 5.** According to a procedure similar to that described above in **d**, a boiling solution of **7c** (178 mg, 0.50 mmol) in toluene was treated with a solution of $(TMS)_3SiH$ and AIBN in toluene for 4 h. To the mixture was added a saturated solution of $NaHCO_3$, and the mixture was stirred vigorously for 1 h. The mixture was extracted with AcOEt, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed (3:1 *n*-hexane/AcOEt) to give **10** (87 mg, 76%). **(f) Table 2, Entry 2.** According to the general procedure, a boiling solution of **7c** (178 mg) and Bu_3SnCl (813 mg, 2.5 mmol) in toluene was treated with a solution of Bu_3SnH and AIBN in toluene for 1 h. Workup and chromatography gave **2** (21 mg, 18%), **8** (23 mg, 20%), **9** (32 mg, 28%), and **10** (10 mg, 9%). **(g) Table 2, Entry 3.** According to the general procedure, a boiling solution of **7c** (178 mg) and Bu_3SnF (771 mg, 2.5 mmol) in toluene was treated with a mixture of Bu_3SnH and AIBN (12 mg, 0.1 mmol) in toluene for 2 h. Workup and chromatography gave **2** (10 mg, 9%) and **8** (61 mg, 54%).

***N*-(Cyclohex-1-enyl)-*N*-methyl-2-iodopropionamide (15b).** A mixture of cyclohexanone (2.1 mL, 20 mmol) and methylamine (3 mL) in toluene (10 mL) was heated in a sealed tube at 100 °C for 2 h. After cooling, the mixture was concentrated under reduced pressure, and the residual crude imine was dissolved in toluene (20 mL). To this solution were added successively pyridine (2.4 mL, 30 mmol) and a solution of 2-bromopropanoyl bromide (4.75 g, 22 mmol) in toluene (50 mL) at 0 °C, and the mixture was stirred under the same temperature for 1 h. The mixture was washed successively with 5% hydrochloric acid, a saturated aqueous solution of $NaHCO_3$, and brine. After drying ($MgSO_4$), the mixture was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (5:1 *n*-hexane/AcOEt) to yield 2-bromo-*N*-(cyclohex-1-enyl)-*N*-methylpropionamide. This material was used in the next step without further purification. According to a procedure similar to that described for the preparation of **1b**, the bromo amide (550 mg, 1.9 mmol) was treated with NaI (330 mg, 2.2 mmol) in dry acetone (30 mL). After workup, the crude material was chromatographed (3:1 *n*-hexane/AcOEt) to give **15b** (460 mg, 8%, two steps) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.58−1.82 (m, 4 H), 1.93 (d, J = 6.9 Hz, 3 H), 2.04−2.31 (m, 4 H), 2.98 (s, 3 H), 4.83 (q, J = 6.9 Hz, 1 H), 5.81 (br s, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.4, 21.3, 22.6, 24.3, 24.5, 26.6, 34.7, 126.5, 139.8, 170.3. Anal. Calcd for $C_{10}H_{16}INO$: C, 40.97; H, 5.50; N, 4.78. Found: C, 40.76; H, 5.65; N, 4.62.

Benzyl-3-methyl-1,4,5,6,7,7a-hexahydroindol-2-one (16b) and *N*-(Cyclohex-1-enyl)-*N*-methylpropionamide (17). According to the general procedure, a boiling solution of **15b** (182 mg, 0.62 mmol) in toluene (20 mL) was treated with Bu_3SnH (198 mg, 0.68 mmol) and AIBN (10 mg, 0.062 mmol) in toluene (45 mL) for 2 h. Workup and chromatography (from 20:1 to 1:5 *n*-hexane/AcOEt) gave **16b** (20 mg, 24%) and **17** (53 mg, 63%). **16b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (qd, J = 11.9, 3.3 Hz, 1 H), 1.26 (tt, J = 13.2, 3.6 Hz, 1 H), 1.48 (qt, J = 13.2, 3.0 Hz, 1 H), 1.78 (t, J = 1.5 Hz, 3 H), 1.82−2.12 (m, 3 H), 2.37−2.42 (m, 1 H), 2.69−2.79 (m, 1 H), 2.95 (s, 3 H), 3.50 (dd, J = 11.2, 5.3 Hz, 1 H); HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1160. **17**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11 (t, J = 7.4 Hz, 3 H), 1.58−1.78 (m, 4 H), 2.08−2.14 (m, 4 H), 2.28 (q, J = 7.4 Hz, 2 H), 2.98 (s, 3 H), 5.63 (br s, 1 H); HRMS calcd for $C_{10}H_{17}NO$ 167.1311, found 167.1313.

Methyl *N*-Benzylpyroglutamate (20) and Methyl 2-(*N*-Benzylethanamido)propenoate (21) (Table 3, Entry 5). According to the general procedure, a boiling solution of **19b** (180 mg) and Bu_3SnCl (813 mg, 2.5 mmol) in benzene was treated with Bu_3SnH (160 mg, 0.55 mmol) and AIBN (12 mg, 0.1 mmol) in benzene for 5 h. After workup, the crude material was chromatographed (2:1 *n*-hexane/AcOEt) to give **20**[3k] (69 mg, 59%) and **21**[3k] (11 mg, 9%). **20**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.02−2.63 (m, 4 H), 3.66 (s, 3 H), 4.01 (d, J = 15.3 Hz, 1 H), 4.05 (dd, J = 12.2, 8.9 Hz, 1 H), 5.00 (d, J = 15.3 Hz, 1 H), 7.19−7.31 (m, 5 H). **21**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.00 (s, 3 H), 3.78 (s, 3 H), 4.68 (s, 2 H), 5.40 (s, 1 H), 6.32 (s, 1 H), 7.26 (m, 5 H). The ^{1}H NMR spectral data of **20** and **21** were identical with those reported.[3k]

***N*-(Cyclohex-1-enyl)-*N*-[(2-iodo-4,5-methylenedioxy)-benzyl]-2-iodoacetamide (26).** According to a procedure similar to that described for the preparation of **7a**, *N*-cyclohex-1-enyl-*N*-[(2-iodo-4,5-methylenedioxy)benzyl]-2-chloroacetamide (1.12 g, 52%) was obtained from cyclohexanone (490 mg, 5 mmol), 2-iodo-4,5-methylendioxybenzylamine[26] (1.38 g, 5 mmol), triethylamine (4.1 mL, 30 mmol), and toluene (50 mL) after chromatography on silica gel (10:1 *n*-hexane/AcOEt). ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.56−1.62 (m, 2 H), 1.70−1.75 (m, 2 H), 2.03−2.10 (m, 4 H), 4.13 (s, 2 H), 4.70 (s, 2 H), 5.48 (br s, 1 H), 5.96 (s, 2 H), 6.98 (s, 1 H), 7.18 (s, 1 H). Anal. Calcd for $C_{16}H_{17}ClINO_3$: C, 44.31; H, 3.95; N, 3.23. Found: C, 44.16; H, 3.97; N, 3.18. According to a treatment similar to that described for the preparation of **7c**, **26** (552 mg, 42%) was obtained from the corresponding chloro amide (1.12 g, 2.5 mmol), NaI (2.0 g), and acetone (20 mL) after chromatography on silica gel (10:1 *n*-hexane/AcOEt): ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.55−1.63 (m, 2 H), 1.70−1.79 (m, 2 H), 2.04−2.09 (s, 2 H), 2.19 (br s, 2 H), 3.84 (s, 2 H), 4.67 (s, 2 H), 5.60 (br s, 1 H), 5.96 (s, 2 H), 6.99 (s, 1 H), 7.18 (s, 1 H). Anal. Calcd for

$C_{16}H_{17}I_2NO_3$: C, 36.67; H, 3.30; N, 2.67. Found: C, 36.67; H, 3.30; N 2.58.

(3a*R,11b*R**,11c*S**)-9,10-(Methylenedioxy)-1,2,3,3a,4,5,-11b,11c-octahydropyrrolo[3,2,1-*de*]phenanthridine-5-one (24a), Its (11b*S**)-Isomer (24b), 9,10-(Methylenedioxy)-1,2,3,3a,4,5-hexahydropyrrolo[3,2,1-*de*]phenanthridine-5-one (28), 1-(3,4-Methylenedioxy)benzyl-1,3,3a,4,5,6-hexahydroindole-2-one (29), and 1-[(3,4-Methylenedioxy)benzyl]octahydroindol-2-one (30): (a) Table 4, Entry 1.** According to the general procedure, a solution of **26** (263 mg) and Bu_3SnF (772 mg, 2.5 mmol) in toluene was treated with a solution of Bu_3SnH and ACN in toluene for 10 h. After workup, the crude material was chromatographed (10:1 *n*-hexane/AcOEt) to give **24a**[24b] (28 mg, 21%), **28** (33 mg, 25%), **29** (18 mg, 13%), and **30** (25 mg, 18%). **24a**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.16−1.25 (m, 1 H), 1.58−1.65 (m, 1 H), 1.72−1.80 (m, 3 H), 2.13−2.30 (m, 2 H), 2.35−2.50 (m, 1 H), 2.50 (dd, J = 16.5, 11.2 Hz, 1 H), 2.56−2.75 (m, 1 H), 3.21 (dd, J = 10.5, 7.2 Hz, 1 H), 4.19 (d, J = 17.1 Hz, 1 H), 4.97 (d, J = 17.1 Hz, 1 H), 5.91−5.93 (m, 2 H), 6.59 (s, 1 H), 6.69 (s, 1 H). The ^{1}H NMR spectral data were identical with those reported for **24a**.[24b] **28**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.45−1.89 (m, 6 H), 2.25 (dd, J = 15.5, 7.6 Hz, 1 H), 2.49−2.59 (m, 1 H), 2.83 (t, J = 14.1 Hz, 1 H), 4.18 (d, J = 14.9 Hz, 1 H), 4.72 (d, J = 14.9 Hz, 1 H), 5.97 (s, 2 H), 6.70 (s, 1 H), 6.86 (s, 1 H); HRMS calcd for $C_{16}H_{15}NO_3$ 269.1052, found 269.1044. **29**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25−1.66 (m, 3 H), 1.83−2.11 (m, 4 H), 2.14 (dd, J = 15.5, 5.9 Hz, 1 H), 2.55−2.67 (m, 2 H), 4.38 (d of a pair of ABq, J = 15.1 Hz, 1 H), 4.66 (d of a pair of ABq, J = 15.1 Hz, 1 H), 4.79 (m, 1 H), 5.93 (s, 2 H), 6.72 (s, 3 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 22.7, 23.5, 28.4, 35.2, 37.2, 43.6, 98.4, 101.4, 108.4, 108.6, 121.2, 131.0, 142.3, 147.2, 148.3, 175.1; HRMS calcd for $C_{16}H_{17}NO_3$ 271.1209, found 271.1209. **30**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.25−1.75 (m, 7 H), 2.01−2.40 (m, 4 H), 3.39 (q, J = 5.6 Hz, 1 H), 3.87 (d, J = 14.8 Hz, 1 H), 4.84 (d, J = 14.8 Hz, 1 H), 5.94 (s, 2 H), 6.70−6.75 (m, 3 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.1, 22.3, 26.7, 27.2, 32.3, 37.0, 43.6, 55.9, 101.0, 108.1, 108.4, 121.2, 130.9, 146.8, 147.9, 175.5; HRMS calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1366. **(b) Table 4, Entry 2.** According to the general procedure, a solution of **26** (263 mg) and Bu_3SnF (771 mg, 2.5 mmol) in benzene was treated with Bu_3SnH and ACN in benzene for 10 h. Workup and chromatography gave **24a** (40 mg, 29%), **24b**[3g] (7 mg, 5%), **28** (37 mg, 27%), and **30** (14 mg, 10%). **24b**: ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.10−1.38 (m, 3 H), 1.67−1.76 (m, 3 H), 2.10 (d, J = 16.1 Hz, 1 H), 2.41 (quintet, J = 5.6 Hz, 1 H), 2.58 (dd, J = 16.1, 6.8 Hz, 1 H), 2.75 (dt, J = 12.2, 4.6 Hz, 1 H), 3.77 (t, J = 4.6 Hz, 1 H), 4.32 (d of a pair of ABq, J = 17.1 Hz, 1 H), 4.54 (d of a pair of ABq, J = 17.1 Hz, 1 H), 5.92 (d of a pair of ABq, J = 1.4 Hz, 1 H), 5.94 (d of a pair of ABq, J = 1.4 Hz, 1 H), 6.59 (s, 1 H), 6.62 (s, 1 H). The ^{1}H NMR spectral data were identical with those reported for **24b**.[3g]

Supporting Information Available: ^{1}H NMR spectra for **8**, **16b**, **17**, and **28**; ^{13}C NMR spectra for **3**, **4b**, **10**, **29**, and **30**; and IR spectra for **1a**, **4b**, **7a**−**c**, **8**, **10**, **15b**, **26**, and **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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