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Kinetic Study of the 7-*endo* Selective Radical Cyclization of *N*-*tert*-Butyl-*o*-bromobenzylmethacryl Amides: Kinetic Investigation of the Cyclization and 1,7-Hydrogen Transfer of Aromatic Radicals

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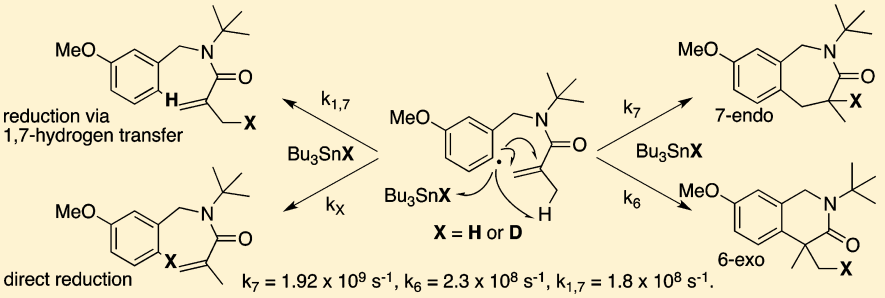
Supporting Information



ABSTRACT: A kinetic investigation of the radical cyclization of *N*-*tert*-butyl-*o*-bromobenzylmethacryl amides to give 2-benzazepines via 7-*endo* selective cyclization was undertaken. The aryl radical generated from the amide precursor by treatment with Bu_3SnH gave the three compounds, which are a 7-*endo* cyclized adduct, a 6-exocyclized adduct, and a reduced product. The cyclization reactions under various Bu_3SnH concentrations were traced by GC analysis. The 7-*endo*/6-*exo* selectivity was constant irrespective of variation in Bu_3SnH concentration. These results revealed that regioselectivity is controlled in a kinetic manner and that there is no possibility of a neophyl rearrangement. The use of Bu_3SnD revealed that 1,7-hydrogen transfer, in which an aryl radical abstracts a hydrogen atom from the methallylic methyl group, occurs during the reaction. Hydrogen abstraction from toluene, the reaction solvent, was also observed. The 1,7-transfer rate depended on the Bu_3SnX (X = H or D), and the reaction kinetics was examined. The k_H/k_D value for the hydrogen abstraction of aryl radical from Bu_3SnX (X = H or D) was estimated using 4-bromoanisol. The utilization of these values revealed the overall reaction kinetics and relative rates for the cyclization and reduction by Bu_3SnX (X = H or D). Kinetic parameters for hydrogen abstraction from toluene by aryl radicals were also estimated.

INTRODUCTION

The radical cyclization is recognized as a useful methodology in organic synthesis.[1] In particular, the formation of a five- or six-membered ring is effectively achieved through the reaction, and many useful molecules have been constructed via radical cyclization. Recently, we established the straightforward preparation of 2-benzazepines,[2] which have been of interest because of their potentially unique biological activity.[3] Our synthesis progressed smoothly via the 7-*endo* selective radical cyclization of the aryl radical. We successfully identified interesting biological activity in these molecules, in which cell migration was stimulated, but cell proliferation was not accelerated.[4] The reagents appear to have potential as a new drug candidate for skin wound healing; therefore, we examined their structure−activity relationship.[4,2b] We also reported a mechanistic study of the 7-*endo* selective radical cyclization and estimated kinetic parameters for 7-*endo* and 6-*exo* cyclization.[5] Although the kinetics was well established, there remains some ambiguity because the cyclization precursor contains rotational isomers due to the presence of a tertiary amide, requiring careful consideration of its conformational analysis.[6] To remove this ambiguity and establish the reaction mechanism, we attempted to use *N*-*tert*-butylamide instead of *N*-methyl amide. Because of the steric bulkiness of the *tert*-butyl group, this new precursor contains only one rotational isomer that is favorable for radical cyclization. With this precursor, we assumed that a kinetic study of the cyclization would afford unambiguous results in terms of the reaction mechanism. In this study, we report the kinetic study of 7-*endo* selective radical cyclization and estimated the kinetic parameters. We also identified a novel 1,7-hydrogen transfer[7,8] during the reaction.[9] Hydrogen transfer from toluene as the reaction solvent is also discussed.

RESULTS AND DISCUSSION

Preparation of Starting Materials and Products. The preparation of the cyclization precursor **1**, 7-*endo* product **2**, 6-*exo* product **3**, and reduced product **4** was carried out in the following manner (Scheme 1). The exposure of 1-bromo-2-(bromomethyl)-4-methoxybenzene **5** to *tert*-butylamine gave

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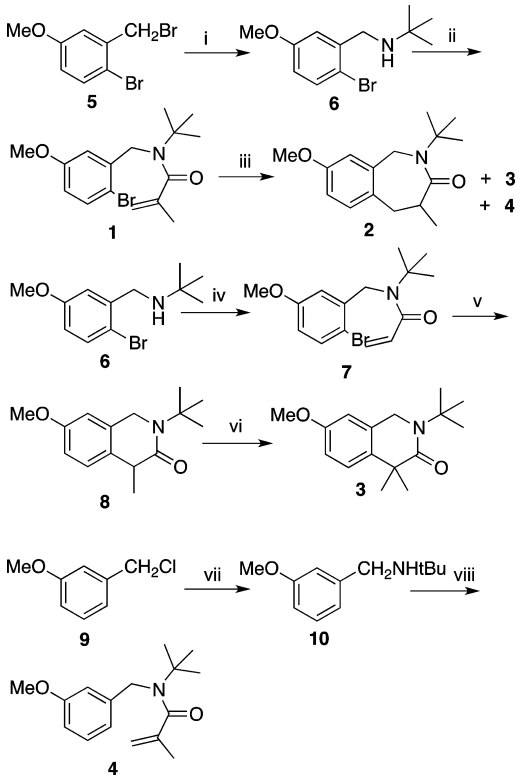
Scheme 1[a]

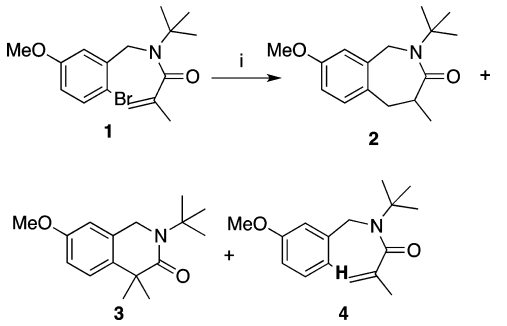


[a]Reagents and conditions: (i) *t*BuNH$_2$, CH_2Cl_2, rt, 98%; (ii) CH_2=C(CH_3)COCl, DMAP, Et_3N, CH_2Cl_2, 78%; (iii) Bu_3SnH, AIBN, toluene, 110 °C, 3 h, 62%; (iv) CH_2=CHCOCl, DMAP, Et_3N, CH_2Cl_2, 77%; (v) Bu_3SnH, AIBN, toluene, 110 °C, 3 h, 67%; (vi) BuLi, THF, −50 °C, then MeI, 80%; (vii) *t*BuNH$_2$, CH_2Cl_2, rt, 92%; (viii) CH_2=CH(CH_3)COCl, DMAP, Et_3N, CH_2Cl_2, 89%.

N-(2-bromo-5-methoxybenzyl)-2-methylpropan-2-amine **6** in 98% yield. The methacroylation of **6** proceeded smoothly by treatment with methacryloyl chloride in the presence of DMAP under standard amidation conditions, and the desired precursor **1** was obtained in 78% yield. ^{1}H NMR spectrum of compound **1** showed sharp signals, suggesting that compound **1** contains only one rotational isomer. Variable-temperature NMR showed no coalescence in any signals. The desired 7-*endo* adduct **2** was prepared by the radical cyclization of **1** to give a mixture of **2**, **3**, and **4**, following flash chromatography separation afforded compound **2** in 62% yield. The yield of **2** was very high compared with the cyclization from *N*-methyl amide.[5] These results clearly indicated that the free rotation around the C−N bond in **1** was fixed, and thus compound **1** contained only one rotamer that is favorable to the radical cyclization. Although the separation of the minor product **3** from the reaction mixture was possible using a recycle GPC apparatus, compound **3** was separately prepared via 6-*exo* selective cyclization followed by methylation reaction. Thus, *tert*-butylamine **6** was acrylated with acryloyl chloride to give **7** in 77% yield, which underwent radical cyclization by treatment with Bu_3SnH to give dihydroisoquinolin-3-one **8** in 67% yield.[10] The methylation of **8** was carried out by treatment with BuLi followed by MeI to give **3** in 80% yield. The reduce product **4** was prepared in a manner similar to the preparation of **1**.

Investigation of the Products Distribution of the Reaction. With all of the materials in the reaction in hand, we examined radical cyclization using various Bu_3SnH concentrations. Three equivalents of Bu_3SnH was used for each reaction, and all products were monitored by GC or GC-MS analyses. The product yields were estimated by a curve-fitting method in the presence of anthracene as an internal standard. Table 1 shows GC yields after 15−120 min of reaction time.

Table 1. Yields of 2, 3, and 4 from 1 under the Various Conditions[a]



entry	[Bu_3SnH]	time (min)	temp (°C)	**2**; yield (%)[b]	**3**; yield (%)[b]	**4**; yield (%)[b]	sum of the yields
1	0.05	60	70	74	9	8	91
2	0.05	120	78	78	7	6	91
3	0.05	15	90	71	9	6	86
4	0.10	60	70	77	9	10	96
5	0.10	60	78	81	10	7	98
6	0.10	17	90	77	7	7	94
7	0.15	20	70	70	8	13	91
8	0.15	120	78	78	9	7	94
9	0.15	6.5	90	68	9	10	87
10	0.20[c]	36	70	70	8	12	90
11	0.20[c]	120	78	77	9	7	93
12	0.20[c]	10	90	71	9	10	90

[a]Reagents and conditions: (i) Bu_3SnH (3 equiv), AIBN, benzene or, *tert*-butylbenzene. [b]GC yields. [c]*tert*-Butylbenzene was used as the reaction solvent.

The reaction was carried out at three temperatures, 70, 78, and 90 °C. *tert*-Butylbenzene was used as the reaction solvent at 90 °C instead of benzene. As the sum of the yields always exceeded 85%, we anticipated that most of the reaction products were traced by this method.

We next investigated the changes in the yields of **2**, **3**, and **4** according to reaction time. Figure 1 shows a typical curve for the reaction at 78 °C, and Figure 2 shows an expansion of the first 15 min of this experiment.

The reaction was completed after approximately 20 min, and from then, the yields of **2** and **3** remained unchanged. The yields of **4** slightly decreased as the reaction time increased, probably due to further polymerization that consumed compound **4**. We investigated the early stage of the reaction and found that the yields of **2**, **3**, and **4** increased in proportion to the reaction time after a short induction period. Yields and time were found to fit to a linear relationship, with correlation factors of greater than 0.99. The calculated slopes represent relative rates for the formation of each product. Their values, k_{7obs}, k_{6obs}, and k_{redobs}, are presented in Table 2 after normalization (see footnote in Table 2). These values also represent the yield of **2**, **3**, and **4** based on the relative reaction rate.

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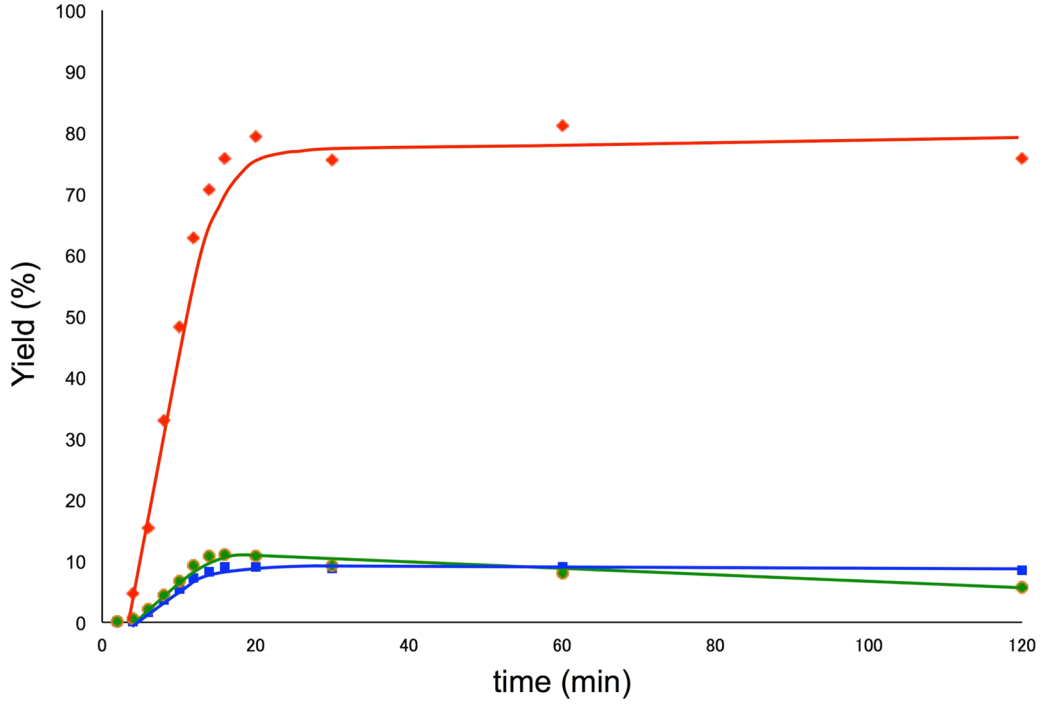

Figure 1. Typical time course for the reaction of **1** with Bu_3SnH (0.1 M), 78 °C. Red: compound **2**; Blue: compound **3**; Green: compound **4**.

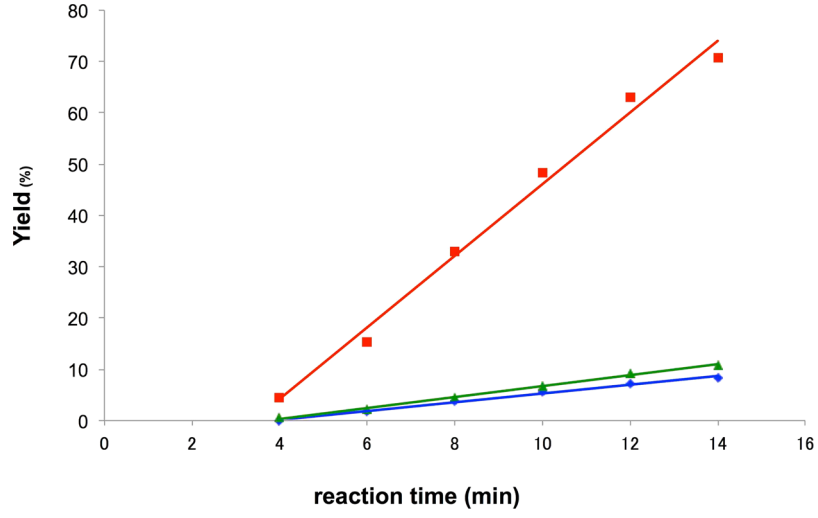

Figure 2. Expansion of Figure 1 for the first 15 min. Red: compound **2**. Blue: compound **3**. Green: compound **4**.

Table 2. Normalized k_{obs} Data and k_7/k_6 Values for the Reaction[a]

entry	[Bu_3SnH] (M)	temp (°C)	k_{7obs} (**2**; yield)	k_{6obs} (**3**; yield)	k_{redobs} (**4**; yield)	k_7/k_6
1	0.05	70	79.88 ± 0.44	9.68 ± 0.15	10.44 ± 0.50	8.25
2	0.10	70	77.83 ± 0.63	9.90 ± 0.27	12.26 ± 0.53	7.86
3	0.15	70	75.45 ± 0.41	8.73 ± 0.07	15.55 ± 0.04	8.64
4	0.20	70	74.84 ± 0.50	9.02 ± 0.11	16.14 ± 0.40	8.30
5	0.05	78	81.20 ± 0.48	9.39 ± 0.22	9.41 ± 0.26	8.65
6	0.10	78	78.45 ± 0.62	9.43 ± 0.43	12.12 ± 0.19	8.32
7	0.15	78	77.58 ± 0.42	9.42 ± 0.28	13.00 ± 0.14	8.24
8	0.20	78	75.67 ± 0.43	9.10 ± 0.14	15.23 ± 0.29	8.31
9	0.05	90	80.37 ± 1.47	9.34 ± 1.04	10.29 ± 0.43	8.61
10	0.10	90	78.61 ± 0.20	10.91 ± 0.17	11.20 ± 0.37	7.71
11	0.15	90	76.78 ± 1.22	9.93 ± 0.42	13.29 ± 0.92	7.74
12	0.20	90	76.13 ± 0.82	9.62 ± 0.19	14.25 ± 0.64	7.91

[a]All k_{obs} values were normalized to $k_{7obs} + k_{6obs} + k_{redobs} = 100$ for each entry.

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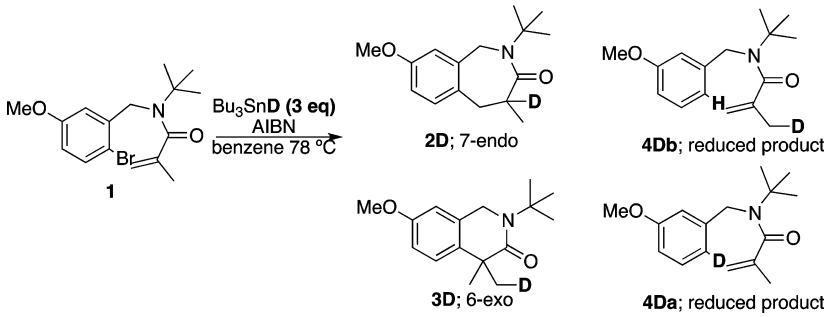
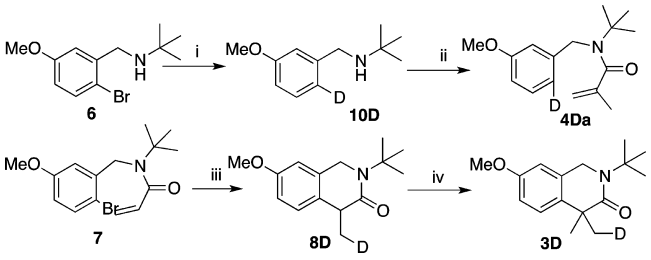
Scheme 2



The experiments were performed at least three times for each entry, and the average values are shown in Table 2. These values reflect how fast each product forms, and their ratios represent the selectivity of the reaction under given conditions. As the Bu_3SnH concentration increased, k_{7obs} and k_{6obs} decreased, while k_{redobs} increased. This means that reduction was preferred with increasing Bu_3SnH concentration. The reaction temperature appeared to have no significant influence on these values. The ratio between k_{7obs} and k_{6obs}, k_7/k_6, represents the relative rate for 7-*endo*/6-*exo* cyclization. The calculated k_7/k_6 ratio was 8.26 ± 0.40 at 70 °C, 8.38 ± 0.27 at 78 °C, and 7.99 ± 0.62 at 90 °C. Thus, the k_7/k_6 ratios were almost constant across these three temperatures. This finding clearly suggests that no rearrangement occurs between 7-*endo* adduct and 6-*exo* adduct radicals and that the 7-*endo*/6-*exo* selectivity of aryl radical cyclization is determined kinetically. This is consistent with our previous reported results.[5] Before discussing these data further, we examined the reaction rate using Bu_3SnD.

1,7-Hydrogen Transfer of the Aryl Radical. Treatment of **1** with Bu_3SnD under the same reaction conditions in benzene gave deuterated products **2D**, **3D**, and **4D** (Scheme 2). Other deuterated products (**4Da** and **3D**) were separately prepared (Scheme 3).

Scheme 3[a]



[a]Reagents and conditions: (i) Bu_3SnD, AIBN, benzene 80 °C, 2.5 h, 87%; (ii) $CH_2{=}C(CH_3)COCl$, DMAP, Et_3N, CH_2Cl_2, 44%; (iii) Bu_3SnD AIBN, benzene 70 °C, 3 h, 44%; (iv) BuLi, THF, −78 °C, then MeI, 97%.

GC-MS data showed that all products had a parent mass peak at m/z = 262; thus, complete D introduction was achieved. **2D** and **3D** showed a single mass pattern indicating that a deuterium atom was introduced at the α-carbon to the carbonyl group in **2** and the terminal methyl group of **3**, respectively. These findings were also confirmed by the ^1H and ^{13}C NMR spectra, which clearly indicated the disappearance of the corresponding protons and $^{13}C{-}^2D$ coupling at the corresponding carbons, respectively. On the other hand, and to our surprise, **4D** contained two products, depending on the Bu_3SnD concentration. Thus, the mass patterns, particularly around m/z = 69 (allylic cation fragment) and m/z 121 (5-methoxybenzyl cation fragment), varied with the Bu_3SnD concentration. One isomer **4Da** contains a deuterium atom at the aromatic carbon, while the other isomer **4Db** contains a deuterium atom at the allylic methyl group. NMR spectra of **4Db**, isolated from the reaction, and **4Da**, prepared separately, were consistent with this assumption. Thus, these data strongly suggest that there is a pathway in which the aryl radical abstracts the allylic hydrogen in an intramolecular manner to give an allylic radical, which then abstracts deuterium from Bu_3SnD giving **4Db**. In other words, a 1,7-hydrogen shift should be included as an alternative route for the formation of reduced product **4**. Scheme 4 shows our revised reaction process. Reduction to **4** has two routes: the direct reduction of an aryl radical by tin deuteride, and reduction via 1,7-hydrogen transfer. Note that these two routes cannot be distinguished by product distribution analysis when Bu_3SnH is used as the reducing reagent.

The estimation of **4Da** and **4Db** ratios by mass fragment patterns was performed. The ratios were estimated by mass fragment pattern simulation. We consulted tables for the fragment at around 69 and 121 and estimated the D contents of these fragments. On the basis of these values, we determined the product ratios of **4Da** and **4Db**. The results are summarized in Table 3. Plots of **4Da**/**4Db** versus the Bu_3SnD concentration in the reaction carried out at 78 °C are depicted in Figure 3.

GC yields revealed that compounds **2D**, **3D**, and **4D** were obtained in yields similar to those obtained by the reaction using Bu_3SnH (entries 1−12). Plots of **4Da**/**4Db** ratios obtained in the reaction at 78 °C versus Bu_3SnD concentration indicated a linear relationship, as shown in Figure 3. Plots from other reaction temperature conditions also showed a clear linear relationship passing through the zero point. The slope was calculated by the least-squares method to be 3.33 for 70 °C, 3.42 for 78 °C, and 3.62 for 90 °C. The correlation coefficients were greater than 0.99 in all cases. Thus, the D distribution ratios in **4D** depended on the Bu_3SnD concentration. As the Bu_3SnD concentration increased, **4Da**, the direct reduction product, became the major product. Based on these plots, the present 1,7-hydrogen transfer should be irreversible because all of the plots pass through zero intercepts. The D content of all compound **4** derivatives was almost 100% as long as the reaction was performed in benzene or *tert*-butylbenzene because we used Bu_3SnD for 97% D content. On the other hand, the reaction performed in toluene produced no D containing **4** in approximately 20% yield (entries 13−16). These results strongly suggest that the aryl radical intermediate

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Scheme 4

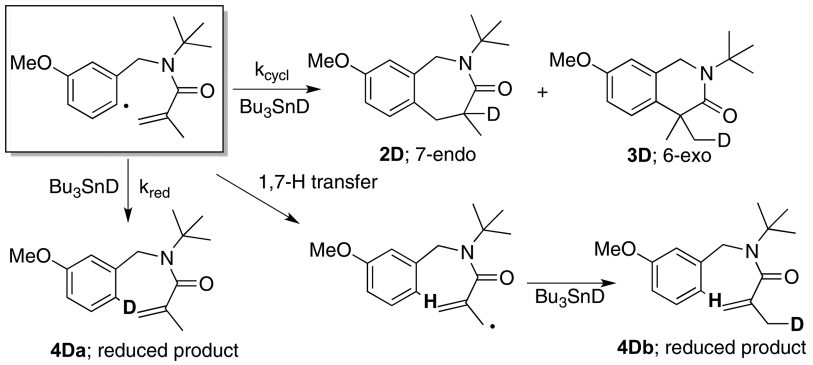

Table 3. Contents of Deuterium Ratios[a]

entry	temp (°C)	[Bu_3SnD] (M)	2D; yield (%)[a]	3D; yield (%)[a]	4D; yield (%)[a]	4Da/4Db[b]	4; D contents
1	70	0.05	73	7	7	15/82	97
2	70	0.10	72	8	8	26/71	97
3	70	0.15	70	8	9	33/64	97
4	70	0.20	68	8	9	38/60	98
5	78	0.05	74	7	5	16/80	96
6	78	0.10	75	8	6	23/74	97
7	78	0.15	75	8	7	34/63	97
8	78	0.20	75	8	7	39/58	97
9[c]	90	0.05	68	7	5	17/75	92
10[c]	90	0.10	67	8	6	24/69	93
11[c]	90	0.15	69	8	6	34/61	95
12[c]	90	0.20	67	8	6	39/55	94
13[d]	70	0.05	65	6	7	12/65	77
14[d]	70	0.10	73	8	9	25/54	79
15[d]	70	0.15	71	8	10	28/55	83
16[d]	70	0.20	62	7	10	34/50	84

[a]GC yield. Yields of **4D** are combined yield of **4Da** and **4Db**. [b]Estimated by *m*/*z* table around 69 and 121. [c]Reaction was carried out in *tert*-butylbenzene. [d]Reaction was carried out in toluene.

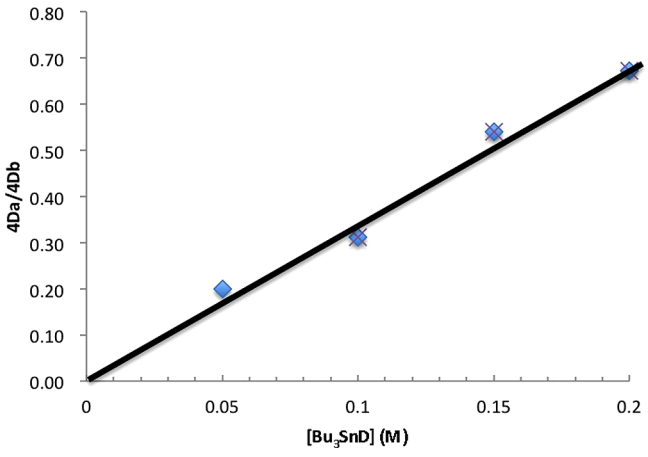

Figure 3. 4Da/4Db ratio plots versus [Bu_3SnD] in the reaction at 78 °C.

abstracts hydrogen from toluene to give the nondeuterated product **4** and a benzyl radical. Thus, toluene works as an effective hydrogen donor for the reaction of aryl radicals, even though the hydrogen abstraction ratio was small. A kinetic estimation of the hydrogen abstraction from toluene will be discussed in a later section.

Estimation of k_H/k_D Using 4-Bromoanisole. These data are useful in the investigation of kinetics of the entire reaction, particularly for the reaction rates of the direct reduction of an aryl radical and 1,7-hydrogen transfer. The former rate should be dependent on the type of reducing reagent (Bu_3SnX, X = H or D), while the latter rate was independent of reagent. Thus, we need to calculate the rate difference of the hydrogen or deuterium abstraction of the aryl radical (k_H/k_D). However, this is not easy to estimate using compound **1**. Therefore, we used 4-bromoanisole as the model of compound **1** to estimate k_H/k_D. Fortunately, the aryl radical is a σ-radical that should not be affected by the aromatic ring substituents.[11] Thus, the reduction of 4-bromoanisol with a 1:1 mixture of Bu_3SnH and Bu_3SnD was performed at 70, 78, and 90 °C (Scheme 5). The results are summarized in Table 4. The k_H/k_D values were estimated from the product ratio of **11-H** and **11-D** obtained by the *m*/*z* peak table at 108 and 109.

Scheme 5

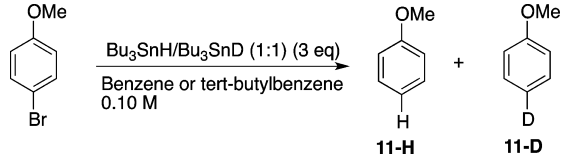

Table 4. Estimation of k_H/k_D Values in the Reduction of 4-Bromoanisole

entry	temp (°C)	11; yield (%)[a]	11-D contents (%)[b]	11-H/11-D	Bu_3SnD/Bu_3SnH	k_H/k_D
1	70	75	36.8 ± 1.1	1.717	0.944	1.622
2	78	86	36.0 ± 1.5	1.778	0.901	1.601
3	90	71	38.7 ± 0.8	1.584	0.936	1.483

[a]GC yield. [b]Estimated by *m*/*z* table at 108 and 109.

The estimated k_H/k_D values were approximately 1.57 ± 0.09 at the temperature range of 70−90 °C. The values depended on the reaction temperature, gradually decreasing with increasing reaction temperature. The k_H/k_D values obtained are reasonably consistent with reported results.[11,12] For example, Ingold and Lusztyk reported that the k_H/k_D value for the aryl radical at 25 °C is 1.6.

Kinetic Estimation for the Whole Reaction Pathways. Whole reaction pathways are depicted in Scheme 6. The aryl

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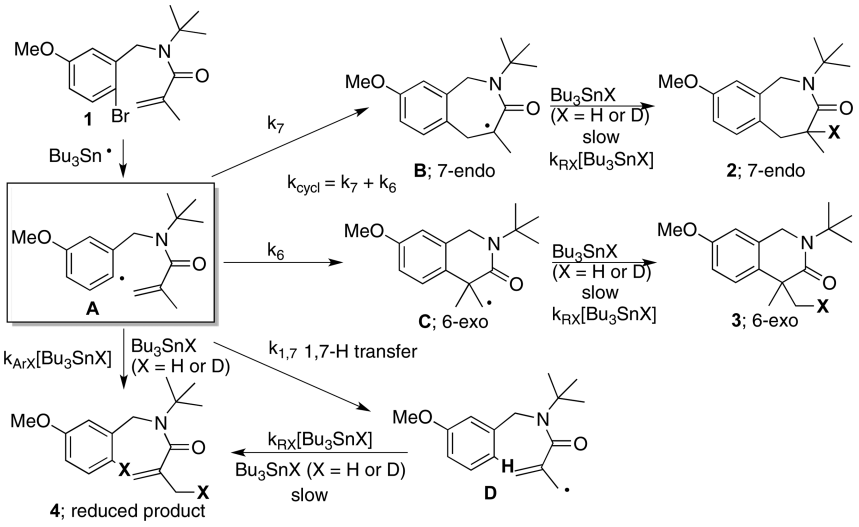
Scheme 6



radical intermediate **A**, which was generated from bromine abstraction using a tin radical, has a two-reaction route; one is the intramolecular reaction of a radical to generate relocated radicals, and the other is the direct hydrogen abstraction from Bu_3SnX (X = H or D) to give compound **4**. The former route includes 7-*endo* and 6-*exo* radical cyclization to give the relocated radicals **B** and **C** as well as 1,7-hydrogen abstraction to give radical **D**. We assume that the reaction rate for the latter reaction, direct hydrogen abstraction, should depend on whether Bu_3SnH or Bu_3SnD is used, while the former reaction rate should not change. Fortunately, the subsequent reactions, such as **B** to **2**, **C** to **3**, and **D** to **4**, are irreversible, and their reaction rates ($k_{RX}[Bu_3SnX]$, X = H or D) should be much slower than the reaction rates such as k_7, k_6, $k_{1,7}$, and k_{ArX} (X = H or D). This is supported by the fact that k_{RX} values are the rate constants for hydrogen abstraction from tin hydride by alkyl radicals, and these values are estimated to be on the order of 10^6 M^{-1} s^{-1},[13] while k_{ArX} is the rate constant for the hydrogen abstraction reaction of an aryl radical and should be on the order of 10^8 or 10^9 M^{-1} s^{-1} at 80 °C.[11,14] Hence, the key parameters for the consideration of the entire reaction process are k_7, k_6, $k_{1,7}$, and k_{ArX}.

There are two types of compound **4** in this scheme; one is a directed reduced product (**A** to **4**), and the other is compound **4** produced via a 1,7-hydrogen transfer (**A** to **D** to **4**). We next attempted to estimate the ratio between the two processes. We considered the product ratios of **4Da** and **4Db** again. Both products were kinetically produced and had no equilibrium between them. This was clearly supported by the kinetic plots shown in Figure 3, in which the graph showed a zero intercept. Thus, the reaction rates for producing these compounds are shown in following equations:

$$d[\mathbf{4Da}]/dt = k_{ArD}[Bu_3SnD][\mathbf{A}]$$

$$d[\mathbf{4Db}]/dt = k_{1,7}[\mathbf{A}]$$

$$[\mathbf{4Da}]/[\mathbf{4Db}] = k_{ArD}[Bu_3SnD]/k_{1,7} = k_{ArD}/k_{1,7}[Bu_3SnD]$$

This assumption is applicable for the virtual product distribution for **4Ha** and **4Hb** (both of which are the same compound **4**, but formed via different process). Here $k_{1,7}$ is constant regardless the reducing reagent used because there is no contribution from Bu_3SnX (X = H or D) to 1,7-hydrogen transfer.

$$[\mathbf{4Ha}]/[\mathbf{4Hb}] = k_{ArH}[Bu_3SnH]/k_{1,7} = k_{ArH}/k_{1,7}[Bu_3SnH]$$

The $k_{ArD}/k_{1,7}$ values were estimated from the kinetic plots such as Figure 3 by calculating the slope. To estimate $k_{ArH}/k_{1,7}$, we needed to convert k_{ArD} to k_{ArH}. These values are the rate constants for the hydrogen abstraction of the aryl radical **A** from Bu_3SnX (X = H or D). We can apply the k_H/k_D values estimated from the reduction of 4-bromoanisole. Thus, the $k_{ArH}/k_{1,7}$ values should be calculated as follows:

$$k_{ArH}/k_{1,7} = k_H/k_D \times k_{ArD}/k_{1,7}$$

Thus, we were now able to estimate the ratio of **4Ha** and **4Hb**, and the values obtained are summarized in Table 5.

Table 5. Kinetic Estimation of the Product Ratio for 4Ha/4Hb

entry	$[Bu_3SnH]$ (M)	temp (°C)	$k_{ArD}/k_{1,7}$	k_H/k_D	$k_{ArH}/k_{1,7}$	**4Ha/4Hb**
1	0.05	70	3.330	1.622	5.401	0.270
2	0.1	70	3.330	1.622	5.401	0.540
3	0.15	70	3.330	1.622	5.401	0.810
4	0.2	70	3.330	1.622	5.401	1.080
5	0.05	78	3.420	1.601	5.475	0.274
6	0.1	78	3.420	1.601	5.475	0.548
7	0.15	78	3.420	1.601	5.475	0.821
8	0.2	78	3.420	1.601	5.475	1.095
9	0.05	90	3.621	1.483	5.370	0.268
10	0.1	90	3.621	1.483	5.370	0.537
11	0.15	90	3.621	1.483	5.370	0.805
12	0.2	90	3.621	1.483	5.370	1.074

The **4Ha**/**4Hb** ratios obtained were useful for the estimation of the origin of compound **4** in the actual reactions. The k_{redobs} values in Table 2 were divided into [**4Ha**] (k_{ArH}) and [**4Hb**] ($k_{1,7}$). The results are summarized in Table 6. [**4Ha**]/([**2**] + [**3**] + [**4Hb**]) ($k_{ArH}/(k_{7obs} + k_{6obs} + k_{1,7})$) plots for the reaction at 78 °C are depicted in Figure 4.

The plots in Figure 4 showed a good linear relationship, with a correlation factor of 0.996. Other plots for the reaction at 70

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Table 6. Kinetic Distribution of the Products of the Reaction (Normalized)

entry	[Bu_3SnH] (M)	temp (°C)	[**2**] (k_{7obs})	[**3**] (k_{6obs})	[**4Hb**] ($k_{1,7}$)	[**4Ha**] (k_{ArH})	[**4Ha**]/([**2**] + [**3**] + [**4Hb**]) ($k_{ArH}/(k_{1,7} + k_7 + k_6)$)
1	0.05	70	79.88 ± 0.44	9.68 ± 0.63	8.22 ± 0.39	2.22 ± 0.11	0.02270 ± 0.00108
2	0.1	70	77.83 ± 0.63	9.90 ± 0.27	7.96 ± 0.35	4.30 ± 0.19	0.04494 ± 0.00195
3	0.15	70	75.45 ± 0.41	8.73 ± 0.07	8.59 ± 0.02	6.96 ± 0.02	0.07503 ± 0.00018
4	0.2	70	74.84 ± 0.50	9.02 ± 0.11	7.76 ± 0.19	8.38 ± 0.21	0.09150 ± 0.00227
5	0.05	78	81.20 ± 0.48	9.39 ± 0.22	7.39 ± 0.21	2.02 ± 0.06	0.02064 ± 0.00057
6	0.1	78	78.45 ± 0.62	9.43 ± 0.43	7.83 ± 0.12	4.29 ± 0.07	0.04479 ± 0.00069
7	0.15	78	77.58 ± 0.42	9.42 ± 0.28	7.14 ± 0.08	5.86 ± 0.07	0.06229 ± 0.00068
8	0.2	78	75.67 ± 0.43	9.10 ± 0.14	7.27 ± 0.14	7.96 ± 0.15	0.08649 ± 0.00166
9	0.05	90	80.37 ± 1.47	9.34 ± 1.04	8.11 ± 0.34	2.18 ± 0.09	0.02227 ± 0.00093
10	0.1	90	78.61 ± 0.20	10.19 ± 0.17	7.29 ± 0.24	3.91 ± 0.13	0.04072 ± 0.00135
11	0.15	90	76.78 ± 1.22	9.93 ± 0.42	7.36 ± 0.51	5.93 ± 0.41	0.06303 ± 0.00436
12	0.2	90	76.13 ± 0.82	9.62 ± 0.19	6.87 ± 0.31	7.38 ± 0.33	0.07967 ± 0.00356

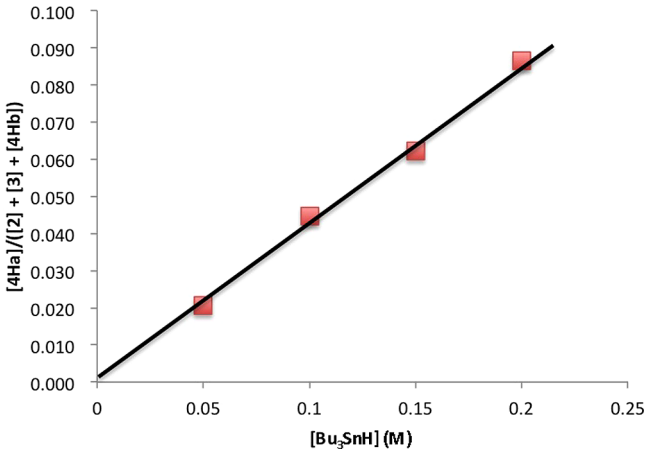


Figure 4. [**4Ha**]/([**2**] + [**3**] + [**4Hb**]) plots versus [Bu_3SnH] in the reaction at 78 °C.

and 90 °C also showed a good linear relationship, with correlation factors of 0.989 and 0.994, respectively. These results clearly suggest that radical rearrangements, including 7-*endo*/6-*exo* cyclization and 1,7-hydrogen transfer, are irreversible. Thus, the product distribution was decided kinetically. The slopes were estimated to be 0.469 at 70 °C, 0.429 at 78 °C, and 0.408 at 90 °C. The values slightly decreased with increasing reaction temperature. The slope values allowed us to estimate actual kinetic values. Unfortunately, no definitive rate constant for the hydrogen abstraction of the 4-methoxy-2-methylphenyl radical from Bu_3SnH is available. However, we can estimate the desired kinetic parameters using the data for the phenyl radical because aryl radicals are σ-radicals and their absolute rate constants are not significantly influenced by the substituents.[11,13,15]

The relative kinetic parameters obtained on the basis of k_{ArH} (=1) are as follows: k_7 = 1.74 (70 °C), 1.92 (78 °C), and 2.01 (90 °C), k_6 = 0.21 (70 °C), 0.23 (78 °C), and 0.25 (90 °C), $k_{1,7}$ = 0.18 (70 °C), 0.18 (78 °C), and 0.19 (90 °C). If the k_{ArH} value is postulated to be the same as the rate constant of a phenyl radical abstracting hydrogen from Bu_3SnH ($k = 1 \times 10^9$ M^{-1} s^{-1} at 80 °C), the kinetic parameters for the reaction at 78 °C would be $k_7 = 1.92 \times 10^9$ s^{-1}, $k_6 = 2.3 \times 10^8$ s^{-1}, $k_{1,7} = 1.8 \times 10^8$ s^{-1}. In the overall reaction conditions, 6-*exo* cyclization appears as a minor process and 7-*endo* selectivity is decided kinetically. The 7-*endo* cyclization reaction is relatively rapid, and the process becomes faster than the direct reduction of the aryl radical by Bu_3SnH if the reaction was performed under sufficiently low Bu_3SnH concentration conditions. On the other hand, under such conditions, intramolecular hydrogen abstraction (the 1,7-hydrogen transfer) becomes a significant process, giving the reduced product **4**, and it is not possible to suppress this side product completely.

The reaction using Bu_3SnD strongly suggested that the aryl radical intermediate **A** is very reactive and abstracts hydrogen from a solvent such as toluene to give compound **4**. To estimate the hydrogen abstraction from toluene, similar kinetic plots, which is shown in Figure 5, were examined (Scheme 7).

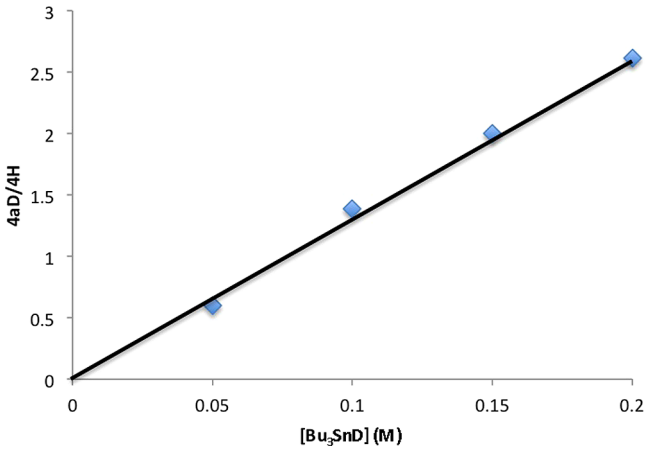
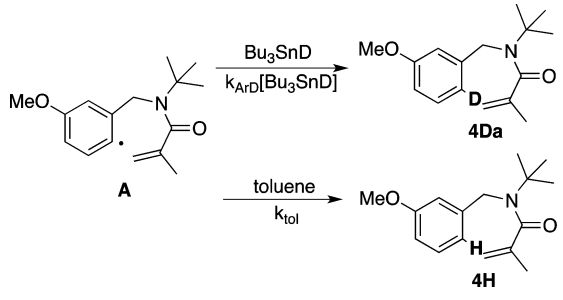


Figure 5. 4Da/4H plots versus [Bu_3SnD] in the reaction at 70 °C in toluene.

The plots clearly suggest that the hydrogen abstraction from toluene is irreversible. The good linear relationship to the Bu_3SnD concentration allowed us to estimate the relative rate.

Scheme 7



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The relative rate constant of k_{tol} should be obtained by the following calculation:

$$k_{tol} = 1/\text{slope} \times k_D/k_H \times k_{ArH}$$

Thus, the value was estimated to be approximately 0.0756 compared with k_{ArH}. This value clearly suggests that the hydrogen abstraction from toluene is not particularly slow and should not be an ignorable process if the reaction is performed under very low Bu_3SnH concentration conditions. Thus, we conclude that toluene is not a good solvent for a radical reaction that involves some rearrangement of the initial radical and toluene should likely be a hydrogen donor that prevents radical rearrangement including radical cyclization.

CONCLUSIONS

We have performed careful product distribution analyses of 7-*endo*/6-*exo* radical cyclization by an aryl radical to give 2-benzazepines in good yields. The investigation of the product distribution study clearly indicated that the regioselectivity of cyclization was determined kinetically. The use of Bu_3SnD enabled us to show that 1,7-hydrogen transfer is included in the reaction pathway. A reduction study using 4-bromoanisole revealed the k_H/k_D value for the aryl radical. These kinetic parameters allowed investigation of the entire reaction process and real product distribution. Furthermore, we have demonstrated the importance of a solvent as a hydrogen donor. These data will be useful for further kinetic studies into radical reaction and improvement of efficiency and/or selectivity of the radical reaction.

EXPERIMENTAL SECTION

Preparation of *N*-(2-Bromo-5-methoxybenzyl)-2-methylpropan-2-amine (6). 1-Bromo-2-(bromomethyl)-4-methoxybenzene **5** (4.2382 g, 15.14 mmol) was dissolved in DMF (30 mL), and *tert*-butylamine (1.9747 g, 27 mmol) and K_2CO_3 (2.6951 g, 19.5 mmol) were added. The reaction mixture was stirred at room temperature for 3 h. Water (150 mL) was added the mixture, and the resulting mixture was extracted with ether (30 mL × 4). The organic phase was combined, washed with brine (30 mL × 1), and dried over Na_2SO_4. Filtration and concentration gave crude **6** in 98% yield (4.0306 g, 14.9 mmol) which was used next step without further purification: pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 3.1 Hz, 1H), 6.66 (dd, J = 8.7, 3.1 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 2H), 1.19 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 141.4, 133.3, 116.2, 114.3, 114.2, 55.6, 51.0, 47.5, 29.3; HRMS (FAB M + H) m/z 272.0641, calcd for $C_{12}H_{18}ONBr$ 272.0650.

Preparation of *N*-(2-Bromo-5-methoxybenzyl)-N-(*tert*-butyl)methacrylamide (1). Compound **6** (3.8670 g, 14.21 mmol) was dissolved in CH_2Cl_2 (120 mL) and Et_3N (4.8 mL, 34.15 mmol), and DMAP (0.4376 g, 3.58 mmol) was added. The reaction mixture was cooled at −50 °C, and methacroyl chloride (2.1 mL, 21.5 mmol) in CH_2Cl_2 (40 mL) was added. The reaction mixture was allowed to warm to room temperature for 1 h. The reaction mixture was stirred for a additional 2 h. Then, 1 M aqueous HCl (50 mL) was added to the reaction mixture, and the resulting biphasic mixture was extracted with CH_2Cl_2 (30 mL × 3). The organic phase was combined, washed with saturated $NaHCO_3$ (40 mL), and dried over Na_2SO_4. Filtration and concentration in vacuo gave crude **1**, which was purified through flash chromatography (silica gel/hexane−EtOAc 15:1 v/v) to give methacrylamide **1** in 78% yield (3.777 g, 11.10 mmol): white solid; mp 47.2−47.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 8.7 Hz, 1 H), 6.94 (d, J = 3.1 Hz, 1 H), 6.68 (dd, J = 8.7, 3.1 Hz, 1 H), 4.93 (t, J = 1.0 Hz, 1 H), 4.88 (p, J = 1.3 Hz, 1 H), 4.58 (s, 2 H), 3.78 (s, 3 H), 1.92 (t, J = 1.3 Hz, 3 H), 1.45 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 159.1, 142.7, 140.1, 133.5, 114.3, 114.0, 113.2, 111.7, 57.9, 55.5, 51.3, 28.6, 20.9; HRMS (FAB M + H) m/z 340.0916, calcd for $C_{16}H_{23}O_2NBr$ 340.0912. Anal. Calcd for $C_{16}H_{22}BrNO_2$: C, 56.48; H, 6.52; N, 4.12. Found: C, 56.53; H, 6.56; N, 4.22.

Preparation of 2-(*tert*-Butyl)-8-methoxy-4-methyl-4,5-dihydro-1*H*-benzo[*c*]azepin-3(2*H*)-one (2). A solution of AIBN (0.0639 g, 0.389 mmol) in benzene (50 mL) was added to a solution of Bu_3SnH (2.34 mL, 8.83 mmol) and compound **1** (1.3598 g, 3.996 mmol) in benzene (150 mL) at 80 °C over 15 min. The reaction mixture was refluxed for an additional 3 h. Then the reaction pot was cooled, and the reaction solution was concentrated by a rotary evaporator. The residue was subjected to flash chromatography (silica gel/hexane−EtOAc 15:0 then 10:1 v/v) to give crude compound **2**, which was purified by recrystallization from hexane/EtOAc, giving compound **2** in 62% yield (0.6472 g, 2.476 mmol): white solid; mp 105.5−105.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, J = 8.4 Hz, 1 H), 6.74 (dd, J = 8.4, 2.7 Hz, 1 H), 6.58 (d, J = 2.7 Hz, 1 H), 4.90 (d, J = 17.1 Hz, 1 H), 4.17 (d, J = 17.2 Hz, 1 H), 3.78 (s, 3H), 3.48−3.40 (m, 1 H), 2.89 (dd, J = 17.1, 4.6 Hz, 1 H), 2.83 (dd, J = 17.2, 12.6 Hz, 1H), 1.41 (s, 9 H), 1.19 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 157.3, 137.1, 131.5, 129.9, 113.8, 112.5, 57.8, 55.4, 47.9, 37.5, 36.6, 29.3, 18.0; HRMS (FAB M + H) m/z 262.1805, calcd for $C_{16}H_{24}O_2N$ 262.1807.

Deuterated **2D** was isolated from kinetic samples. Combined samples after four kinetic experiments, starting from **1** (0.274 g of 0.81 mmol) treated with Bu_3SnD (0.6978 g, 2.39 mmol) under 0.15 M conditions in benzene at 78 °C were concentrated, and the residue was subjected to flash chromatography (silica gel/hexane then hexane−EtOAc 1:1 v/v) to give crude **2D** which was purified through preparative GPC apparatus three times to give **2D** in 59% yield (0.1249 g, 0.477 mmol): white solid; mp 106−106.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (d, J = 8.4 Hz, 1H), 6.73 (dd, J = 8.4, 2.7 Hz, 1H), 6.57 (d, J = 2.7 Hz, 1H), 4.89 (d, J = 17.1 Hz, 1H), 4.16 (d, J = 17.2 Hz, 1H), 3.78 (s, 3H), 2.88 (d, J = 17.1 Hz, 1H), 2.82 (d, J = 17.2 Hz, 1H), 1.39 (s, 9H), 1.18 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.7, 157.3, 137.1, 131.5, 129.9, 113.8, 112.5, 57.8, 55.4, 47.9, 37.4, 36.2 (weak t, J^2H−^{13}C = 19.1 Hz), 29.2, 17.8; HRMS (ESI M + H) m/z 263.1887, calcd for $C_{16}H_{23}DO_2N$ 263.1870.

Preparation of *N*-(2-Bromo-5-methoxybenzyl)-*N*-(*tert*-butyl)acrylamide (7). Under nitrogen atmosphere, a solution **6** (3.7494 g, 13.78 mmol) in CH_2Cl_2 (60 mL) was cooled at −50 °C, and DMAP (0.5083 g, 4.16 mmol) and Et_3N (2.7860 g, 27.56 mmol) were added. A solution of acryloyl chloride (1.8708 g, 20.67 mmol) in CH_2Cl_2 (40 mL) was added to the solution over 30 min. The reaction mixture was allowed to warm to room temperature and stirred for 3.5 h. Then, 1 M aqueous HCl (50 mL) was added to the reaction mixture, and the resulting biphasic mixture was extracted with CH_2Cl_2 (4 × 30 mL). The organic phase was washed with aqueous K_2CO_3 (30 mL) and dried over Na_2SO_4. Filtration and concentration gave crude **7** which was purified by flash chromatography (silica gel/hexane−EtOAc 20:1 then 10:1 v/v) to give **7** in 77% yield (3.442 g): white solid; mp 99.0−99.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 3.0 Hz, 1H), 6.70 (dd, J = 8.8, 3.0 Hz, 1H), 6.32 (dd, J = 16.6, 2.3 Hz, 1H), 6.22 (dd, J = 16.6, 10.2 Hz, 1H), 5.54 (dd, J = 10.2, 2.2 Hz, 1H), 4.51 (s, 2H), 3.75 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 159.5, 139.3, 133.5, 131.1, 127.8, 114.2, 113.9, 111.6, 57.7, 55.4, 49.8, 28.3; HRMS (FAB M + Na) m/z 348.0573, calcd for $C_{15}H_{20}O_2NNaBr$ 348.0575.

Preparation of 2-(*tert*-Butyl)-7-methoxy-4-methyl-1,2-dihydroisoquinolin-3(4*H*)- one (8). A solution of Bu_3SnH (5.9607 g, 20.48 mmol) and AIBN (0.4036 g, 2.46 mmol) in benzene (50 mL) was added dropwise to a solution of **7** (3.3405 g, 10.24 mmol) in benzene (250 mL) at 78 °C over 1 h. After additional heating at 78 °C for 4 h, the reaction mixture was cooled and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel/hexane−EtOAc 100:1, 50:1, 30:1, then 10;1 v/v) to give **8** in 67% yield (1.6886 g): pale yellow solid; mp 52.5−53 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 1H), 7.06 (dd, J = 8.5, 2.5 Hz, 1H), 6.96 (d, J = 2.6 Hz, 1H), 4.73 (d, J = 15.7 Hz, 1H), 4.62 (d, J = 15.3 Hz, 1H), 4.04 (s, 3H), 3.63 (q, J = 7.1 Hz, 1H), 1.74 (s, 9H), 1.67 (d, J = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 158.2, 134.3, 130.8, 126.2, 113.1, 110.8, 57.4, 55.4,

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46.6, 43.0, 28.5, 16.1; HRMS (FAB M + H) m/z 248.1640, calcd for $C_{15}H_{22}NO_2$ 248.1651.

Preparation of 2-(*tert*-Butyl)-7-methoxy-4,4-dimethyl-1,2-dihydroisoquinolin-3(4*H*)-one (3). Under nitrogen atmosphere, BuLi (1.6 M, 2.44 mL, 3.9 mmol) was added to a solution of **8** (0.7514 g, 3.04 mmol) in THF (5 mL) at −50 °C. MeI (1.12 mL, 18 mmol) was added immediately, and the reaction mixture was stirred for 20 min at the same temperature and for 1 h with warming to room temperature. Aqueous NH_4Cl (20 mL) was added to the reaction mixture, and THF was removed by a rotary evaporator. The resulting aqueous mixture was extracted with EtOAc (4 × 20 mL). The organic phase was washed with aqueous $Na_2S_2O_3$ (2 × 10 mL) and dried over Na_2SO_4. After filtration, the filtrate was concentrated and the residue was purified by flash chromatography (silica gel/hexane−EtOAc 20:1 v/v) to give **3** in 80% yield (0.6315 g, 2.42 mmol): white solid; mp 69.0−69.2 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, J = 8.7 Hz, 1H), 6.77 (dd, J = 8.6, 2.7 Hz, 1H), 6.61 (d, J = 2.6 Hz, 1H), 4.42 (s, 2H), 3.74 (s, 3H), 1.45 (s, 9H), 1.35 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 158.1, 134.4, 133.2, 125.7, 113.5, 110.9, 57.6, 55.4, 46.6, 43.3, 28.4, 25.8; HRMS (FAB M + H) m/z 262.1812, calcd for $C_{16}H_{24}O_2N$ 262.1807.

Preparation of *N*-(3-Methoxybenzyl)-2-methylpropan-2-amine (10). NaI (0.7495 g, 5 mmol) and *t*BuNH$_2$ (2.9225 g, 39.97 mmol) were added to a solution of *m*-methoxybenzylchloride (1.5661 g, 10 mmol) in THF (20 mL), and the reaction mixture was stirred at room temperature for 140 h. THF was removed in vacuo, and aqueous $NaHCO_3$ (30 mL) was added to the residue. The resulting aqueous mixture was extracted with EtOAc (4 × 20 mL). The organic phase was combined and dried over Na_2SO_4. After filtration, crude product was isolated by concentration to give compound **10** in 92% yield (1.7859 g, 9.24 mmol), which was used for the next stage without further purification: pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, J = 7.8 Hz, 1H), 6.91 (d, J = 8.9 Hz, 1H), 6.90 (s, 1H), 6.77 (dd, J = 8.2, 2.6 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 2H), 1.20−1.40 (br, 1H), 1.17 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 143.3, 129.5, 120.6, 113.9, 112.3, 55.3, 50.8, 47.4, 29.3; HRMS (ESI M + H) m/z 194.1554, calcd for $C_{12}H_{20}NO$ 194.1545.

Preparation of *N*-(*tert*-Butyl)-*N*-(3-methoxybenzyl)methacrylamide (4). Compound **10** (1.6446 g, 8.51 mmol) was dissolved in CH_2Cl_2 (80 mL), and Et_3N (2.36 mL, 17.02 mmol) and DMAP (0.3115 g, 2.55 mmol) were added. Under nitrogen atmosphere, the reaction mixture was cooled at −50 °C and a solution of methacroyl chloride (1.25 mL, 12.77 mmol) in CH_2Cl_2 (40 mL) was added. The reaction mixture was allowed to warm to room temperature for 20 h. Aqueous HCl (1 M, 50 mL) was added to the reaction mixture, and the resulting biphasic mixture was extracted with CH_2Cl_2 (40 mL × 3). The organic phase was washed with aqueous $NaHCO_3$ (20 mL) and dried over Na_2SO_4. Filtration and concentration in vacuo gave crude **4**, which was purified through flash chromatography (silica gel/hexane−EtOAc 100:1 then 10:1 v/v) to give methacrylamide **4** in 89% yield (1.9869 g): white solid; mp 34−35 °C, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 7.6 Hz, 1 H), 6.85−6.75 (m, 3 H), 5.02 (s, 1 H), 4.93 (s, 1 H), 4.65 (s, 2 H), 3.80 (s, 3 H), 1.93 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 159.9, 143.1, 142.1, 129.7, 118.4, 113.5, 112.2, 111.9, 57.8, 55.3, 50.9, 28.7, 21.0; HRMS (FAB M + H) m/z 262.1809, calcd for $C_{16}H_{24}O_2N$ 262.1807.

Allylic deuterated **4Db** was isolated from kinetic samples. A combined five times samples, containing the reaction mixture starting from **1** (0.342 g of 1 mmol) treated with Bu_3SnD (0.9196 g, 3.15 mmol) under 0.025 M conditions in benzene at 78 °C, was concentrated, and the residue was subjected to flash chromatography (silica gel/hexane then hexane/EtOAc 1:1 v/v) to give crude **4Db** which was purified through preparative GPC apparatus three times to give **4Db** in 2% yield (0.0042 g, 0.016 mmol). GC-MS peak showed that the **4Db**/**4 Da** ratio was 96/4: yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 7.9 Hz, 1H), 6.82−6.74 (m, 3H), 5.01 (d, J = 1.0 Hz, 1H), 4.92 (d, J = 1.3 Hz, 1H), 4.64 (s, 2H), 3.79 (s, 3H), 1.91 (s, 2H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 159.9, 143.1, 142.1, 129.7, 118.5, 113.5, 112.3, 111.9, 57.8, 55.3, 50.8, 28.7, 20.7 (weak, t, J^2H−^{13}C = 19.5 Hz); HRMS (ESI M + H) m/z 263.1872, calcd for $C_{16}H_{23}DO_2N$ 263.1870.

Preparation of *N*-(3-Methoxy-5-deuteriobenzyl)-2-methylpropan-2-amine (10D). A solution of AIBN (0.025 g, 0.15 mmol), compound **6** (0.206 g, 0.755 mmol), and Bu_3SnD (0.41 mL, 1.5 mmol) in benzene (8 mL) was heated at 80 °C, and the reaction mixture was heated at refluxing temperature for 2 h. AIBN (0.036 g, 0.22 mmol) wad added to the reaction mixture and heated at the same temperature for 30 min. The reaction mixture was poured into concentrated HCl (10 mL), and the resulting biphasic mixture was washed with EtOAc (3 × 20 mL). The water layer was then basified by adding 6 M aqueous NaOH (30 mL). The resulting basic aqueous solution was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was combined and dried with Na_2SO_4. After filtration, the filtrate was concentrated in vacuo to give **10D** in 87% yield (0.127 g, 0.654 mmol): yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.2 Hz, 1H), 6.90 (d, J = 2.7 Hz, 1H), 6.77 (dd, J = 8.2, 2.6 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 2H), 1.40−1.20 (br, 1H), 1.17 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.8, 143.2, 129.4, 120.3 (weak, t, J^2H−^{13}C = 24.2 Hz), 113.8, 112.3, 55.3, 50.8, 47.3, 29.3; HRMS (ESI M + H) m/z 195.1616, calcd for $C_{12}H_{19}DNO$ 195.1608.

Preparation of *N*-(*tert*-Butyl)-*N*-(3-methoxy-5-deuteriobenzyl)methacrylamide (4Da). Methacroyl chloride (0.07 mL, 0.72 mmol) was added slowly to a solution of **10D** (0.0839 g, 0.432 mmol), Et_3N (0.12 mL, 0.83 mmol), and DMAP (0.0175 g, 0.14 mmol) in CH_2Cl_2 (10 mL) at −50 °C, and the reaction mixture was gradually warmed to room temperature for 9 h. Aqueous 1 M HCl (5 mL) was added to the reaction mixture, and the resulting biphasic mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was combined, washed with aqueous $NaHCO_3$ (1 × 20 mL), and dried over Na_2SO_4. After filtration, the filtrate was concentrated in vacuo and the residue was subjected to flash chromatography (silica gel/hexane−EtOAc 9:1 then 3:1) to give **4Da** in 44% yield (0.0494 g, 0.188 mmol): pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.20 (m, 1H), 6.82−6.73 (m, 2H), 5.01 (s, 1H), 4.92 (s, 1H), 4.64 (s, 2H), 3.78 (s, 3H), 1.92 (s, 3H), 1.42 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 159.9, 143.2, 142.0, 129.6, 118.4 (weak, m), 113.5, 112.2, 111.9, 111.8, 57.8, 55.3, 50.8, 28.7, 20.9; HRMS (ESI M + H) m/z 263.1884, calcd for $C_{16}H_{23}DO_2N$ 263.1870.

Preparation of 2-(*tert*-Butyl)-7-methoxy-4-deuteriomethyl-1,2-dihydroisoquinolin-3(4*H*)-one (8D). A solution of Bu_3SnD (0.34 mL, 1.26 mmol) and AIBN (0.0202 g, 0.12 mmol) in benzene (5 mL) was added to a solution of **7** (0.2012 g, 0.62 mmol) in benzene (20 mL) at 78 °C over 90 min using a syringe pump. After additional heating at 78 °C for 90 min, the reaction mixture was cooled and concentrated in vacuo. The residue was subjected to flash chromatography (silica gel/hexane−EtOAc 15:1, 12:1, 10:1, then 8:1 v/v) to give crude **8D** (0.092 g, 0.35 mmol), which was purified again using flash chromatography (silica gel/hexane−EtOAc 12:1 then 8:1 v/v) to give **8D** in 44% yield (0.0666 g, 0.268 mmol): pale yellow solid; mp 50.5−51.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J = 8.4 Hz, 1H), 6.82 (dd, J = 8.3, 2.3 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 4.48 (d, J = 15.4 Hz, 1H), 4.37 (d, J = 15.4 Hz, 1H), 3.80 (s, 3H), 3.38 (t, J = 7.1 Hz, 1H), 1.50 (s, 9H), 1.41 (d, J = 7.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 158.2, 134.4, 130.9, 126.2, 113.10, 110.8, 57.5, 55.5, 46.8, 43.0, 28.7, 16.0 (weak, t, J^2H−^{13}C = 20.8 Hz); HRMS (ESI M + H) m/z 249.1688, calcd for $C_{15}H_{21}DO_2N$ 249.1713.

Preparation of 2-(*tert*-Butyl)-7-methoxy-4-deuteriomethyl-4-methyl-1,2-dihydroisoquinolin-3(4H)-one (3D). Under nitrogen atmosphere, BuLi (1.6 M, 0.1 mL, 0.16 mmol) was added to a solution of **8D** (0.0312 g, 0.126 mmol) in THF (5 mL) at −50 °C. MeI (0.05 mL, 0.8 mmol) was added after 20 min, and the reaction mixture was stirred for 2 h with warming up to room temperature. Aqueous NH_4Cl (20 mL) was added to the reaction mixture, and THF was removed by an evaporator. The resulting aqueous mixture was extracted with EtOAc (3 × 20 mL). The organic phase was washed with aqueous $Na_2S_2O_3$ (2 × 10 mL) and dried over Na_2SO_4. After filtration, the filtrate was concentrated and the residue was purified by flash chromatography (silica gel/hexane−EtOAc 12:1 then 6:1) to give **3D** in 97% yield (0.0319 g, 0.122 mmol): white solid, mp 63.0−63.5

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°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 1H), 6.83 (dd, J = 8.6, 2.7 Hz, 1H), 6.68 (d, J = 2.6 Hz, 1H), 4.48 (s, 2H), 3.80 (s, 3H), 1.51 (s, 9H), 1.41 (s, 3H), 1.40 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 158.0, 134.3, 133.1, 125.6, 113.5, 110.8, 57.6, 55.4, 46.7, 43.3, 28.4, 25.8, 25.5 (t, J^2H−^{13}C = 19.4 Hz); HRMS (ESI M + H) m/z 263.1859, calcd for $C_{16}H_{23}DO_2N$ 263.1870.

General Procedure for Kinetic Estimation: Typical Procedure. A solution of compound **1** (0.3425 g, 1.006 mmol, 0.1 M) and anthracene (5.08 mg, 0.285 mmol) in benzene (10 mL) was prepared using a 10 mL measuring flask. A solution of Bu_3SnH (0.8690 g, 2.99 mmol) in benzene (5 mL) was prepared using a 5 mL measuring flask. AIBN (0.0398 g) was added to a 30 mL test tube, and 2 mL of the former solution and 1 mL of the latter solution were mixed. The resulting 3 mL solution (0.20 M for Bu_3SnH) was used directly or diluted with benzene to adjust its concentration to be 0.15 M (add 1 mL of benzene), 0.10 M (add 3 mL of benzene), and 0.05 M (add 9 mL of benzene). The reaction solution was then purged by N_2 gas for 5 min and sealed. The test tube was placed into a preheated oil bath (70 °C). 10 μL of the reaction mixture was taken as a sample for every 4 min, and the sample was analyzed and quantified by GC-MS using a Cap-5 capillary column. The amounts of compounds **2**, **3**, and **4** were estimated using a curve-fitting method with anthracene as an internal standard. The reaction was carried out at least three times for each concentration and temperature.

■ ASSOCIATED CONTENT

Supporting Information

Spectroscopic charts for compounds **1**, **2**, **2D**, **3**, **3D**, **4**, **4Da**, **4Db**, **6**, **7**, **8**, **8D**, **10**, and **10D**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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