

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/11684262>

# General and Efficient Insertions of Carbons Carrying Aryl and Heteroaryl Groups: Synthesis of $\alpha$ -Aryl- and $\alpha$ -Heteroaryl-Substituted Ketones

ARTICLE in THE JOURNAL OF ORGANIC CHEMISTRY · NOVEMBER 1996

Impact Factor: 4.72 · DOI: 10.1021/jo960841h · Source: PubMed

---

CITATIONS

28

---

READS

8

3 AUTHORS, INCLUDING:



Dorin Toader

MedImmune, LLC

45 PUBLICATIONS 462 CITATIONS

SEE PROFILE



Linghong Xie

Sunovion Respiratory Development

34 PUBLICATIONS 634 CITATIONS

SEE PROFILE

# General and Efficient Insertions of Carbons Carrying Aryl and Heteroaryl Groups: Synthesis of $\alpha$ -Aryl- and $\alpha$ -Heteroaryl-Substituted Ketones

Alan R. Katritzky,\* Dorin Toader, and Linghong Xie

Center for Heterocyclic Compounds, Department of Chemistry, University of Florida,  
Gainesville, Florida 32611-7200

Received May 7, 1996<sup>®</sup>

Anions formed from the lithiation of a variety of 1-(arylmethyl)- and 1-(heteroarylmethyl)-benzotriazoles **1** with *n*-BuLi underwent addition to aliphatic and aromatic aldehydes and cyclic and acyclic ketones. Subsequent *in situ* thermal rearrangements of the intermediates in the presence of zinc bromide provided one-carbon chain-extended or ring-expanded  $\alpha$ -aryl- and  $\alpha$ -heteroaryl-substituted ketones **2** in moderate to excellent yields in simple one-pot operations with excellent regioselectivity in most cases. Substituent effects on the relative migration rates were investigated in the insertion reactions of 1-(4-methoxybenzyl)benzotriazole (**1e**) with XC<sub>6</sub>H<sub>4</sub>-COPh. The small and negative Hammett  $\rho^+$  value (−0.92) suggested that the rearrangements proceed *via* early, reagent-like, electron deficient transition states.

## Introduction

Carbon chain extension or ring expansion of carbonyl compounds by a one-carbon unit is a frequently encountered synthetic objective and has attracted widespread and continuing interest (for recent examples, see refs 1–5). Carbon insertion is the most straightforward and most commonly used strategy for this purpose. The numerous procedures for the insertions of carbons bearing C-linked substituents into aldehydes and ketones available in the literature can be classified into the following categories: (i) diazo insertion reactions utilizing ethyl diazoacetate,<sup>6–8</sup>  $\alpha$ -diazo ketones and aldehydes,<sup>9</sup> diazoalkanes,<sup>2</sup> and aryl diazomethanes;<sup>10,11</sup> (ii)  $\beta$ -oxido carbenoid chemistry as initiated by Yamamoto using dihalomethylolithiums<sup>12</sup> and recently extensively developed by Yamakawa<sup>1</sup> with chloromethyl sulfoxides as advantageous reagents for the insertions of carbons bearing an alkyl<sup>1c,13</sup> and an aryl<sup>13</sup> groups into aldehydes and ketones; (iii) semipinacol-type rearrangements, alkylidene insertions utilizing  $\alpha$ -lithioalkyl sulfoxides<sup>14</sup> and

selenoxides<sup>14–16</sup> and arylmethylene insertions *via* the rearrangement of halohydrins, derived from the addition of benzylmagnesium chloride to carbonyl compounds, followed by  $\alpha$ -bromination;<sup>17</sup> and (iv) other approaches include ring expansions of cyclic ketones *via* radical processes<sup>18–20</sup> and more complex pathways.<sup>21</sup>

While several arylmethylene insertion routes to one-carbon-homologated  $\alpha$ -aryl-substituted ketones are available as mentioned above, insertions of carbons carrying heteroaryl groups into carbonyl compounds were previously unknown. Moreover, all the previous approaches possess limitations: (i) Direct insertions of the corresponding aryl diazomethanes<sup>10–11</sup> are not suitable for large-scale preparations and often suffer from epoxide formation and multiple homologation. (ii) The original  $\beta$ -oxido carbenoid route is limited by the extreme thermal instability of the ( $\alpha,\alpha$ -dibromobenzyl)lithium reagent.<sup>16a</sup> (iii) Sisti's semipinacol-type rearrangement<sup>17</sup> involves three steps and is limited to cyclic ketones.

Since our preliminary paper,<sup>22</sup> we have undertaken a systematic investigation of the benzotriazole-mediated insertion route to one-carbon-chain extended or ring-expanded  $\alpha$ -functionalized ketones. In the preceding paper,<sup>23</sup> we have described the efficient benzotriazole-mediated insertions of carbons carrying O-, S-, and N-linked substituents to give  $\alpha$ -alkoxyalkyl-,  $\alpha$ -(alkylthio)alkyl-, and  $\alpha$ -(carbazol-9-yl)alkyl-substituted ketones. We now provide full details for the insertions of carbons carrying aryl and heteroaryl groups to furnish one-carbon-homologated  $\alpha$ -aryl- and  $\alpha$ -heteroaryl-substituted ketones and comment on the generality of and

<sup>®</sup> Abstract published in *Advance ACS Abstracts*, October 1, 1996.

(1) (a) Satoh, T.; Mizu, Y.; Kawashima, T.; Yamakawa, K. *Tetrahedron* **1995**, *51*, 703. (b) Satoh, T.; Itoh, N.; Gengyo, K.; Yamakawa, K. *Tetrahedron Lett.* **1992**, *33*, 7543. (c) Satoh, T.; Hayashi, Y.; Mizu, Y.; Yamakawa, K. *Tetrahedron Lett.* **1992**, *33*, 7181. (d) Satoh, T.; Fujii, T.; Yamakawa, K. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1266.

(2) (a) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *J. Org. Chem.* **1994**, *59*, 4725. (b) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283.

(3) Montana, J. G.; Phillipson, N.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1994**, 2289.

(4) Trost, B. M.; Mikhail, G. K. *J. Am. Chem. Soc.* **1987**, *109*, 4124.

(5) Krow, G. R. *Tetrahedron* **1987**, *43*, 3.

(6) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

(7) Nagao, K.; Chiba, M.; Kim, S.-W. *Synthesis* **1983**, 197.

(8) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459.

(9) Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297.

(10) Loeschorn, C. A.; Nakajima, M.; McCloskey, P. J.; Anselme, J.-P. *J. Org. Chem.* **1983**, *48*, 4407.

(11) Gutsche, C. D.; Johnson, H. E. *J. Am. Chem. Soc.* **1955**, *77*, 109.

(12) (a) Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6510. (b) Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1976**, 2617.

(13) Villieras, J.; Perriot, P.; Normant, J. F. *Synthesis* **1979**, 968.

(14) Gadwood, R. C.; Mallick, I. M.; DeWinter, A. J. *J. Org. Chem.* **1987**, *52*, 774.

(15) Gadwood, R. C. *J. Org. Chem.* **1983**, *48*, 2098.

(16) (a) Labar, D.; Laboureur, J. L.; Krief, A. *Tetrahedron Lett.* **1982**, *23*, 983. (b) Krief, A.; Dumont, W.; Laboureur, J. L. *Tetrahedron Lett.* **1988**, *29*, 3265. (c) Laboureur, J. L.; Krief, A. *Tetrahedron Lett.* **1984**, *25*, 2713.

(17) (a) Sisti, A. J. *Tetrahedron Lett.* **1967**, 5327. (b) Sisti, A. J. *J. Org. Chem.* **1970**, *35*, 2670. (c) Sisti, A. J.; Rusch, G. M.; Sukhon, H. K. *J. Org. Chem.* **1971**, *36*, 2030.

(18) Kim, S.; Lee, S. *Tetrahedron Lett.* **1991**, *32*, 6575.

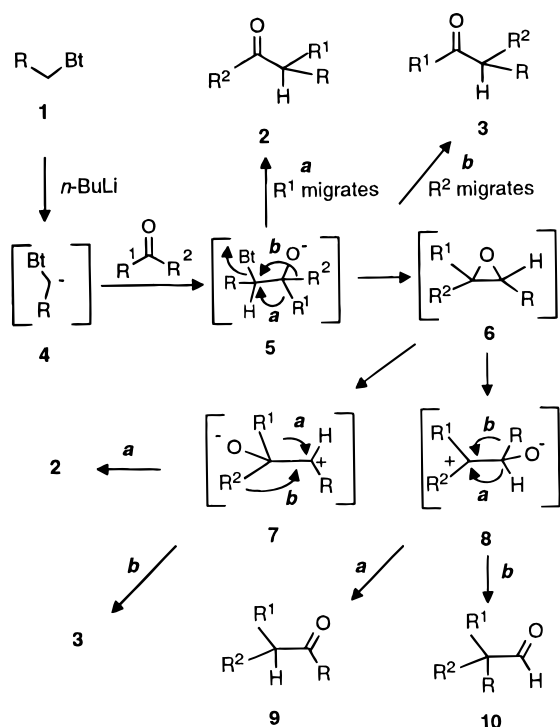
(19) Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493.

(20) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1990**, *55*, 5442.

(21) Bunce, R. A.; Schilling, C. L., III. *J. Org. Chem.* **1995**, *60*, 2748.

(22) Katritzky, A. R.; Xie, L.; Toader, D.; Serdyuk, L. *J. Am. Chem. Soc.* **1995**, *117*, 12015.

(23) Katritzky, A. R.; Xie, L.; Serdyuk, L. *J. Org. Chem.* **1996**, *61*, 7564.

Scheme 1 <sup>a</sup>

<sup>a</sup> Bt = benzotriazol-1-yl; R = aryl, heteroaryl (see Tables 1 and 2 for the designation of R).

significant exceptions to the scope of this synthetic transformation. Substituent effects on relative migration rates are also described.

## Results and Discussion

**Preparation of 1-(Arylmethyl)- and 1-(Heteroarylmethyl)benzotriazoles 1a–f and *in Situ* Preparation of Their Lithio Derivatives 4a–f.** 1-(4-Methylbenzyl)benzotriazole (**1a**),<sup>24</sup> 1-[4-(*N,N*-dimethylamino)benzyl]benzotriazole (**1b**),<sup>25</sup> 1-[(1-methylindol-3-yl)methyl]benzotriazole (**1d**),<sup>26</sup> and 1-(4-methoxybenzyl)benzotriazole (**1e**)<sup>27</sup> were made according to previously reported procedures. 1-[(5-Methylthien-2-yl)methyl]benzotriazole (**1c**) was produced by treatment of 1-(hydroxymethyl)benzotriazole with 2-methylthiophene in refluxing acetic acid in 50% yield. 1-(4-Chlorobenzyl)benzotriazole (**1f**) was prepared in good yield from the reaction of 4-chlorobenzyl chloride with benzotriazole in refluxing toluene. All these benzotriazole derivatives **1a–f** can easily be prepared on a large scale; novel compound **1c** was characterized by NMR spectroscopy and elemental analyses.

Lithio derivatives **4a–f** were prepared *in situ* as deep green solutions in THF under argon by stirring compounds **1** with *n*-butyllithium at  $-78\text{ }^{\circ}\text{C}$  for *ca.* 30 min (Scheme 1). Anions **4d** and **4e** have been previously documented to react readily with electrophiles followed by the displacement of the benzotriazolyl group to furnish functionalized indoles,<sup>26</sup> carbazoles,<sup>28</sup> and methoxybenzenes.<sup>27</sup>

## Arylmethylene and Heteroarylmethylene Insertions into Aldehydes and Ketones: Preparation of

**$\alpha$ -Aryl and  $\alpha$ -Heteroaryl-Substituted Ketones.** Treatment of the deep green solutions of **4** prepared *in situ* with aldehydes or ketones at  $-78\text{ }^{\circ}\text{C}$  for 4 h gave the intermediate products **5** (Scheme 1). The intermediates **5** thus produced were shown in each case to be capable of *in situ* rearrangement promoted by a *ca.* 3-fold molar excess of zinc bromide upon heating to furnish one-carbon-homologated  $\alpha$ -aryl- and  $\alpha$ -heteroaryl-substituted ketones **2a–u** in moderate to excellent yields (Tables 1 and 2). All compounds prepared showed the expected NMR spectra, and all new compounds were further characterized by elemental analyses (see Experimental Section).

As discussed in our preceding paper,<sup>23</sup> zinc bromide is necessary for the departure of the benzotriazolyl group. An excess of the Lewis acid and complete coordination of the oxygen anion with zinc cation were found to be crucial to suppress the tendency of intermediates **5** to revert back to the starting materials. The reaction temperatures necessary for the rearrangement vary as listed in Tables 1 and 2. As expected, the greater the R group stabilization (Scheme 1) of the transient cation, the lower the temperature needed to complete the rearrangement. In those cases where the required temperature was higher than the boiling point of THF, the THF was distilled off and an appropriate solvent (or no solvent) was added for the rearrangement stage.

Of special importance is the general applicability of these insertions to diverse aldehydes and ketones. While Table 1 shows examples of insertions into aliphatic and aromatic aldehydes and acyclic ketones to give chain-extended products, Table 2 illustrates the successful insertions into cyclic ketones to provide ring-expanded ketones. The regioselectivity of these insertions is also significant. In most cases (entries 1–11 in Table 1 and entries 1–7 in Table 2), single regioisomers were produced by migration of the group ( $R^1$ , see Scheme 1) that can best stabilize an electron deficiency in the transition state, *i.e.*, in general,  $\text{H} > \text{Ar} > \text{alkyl}$ ; *tert*-alkyl > *sec*-alkyl > *n*-alkyl. Similar migration aptitudes were found in other pinacol-type rearrangements.<sup>29</sup> Although the yields of **2e** and **2g** were only moderate, no other regioisomers were detected according to GCMS analysis of the crude products; the relatively low yields of **2e** and **2g** were due either to the partial recovery of the intermediates **5** or to the reverse reaction of **5** to the starting materials. In the case of **2l** (entry 12 in Table 1), the alternative regioisomer **3l**, derived from the migration of the trifluorophenyl group ( $R^2$ , see Scheme 1), was formed in 27% yield based on the GCMS and NMR results of the crude product, although its separation was not achieved.

Two different insertion reagents each reacted with 2-methylcyclohexanone (entries 8 and 9 in Table 2) to afford two regioisomers (**2** and **3**) in each case. In the case of entry 8, **2t** and **3t** were separated in yields of 81% and 3%, and the GCMS analysis of the crude reaction mixture indicated that they were formed in a ratio of 11:1. In the case of entry 9, **2u** and **3u** were formed in a ratio of 5:1 according to the GCMS of the crude product, although only **2u** was separated in 66% yield. These results again reveal preferential migrations of the most substituted alkyl group.

In the preceding paper, it was demonstrated that the

(24) Gibson, M. S. *J. Chem. Soc.* **1956**, 1076.

(25) Katritzky, A. R.; Lan, X.; Lam, J. N. *Synthesis* **1990**, 341.










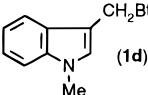
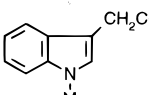
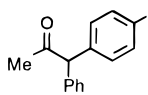

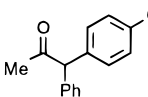
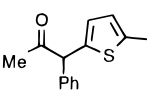

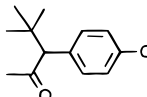

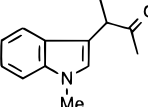
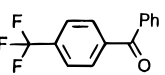
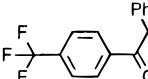
(26) Katritzky, A. R.; Xie, L.; Cundy, D. *Synth. Commun.* **1995**, *25*, 539.

(27) Katritzky, A. R.; Lan, X.; Lam, J. N. *Chem. Ber.* **1991**, *124*, 1819.

(28) Katritzky, A. R.; Xie, L. *J. Org. Chem.* **1995**, *60*, 3707.

(29) Hanson, J. R. (Section 3.1); Rickborn, B. (Section 3.2 and 3.3); Coveney, D. J. (Section 3.4) In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 3, p 705.

**Table 1. Arylmethylene and Heteroarylmethylene Insertions into Aldehydes and Acyclic Ketones: Preparation of One-Carbon Chain-Extended Ketones**

| entry | carbonyl compound   | Bt-reagent  | temp, °C/ time, h <sup>a</sup><br>/ solvent       | product  | yield <sup>b</sup><br>(%) |
|-------|---|---|---|--|---------------------------|
| 1     | PhCH <sub>2</sub> CH <sub>2</sub> CHO   | Me-  -CH <sub>2</sub> Bt (1a)  | 150 / 10 /<br>neat                                | Me-  -CH <sub>2</sub> COCH <sub>2</sub> CH <sub>2</sub> Ph (2a)      | 65                        |
| 2     | PhCH <sub>2</sub> CH <sub>2</sub> CHO   |  -CH <sub>2</sub> Bt (1b)      | 115 / 5 /<br>CHCl <sub>2</sub> CH <sub>2</sub> Cl |  -CH <sub>2</sub> COCH <sub>2</sub> CH <sub>2</sub> Ph (2b)          | 63                        |
| 3     | PhCH <sub>2</sub> CH <sub>2</sub> CHO   |  -CH <sub>2</sub> Bt (1c)      | 115 / 8 /<br>CHCl <sub>2</sub> CH <sub>2</sub> Cl |  -CH <sub>2</sub> COCH <sub>2</sub> CH <sub>2</sub> Ph (2c)          | 76                        |
| 4     |    | 1b  | 140 / 0.5 /<br>neat                               |  -CH <sub>2</sub> COC(Me) <sub>3</sub> (2d)                          | 76                        |
| 5     | PhCHO   | 1b  | 65 / 10 /<br>THF                                  |  -CH <sub>2</sub> COPh (2e)  | 40                        |
| 6     | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub> CHO                                       |  (1d)                          | 65 / 5 /<br>THF                                   |  -CH <sub>2</sub> COC <sub>6</sub> H <sub>4</sub> -Cl- <i>p</i> (2f) | 70                        |
| 7     | PhCOMe  | 1a  | 210 / 3 /<br>neat                                 |  (2g)  | 32                        |
| 8     | PhCOMe  | MeO-  -CH <sub>2</sub> Bt (1e) | 180 / 3 /<br>neat                                 |  (2h)  | 79                        |
| 9     | PhCOMe  | 1c  | 115 / 8 /<br>CHCl <sub>2</sub> CH <sub>2</sub> Cl |  (2i)  | 90                        |
| 10    |   | 1e  | 175 / 3 /<br>neat                                 |  (2j)   | 63                        |
| 11    |  | 1d  | 65 / 3 /<br>THF                                   |  (2k)  | 87                        |
| 12    |  | 1e  | 155 / 3 /<br>neat                                 |  (2l)  | 35                        |

<sup>a</sup>Conditions for the *in situ* rearrangement step. <sup>b</sup>Overall yield for the isolated pure product from carbonyl compound.

alkoxymethylene and (alkylthio)methylene insertions proceeded through the epoxide intermediates by successful isolation of the latter.<sup>23</sup> Epoxide intermediates seem unlikely in most of the present reactions, since in not one of the cases described in Tables 1 and 2 were any of the regioisomers **9** and **10** (Scheme 1) detected. If epoxides **6** were intermediates, formation of compounds **9** and **10** would be expected alongside insertion products **2** and **3**, especially in the cases of entries 7–9 and 12 of Table 1 where the corresponding tertiary cationic species **8** should be more stable than secondary cationic species **7**. However, the epoxide mechanism was implicated in one experiment as shown in Scheme 2. Treatment of the anion of 1-(4-methoxybenzyl)benzotriazole (**1e**) with *p*-tolualdehyde, followed by zinc bromide-assisted rearrangement, gave an inseparable mixture of ketones **2w** and **9w** together with aldehyde **10w** in the ratio of 3:1:12 in total 88% yield based on the NMR and GCMS results of the crude product. These results suggest that epoxide **6** is the intermediate (Scheme 1), which can open up from both sides to give cationic intermediates **7** and **8**. While **7** leads to the “normal” insertion product **2w**

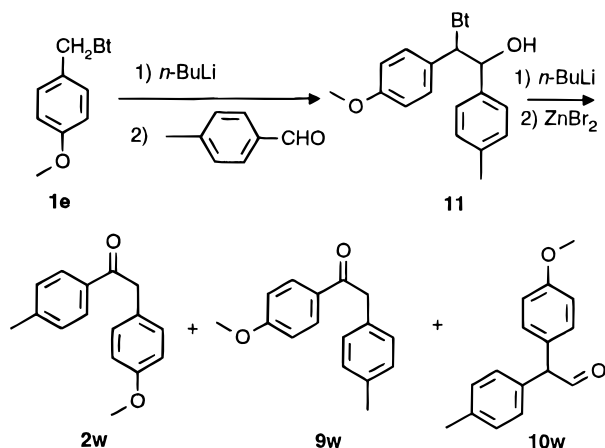
(*via* path a, hydride migration), subsequent hydride (path a) and 4-methoxyphenyl (path b) migrations of **8** furnish ketone **9w** and aldehyde **10w**. It is noteworthy that in this case the 4-methoxyphenyl group migrates preferentially over the hydrogen due to the existence of the electron-donating methoxy group, which reflects a significant substituent effect on the migration aptitude. The reason for the different behavior in the case of **1e** from all those in Tables 1 and 2 has not yet been fully clarified. However, the diastereoselectivity of the initial addition does not determine product structures since for the reaction described in Scheme 2 the same products were obtained in the same proportions when the two diastereoisomers of adduct intermediate **11** were isolated and treated with ZnBr<sub>2</sub> separately.

To explore further the generality of this insertion methodology, 1-(3-phenylallyl)benzotriazole (**1g**) was prepared from the reaction of cinnamyl bromide with benzotriazole in the presence of sodium ethoxide in ethanol in 52% yield. The scope of this methodology was thus extended to vinyl-substituted methylene insertions as exemplified by the successful preparation of 2-(2-phen-

**Table 2. Arylmethylene and Heteroarylmethylene Insertions into Cyclic Ketones: Preparation of One-Carbon Ring-Expanded Ketones**

| entry | carbonyl compound | Bt-reagent  | temp, °C/ time, h <sup>a</sup><br>/ solvent        | product | yield <sup>b</sup><br>(%) |
|-------|-------------------|---|--|---------|---------------------------|
| 1     |                   | MeO-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> Bt ( <b>1e</b> ) | 115 / 5 /<br>CHCl <sub>2</sub> CH <sub>2</sub> Cl  |         | 40                        |
| 2     |                   |   | 115 / 5 /<br>CHCl <sub>2</sub> CH <sub>2</sub> Cl  |         | 66                        |
| 3     |                   |   | 65 / 6 /<br>THF                                    |         | 76                        |
| 4     |                   |   | 140 / 1 /<br>neat                                  |         | 40                        |
| 5     |                   | Cl-C <sub>6</sub> H <sub>4</sub> -CH <sub>2</sub> Bt ( <b>1f</b> )  | 170 / 12 /<br>neat                                 |         | 85                        |
| 6     |                   | <b>1d</b>   | 65 / 10 /<br>THF                                   |         | 85                        |
| 7     |                   | <b>1c</b>   | 115 / 10 /<br>CHCl <sub>2</sub> CH <sub>2</sub> Cl |         | 67                        |
| 8     |                   | <b>1d</b>   | 65 / 10 /<br>THF                                   |         | 81 <sup>c</sup>           |
|       |                   |   |  |         | 3                         |
|       |                   |   |  |         |                           |
| 9     |                   | <b>1c</b>   | 115 / 10 /<br>CHCl <sub>2</sub> CH <sub>2</sub> Cl |         | 66 <sup>c</sup>           |
|       |                   |   |  |         | 16 <sup>d</sup>           |
| 10    |                   | Bt-CH=CH-Ph ( <b>1g</b> )   | 110 / 10 /<br>toluene                              |         | 60                        |

<sup>a</sup> Conditions for the *in situ* rearrangement step. <sup>b</sup> Overall yield for the isolated pure product from carbonyl compound. <sup>c</sup> Total yield of *cis* and *trans* isomers. <sup>d</sup> GC yield.

**Scheme 2**

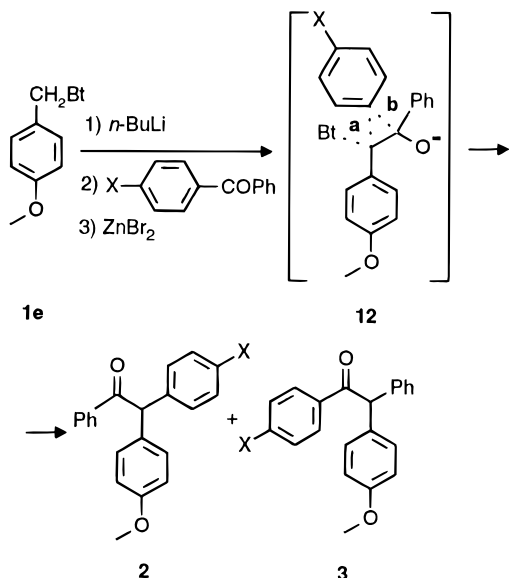
ylvinyl)cycloheptanone (**2v**) from 1-(3-phenylallyl)benzotriazole (**1g**) and cyclohexanone (Table 2, entry 10). However, a stabilizing group such as phenyl at the vinylic

terminal to assist the departure of the benzotriazolyl group in **5** (Scheme 1) was found to be essential since the simple allyl analog 1-allylbenzotriazole failed to give homologation products: even at 220 °C for 10 h, the intermediate **5** was still present, while higher temperatures caused tar formation. Vinyl-substituted methylene homologations of ketones have previously been accomplished by direct insertion of the corresponding diazo compounds<sup>2</sup> and a rather complex radical process.<sup>18</sup>

**Substituent Effects on Relative Migration Rates.**

To gain insight into the mechanism of this reaction, we examined the electronic effects of the substituents on the transition state. 1-(4-Methoxybenzyl)benzotriazole (**1e**) was used for insertion into a series of *p*-substituted benzophenones according to our methodology (Scheme 3). The reaction conditions were the ones used for the synthesis of **2l** (Table 1, entry 12), *i.e.*, heating at 155 °C for 3 h without solvent. Under these conditions, solvent and steric influences upon variation in the migration rates are minimized. The crude mixture of products was

Scheme 3



analyzed by GCMS, and the identities of the two products **2** and **3** were assigned according to their fragmentation patterns: a peak at *m/z* 105 was diagnostic for the product containing an unsubstituted benzoyl group. The migration ratio of substituted phenyl to give product **2** and of unsubstituted phenyl to form product **3** was calculated. This ratio represents the relative migration aptitude of a substituted phenyl free of steric and solvent effects. The data are presented in Table 3. When  $\log(k_X/k_H)$  was plotted against the corresponding  $\sigma$  and  $\sigma^+$  values,<sup>30</sup> the corresponding  $\rho$  and  $\rho^+$  values were obtained (Table 3). The linear correlation is better for  $\rho^+$  (correlation coefficient 0.982) than for  $\rho$  (correlation coefficient 0.931). The negative value for the selectivity parameter ( $\rho^+$ ) signifies that electron-donating substituents accelerate the migration rate and suggests that bond making (of bond **a**) is further advanced in the transition state **12** than bond breaking (of bond **b**) (see Scheme 3). A correlation is with  $\sigma^+$  rather than with  $\sigma$ , indicating that conjugative electronic interaction in the transition state between ring substituent and the cationic center dominates over field effects. The small  $|\rho^+|$  value indicates (i) an early, reagent-like transition state,<sup>31</sup> similar to a phenonium ion where  $\beta$ -aryl group assists leaving of the benzotriazole,<sup>32</sup> and (ii) a small contribution from cationic structures of types **8** to the transition state (Scheme 1) since if **8** was important, the  $|\rho^+|$  value should have been much higher (higher than 3) due to strong interaction between the C<sub>α</sub> carbocation and the substituent.

Thus, the Hammett correlation implicates an early reagent-like transition state with cationic character for this process.

### Conclusion

Various 1-(arylmethyl)- and 1-(heteroarylmethyl)benzotriazoles are excellent insertion reagents for the transformations of aldehydes and ketones into one-carbon chain-extended or ring-expanded  $\alpha$ -aryl- and  $\alpha$ -heteroaryl-substituted ketones. Advantages of this methodology include wide generality, excellent regioselectivity

in many cases, ready availability of starting materials, and simple one-pot procedures.

### Experimental Section

**General Procedures.** Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were taken in CDCl<sub>3</sub> with tetramethylsilane as the internal standard for <sup>1</sup>H (300 MHz) or solvent as the internal standard for <sup>13</sup>C (75 MHz). Tetrahydrofuran was distilled under nitrogen immediately prior to use from sodium/benzophenone. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230–400 mesh. 1-(4-Methylbenzyl)benzotriazole (**1a**),<sup>24</sup> 1-[4-(*N,N*-dimethylamino)benzyl]benzotriazole (**1b**),<sup>25</sup> 1-[(1-methylindol-3-yl)methyl]benzotriazole (**1d**),<sup>26</sup> and 1-(4-methoxybenzyl)benzotriazole (**1e**)<sup>27</sup> were prepared according to previously reported procedures.

**Preparation of 5-Methyl-2-(benzotriazol-1-ylmethyl)-thiophene (1c).** A mixture of (hydroxymethyl)benzotriazole (4.5 g, 30 mmol) and 2-methylthiophene (3.4 g, 35 mmol) in glacial acetic acid (50 mL) was refluxed for 48 h. After the acetic acid was distilled off under reduced pressure, aqueous sodium hydroxide (5%, 30 mL) and chloroform (50 mL) were added. The organic layer was separated, washed with water (50 mL), and dried (MgSO<sub>4</sub>). After the solvent was removed, the residue was crystallized from methylene chloride and hexanes to give the pure product as a brownish solid (3.4 g, 50%): mp 108–109 °C; <sup>1</sup>H NMR  $\delta$  2.40 (s, 3 H), 5.92 (s, 2 H), 6.60 (d, *J* = 3.4 Hz, 1 H), 6.90 (d, *J* = 3.4 Hz, 1 H), 7.35 (dd, *J*<sub>1</sub> = *J*<sub>2</sub> = 6.7 Hz, 1 H), 7.46 (m, 2 H), 8.05 (d, *J* = 8.3 Hz, 1 H); <sup>13</sup>C NMR  $\delta$  15.4, 47.2, 109.6, 120.0, 123.8, 125.0, 127.3, 127.4, 132.3, 134.0, 141.3, 146.2. Anal. Calcd for C<sub>12</sub>H<sub>11</sub>N<sub>3</sub>S: C, 62.86; H, 4.84; N, 18.33. Found: C, 62.52; H, 4.79; N, 18.33.

**Preparation of 1-(4-Chlorobenzyl)benzotriazole (1f).** A solution of benzotriazole (23.8 g, 200 mmol) and 4-chlorobenzyl chloride (22.5 g, 140 mmol) in toluene (200 mL) was refluxed for 48 h. After being cooled to room temperature, the solution was washed with aqueous sodium hydroxide (5%, 2 × 100 mL) and water (100 mL) to remove excess benzotriazole. The toluene solution was then extracted with cold hydrochloric acid (25%, 5 × 50 mL) to allow complete extraction of the product into the aqueous layer. To the combined aqueous extract was added water (500 mL), and the solution was then extracted with benzene (3 × 100 mL). The combined benzene solution was washed with water (2 × 50 mL) and dried (MgSO<sub>4</sub>). After the solvent was removed, the residue was crystallized from methanol to give a white solid (22.5 g, 66%): mp 101–102 °C (lit.<sup>33</sup> mp 90 °C); <sup>1</sup>H NMR  $\delta$  5.78 (s, 2 H), 7.18 (d, *J* = 8.3 Hz, 2 H), 7.27 (d, *J* = 8.3 Hz, 2 H), 7.33–7.42 (m, 3 H), 8.04 (d, *J* = 8.0 Hz, 1 H); <sup>13</sup>C NMR  $\delta$  51.2, 109.4, 119.8, 123.9, 127.4, 128.8, 129.0, 132.5, 133.1, 134.2, 146.1. Anal. Calcd for C<sub>13</sub>H<sub>10</sub>ClN<sub>3</sub>: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.02; H, 3.88; N, 17.36.

**Preparation of (E)-3-(Benzotriazol-1-yl)-1-phenyl-1-propene (1g).** To a solution of sodium ethoxide prepared from sodium metal (2.3 g, 100 mmol) in ethanol (200 mL) were added benzotriazole (13.1 g, 110 mmol) and cinnamyl bromide (19.7 g, 100 mmol). The mixture was refluxed overnight. After the ethanol was removed, benzene (200 mL) was added, and the solution was washed with aqueous sodium hydroxide (5%, 2 × 100 mL) and water (100 mL) to remove excess benzotriazole. The benzene solution was then extracted with cold hydrochloric acid (25%, 3 × 100 mL) to allow complete extraction of the product into the aqueous solution. To the combined aqueous extract was added water (500 mL), and the solution was then extracted with benzene (3 × 100 mL). The combined benzene solution was washed with water (2 × 50 mL) and dried (MgSO<sub>4</sub>). Removal of the solvent gave white prisms (12.2 g, 52%): mp 79 °C (lit.<sup>34</sup> mp 75–76 °C); <sup>1</sup>H NMR  $\delta$  5.37 (dd, *J* = 6.2, 1.4 Hz, 2 H), 6.34 (dt, *J* = 15.8, 6.2 Hz, 1 H), 6.62 (dt, *J* = 15.8, 1.4 Hz, 1 H), 7.21–7.35 (m, 6 H), 7.41

(30) Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

(31) Ruasse, M.-F.; Dubois, J.-E. *J. Am. Chem. Soc.* **1984**, *106*, 3230.

(32) Lancelot, C. J.; Cram, D. J.; Schleyer, P. v. R. Phenonium Ions. in *Carbonium Ions*; Olah, G. A., Schleyer, P. v. R., Eds.; Wiley: New York, 1972; Vol. III.

(33) Kreutzberger, A.; Stratmann, J. *Arch. Pharm. (Weinheim)* **1979**, *312*, 806.

(34) Arnau, N.; Arredondo, Y.; Moreno-Manas, M.; Pleixats, R.; Villarroya, M. *J. Heterocycl. Chem.* **1995**, *32*, 1325.

Table 3. Hammett Correlations

| X               | <i>p</i> -OCH <sub>3</sub> | <i>p</i> -CH <sub>3</sub> | <i>p</i> -F | <i>p</i> -H                             | <i>p</i> -Cl | <i>p</i> -Br | <i>p</i> -CF <sub>3</sub> |
|-----------------|----------------------------|---------------------------|-------------|---|--------------|--------------|---------------------------|
| $k_X/k_H$       | 5.75                       | 2.45                      | 1.24        | 1                                       | 0.74         | 0.59         | 0.37                      |
| $\log(k_X/k_H)$ | 0.760                      | 0.389                     | 0.093       | 0                                       | -0.131       | -0.229       | -0.432                    |
| $\rho^+(r)$     |                            |                           |             | -0.92 <sup>a</sup> (0.982) <sup>b</sup> |              |              |                           |
| $\rho(r)$       |                            |                           |             | -1.34 <sup>c</sup> (0.931) <sup>b</sup> |              |              |                           |

<sup>a</sup>  $\log(k_X/k_H)$  plotted against  $\sigma^+$  for  $\rho^+$ . Constants were taken from ref 30. <sup>b</sup> Correlation coefficient. <sup>c</sup>  $\log(k_X/k_H)$  plotted against  $\sigma$  for  $\rho$ .

(td,  $J = 8.3, 1.0$  Hz, 1 H), 7.52 (dd,  $J = 8.3, 1.0$  Hz, 1 H), 8.05 (dd,  $J = 8.3, 1.0$  Hz, 1 H); <sup>13</sup>C NMR  $\delta$  50.3, 109.6, 119.8, 122.0, 123.7, 126.4, 127.1, 128.1, 128.5, 132.7, 134.2, 135.4, 146.1. Anal. Calcd for C<sub>15</sub>H<sub>13</sub>N<sub>3</sub>: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.52; H, 5.55; N, 17.90.

**General Procedure for the Insertions into Aldehydes and Ketones: Preparation of  $\alpha$ -Aryl- and  $\alpha$ -Heteroaryl-Substituted Ketones 2a–u, 3t, and 2-((*E*)-2-Phenylethen-yl)cycloheptanone (2v).** To a solution of an appropriate benzotriazole derivative (5 mmol) in THF (50 mL) at  $-78^\circ\text{C}$  under argon was added *n*-BuLi (2 M, 2.8 mL, 5.5 mmol). After 30 min, a solution of an appropriate aldehyde or ketone (5.5 mmol) in THF (10 mL) was added. The mixture was stirred at  $-78^\circ\text{C}$  for an additional 4 h and allowed to warm to room temperature overnight. A solution of zinc bromide (15 mmol) in THF (15 mL) was then added. As indicated in Table 1, (i) the mixture was refluxed in THF (for entries 5, 6, and 11 in Table 1 and entries 3, 6 and 8 in Table 2), (ii) the THF was removed, an appropriate solvent (15 mL) added, and the mixture refluxed (for entries 2, 3, and 9 in Table 1 and entries 1, 2, 7, 9, and 10 in Table 2), or (iii) the THF was removed and the residue was heated at an appropriate temperature (for entries 1, 4, 7, 8, 10, and 12 in Table 1, 4, and 5 in Table 2). Ethyl acetate (150 mL) and diethyl ether (100 mL) were added to the residue, and the mixture was stirred for 1 h at room temperature. The solid was filtered off, and the solution was washed with water (2  $\times$  100 mL) and dried (MgSO<sub>4</sub>). After the solvent was removed, the residue was subjected to column chromatography to give the pure product.

**1-(4-Methylphenyl)-4-phenyl-2-butanone (2a).** Hexanes: diethyl ether (3:1) was used as the eluent to give a white solid: mp 65–66  $^\circ\text{C}$ ; <sup>1</sup>H NMR  $\delta$  2.31 (s, 3 H), 2.70–2.76 (m, 2 H), 2.81–2.87 (m, 2 H), 3.59 (s, 2 H), 7.01–7.26 (m, 9 H); <sup>13</sup>C NMR  $\delta$  21.0, 29.7, 43.3, 49.9, 126.0, 128.2, 128.4, 129.2, 129.4, 131.0, 136.5, 140.9, 207.5. Anal. Calcd for C<sub>17</sub>H<sub>18</sub>O: C, 85.67; H, 7.61. Found: C, 86.00; H, 7.74.

**1-[4-(*N,N*-Dimethylamino)phenyl]-4-phenyl-2-butanone (2b).** Hexanes:diethyl ether (3:1) was used as the eluent to give a white solid: mp 42–43  $^\circ\text{C}$ ; <sup>1</sup>H NMR  $\delta$  2.71 (t,  $J = 8.0$  Hz, 2H), 2.83 (t,  $J = 8.0$  Hz, 2H), 2.89 (s, 6H), 3.52 (s, 2H), 6.65 (d,  $J = 8.6$  Hz, 2H), 7.01 (d,  $J = 8.6$  Hz, 2H), 7.08–7.24 (m, 5H); <sup>13</sup>C NMR  $\delta$  29.7, 40.4, 42.9, 49.4, 112.8, 121.7, 125.8, 128.2, 128.3, 129.8, 141.0, 149.5, 208.2. Anal. Calcd for C<sub>18</sub>H<sub>21</sub>NO: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.11; H, 8.09; N, 4.94.

**1-(5-Methylthien-2-yl)-4-phenyl-2-butanone (2c).** Hexanes:diethyl ether (2:1) was used as the eluent to give a white solid: mp 43–44  $^\circ\text{C}$ ; <sup>1</sup>H NMR  $\delta$  2.42 (s, 3H), 2.65–2.92 (m, 4H), 3.73 (s, 2H), 6.57–6.59 (m, 2H), 7.12–7.25 (m, 5H); <sup>13</sup>C NMR  $\delta$  15.2, 29.7, 43.0, 44.0, 125.0, 126.0, 126.6, 128.2, 128.4, 132.7, 139.5, 140.8, 206.0. Anal. Calcd for C<sub>15</sub>H<sub>16</sub>OS: C, 73.73; H, 6.60. Found: C, 73.88; H, 6.64.

**1-[4-(*N,N*-Dimethylamino)phenyl]-3,3-dimethyl-2-butanone (2d).** Hexanes:diethyl ether (3:1) was used as the eluent to give a white solid: mp 34–36  $^\circ\text{C}$ ; <sup>1</sup>H NMR  $\delta$  1.17 (s, 9H), 2.89 (s, 6H), 3.68 (s, 2H), 6.68 (d,  $J = 8.8$  Hz, 2H), 7.04 (d,  $J = 8.8$  Hz, 2H); <sup>13</sup>C NMR  $\delta$  26.4, 40.6, 42.3, 44.4, 112.7, 122.7, 130.0, 149.4, 213.4. Anal. Calcd for C<sub>14</sub>H<sub>21</sub>NO: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.26; H, 9.72; N, 6.36.

**1-Phenyl-2-[4-(*N,N*-dimethylamino)phenyl]ethanone (2e).** Hexanes:diethyl ether (1:1) was used as the eluent to give a white solid: mp 119–120  $^\circ\text{C}$  (lit.<sup>35</sup> mp 128  $^\circ\text{C}$ ); <sup>1</sup>H NMR  $\delta$  2.88 (s, 6H), 4.15 (s, 2H), 6.67 (d,  $J = 7.0$  Hz, 2H), 7.12 (d,  $J = 7.0$  Hz, 2H), 7.37–7.52 (m, 3H), 7.99 (d,  $J = 8.6$  Hz, 2H); <sup>13</sup>C NMR  $\delta$  40.5, 44.5, 112.8, 122.1, 128.4, 128.5, 129.9, 132.8,

136.6, 149.5, 198.1. Anal. Calcd for C<sub>16</sub>H<sub>17</sub>NO: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.59; H, 7.19; N, 5.75.

**1-(4-Chlorophenyl)-2-(1-methylindol-3-yl)ethanone (2f).** Hexanes:ethyl acetate (2:1) was used as the eluent to give a white powder: mp 114–115  $^\circ\text{C}$ ; <sup>1</sup>H NMR  $\delta$  3.68 (s, 3H), 4.32 (s, 2 H), 6.93 (s, 1H), 7.13 (t,  $J = 7.9$  Hz, 1H), 7.23 (m, 2H), 7.36 (d,  $J = 6.8$  Hz, 2H), 7.57 (d,  $J = 7.9$  Hz, 1H), 7.95 (d,  $J = 6.8$  Hz, 2H); <sup>13</sup>C NMR  $\delta$  32.6, 35.5, 106.9, 109.3, 118.7, 119.2, 121.8, 127.6, 127.7, 128.8, 130.0, 134.9, 136.9, 139.3, 196.5. Anal. Calcd for C<sub>17</sub>H<sub>14</sub>ClNO: C, 71.96; H, 4.97; N, 4.94. Found: C, 71.63; H, 4.91; N, 4.79.

**1-(4-Methylphenyl)-1-phenyl-2-propanone (2g).** Hexanes:diethyl ether (3:1) was used as the eluent to give a colorless oil (lit.<sup>36</sup> bp 143–148  $^\circ\text{C}/0.25\text{mm}$ ): <sup>1</sup>H NMR  $\delta$  2.19 (s, 3H), 2.29 (s, 3H), 5.06 (s, 1H), 7.11 (m, 4H), 7.19–7.31 (m, 5H); <sup>13</sup>C NMR  $\delta$  20.9, 29.8, 64.5, 127.0, 128.5, 128.7, 128.8, 129.3, 135.2, 136.8, 138.4, 206.5; HRMS calcd for C<sub>16</sub>H<sub>16</sub>O 224.1201, found 224.1211.

**1-(4-Methoxyphenyl)-1-phenyl-2-propanone (2h).** Hexanes:diethyl ether (3:1) was used as the eluent to give a colorless oil (lit.<sup>37</sup> bp 225  $^\circ\text{C}/25\text{mm}$ ): <sup>1</sup>H NMR  $\delta$  2.20 (s, 3H), 3.75 (s, 3H), 5.05 (s, 1H), 6.85 (d,  $J = 8.8$  Hz, 2H), 7.13 (d,  $J = 8.8$  Hz, 2H), 7.19–7.31 (m, 5H); <sup>13</sup>C NMR  $\delta$  29.8, 55.1, 64.1, 114.0, 127.0, 128.6, 128.8, 129.9, 130.3, 138.6, 158.7, 206.6; HRMS calcd for C<sub>16</sub>H<sub>16</sub>O<sub>2</sub> 241.1229 (M + 1), found 241.1227.

**1-(5-Methylthien-2-yl)-1-phenyl-2-propanone (2i).** Hexanes:diethyl ether (2:1) was used as the eluent to give a colorless oil: <sup>1</sup>H NMR  $\delta$  2.19 (s, 3H), 2.39 (s, 3H), 5.17 (s, 1H), 6.56–6.57 (m, 1H), 6.61–6.63 (m, 1H), 7.26–7.31 (m, 5H); <sup>13</sup>C NMR  $\delta$  15.1, 29.0, 59.9, 124.5, 126.0, 127.4, 128.4, 128.7, 138.1, 138.2, 139.6, 204.7. Anal. Calcd for C<sub>14</sub>H<sub>14</sub>OS: C, 73.01; H, 6.13. Found: C, 72.83; H, 6.17.

**3-(4-Methoxyphenyl)-4,4-dimethyl-2-pentanone (2j).** Hexanes:diethyl ether (3:1) was used as the eluent to give a colorless oil: <sup>1</sup>H NMR  $\delta$  0.97 (s, 9H), 2.06 (s, 3H), 3.54 (s, 1H), 3.79 (s, 3H), 6.84 (d,  $J = 8.8$  Hz, 2H), 7.17 (d,  $J = 8.8$  Hz, 2H); <sup>13</sup>C NMR  $\delta$  27.8, 32.3, 34.3, 55.1, 67.1, 113.4, 127.9, 131.3, 158.7, 209.1; HRMS calcd for C<sub>14</sub>H<sub>20</sub>O<sub>2</sub> 221.1542 (M + 1), found 221.1541.

**4,4-Dimethyl-3-(1-methylindol-3-yl)-2-pentanone (2k).** Hexanes:diethyl ether (3:1) was used as the eluent to give a white solid: mp 65  $^\circ\text{C}$ ; <sup>1</sup>H NMR  $\delta$  1.04 (s, 9 H), 2.10 (s, 3H), 3.73 (s, 3H), 3.96 (s, 1H), 6.99 (s, 1H), 7.12 (dd,  $J_1 = J_2 = 8.0$  Hz, 1H), 7.21 (dd,  $J_1 = J_2 = 8.0$  Hz, 1H), 7.28 (d,  $J = 8.0$  Hz, 1H), 7.65 (d,  $J = 8.0$  Hz, 1H); <sup>13</sup>C NMR  $\delta$  28.1, 32.5, 32.7, 34.9, 58.1, 109.0, 109.2, 119.0, 119.1, 121.4, 128.8, 129.0, 136.6, 209.7. Anal. Calcd for C<sub>16</sub>H<sub>21</sub>NO: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.96; H, 8.91; N, 5.53.

**1-[4-(Trifluoromethyl)phenyl]-2-(4-methoxyphenyl)-phenylethanone (2l).** Hexanes:diethyl ether (4:1) was used as the eluent to give colorless prisms: mp 84–85  $^\circ\text{C}$ ; <sup>1</sup>H NMR  $\delta$  3.75 (s, 3H), 5.95 (s, 1H), 6.86 (d,  $J = 8.8$  Hz, 2H), 7.18 (d,  $J = 8.8$  Hz, 2H), 7.22–7.35 (m, 5H), 7.64 (d,  $J = 8.0$  Hz, 2H), 8.07 (d,  $J = 8.0$  Hz, 2H); <sup>13</sup>C NMR  $\delta$  55.2, 59.1, 114.3, 123.5 (q,  $J = 271.0$  Hz), 125.6 (q,  $J = 4.8$  Hz), 127.3, 128.8, 129.8, 129.2, 130.1, 130.4, 134.1 (q,  $J = 32.6$  Hz), 138.8, 139.5, 158.9, 197.5. Anal. Calcd for C<sub>22</sub>H<sub>17</sub>OF<sub>3</sub>: C, 71.35; H, 4.63. Found: C, 71.22; H, 4.47.

**2-(4-Methoxyphenyl)cycloheptanone (2m).** Hexanes: diethyl ether (3:1) was used as the eluent to give colorless plates: mp 59–60  $^\circ\text{C}$  (from petroleum ether) (lit.<sup>38</sup> mp 59–60

(36) Gragoe, E. J., Jr.; Pietruszkiewicz, A. M.; Robb, C. M. *J. Org. Chem.* **1958**, *23*, 971.

(37) Levy, J.; Gallais, P.; Agram, D. *Bull. Chem. Soc. Fr.* **1928**, *43*, 868.

(38) Gutsche, C. D.; Strohmayer, H. F.; Chang, J. M. *J. Org. Chem.* **1958**, *23*, 1.

(35) Jenkins, S. S.; Buck, J. S.; Bigelow, L. A. *J. Am. Chem. Soc.* **1930**, *52*, 4495.

°C);  $^1\text{H}$  NMR  $\delta$  1.39–1.64 (m, 3H), 1.89–2.15 (m, 5H), 2.44–2.52 (m, 1H), 2.61–2.71 (m, 1H), 3.65 (dd,  $J$  = 11.3, 4.1 Hz, 1H), 3.77 (s, 3H), 6.85 (d,  $J$  = 8.8 Hz, 2H), 7.14 (d,  $J$  = 8.4 Hz, 2H);  $^{13}\text{C}$  NMR  $\delta$  25.3, 28.4, 29.9, 31.9, 42.3, 55.1, 57.8, 113.8, 128.7, 132.3, 158.4, 213.6.

**2-(5-Methylthien-2-yl)cycloheptanone (2n).** Hexanes: diethyl ether (3:1) was used as the eluent to give a colorless oil:  $^1\text{H}$  NMR  $\delta$  1.27–1.62 (m, 3H), 1.78–2.10 (m, 4H), 2.15–2.30 (m, 1H), 2.41 (s, 3H), 2.42–2.50 (m, 1H), 2.65–2.73 (m, 1H), 3.85 (dd,  $J$  = 11.1, 4.7 Hz, 1H), 6.58 (d,  $J$  = 3.5 Hz, 1H), 6.65 (d,  $J$  = 3.5 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  15.1, 25.5, 27.8, 29.8, 32.6, 41.2, 54.2, 124.1, 124.6, 138.6, 139.8, 211.6. Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{OS}$ : C, 69.19; H, 7.74. Found: C, 69.33; H, 7.88.

**2-(1-Methylindol-3-yl)cycloheptanone (2o).** Hexanes: ethyl acetate (2:1) was used as the eluent to give a colorless oil:  $^1\text{H}$  NMR  $\delta$  1.43–1.50 (m, 2H), 1.55–1.72 (m, 1H), 1.92–2.04 (m, 4H), 2.24–2.35 (m, 1H), 2.38–2.45 (m, 1H), 2.70–2.79 (m, 1H), 3.73 (s, 3H), 4.04 (dd,  $J$  = 11.3, 4.7 Hz, 1H), 7.00 (s, 1H), 7.11 (t,  $J$  = 8.0 Hz, 1H), 7.19–7.28 (m, 2H), 7.67 (d,  $J$  = 9.9 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  25.6, 28.1, 30.0, 31.3, 32.6, 41.2, 50.4, 109.1, 113.3, 119.0, 119.5, 121.7, 126.2, 127.1, 136.9, 213.1. Anal. Calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}$ : C, 79.63; H, 7.94; N, 5.80. Found: C, 79.27; H, 8.03; N, 5.92.

**2-[4-(*N,N*-Dimethylamino)phenyl]cycloheptanone (2p).** Hexanes: diethyl ether (1:1) was used as the eluent to give a yellowish solid: mp 70–72 °C;  $^1\text{H}$  NMR  $\delta$  1.36–1.60 (m, 3H), 1.85–2.15 (m, 5H), 2.39–2.46 (m, 1H), 2.63–2.72 (m, 1H), 2.90 (s, 6H), 3.59 (dd,  $J$  = 11.3, 4.2 Hz, 1H), 6.68 (d,  $J$  = 8.5 Hz, 2H), 7.11 (d,  $J$  = 8.5 Hz, 2H);  $^{13}\text{C}$  NMR  $\delta$  25.6, 28.1, 30.1, 31.5, 40.5, 42.0, 57.9, 112.7, 127.8, 128.2, 149.5, 213.8. Anal. Calcd for  $\text{C}_{15}\text{H}_{21}\text{NO}$ : C, 77.88; H, 9.15; N, 6.05. Found: C, 77.63; H, 9.32; N, 5.80.

**2-(4-Chlorophenyl)cyclohexanone (2q).** Hexanes: diethyl ether (3:1) was used as the eluent to give white plates: mp 81–82 °C (lit.<sup>38</sup> mp 77–78 °C);  $^1\text{H}$  NMR  $\delta$  1.77–2.50 (m, 8H), 3.57 (dd,  $J$  = 11.9, 5.4 Hz, 1H), 7.05 (d,  $J$  = 8.5 Hz, 2H), 7.28 (d,  $J$  = 8.5 Hz, 2H);  $^{13}\text{C}$  NMR  $\delta$  25.3, 27.7, 35.2, 42.1, 56.7, 128.4, 129.9, 132.6, 137.2, 209.6. Anal. Calcd for  $\text{C}_{12}\text{H}_{13}\text{OCl}$ : C, 69.07; H, 6.28. Found: C, 68.91; H, 6.25.

**2-(1-Methylindol-3-yl)-3-methylcyclohexanone (2r).** Hexanes: diethyl ether (4:1) was used as the eluent to give a colorless thick oil as a mixture of *cis* and *trans* isomers in a ratio of 1.35:1 (signals for *trans* isomer in square brackets):  $^1\text{H}$  NMR  $\delta$  0.81 [0.87] (d,  $J$  = 7.1 [7.2] Hz, 3H), 1.83–2.58 (m, 7H), 3.70 [3.73] (s, 3H), 4.25 [3.45] (d,  $J$  = 4.8 [11.2] Hz, 1H), 6.86 [7.35] (s, 1H), 7.04–7.28 (m, 3H), 7.53 [7.40] (d,  $J$  = 7.8 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  15.3 [21.5], 23.7 [25.9], 31.2 [29.6], 34.2 [32.6], 38.1 [40.6], 41.1 [41.6], 52.6 [56.0], 109.0 [109.2], 110.5, 118.5 [118.6], 119.4, 121.2 [121.3], 127.9 [127.5], 128.0, 136.1 [136.9], 210.6 [210.5]; HRMS calcd for  $\text{C}_{16}\text{H}_{19}\text{NO}$  242.1545 ( $M$  + 1), found 242.1517.

**2-(5-Methylthien-2-yl)-3-methylcyclohexanone (2s).** Hexanes: diethyl ether (10:1) was used as the eluent to give a colorless oil in *trans* form:  $^1\text{H}$  NMR  $\delta$  0.94 (d,  $J$  = 6.2 Hz, 3H), 1.55–2.13 (m, 5H), 2.34–2.56 (m, 2H), 2.46 (s, 3H), 3.44 (d,  $J$  = 7.8 Hz, 1H), 6.55 (d,  $J$  = 3.3 Hz, 1H), 6.60 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  15.2, 21.1, 25.6, 33.9, 41.4, 41.7, 59.8, 124.4, 125.9, 137.4, 138.8, 208.8; HRMS calcd for  $\text{C}_{12}\text{H}_{16}\text{OS}$  209.1000 ( $M$  + 1), found 209.1018.

**3-Methyl-2-(1-methylindol-3-yl)cycloheptanone (2t) and 2-Methyl-7-(1-methylindol-3-yl)cycloheptanone (3t).** Hexanes: ethyl acetate (20:1) was used as the eluent to give pure *cis*- and *trans*-2t and *trans*-3t. *cis*-2t: yellowish oil, yield (68%);  $^1\text{H}$  NMR  $\delta$  0.87 (d,  $J$  = 7.2 Hz, 3H), 1.50–1.64 (m, 1H), 1.83–2.00 (m, 5H), 2.33–2.50 (m, 2H), 2.68 (dt,  $J$  = 17.2, 4.9 Hz, 1H), 3.78 (s, 3H), 4.56 (d,  $J$  = 2.5 Hz, 1H), 7.06–7.12 (m, 1H), 7.18–7.31 (m, 2H), 7.43 (s, 1H), 7.46 (d,  $J$  = 7.9 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  15.3, 24.1, 24.3, 32.6, 35.7, 37.0, 44.4, 51.7, 109.1, 111.9, 118.1, 118.6, 121.3, 127.6, 127.8, 136.2, 212.5. Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}$ : C, 79.96; H, 8.29; N, 5.49. Found: C, 79.77; H, 8.47; N, 5.26. *trans*-2t: white plates; mp 86–87 °C; yield (13%);  $^1\text{H}$  NMR  $\delta$  1.00 (d,  $J$  = 6.7 Hz, 3H), 1.32–1.67 (m, 3H), 1.80–2.02 (m, 3H), 2.14–2.26 (m, 2H), 2.78–2.86 (m, 1H), 3.58 (d,  $J$  = 10.5 Hz, 1H), 3.77 (s, 3H), 7.04 (s, 1H), 7.10–7.15 (m, 1H), 7.19–7.29 (m, 2H), 7.72 (dd,  $J$  = 7.7, 1.2 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  21.7, 27.5, 29.6, 32.8, 36.1, 36.6, 40.1, 59.0, 109.1, 112.0, 119.2, 119.8, 121.9, 126.0, 127.8, 137.0, 212.1. Anal. Calcd

for  $\text{C}_{17}\text{H}_{21}\text{NO}$ : C, 79.96; H, 8.29; N, 5.49. Found: C, 79.98; H, 8.47; N, 5.40. *trans*-3t: white plates; mp 83–84 °C; yield (3%);  $^1\text{H}$  NMR  $\delta$  1.11 (d,  $J$  = 6.7 Hz, 3H), 1.42–1.92 (m, 6H), 2.02–2.21 (m, 2H), 2.91–3.00 (m, 1H), 3.76 (s, 3H), 4.32 (dd,  $J$  = 9.7, 4.2 Hz, 1H), 7.06–7.11 (m, 1H), 7.16 (s, 1H), 7.17–7.30 (m, 2H), 7.48 (d,  $J$  = 7.9 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  16.3, 25.4, 28.2, 32.5, 32.7, 33.2, 46.0, 47.9, 109.2, 113.9, 118.5, 118.7, 121.4, 127.0, 127.2, 136.6, 214.9. Anal. Calcd for  $\text{C}_{17}\text{H}_{21}\text{NO}$ : C, 79.96; H, 8.29; N, 5.49. Found: C, 79.56; H, 8.61; N, 5.29.

**3-Methyl-2-(5-methylthien-2-yl)cycloheptanone (2u).** Hexanes: diethyl ether (10:1) was used as the eluent to give pure *cis* and *trans* isomers. *cis* Isomer: colorless oil; yield (55%);  $^1\text{H}$  NMR  $\delta$  0.92 (d,  $J$  = 7.2 Hz, 3H), 1.50–1.65 (m, 1H), 1.72–1.90 (m, 5H), 2.25–2.35 (m, 1H), 2.40–2.50 (m, 1H), 2.45 (s, 3H), 2.65 (dt,  $J$  = 17.2, 5.0 Hz, 1H), 4.35 (d,  $J$  = 2.8 Hz, 1H), 6.58–6.60 (m, 1H), 6.68 (d,  $J$  = 3.6 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  15.0, 16.2, 23.8, 24.8, 36.2, 37.0, 43.5, 56.8, 123.8, 125.4, 138.5–(2C), 210.7; HRMS calcd for  $\text{C}_{13}\text{H}_{18}\text{OS}$  222.1078, found 222.1074. *trans* Isomer: colorless oil; yield (11%);  $^1\text{H}$  NMR  $\delta$  0.98 (d,  $J$  = 6.7 Hz, 3H), 1.26–1.31 (m, 1H), 1.51–1.58 (m, 2H), 1.77–2.03 (m, 4H), 2.30–2.36 (m, 1H), 2.43 (s, 3H), 2.77–2.85 (m, 1H), 3.40 (d,  $J$  = 10.7 Hz, 1H), 6.69 (m, 1H), 6.70 (d,  $J$  = 3.3 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  15.2, 21.4, 27.2, 29.2, 36.4, 37.9, 40.4, 62.9, 124.9, 125.1, 138.6, 138.8, 211.1. Anal. Calcd for  $\text{C}_{13}\text{H}_{18}\text{OS}$ : C, 70.23; H, 8.16. Found: C, 70.11; H, 8.41.

**2-((*E*)-2-Phenylethenyl)cycloheptanone (2v).** Hexanes: diethyl ether (6:1) was used as the eluent to give a colorless oil:  $^1\text{H}$  NMR  $\delta$  1.37–1.99 (m, 8H), 2.49–2.56 (m, 2H), 3.28–3.35 (m, 1H), 6.30 (dd,  $J$  = 16.0, 7.1 Hz, 1H), 6.40 (d,  $J$  = 16.0 Hz, 1H), 7.19–7.35 (m, 5H);  $^{13}\text{C}$  NMR  $\delta$  24.7, 27.8, 29.5, 31.4, 42.3, 56.1, 126.1, 127.2, 128.4, 128.5, 130.7, 137.0, 213.4. Anal. Calcd for  $\text{C}_{15}\text{H}_{18}\text{O}$ : C, 84.07; H, 8.47. Found: C, 83.90; H, 8.54.

**Preparation of 2-(Benzotriazol-1-yl)-2-(4-methoxyphenyl)-1-(4-methylphenyl)ethanol (11).** To a solution of 1-(4-methoxybenzyl)benzotriazole (**1e**) (0.239 g, 1 mmol) in THF (30 mL) at –78 °C under argon was added dropwise *n*-BuLi (2.2 M, 0.5 mL, 1.1 mmol). After 30 min, *p*-tolualdehyde (0.13 mL, 1 mmol) in THF (10 mL) was added. The mixture was stirred at –78 °C for an additional 4 h and allowed to warm to rt overnight. A saturated aqueous  $\text{NH}_4\text{Cl}$  solution (30 mL) was added, and the mixture was extracted with diethyl ether (3  $\times$  50 mL). The combined organic layer was washed with brine and dried ( $\text{MgSO}_4$ ) and solvent removed under vacuum. The remaining oil was subjected to column chromatography (hexane:ether = 1:1) to give *threo* (0.155 g, 42%) as the first fraction and *erythro* (0.075 g, 21%) as the second fraction. *threo*: mp 146–147 °C;  $^1\text{H}$  NMR  $\delta$  2.28 (s, 3H), 3.69 (s, 3H), 3.88 (d,  $J$  = 4.4 Hz, 1H), 5.75 (d,  $J$  = 8.7 Hz, 1H), 5.89 (dd,  $J$  = 8.6, 4.1 Hz, 1H), 6.66 (d,  $J$  = 8.8 Hz, 2H), 6.98 (d,  $J$  = 8.8 Hz, 2H), 7.03 (d,  $J$  = 8.2 Hz, 2H), 7.10 (d,  $J$  = 8.0 Hz, 2H), 7.28–7.37 (m, 3H), 8.01–8.04 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  21.1, 55.1, 70.0, 76.2, 110.0, 113.9, 119.8, 124.2, 126.9, 126.9, 127.5, 128.2, 128.9, 133.5, 136.4, 137.7, 145.8, 159.4. Anal. Calcd for  $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2$ : C, 73.52; H, 5.89; N, 11.69. Found: C, 73.54; H, 5.85; N, 11.76. *erythro*: mp 86–87 °C;  $^1\text{H}$  NMR  $\delta$  2.28 (s, 3H), 3.69 (m, 1H), 3.75 (s, 3H), 5.69 (d,  $J$  = 5.4 Hz, 1H), 5.98 (m, 1H), 6.79 (d,  $J$  = 8.7 Hz, 2H), 7.00 (d,  $J$  = 8.0 Hz, 2H), 7.09–7.32 (m, 7H), 8.00 (d,  $J$  = 8.0 Hz, 1H);  $^{13}\text{C}$  NMR  $\delta$  21.1, 55.2, 68.7, 75.0, 109.7, 113.7, 119.8, 124.1, 126.5, 126.7, 127.4, 128.8, 129.9, 132.9, 136.5, 137.7, 145.4, 159.4. Anal. Calcd for  $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2$ : C, 73.52; H, 5.89; N, 11.69. Found: C, 73.64; H, 5.97; N, 11.88.

**Supporting Information Available:**  $^1\text{H}$  and  $^{13}\text{C}$  spectra for compounds **2g**, **2j**, **2r**, **2s**, and *cis*-**2u** (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.