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Regioselective Synthesis of Heterocycles Containing Nitrogen Neighboring an Aromatic Ring by Reductive Ring Expansion Using Diisobutylaluminum Hydride and Studies on the Reaction Mechanism

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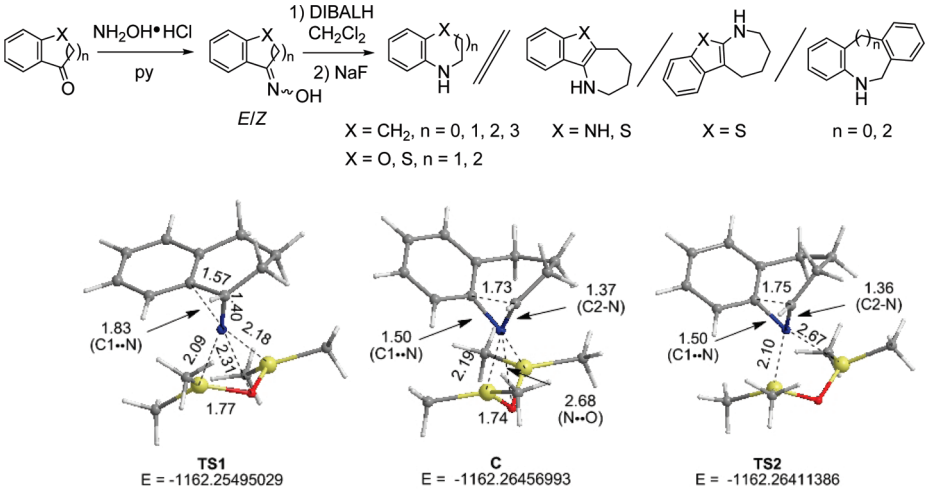

A systematic investigation of the reductive ring-expansion reaction of cyclic ketoximes fused to aromatic rings with diisobutylaluminum hydride (DIBALH) is described. This reaction regioselectively afforded a variety of five- to eight-membered bicyclic heterocycles or tricyclic heterocycles containing nitrogen neighboring an aromatic ring, including indoline, 1,2,3,4,5,6-hexahydrobenz[*b*]azocine, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine, 2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine, 1,2,3,4,5,6-hexahydroazepino[3,2-*b*]-indole, 2,3,4,5-tetrahydro-1*H*-benzothieno[2,3-*b*]azepine, 2,3,4,5-tetrahydro-1*H*-benzothieno[3,2-*b*]-azepine, 5,6-dihydrophenanthridine, and 5,6,11,12-tetrahydrodibenz[*b*,*f*]azocine. The reaction mechanism leading to the rearrangement was investigated on the basis of the restricted Becke three-parameter plus Lee−Yang−Parr (B3LYP) density functional theory (DFT) with the 6-31G (d) basis set. It was found that the reaction proceeds through a three-centered transition state via a stepwise mechanism because the potential energy curve along the intrinsic reaction coordinate (IRC) had two maxima (saddle points; **TS1** and **TS2**) and the partial phenonium cation intermediate **C**. In addition to cyclic ketoximes fused to aromatic rings, the reactions of various cyclic and acyclic ketoximes were examined to investigate preference of migrating group. It was found that the more electron-rich group migrated preferentially to give the corresponding secondary amines.

Introduction

Development of new synthetic methods for the unsubstituted basic skeletons of heterocycles is important from the viewpoint of both synthetic and medicinal chemistry. Synthesis of five- to eight-membered bicyclic or tricyclic fused heterocycles containing nitrogen neighboring an aromatic ring, such as hydrogenated benzazepine, benzoxazine,

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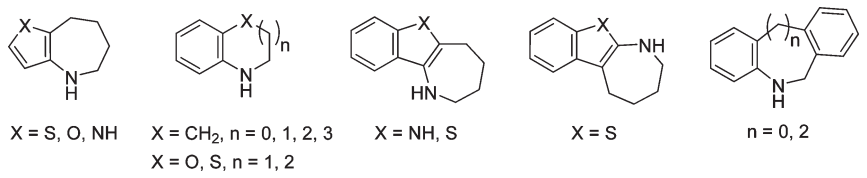
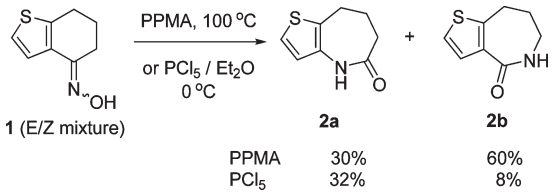
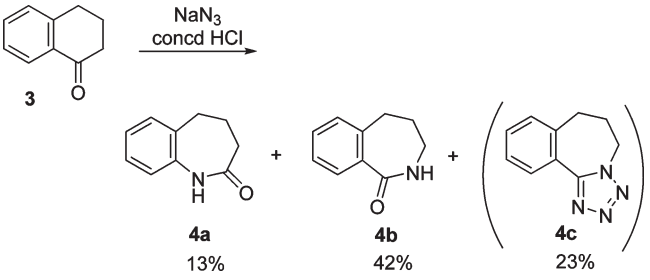


FIGURE 1. Heterocycles containing nitrogen neighboring an aromatic ring.

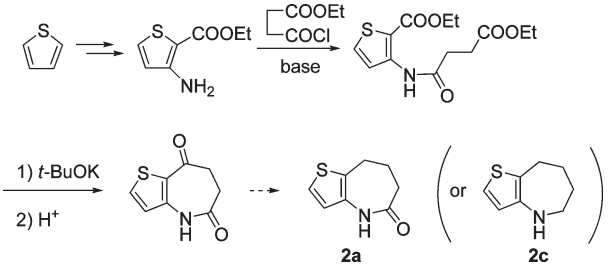
SCHEME 1. Regiochemical Problem with Beckmann Rearrangement



SCHEME 2. Regiochemical Problem with Schmidt Rearrangement



SCHEME 3. Step-by-Step Synthesis of a Lactam Derivative



benzoxazepine, benzthiazine, or benzthiazepine (Figure 1), is particularly important because these are the core structures of medicines or clinical candidates. In addition, hydrogenated benzazocine, dibenzoazocine, phenanthridine, azepino[3,2-*b*]-indole, and so on are also attractive as partial structures for medicines, although these compounds have not been widely used due to lack of synthetic methods.

Despite their importance, the formation of unsubstituted core structures of bicyclic or tricyclic heterocycles containing nitrogen neighboring an aromatic ring has not yet been well investigated because of the difficulty in synthesizing these simple structures. There are only a few straightforward methods available for selective synthesis of these compounds. While Beckmann rearrangement or Schmidt rearrangement of bicyclic aryl ketones would be the method of choice, these methods generally give rise to a mixture of two isomeric lactam derivatives without high selectivity. For example, Beckmann rearrangement of **1** with PPMA[1,2] or PCl_5[3] (Scheme 1) or Schmidt rearrangement of **3** with NaN_3−HCl[4] (Scheme 2) provides a mixture of two isomeric lactam derivatives **2a** and **2b** with low selectivity. In order to synthesize compound **2a** (or **2c**) exclusively, conventional lengthy step-by-step synthesis of ketolactam via Dieckmann condensation with further transformations are required (Scheme 3).[5]

During their investigations into the synthesis of arginine vasopressin (AVP) antagonists (Figure 2), Cho and coworkers developed a straightforward method for the synthesis of bicyclic heterocycles containing nitrogen neighboring an aromatic ring by reductive ring-expansion reaction of oximes with DIBALH[2,6] (Scheme 4). Significantly, the desired bicyclic heterocycle containing nitrogen neighboring an aromatic ring could be obtained exclusively from either *syn* or *anti* oximes, suggesting that the reaction mechanisms were different from Beckmann rearrangement. This method has made it feasible to perform the regioselective synthesis of a series of unsubstituted basic skeletons of heterocycles, such as 5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]-azepine, 5,6,7,8-tetrahydro-4*H*-furo[3,2-*b*]azepine, and 5,6,7,8-tetrahydro-4*H*-pyrro[3,2-*b*]azepine, as the sole product in good yield.

As a seminal study in this area, Yamamoto and Maruoka reported on the reductive rearrangement of oximes with DIBALH providing the corresponding secondary amines.[7] They also reported several examples of exclusive generation of secondary amines from unsymmetrical ketoximes, although the detailed reaction mechanisms were not described. After Cho's preliminary report,[2a] Torisawa[8] and Willand[9] more recently applied the ring-expansion reaction with DIBALH to synthesis

(1) Danaruma, L. G.; Heldt, W. E. *Org. React.* **1960**, *11*, 1–156.
(2) (a) Cho, H.; Murakami, K.; Nakanishi, H.; Isoshima, H.; Hayakawa, K.; Uchida, I. *Heterocycles* **1998**, *48*, 919–927. (b) Cho, H.; Matsuki, S. *Heterocycles* **1996**, *43*, 127–131.
(3) Aparajithan, K.; Thompson, A. C.; Sam, J. *J. Heterocycl. Chem.* **1966**, *3*, 466–469.
(4) Wolff, H. *Org. React.* **1946**, 307–336.
(5) Kunick, C. *Arch. Pharm.* (*Weinheim*) **1991**, *324*, 579–581.
(6) (a) Cho, H.; Murakami, K.; Nakanishi, H.; Fujisawa, A.; Isoshima, H.; Niwa, M.; Hayakawa, K.; Hase, Y.; Uchida, I.; Watanabe, H.; Wakitani, K.; Aisaka, K. *J. Med. Chem.* **2004**, *47*, 101–109. (b) Cho, H.; Wakitani, K. *Japan Patent Application*, H7-291540 (Nov 9, **1995**), WO97/17349. (c) Cho, H.; Murakami, K.; Fujisawa, A.; Niwa, M.; Nakanishi, H.; Uchida, I. *Heterocycles* **1998**, *48*, 1555–1566.
(7) (a) Hattori, K.; Matsumura, Y; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1981**, *103*, 7368–7370. (b) Sasatani, S.; Miyazaki, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4711–4712. (c) Fujiwara, J.; Sano, H.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 2367–2370.
(8) Torisawa, Y.; Nishi, T.; Minamikawa, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 387–390.
(9) Willand, N.; Beghyn, T.; Nowogrocki, G.; Gesquiere, J.-C.; Deprez, B. *Tetrahedron Lett.* **2004**, *45*, 1051–1054.

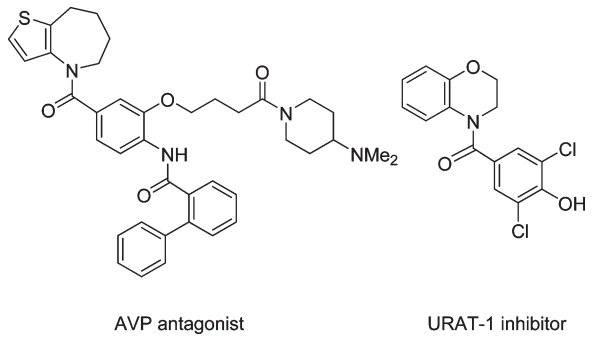
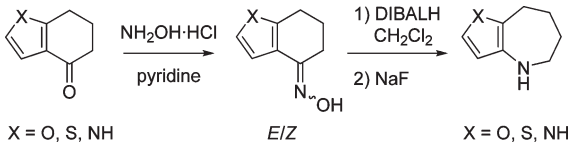


FIGURE 2. Structures of an arginine vasopressin (AVP) antagonist and a human urate transporter-1 (URAT-1) inhibitor.

SCHEME 4. Preliminary Studies for the Reductive Ring-Expansion Reaction of Oximes with DIBALH



of heterocyclic compounds. On the other hand, Ortiz-Marciales[10] reported the synthesis of similar heterocycles by rearrangement of *O*-silylated oximes via reduction with borane in the presence of boron trifluoride. In addition, Naito and Miyata described treatment of oxime ethers with alkyl metal species, such as Grignard reagents or alkyllithium, to achieve alkylative ring expansion.[11]

Although several analogous reactions have been reported, both the general applicability[12] and the detailed reaction mechanisms have not yet been studied. In particular, there remains some confusion about the mechanisms of reductive rearrangement reactions compared with that of Beckmann rearrangement. In this paper, we describe the scope and limitation of reductive rearrangement of oximes with DIBALH, including application to synthesis of five- to eight-membered bicyclic or tricyclic heterocycles. The results of detailed mechanistic studies based on density functional theory (DFT) are also reported.

Results and Discussion

1. Scope and Limitations of Reductive Rearrangement of Oximes with DIBALH. A series of oximes **5a**−**z**[13] were prepared in pyridine from 2−4 equiv of hydroxylamine hydrochloride and the corresponding aryl ketones, which are commercially available or reported in the literature,[14] and were subjected to reductive rearrangement (Tables 1, 2, and 4−6). The general procedure involved reaction of an *E*, *Z* mixture of oximes with 6 equiv of a hexane solution of DIBALH at 0 °C to room temperature, after which the reaction mixture was treated with NaF to obtain the corresponding linear, bicyclic, or tricyclic secondary amines in good to excellent yields.

1.1. Reaction of Carbocyclic or Heterocyclic Ketoximes Fused to a Benzene Ring. The reductive rearrangement reaction was widely applicable, and oximes derived from four- to seven-membered cyclic ketones could be used to provide the corresponding ring expanded cyclic secondary amines in good to excellent yields (Table 1). For instance, reaction of carbocyclic ketoximes **5a**, **5b**, **5c**, or **5d** resulted in indoline **6a**, 1,2,3,4-tetrahydroquinoline **6b**, 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine **6c**,[10] and 1,2,3,4,5,6-hexahydrobenz[*b*]azocine **6d**,[15] respectively (entries 1−4). Interestingly, the relatively strained benzocyclobutenone oxime smoothly underwent reductive rearrangement to give indoline with a small amount (4%) of an indole byproduct. In addition, a variety of heterocyclic ketoximes with five- or six-membered oxygen- or sulfur-containing rings served as good substrates for the reaction. Thus, coumaran-3-one oxime **5e**, chroman-4-one oxime **5f**, thioindoxyl oxime **5g**, and thiochroman-4-one oxime **5h** were converted to 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **6e**,[16] 2,3,4,5-tetrahydrobenzo[*b*][1,4]oxazepine **6f**,[10] 3,4-dihydro-2*H*-benzo[*b*][1,4]thiazine **6g**,[17] and 2,3,4,5-tetrahydrobenzo-[*b*][1,4]thiazepine **6h**,[17] respectively (entries 5−8). These compounds should be valuable in the field of medicinal chemistry. In particular, 3,4-dihydro-2*H*-benzo[*b*][1,4]oxazine **6e** is important as a precursor of a human URAT-1 (urate transporter-1) inhibitor, 2,6-dichloro-4-(2,3-dihydro-1,4-benzoxazin-4-ylcarbonyl)phenol (Figure 2), which was synthesized in one step by acylation of **6e** with 3,5-dichloro-4-hydroxybenzoyl chloride.[18]

1.2. Reductive Ring-Expansion Reaction of Tricyclic Heteroaryl Ketoximes. Next, we examined the reductive ring-expansion reaction of tricyclic ring systems (Table 2).

(10) Ortiz-Marciales, M.; Rivera, L. D.; Jesús, M. D.; Espinosa, S.; Benjamin, J. A.; Casanova, O. E.; Figueroa, I. G.; Rodríguez, S.; Correa, W. *J. Org. Chem.* **2005**, *70*, 10132–10134.

(11) Mukhopadhyay, P. P.; Miyata, O.; Naito, T. *Synlett* **2007**, 1403–1406.

(12) Cho, H.; Iwama, Y.; Sugimoto, K.; Kwon, E.; Tokuyama, H. *Heterocycles* **2009**, *78*, 1183–1190.

(13) The spectral data of oximes **5a**, **5b**, **5c**, **5d**, **5e**, **5f**, and **5m** are identical with those reported previously. (a) For **5a**, see: Bubb, W. A.; Sternhell, S. *Aust. J. Chem.* **1976**, *29*, 1685–1697. (b) For **5b** and **5c**, see: Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505–507. (c) For **5d**, see: Bonvallet, P. A.; Todd, E. M.; Kim, Y. S.; McMahon, R. J. *J. Org. Chem.* **2002**, *67*, 9031–9042. (d) For **5e** and **5f**, see: Clive, D. L. J.; Pham, M. P.; Subedi, R. *J. Am. Chem. Soc.* **2007**, *129*, 2713–2717. (e) For **5i**, see: Bascop, S.-I.; Laronze, J.-Y.; Sapi, J. *Monatsh. Chem.* **1999**, *130*, 1159–1166. (f) For **5m**, see: Jain, N.; Kumar, A.; Chauhan, S. M. S. *Tetrahedron Lett.* **2005**, *46*, 2599–2602.

(14) The precursor ketones of **5b**, **5c**, **5d**, **5f**, **5h**, **5k**, and **5n** are commercially available. Precursor ketones of **5a**, **5e**, **5g**, and **5i** were prepared according to procedures in the literature. (a) For the precursor ketone of **5a**, see: Bubb, W. A.; Sternhell, S. *Aust. J. Chem.* **1976**, *29*, 1685–1697. (b) For the precursor ketone of **5e**, see: Inoue, A.; Kitagawa, K.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **2001**, *66*, 4333–4339. (c) For the precursor ketone of **5g**, see: Mukherjee, C.; Kamila, S.; De, A. *Tetrahedron* **2003**, *59*, 4767–4774. (d) For the precursor ketone of **5i**, see: Li, X; Vince, R. *Bioorg. Med. Chem.* **2006**, *14*, 2942–2955. (e) For cyclization from the carboxylic acid to the precursor ketone of **5j**, see: Cho, H.; Matsuki, S. *Heterocycles* **1996**, *43*, 127–131. Maertens, F.; Toppet, S.; Hoornaert, G. J.; Compernolle, F. *Tetrahedron* **2005**, *61*, 1715–1722. (f) For new synthesis of the precursor ketone of **5k**, see Scheme S1 shown in the Supporting Information. (As for the starting material, 2-iodobenzo[*b*]thiophene, consult ref S1 in the Supporting Information.) (g) For the precursor ketone of **5l**, see: Horaguchi, T.; Kubo, T.; Tanemura, K.; Suzuki, T. *J. Heterocyclic. Chem.* **1998**, *35*, 649–653.

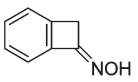
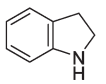
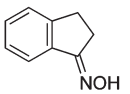
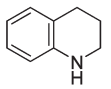
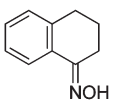
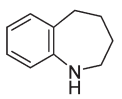
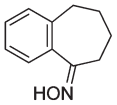
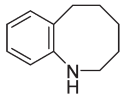
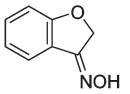
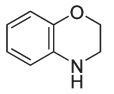
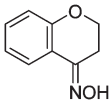
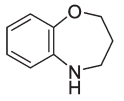
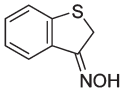
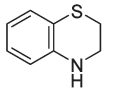
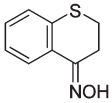
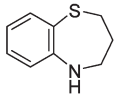
(15) Ahlbrecht, H.; Düber, E. O.; Epsztajn, J.; Marcinkowski, R. M. K. *Tetrahedron* **1984**, *40*, 1157–1165.

(16) Torraca, K. E.; Kawabe, S.-I.; Buchwald, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 12907–12908.

(17) Mukheerjee, C.; Biehl, E. *Heterocycles* **2004**, *63*, 2309–2318.

(18) Hirata, K.; Ogawa, N.; Sinagawa, Y.; Kiguchi, T.; Inoue, T.; Komeda, Y.; Yamashita, I.; Kamiya, Y. Application WO 2007139002, WO 2007-JP60678, Priority: JP 2006-147261, US 2006-809966. Hirata et. al. synthesized the human URAT-1 inhibitor in several steps by using compound **6e** obtained from the reaction of 2*H*-1,4-benzoxazin-3(4*H*)-one with sodium bis(2-methoxyethoxy)aluminum hydride in toluene at rt.

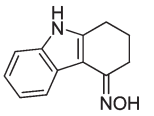
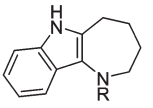
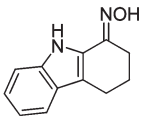
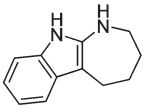
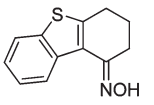
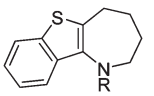
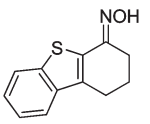
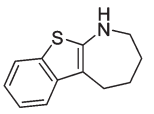
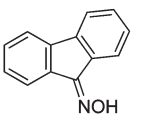
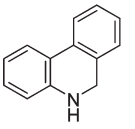
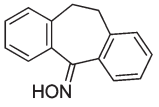
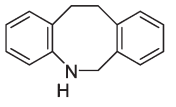
TABLE 1. Reductive Ring-Expansion Reaction of Carbocyclic or Heterocyclic Ketoximes Fused to a Benzene Ring

Entry	Oxime (% yield)[a]	Aromatic amine (% yield)[b]
1	 **5a** (92)	 **6a** (52)
2	 **5b** (90)	 **6b** (92)
3	 **5c** (96)	 **6c** (80)
4	 **5d** (90)	 **6d** (80)
5	 **5e** (69)	 **6e** (80)
6	 **5f** (80)	 **6f** (87)
7	 **5g** (75)[c]	 **6g** (60)
8	 **5h** (96)	 **6h** (71)

[a]Ketone (1 equiv) and hydroxylamine hydrochloride (2 equiv) were used in pyridine at rt for 1−6 h. [b]Oxime (1 equiv) and DIBALH (6 equiv) were used in CH_2Cl_2 at rt for 2−2.5 h. [c]Ketone (1 equiv) and hydroxylamine hydrochloride (4 equiv) were used in pyridine for 4 h.

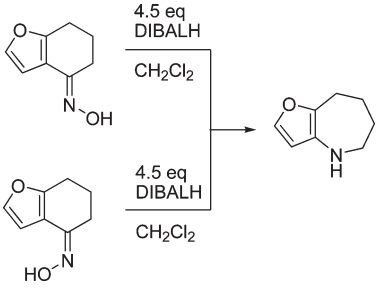
We found that the reaction was also applicable to cyclic ketoximes fused to indole and benzothiophene. Reaction of oxime **5i**,[14] prepared from 1,2,3,4-tetrahydrocarbazol-4-one,[13] proceeded as expected to furnish 1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole **6i** as the sole product. Due to its instability, the yield of **6i** was determined after transformation to 6-(4-nitrobenzoyl)-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]-indole **7i** by benzoylation with *p*-nitrobenzoyl chloride and Et_3N in CH_2Cl_2 (entry 1). The structure of **7i** was unambiguously determined by X-ray crystallographic analysis, as reported previously.[12] In contrast, reaction of oxime **5j** derived from 2,3,4,9-tetrahydrocarbazol-1-one gave a complex mixture under the same reaction conditions and the desired tricyclic compound **6j** was not detected. On the other hand, benzothiophene derivatives behaved in different manner. Thus, reaction of **5l** furnished 2,3,4,5-tetrahydro-1*H*-benzothieno[2,3-*b*]azepine **6l** in 73% yield, while oxime **5k**

TABLE 2. Reductive Ring Expansion of Tricyclic Ketoximes

Entry	Oxime (% yield)[a]	Aromatic amine (% yield)[b]
1	 **5i** (91)	 **6i** R = H (not isolated)[c] **7i** R = *p*-nitrobenzoyl (63)[d]
2	 **5j** (99)	 **6j** (0)
3	 **5k** (77)[e]	 **6k** R = H (not isolated)[f] **7k** R = *p*-nitrobenzoyl (21)[d]
4	 **5l** (18)	 **6l** (73)
5	 **5m** (99)	 **6m** (83)
6	 **5n** (54)[g]	 **6n** (73)

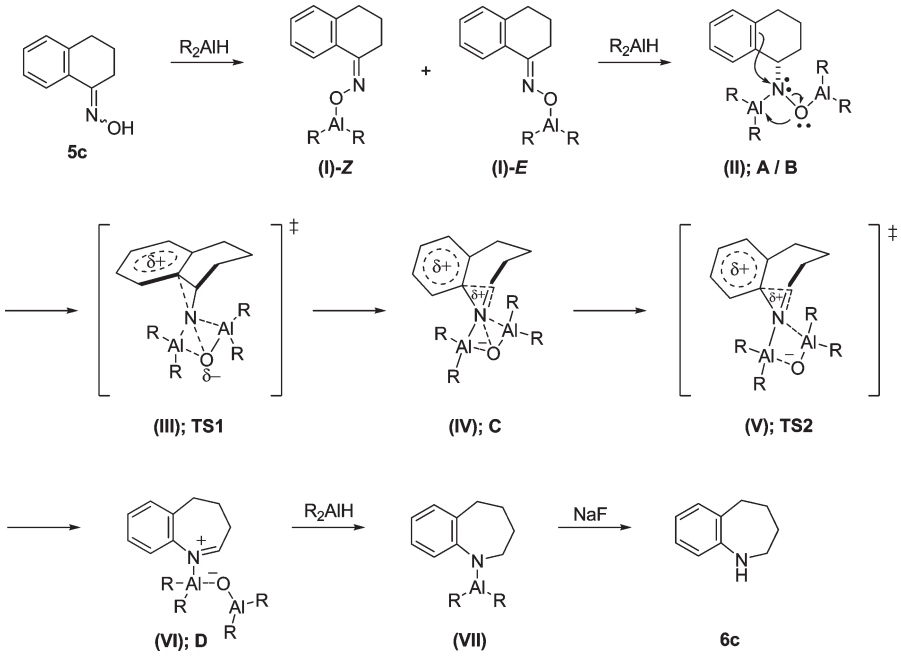
[a]Ketone (1 equiv) and hydroxylamine hydrochloride (2 equiv) were used in pyridine at rt for 2−6 h. [b]Oxime (1 equiv) and DIBALH (6 equiv) were used in CH_2Cl_2 at 0 °C to rt for 2−4 h. [c]Oxime (1 equiv) and DIBALH (9 equiv) were used in CH_2Cl_2/THF (2:1) at 0 °C to rt for 1 h. [d]The yield was based on the oximes. [e]Ketone (1 equiv) and hydroxylamine hydrochloride (6 equiv) were used in pyridine at rt for 3.5 h. [f]Oxime (1 equiv) and DIBALH (7 equiv) were used in CH_2Cl_2 at −10 °C for 3 h. [g]Ketone (1 equiv) and hydroxylamine hydrochloride (4 equiv) were used in pyridine at 115 °C for 11 h.

SCHEME 5. Same Product obtained from Isolated (*E*)- and (*Z*)-Oxime



derived from the corresponding ketone[14f] gave 2,3,4,5-tetrahydro-1*H*-benzothieno[3,2-*b*]azepine **6k** in only a modest yield. Compound **6k** was determined after conversion to **7k**, and was found to be a mixture (6.6:1.0) of rotamers according to ^1H NMR and ^{13}C NMR spectra.

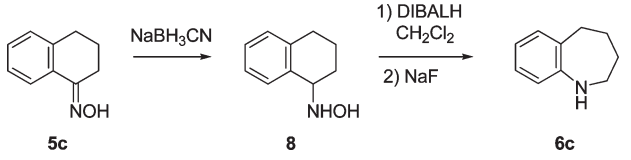
SCHEME 6. Stepwise Mechanism Proceeding through a Three-Centered Transition State Proposed by the Aid of B3LYP Method



The reaction was also tested using tricyclic ketoximes derived from cyclic diaryl ketone derivatives. For example, 9-fluorenone oxime **5m** underwent rearrangement to give 5,6-dihydrophenanthridine **6m**[19] in good yield. The ring-expansion reaction of the seven-membered ring cyclic ketoxime **5n** prepared from the corresponding ketone under relatively strong conditions (refluxed in pyridine for 11 h) required a longer reaction time (3−4 h) but afforded 5,6,11,12-tetrahydrodibenz[*b*,*f*]azocine **6n** in 73% yield.

2. Theoretical Studies on the Mechanisms of Reductive ring-expansion Reactions. As mentioned in the Introduction, the mechanism of the reductive ring-expansion reaction of oximes with DIBALH has not yet been well investigated, although it has been suggested to be similar to Beckmann-type rearrangement. In a previous report,[2a] we proposed a mechanism that was different from Beckmann-type rearrangement[7a] based on several experimental findings. For example, both (*E*)- and (*Z*)-oximes derived from 4,5,6,7-tetrahydro-4-oxobenzo[*b*]furan were separated, and treatment of each oxime with excess DIBALH gave the same product, 5,6,7,8-tetrahydrofuro[3,2-*b*]azepine (Scheme 5).[2a] In addition, the same reaction using a mixture of (*E*)- and (*Z*)-oximes derived from 4,5,6,7-tetrahydro-4-oxobenzo-[*b*]thiophen gave 5,6,7,8-tetrahydrothieno[3,2-*b*]azepine as a single isomer (Scheme 4), while Beckmann rearrangement gave a mixture of isomeric lactams (Scheme 1). Since the structure of the reductive ring-expansion product was independent of the geometry of the oximes, we considered that the initial step was probably DIBALH reduction of the C−N double bond, followed by rearrangement involving N−O bond cleavage assisted by the aromatic ring to furnish the ring-expansion product with nitrogen attached to the aromatic ring.[2a] While the initial step of the reaction is reasonable, the detailed mechanism of the rearrangement process remains unclear. Against this background, we carried out an extensive investigation into the mechanism of the reductive ring-expansion reaction based on theoretical calculations and eventually proved that the reaction proceeds by reduction of the C−N double bond and subsequent rearrangement by a stepwise mechanism through a three-centered transition state (Scheme 6).

SCHEME 7. Rearrangement from Hydroxylamine Derivative 8 to 2,3,4,5-Tetrahydro-1*H*-benz[*b*]azepine 6c



2.1. Confirmation of Intermediacy of Hydroxylamine Derivative. Before starting the theoretical studies, we confirmed that hydroxylamine acts as an intermediate in the reductive ring-expansion reaction. Oxime **5c** was chosen as the test substrate. The corresponding hydroxylamine **8**, prepared by reduction of oxime **5c** with $NaBH_3CN$, was treated with excess DIBALH (Scheme 7). As expected 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine **6c** was isolated in 72% yield as the sole product, indicating that the reaction proceeds via initial formation of aluminum complex (**I**)-***E*** and ***Z***, followed by 1,2-reduction of the C−N double bond to generate intermediate **II** coordinated by two molecules of dialkyl aluminum (R = *i*-Bu). Finally, reductive rearrangement takes place to furnish the cyclic secondary amine aluminum amide **VII** (R = *i*-Bu).

2.2. Theoretical Studies on the Reaction Mechanisms. Subsequently, the reaction processes from **II** to **6c** was investigated by the aid of 3-parameter hybrid Becke exchange/Lee−Yang−Parr correlation functional (B3LYP) method.[20]

(19) Barluenga, J.; Fañanás, F. J.; Sanz, R.; Fernández, Y. *Chem.—Eur. J.* **2002**, *8*, 2034–2046.

(20) Hehre, W. J.; Radom, L.; Schleyer, P. V. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; John Wiley: New York, 1986. References cited therein.

For simplicity, $(i\text{-Bu})_2$AlH was modeled as Me_2AlH. Two Me_2AlH molecules were added to assess the mechanism, because at least two equivalents of the molecule are necessary for completion of the reaction (one for formation of an aluminum oxide **II** from (**I**)-***E*** or (**I**)-***Z***, and the other for reduction of a C=N bond of **VI**).

The 3D structures of representative intermediates and a saddle point (**TS1**) (**III**) with twist-chair conformation on the potential energy surface and the potential energy profile are shown in Figures 3 and 4, respectively. Reduction of ***E***/***Z*** oxime **I** by dialkylaluminum hydride led to two possible conformers **II**, which were two aluminum-bound hydroxylamine residues (one with pseudoequatorial substitution and the other with pseudoaxial substitution). The pseudoequatorially substituted hydroxylamine A with twist-chair conformation of **II** (R = Me) has a slightly lower energy than the pseudoaxially substituted hydroxylamine **B** of **II**, with the difference being 0.1 kJ/mol. Since the π-orbital symmetry of C1 in **A** does not allow further rearrangement of aromatic carbon into nitrogen, **B** is a direct precursor of the rearrangement. The transition state (**TS1**) **III** of the ring opening has an energy level 64.2 kJ/mol higher than the conformer **A** and 64.1 kJ/mol higher than the conformer **B** based on data shown in Figures 3 and 4 (see the Experimental Section and Supporting Information). We performed intrinsic reaction coordinate (IRC) analysis descending from **TS1** toward two-aluminum-bound hydroxylamine derivative **B** and aluminum-coordinated intermediate **C** (**IV**). Calculations following the IRC path toward **C** terminated at a nonstationary point **I1** because the potential surfaces around **I1** were too flat. Subsequent geometric optimization from **I1** is connected to **C**. The other IRC path from **TS1** is connected toward **B** smoothly. When the benzene C1 atom moves closer to a nitrogen atom, N−O bond cleavage occurs. During the stage between **B** to **TS1**, electrons from a benzene ring, C2, and N flow into the O atom (Table 3). The dipole moments at **B** and **TS1** of 2.3 and 8.8 D, respectively, show that **TS1** is more polar than **B**. Then, we employed calculations of solvent polarity effects of CH_2Cl_2 using polarized continuum model (PCM)[21] at the B3LYP/6-31+G(d) level. We found that the activation energy of 64.1 kJ/mol decreases to 35.6 kJ/mol. At **I1**, the C1−N distance of 1.60 Å is closer to the C2−N bond length of 1.37 Å, indicating that the C1−C2−N moiety of **I1** more closely resembles an aziridine-like structure than **TS1**. During the stage between **TS1** and **I1**, the C1−C2 bond is only cleaved partially (1.57 Å in the **TS1** and 1.64 Å in **I1**) and C1−N bond formation (1.83 Å in the **TS1** and 1.60 Å in **I1**) is more advanced. Additional electron flow from the benzene ring and C2 into N and O then occurs to produce an electron-deficient imine carbon (Table 3). During ring expansion (from **III** to **VI**), the N−O bond is cleaved along with Al1−O shortening and N−Al1 bond lengthening (Figure 3 and Scheme 6). In equilibrium structure **C** (**IV**) which is higher in energy than **B** by 38.8 kJ/mol, two aluminum atoms interact with N, and C2 is still interacting with C1. The natural charge of O changes from −0.861 in **B** to −1.327 in **C** (Table 3), and bonds between O and two Al atoms become stronger. Since

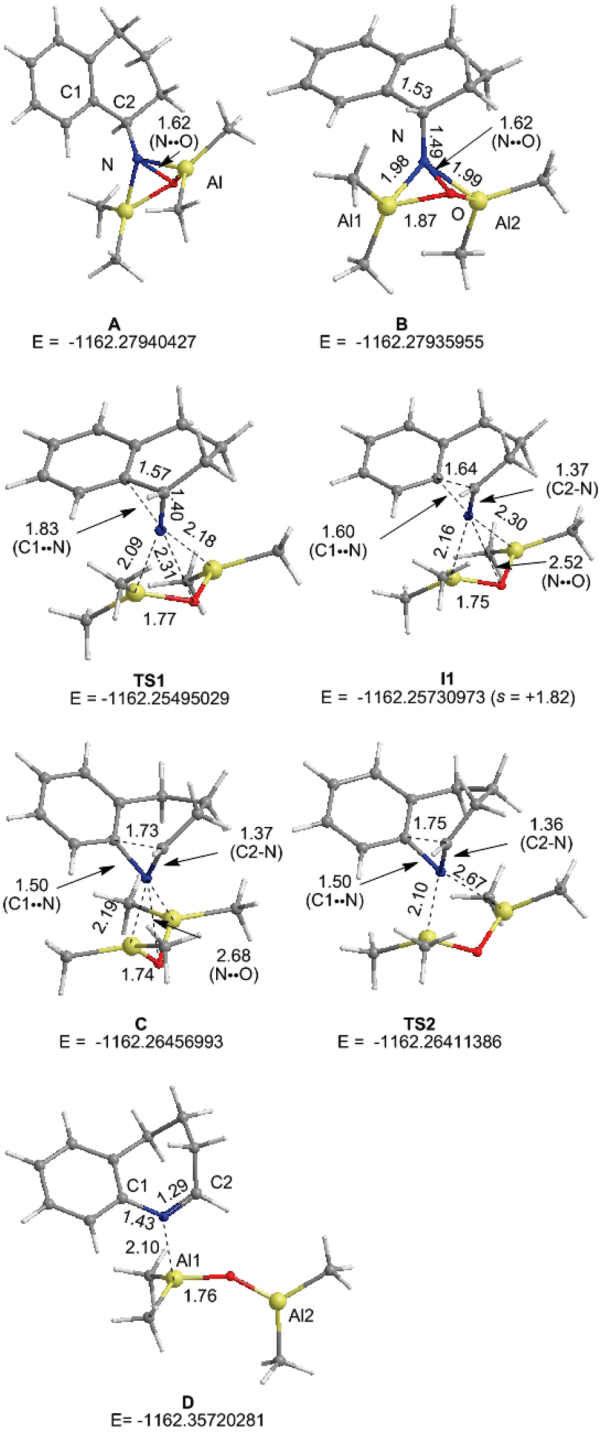


FIGURE 3. Structures of representative intermediates (**B**, **C**, and **D**), TSs (**TS1** and **TS2**), and representative nonstationary point (**I1**) along the IRC. Bond lengths are in angstroms. Total electronic energies (E) at the B3LYP/6-31G(d) level are shown in a.u. The *s* value refers to the reaction coordinate in $amu^{1/2}$ bohr.

the additional positive charge is developed in the benzene ring (+0.400), the intermediate **C** possesses a partial phenonium cation structure. The decrease of the natural charge of C2 from **TS1** (+0.003) to **C** (+0.202) indicates that C2 changes to an imine carbon character. Once C1−C2 bond cleavage occurs with concomitant Al2−N dissociation through the

(21) Cances, M. T.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032–3041. Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43–54.

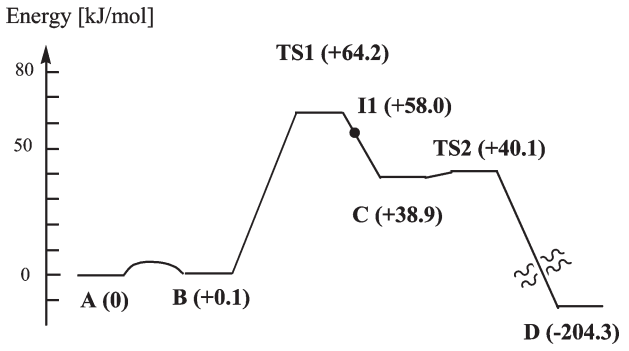


FIGURE 4. Potential energy diagram of ring expansion. Relative energies (kJ/mol) are shown in parentheses (B3LYP/6-31G(d)).

TABLE 3. Natural Charges of Stationary Points (B, TS1, C, TS2, D) and Representative Nonstationary Points (I1) along the IRC at the B3LYP/6-31G(d) Level

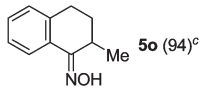
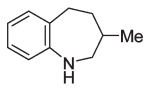
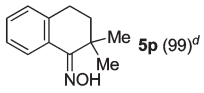
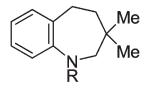
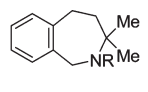
	C1	C2	N	Al1	O	C_6H_4
B	−0.048	−0.070	−0.707	+1.860	−0.861	−0.008
TS1	+0.006	+0.003	−0.701	+1.856	−1.188	+0.300
I1	+0.030	+0.107	−0.762	+1.855	−1.293	+0.389
C	+0.074	+0.202	−0.820	+1.852	−1.327	+0.400
TS2	+0.080	+0.213	−0.792	+1.845	−1.332	+0.368
D	+0.130	+0.194	−0.567	+1.850	−1.350	+0.172

second transition state (**TS2**), ring expansion takes place smoothly to furnish **D** (**VI**). The activation energy of the step from **C** to **TS2** is only 1.2 kJ/mol. The exothermic energy of the nitrogen shift to produce **D** (**VI**) relative to **A** is 204.3 kJ/mol (Figure 4). Thus, we cannot find aziridine as a local minimum (point **I1** along the IRC *s* of +1.82 amu$^{1/2}$ bohr), but can indicate that the reaction proceeds through a three-centered transition state with the stepwise mechanism, because the potential energy curve along the reaction coordinate from **B** to **D** has two maxima (saddle points; **TS1** and **TS2**). Subsequently, reduction of a C=N bond of **VI** with the third molecule of R_2AlH affords compound **VII**.

3. Preference of the Migrating Group. As shown in Tables 1 and 2, the reductive rearrangement reaction gave exclusive product due to migration of the aryl group. However, we found that this was not always the case. The oximes **5c** and **5o**[22] (Tables 1 and 4) derived from 1-tetralone and 2-methyl-1-tetralone, respectively, provided the expected products 2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine **6c** and 3-methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine **6o**[23] due to exclusive migration of the aryl groups. However, contrary to our speculation, rearrangement of oxime **5p** prepared from 2,2-dimethyl-1-tetralone gave a mixture of 3,3-dimethyl-1-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine **7p** (57%) and 3,3-dimethyl-2-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine **10p** (22%) after benzoylation of 3,3-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepine **6p** and 3,3-dimethyl-2,3,4,5-tetrahydro-1*H*-benzo-[*c*]azepine **9p**, respectively. This result prompted us to investigate the migratory preferences of various substituents.

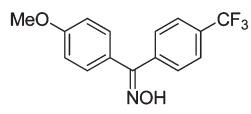
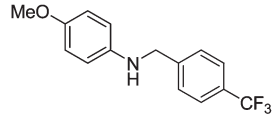
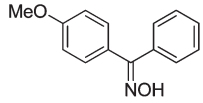
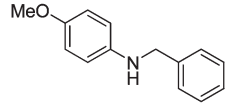
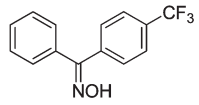
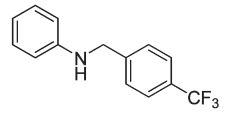
After choosing unsymmetrical benzophenone oximes bearing different substituents at two para positions each, the influence of electron density on the preference of the migrating group was investigated (Table 5). It was found that the migrating group was clearly dependent on the substituents on the benzene ring and that only the more electron-rich benzene ring underwent migration. Thus, in the case of oxime **5q**, exclusive migration of the *p*-anisyl group took place to give

TABLE 4. Products from 2-Substituted Oximes

Entry	Oxime (% yield)[a]	Amine (% yield)[b]
1	 **5o** (94)[c]	 **6o** (77)
2	 **5p** (99)[d]	 **6p** R = H (not isolated) **7p** R = *p*-nitrobenzoyl (57)[e, f]  **9p** R = H (not isolated) **10p** R = *p*-nitrobenzoyl (22)[e, f]

[a]Ketone (1 equiv) and hydroxylamine hydrochloride (2 equiv) were used in pyridine at rt for 2−6 h. [b]Oxime (1 equiv) and DIBALH (6 equiv) were used in CH_2Cl_2 at 0 °C to rt for 2 h. [c]Ketone (1 equiv) and hydroxylamine hydrochloride (4 equiv) were used in pyridine at rt for 6 h. [d]Ketone (1 equiv) and hydroxylamine hydrochloride (4 equiv) were used in pyridine at 80 °C for 30 h. [e]The yield was based on the oximes. [f]The yields of the regioisomers were determined from ^{1}H NMR spectra of mixtures of the benzoylamides.

TABLE 5. Reductive Rearrangement of Diaryl Ketone Oximes

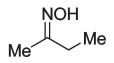
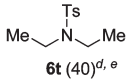
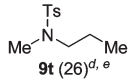
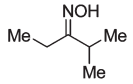
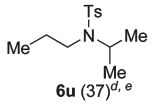
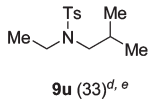
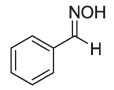
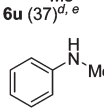
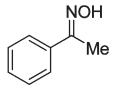
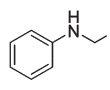
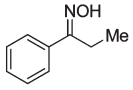
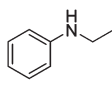
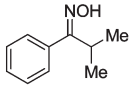
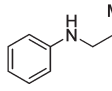
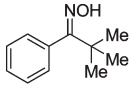
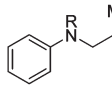
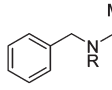
Entry	Oxime (% yield)[a]	Amine (% yield)[b]
1	 **5q** (86)	 **6q** (79)
2	 **5r** (99)	 **6r** (90)
3	 **5s** (98)	 **6s** (65)

[a]Ketone (1 equiv) and hydroxylamine hydrochloride (4 equiv) were used in pyridine at rt for 8−12 h. [b]Oxime (1 equiv) and DIBALH (6 equiv) were used in CH_2Cl_2 at 0 °C to rt for 2 h.

(22) The spectral data of oximes **5o**, **5w**, **5x**, **5y**, and **5z** are identical with those reported previously. (a) For **5o**, **5x**, and **5y**, see: Zhao, H.; Vandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505–507. (b) For **5w**, see: Hwu, J. R.; Tseng, W. N.; Patel, H. V.; Wong, F. F.; Horng, D.-N.; Liaw, B. R.; Lin, L. C. *J. Org. Chem.* **1999**, *64*, 2211–2218. (c) For **5z**, see: Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947–1950.

(23) The spectral data of amines **6o**, **6v**, **6w**, **6x**, and **6y** are identical with those reported previously. (a) For **6o**, see: Ventrice, T.; Campi., E. M.; Roy Jackson, W.; Patti, A. F. *Tetrahedron* **2001**, *57*, 7557–7574. (b) For **6v**, **6w**, **6x**, and **6y**, see: Byun, E.; Hong, B.; De Castro, K. A.; Lim, M.; Rhee, H. *J. Org. Chem.* **2007**, *72*, 9815–9817.

TABLE 6. Preferred Migrating Group During the Reductive Rearrangement of Various Oximes

Entry	Oxime (% yield)[a]	Amine (% yield)[b]	
1	 **5t** (77)[c]	 **6t** (40)[d, e]	 **9t** (26)[d, e]
2	 **5u** (89)[c]	 **6u** (37)[d, e]	 **9u** (33)[d, e]
3	 **5v** (91)[f]	 **6v** (49)	
4	 **5w** (99)[c]	 **6w** (82)	
5	 **5x** (99)	 **6x** (72)	
6	 **5y** (99)[g]	 **6y** (96)	
7	 **5z** (72)	 **6z** R = H (not isolated) **7z** R = *p*-nitrobenzoyl (37)[d, h]  **9z** R = H (not isolated) **10z** R = *p*-nitrobenzoyl (31)[d, h]	

[a]Ketone (1 equiv) and hydroxylamine hydrochloride (2 equiv) were used in pyridine at rt for 2−6 h. [b]Oxime (1 equiv) and DIBALH (6 equiv) were used in CH_2Cl_2 at 0 °C to rt for 2 h. [c]Ketone (1 equiv), hydroxylamine hydrochloride (1.5−2 equiv), and NaOAc (3−5 equiv) were used in MeOH at rt for 1.5 h. [d]The yield was based on the oximes. [e]The yields of the regioisomers were determined from ^{1}H NMR spectra of mixtures of the tosylamides. [f]Aldehyde (1 equiv), hydroxylamine hydrochloride (2 equiv), and pyridine (5 equiv) were used in MeOH at rt for 30 min. [g]Ketone (1 equiv), hydroxylamine hydrochloride (1.5 equiv) and NaOAc (3 equiv) were used in EtOH at rt for 6 h. [h]The yields of the regioisomers were determined from ^{1}H NMR spectra of mixture of the benzoylamides.

compound **6q**[24] in 79% yield. Oxime **5r** derived from phenyl *p*-anisyl ketone gave **6r**[25] with complete control due to the difference between the methoxy group and hydrogen on the benzene rings. In addition, the CF_3 group controlled migration to furnish **6s**[24] as the sole product from the reaction of oxime **5s**.

We then prepared a variety of oximes and investigated general trends in the preference of migration. As shown in Table 6, reaction of ethyl methyl ketone oxime **5t** gave a mixture of diethylamine and *N*-methyl-*n*-propylamine, which was determined as (*N*-diethyl)tosylamide **6t**[26] and (*N*-methyl-*N*-*n*-propyl)-tosylamide **9t** (3:2) after tosylation. The results indicate that the primary alkyl group migrates in preference to the methyl group (entry 1). Predominant generation of (*N*-isopropyl-*n*-propyl)-tosylamide **6u** by successive reduction and tosylation of ethyl isopropyl ketone oxime **5u** demonstrated that secondary alkyl group is more likely to migrate than the primary alkyl group (entry 2). Reactions using benzaldehyde oxime **5v**, acetophenone oxime **5w**,[22] propiophenone oxime **5x**,[22] and isopropyl phenyl ketone oxime **5y**[22] exclusively gave the corresponding aniline derivatives, *N*-methylaniline **6v**,[23] *N*-ethylaniline **6w**,[23] *N*-*n*-propylaniline **6x**,[23] and *N*-isobutylaniline **6y**,[23]respectively, due to migration of the benzene ring, showing that benzene ring migration was preferred over migration of proton, methyl, primary, and secondary alkyl groups. Similar to the rearrangement of oxime **5p** shown in Table 4, the exceptional example of generating a mixture of isomeric rearrangement product was **5z**,[22] which afforded a mixture of **7z** (37%) and **10z** (31%) after *p*-nitrobenzoylation of the resulting secondary amines 2,2-dimethylpropylaniline **6z** and (*N*-*t*-butyl)benzylamine **9z**. According to the above data, we concluded that the preference for migration has the following order: phenyl group ≈ tertiary alkyl group > secondary alkyl group > primary alkyl group. In addition, an electron-rich phenyl group migrates preferentially in the case of unsymmetrical benzophenone oximes.

Conclusions

We performed a systematic investigation into the reductive ring-expansion reaction of oximes with DIBALH. This method makes it feasible to synthesize a variety of bicyclic or tricyclic heterocycles containing nitrogen attached to an aromatic ring, which are the core structures of medicines or clinical candidates or may have potential as core structure of new drugs. For instance, compound **6e**, obtained by reaction of coumaran-3-one oxime **5e**, is particularly important because it could be converted to 2,6-dichloro-4-(2,3-dihydro-1,4-benzoxazin-4-ylcarbonyl)phenol, which is known to inhibit URAT-1 (urate transporter-1) and could be useful for the treatment of hyperuricemia and gout (Figure 2).[18]

Both experimental and theoretical studies were performed to investigate the mechanisms and we obtained some important information. First, it was demonstrated that the reaction proceeds through a hydroxylamine intermediate. Second, DFT calculations revealed that aryl migration occurred by a stepwise mechanism through a three-centered transition state (Figures 3 and 4).

We also clarified the preferences of migrating groups during the reductive rearrangement reaction, and found that the electronic nature of substituents is a crucial factor governing migration preference. For example, the electron-rich phenyl group of unsymmetrical benzophenone migrated exclusively and alkyl groups with more substituents migrated more easily, which is similar to the processes observed in Baeyer−Villiger oxidation. We concluded that the order of migration was as follows; phenyl ≈ tertiary alkyl group > secondary alkyl group > primary alkyl group.

Finally, considering the practical utility of DIBALH on an industrial scale,[27] this reaction may find widespread use not

(24) As to determination of the chemical structure of the products, the ^{1}H NMR data of **6q** and **6s** were respectively identified with those of the compounds synthesized by reductive amination of (*p*-trifluoromethyl)-benzaldehyde with *p*-anisidine or aniline, followed by $NaBH_4$ (Supporting Information, Scheme S2).

(25) Sydnes, M. O.; Kuse, M.; Isobe, M. *Tetrahedron* **2008**, *64*, 6406–6414.

(26) Harmata, M.; Zheng, P.; Huang, C.; Gomes, M. G.; Ying, W.; Ranyanil, K.-O.; Balan, G.; Calkins, N. L. *J. Org. Chem.* **2007**, *72*, 683–685.

(27) (a) For an example of using DIBALH in process chemistry, see: Hobson, L. A.; Nugent, W. A.; Anderson, S. R.; Deshmukh, S. S.; Haley, J. J. III; Liu, P.; Magnus, N. A.; Sheeran, P.; Sherbine, J. P.; Stone, B. R. P.; Zhu, J. *Org. Process Res. Dev.* **2007**, *11*, 985–995. (b) In the case of cyclohexanone oxime, large-scale production using DIBALH is also underway at a chemical corporation.

only in the field of medicinal chemistry but also in process chemistry for creation of novel drugs as well as for the synthesis of related natural products.

Experimental Section

General Procedure for the Ring-Expansion Reaction Using DIBALH. Thiochroman-4-one Oxime (5h). To a stirred solution of 1-thiochroman-4-one (4.40 g, 26.8 mmol) in pyridine (50.0 mL) was added hydroxylamine hydrochloride (3.76 g, 54.1 mmol) at rt. After the mixture was stirred for 1.5 h, pyridine was removed under reduced pressure. The residue was diluted with water and extracted with EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give the crude material. Purification by column chromatography on a silica gel (EtOAc:*n*-hexane = 1:3) afforded oxime **5h** (4.61 g, 96%): colorless crystals; mp 98−100 °C; IR (KBr) 3233, 2920, 1587, 1475, 1310 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.13 (1H, brs), 7.87 (1H, dd, J = 1.6 and 8.0 Hz), 7.25 (1H, dd, J = 1.6 and 8.0 Hz), 7.23 (1H, ddd, J = 1.6, 7.2, and 8.0 Hz), 7.13 (1H, ddd, J = 1.6, 7.2, and 8.0 Hz), 3.19 (2H, t, J = 6.0 Hz), 2.97 (2H, t, J = 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 136.3, 129.5, 129.3, 128.4, 125.9, 125.5, 26.2, 25.9; LRMS (EI) m/z 179 (M^+). Anal. Calcd for C_9H_9NOS: C, 60.31; H, 5.06; N, 7.81. Found: C, 60.40; H, 5.16; N, 7.72.

2,3,4,5-Tetrahydrobenzo[*b*][1,4]thiazepine Hydrochloride (6h). To a stirred solution of **5h** (1.01 g, 5.63 mmol) in CH_2Cl_2 (56.0 mL) was added DIBALH (33.0 mL, 33.7 mmol, 1.02 M in *n*-hexane) over 10 min at 0−5 °C (internal temperature) under an argon atmosphere. Stirring was continued for 5 min at 0 °C and for 2 h at rt. NaF powder (6.76 g, 161 mmol) and water (2.2 mL) were added at 0 °C, and the resulting mixture was stirred for 30 min at the same temperature. Then the reaction mixture was filtered through a Celite pad. The filter cake was washed with EtOAc, and the combined organic solutions were evaporated to give the crude product. Purification by column chromatography on a silica gel (Et_2O:*n*-hexane = 1:3) yielded 2,3,4,5-tetrahydrobenzo[*b*][1,4]thiazepine **6h** (662 mg, 71%). The ^1H NMR spectrum was identified with that reported in ref 17. Although 3 mol equiv of DIBALH is theoretically sufficient for this method, we often employed 6−9 mol equiv of the reagent to finish each reaction. To a solution of **6h** in Et_2O was added HCl in Et_2O (1 M) at rt. After stirring for 20 min, Et_2O was removed under reduced pressure. The residue was purified by recrystallization (EtOH) to give HCl salts of **6h**: colorless crystals; mp 138−142 °C; IR (KBr) 2914, 2687, 1558, 1456, 764 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.74 (1H, dd, J = 1.6 and 7.6 Hz), 7.56 (1H, dd, J = 1.6 and 7.6 Hz), 7.51 (1H, ddd, J = 1.6, 7.6, and 7.6 Hz), 7.46 (1H, ddd, J = 1.6, 7.6, and 7.6 Hz), 3.51 (2H, t, J = 5.6 Hz), 2.95 (2H, t, J = 5.6 Hz), 2.40 (2H, tt, J = 5.6 and 5.6 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 140.9, 136.0, 132.6, 131.3, 131.0, 124.7, 50.9, 32.7, 29.9; LRMS (FAB) m/z 166 (M − Cl). Anal. Calcd for $C_9H_{12}ClNS$: C, 53.59; H, 6.00; N, 6.94. Found: C, 53.47; H, 5.85; N, 6.89.

6-(4-Nitrobenzoyl)-1,2,3,4,5,6-hexahydroazepino[3,2-*b*]indole (7i). 1,2,3,4,5,6-Hexahydroazepino[3,2-*b*]indole **6i** was prepared from oxime **5i**, but was unstable. Without purification, benzoylation of **3i** was carried out with *p*-nitrobenzoyl chloride (68.7 mg, 0.370 mmol) and Et_3N (0.100 mL, 0.717 mmol) in CH_2Cl_2 (3.0 mL). Then the reaction mixture was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by preparative TLC (EtOAc:*n*-hexane = 1:1) to afford compound **7i** in 63% yield for two steps: colorless crystals; mp 216−217 °C (EtOAc/*n*-hexane); IR (KBr) 3271, 2934, 1632, 1520, 1346, 858, 843 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (1H, s), 7.90 (2H, d, J = 8.8 Hz), 7.55 (2H, d, J = 8.8 Hz), 7.14 (1H, d, J = 8.0 Hz), 6.98 (1H, t, J = 7.6 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.84 (1H, t, J = 7.6 Hz), 5.11 (1H, m), 3.08 (1H, t, J = 13.8 Hz), 2.91 (1H, m), 2.82 (1H, t, J = 12.2 Hz), 2.16−2.03 (3H, m), 1.61 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 147.8, 143.1, 133.7, 132.9, 128.7, 123.4, 122.7, 121.8, 120.3, 118.7, 116.6, 110.9, 47.6, 31.1, 28.0, 25.3; LRMS (EI) m/z 335 (M^+). Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.79; H, 5.36; N, 12.45.

1-(4-Nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-benzothieno[3,2-*b*]-azepine (7k). Compound **7k** (rotamers; 6.6:1.0) was synthesized from 2,3,4,5-tetrahydro-1*H*-benzothieno[3,2-*b*]azepine **6k** in a similar manner: pale yellow crystals; mp 180−183 °C; IR (KBr) 2941, 1647, 1522, 1348, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (0.26H, d, J = 8.8 Hz), 7.90 (1.74H, d, J = 8.8 Hz), 7.68 (0.26H, d, J = 0.8 Hz), 7.58 (0.87H, d, J = 8.4 Hz), 7.48 (1.74H, d, J = 8.8 Hz), 7.38 (0.13H, d, J = 8.4 Hz), 7.16−7.11 (3H, m), 5.10−5.06 (0.87H, m), 3.87−3.84 (0.13H, m), 3.11−3.04 (2H, m), 2.87−2.76 (1H, m), 2.20−2.09 (3H, m); 1.63−1.50 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 148.1, 142.3, 138.3, 136.0, 135.4, 134.8, 133.9, 128.9, 128.4, 127.4, 125.2, 124.5, 124.45, 124.43, 124.0, 123.8, 122.8, 122.7, 120.0, 48.3, 46.8, 37.1, 31.0, 29.1, 25.7, 23.8, 21.7; LRMS (EI) m/z 352 (M^+); HRMS (EI) m/z calcd for $C_{19}H_{16}N_2O_3S$ 352.0882 (M^+), found 352.0862.

2,3,4,5-Tetrahydro-1*H*-benzothieno[2,3-*b*]azepine (6l): colorless oil; IR (KBr) 3254, 2924, 1645, 1435, 752 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (1H, dd, J = 1.2 and 8.0 Hz), 7.42 (1H, dd, J = 1.2 and 8.0 Hz), 7.27 (1H, ddd, J = 1.2, 8.0, and 8.0 Hz), 7.11 (1H, ddd, J = 1.2, 8.0, and 8.0 Hz), 4.08 (1H, br s), 3.18 (2H, t, J = 5.6 Hz), 2.77 (2H, t, J = 6.0 Hz), 1.89 (2H, tt, J = 5.2 and 5.6 Hz), 1.73 (2H, tt, J = 5.2 and 6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 141.4, 132.6, 124.1, 121.65, 121.61, 119.4, 116.8, 49.1, 32.3, 26.7, 26.5; LRMS (EI) m/z 203 (M^+); HRMS (EI) m/z calcd for $C_{15}H_{13}NO$ 203.0769 (M^+), found 203.0753.

Dibenzosuberone oxime (5n): colorless crystals; mp 167−170 °C; IR (KBr) 3227, 1489, 1445, 1423, 997 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.86 (1H, br s), 7.56 (1H, d, J = 8.0 Hz), 7.45 (1H, d, J = 7.2 Hz), 7.31−7.23 (4H, m), 7.18 (1H, dd, J = 7.2 and 7.6 Hz), 7.11 (1H, d, J = 7.6 Hz), 3.15−3.12 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 138.8, 138.4, 134.4, 133.7, 130.4, 129.3, 129.2, 128.6, 128.3, 126.2, 125.6, 33.6, 32.1; LRMS (EI) m/z 223 (M^+); HRMS (EI) m/z calcd for $C_{15}H_{13}NO$ 223.0997 (M^+), found 223.0993.

5,6,11,12-Tetrahydrodibenz[*b*,*f*]azocine (6n): colorless crystals; mp 128−130 °C; IR (KBr) 3364, 2924, 1603, 1477 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.10−7.05 (3H, m), 7.02 (1H, dd, J = 1.6 and 8.0 Hz), 6.97 (1H, dd, J = 1.6 and 7.6 Hz), 6.89 (1H, ddd, J = 1.6, 7.6, and 8.0 Hz), 6.68 (1H, ddd, J = 1.6, 7.6, and 7.6 Hz), 6.49 (1H, dd, J = 1.6 and 8.0 Hz), 4.42 (2H, s), 3.93 (1H, br s), 3.29 (2H, t, J = 7.2 Hz), 3.17 (2H, t, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 140.6, 137.3, 131.1, 130.3, 129.5, 129.3, 127.3, 126.8, 126.5, 120.0, 119.0, 51.8, 35.5, 32.5; LRMS (EI) m/z 209 (M^+); HRMS (EI) m/z calcd for $C_{15}H_{15}N$ 209.1204 (M^+), found 209.1179.

1,2,3,4-Tetrahydro-*N*-hydroxy-1-naphthalenamine (8). To a stirred solution of tetralone oxime **5c** (161 mg, 1.00 mmol) in MeOH (2.0 mL) was added sodium cyanoborohydride (189 mg, 3.00 mmol) at rt followed by hydrogen chloride in MeOH (1.0 M, 5.0 mL) at 0 °C. After the mixture was stirred for 5 h at rt, the reaction was quenched with saturated aqueous $NaHCO_3$. The reaction mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash column chromatograpy on silica gel (EtOAc:*n*-hexane = 1:1) to give hydroxylamine **8** (124 mg, 76%) as a colorless solid: IR (KBr) 3155, 2941, 2882, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (1H, dd, J = 2.0 and 6.4 Hz), 7.25−7.09 (3H, m), 4.09 (1H, dd, J = 4.0 and 4.0 Hz), 2.84−2.68 (2H, m), 2.25−2.20 (1H, m), 1.95−1.89 (1H, m),

1.85−1.75 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5, 134.3, 129.6, 129.2, 127.4, 125.8, 59.3, 29.4, 25.8, 18.3; LRMS (EI) m/z 163 (M^+); HRMS (EI) m/z calcd for $C_{10}H_{13}NO$ (M^+) 163.0997, found 163.1015.

2,2-Dimethyl-1-tetralone oxime (5p) (1.4:1.0 mixture of (*E*)- and (*Z*)-isomers): colorless solid; IR (KBr) 3198, 2916, 1456, 949, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.32 (1H, br s), 8.48 (0.42H, d, J = 7.6 Hz), 7.80 (0.58H, d, J = 7.6 Hz), 7.29−7.14 (3H, m), 2.91 (0.83H, t, J = 6.8 Hz), 2.74 (1.17H, t, J = 6.0 Hz), 1.84 (0.83H, t, J = 6.8 Hz), 1.68 (1.17H, t, J = 6.0 Hz), 1.50 (3.50H, s), 1.21 (2.5H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 158.2, 140.5, 139.4, 132.4, 131.6, 129.4, 128.6, 127.9, 127.3, 126.5, 125.5, 125.3, 40.9, 37.09, 37.05, 36.8, 27.0, 26.5, 26.2, 24.3; LRMS (EI) m/z 189 (M^+); HRMS (EI) m/z calcd for $C_{12}H_{15}NO$ (M^+) 189.1154, found 189.1159.

3,3-Dimethyl-2-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine (7p): colorless oil; IR (neat) 2918, 1651, 1524, 1313, 862, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (2H, d, J = 8.0 Hz), 7.39 (2H, d, J = 8.0 Hz), 7.22 (1H, d, J = 7.6 Hz), 7.08 (1H, dd, J = 7.6 and 7.6 Hz), 6.87 (1H, dd, J = 7.6 and 7.6 Hz), 6.54 (1H, d, J = 7.6 Hz), 4.76 (1H, d, J = 13.2 Hz), 3.19 (1H, dd, J = 13.6 and 14.0 Hz), 2.73 (1H, dd, J = 6.0 and 14.0 Hz), 2.58 (1H, d, J = 13.2 Hz), 1.73 (1H, dd, J = 6.0 and 13.6 Hz), 1.45 (1H, dd, J = 13.6 and 13.6 Hz), 1.22 (3H, s), 1.02 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 147.9, 143.6, 142.4, 139.3, 130.2, 129.0, 128.0, 127.5, 127.1, 122.9, 56.6, 39.9, 35.7, 30.7, 29.4, 23.2; LRMS (EI) m/z 324 (M^+); HRMS (EI) m/z Calcd for $C_{19}H_{20}N_2O_3$ (M^+) 324.1474, found 324.1471.

3,3-Dimethyl-2-(4-nitrobenzoyl)-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (10p): pale yellow solid; IR (KBr) 2957, 1651, 1520, 1350, 860, 756 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (2H, dd, J = 1.2 and 8.0 Hz), 7.34 (2H, d, J = 8.0 Hz), 7.25−7.21 (2H, m), 7.05 (1H, dd, J = 7.6 and 7.6 Hz), 6.42 (1H, d, J = 7.6 Hz), 4.33 (2H, br s), 3.18 (2H, t, J = 5.2 Hz), 2.11 (2H, t, J = 5.2 Hz), 1.69 (6H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 148.5, 144.1, 138.7, 135.8, 130.3, 128.7, 128.3, 127.6, 125.9, 123.2, 59.5, 50.5, 40.8, 29.6, 25.0; LRMS (EI) m/z 324 (M^+); HRMS (EI) m/z calcd for $C_{19}H_{20}N_2O_3$ (M^+) 324.1474, found 324.1487.

4-(Methoxyphenyl) 4-(trifluoromethyl)phenyl ketone oxime (5q) (1:1 mixture of (*E*)- and (*Z*)-isomers): colorless solid; IR (KBr) 3256, 1605, 1512, 1325, 1256, 1163, 1130, 837 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (1H, d, J = 8.0 Hz), 7.58−7.61 (2H, m), 7.51 (1H, d, J = 8.0 Hz), 7.40−7.36 (2H, m), 6.99 (1H, d, J = 9.2 Hz), 6.87 (1H, d, J = 9.2 Hz), 3.87 (1.5H, s), 3.82 (1.5H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 160.4, 156.54, 156.50, 140.2, 136.6, 131.24 (q, J_{C-F} = 329 Hz), 131.21, 131.0 (q, J_{C-F} = 329 Hz), 129.6, 129.1, 128.5, 127.8, 125.3−125.2 (2C, m), 123.9, 114.0, 113.7, 55.32, 55.30; LRMS (EI) m/z 295 (M^+); HRMS (EI) m/z calcd for $C_{15}H_{12}F_3NO_2$ 295.0820 (M^+), found 295.0822.

***N*-(4-Trifluoromethyl)benzyl-4-methoxyaniline (6q):** yellow solid; IR (KBr) 3406, 1514, 1327, 1236, 1121, 1067, 820 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, J = 8.4 Hz), 7.46 (2H, d, J = 8.4 Hz), 6.76 (2H, d, J = 9.2 Hz), 6.55 (2H, d, J = 9.2 Hz), 4.34 (2H, s), 3.89 (1H, br s), 3.72 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 144.0 (d, J_{C-F} = 23 Hz), 141.9, 129.4 (q, J_{C-F} = 329 Hz), 127.5, 125.5 (q, J_{C-F} = 33 Hz), 122.8, 115.0, 114.2, 55.7, 48.7; LRMS (EI) m/z 281 (M^+); HRMS (EI) m/z calcd for $C_{15}H_{14}F_3NO$ 281.1027 (M^+), found 281.1032.

Phenyl 4-(trifluoromethyl)phenyl ketone oxime (5s) (mixture of (*E*)- and (*Z*)-isomers): colorless solid; IR (KBr) 3252, 2918, 1616, 1456, 1408, 1323, 1113, 1069, 994 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (1H, br s), 7.74−7.32 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 156.9, 139.7, 136.3, 135.4, 131.9, 131.0 (q, J_{C-F} = 321 Hz), 131.1 (q, J_{C-F} = 321 Hz), 129.9, 129.7, 129.5, 129.2, 128.6, 128.4, 128.2, 127.7, 125.3 (2C, m), 122.6, 122.5; LRMS (EI) m/z 265 (M^+); HRMS (EI) m/z calcd for $C_{14}H_{10}F_3NO$ 265.0714 (M^+), found 265.0707.

***N*-[4-(Trifluoromethyl)benzyl]aniline (6s):** pale yellow oil; IR (neat) 3420, 1605, 1504, 1327, 1163, 1123, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, J = 8.0 Hz), 7.45 (2H, d, J = 8.0 Hz), 7.15 (2H, dd, J = 7.2 and 8.0 Hz), 6.72 (1H, t, J = 7.2 Hz), 6.58 (2H, d, J = 8.0 Hz), 4.38 (2H, s), 4.09 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 143.7, 129.3 (q, J_{C-F} = 322 Hz), 129.2, 127.3, 125.5 (q, J_{C-F} = 37 Hz), 122.8, 117.9, 112.8, 47.8; LRMS (EI) m/z 251 (M^+); HRMS (EI) m/z calcd for $C_{14}H_{12}F_3N$ 251.0922 (M^+), found 251.0923.

Computational Details

All calculations in the present study were performed with the Gaussian 03 program[28] and by using the restricted Becke three-parameter plus Lee−Yang−Parr (B3LYP) DFT method with the 6-31G(d) basis set.[20] Stationary points were optimized without any symmetry assumption unless otherwise noted. By normal coordination analyses, zero and one imaginary frequency were confirmed for all minima and the saddle points, respectively. Then intrinsic reaction coordinate (IRC) analysis was performed from the saddle point.[29] Reaction coordinate s was based on a transition state as zero [1 hartree (au) = 2625.4997 kJ/mol]. Cartesian coordinates for representative stationary points are provided in Table S1 (Supporting Information).

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Supporting Information Available: Additional experimental, spectral data on compounds **5a**, **5g**, (*E*)-**5j**, (*Z*)-**5j**, **5k**, **5l**, **5r**, **6t**, **9t**, **5u**, **6u**, **9u**, **7z**, and **10z**, the new synthetic scheme (five steps) for the precursor ketone of **5k** from 2-iodobenzo[*b*]thiophene, the synthetic scheme of authentic samples for **6q** and **6s**, and tables of Cartesian coordinates for the representative stationary points. This material is available free of charge via the Internet at http://pubs.acs.org.

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