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# Contiguous radical pivaloyloxymethylation–directed C($sp^3$)–H iodination of *N*-tosyl cycloalkanecarbaldimine†

Shintaro Fujii,[a] Mayu Nakano,[a] Yousuke Yamaoka,[a] Kiyosei Takasu,[a] Ken-ichi Yamada,[a]* and Kiyoshi Tomioka[a,b]

[a]*Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan*
[b]*Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe 610-0395, Japan*

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ABSTRACT

A reaction of *N*-tosyl cycloalkanecarbaldimines with iodomethyl pivalate was initiated by triethylborane to give pivaloyloxymethylated products bearing 3-iodocycloalkyl groups. Radical addition of pivaloyloxymethyl to imines generates aminyl radicals, which then regioselectively cleave C–H bonds at the 3-position of the cycloalkane moieties. The resulting carbon-centered radicals are trapped with iodine. DFT calculations rationalized stereo- and regioselectivity.





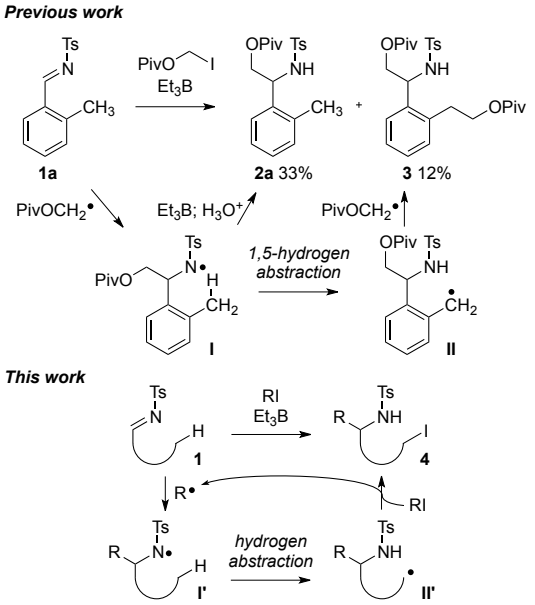
Regioselective functionalization of an unactivated (non-acidic) C–H bond is an important target of modern organic chemistry, and has become one of the most extensively studied research fields in recent years. Many examples have been reported on directed functionalization of C($sp^2$)–H and allylic or benzylic C–H bonds by transition metal catalysis.[1] Recently, C($sp^3$)–H bond functionalization has also been reported.[2] On the other hand, functionalization of C($sp^3$)–H bonds by radical chemistry has a long history.[3] For example, radical halogenation of hydrocarbons and autoxidation of cumene for phenol/acetone production are important processes in industry. Regioselectivity of radical C($sp^3$)–H bond functionalization depends on bond dissociation energy, and the weakest C–H bond in a molecule is preferentially cleaved and functionalized. Hence, benzylic and allylic positions, and α-positions of heteroatoms are usually the site of functionalization,[4] and it is difficult to control the regioselectivity when a molecule has several C–H bonds with similar dissociation energies.[5] Directed C($sp^3$)–H functionalization by a radical process was also developed to control regioselectivity.[6] The Barton nitrite ester reaction[7] and the Hofmann–Löffler reaction[8] are well-known examples. In these reactions, oxyl and aminyl radicals are generated by the scission of O–heteroatom and N–heteroatom bonds, respectively, and abstract a hydrogen atom in a 1,6-relationship (1,5-hydrogen abstraction). Another strategy to generate oxyl and aminyl radicals involves the addition of a C-centered radical to C=O and C=N bonds. This strategy has an attractive aspect that C–C bond formation and the generation of a reactive oxyl or aminyl radical are realized at the same time. However, to the best of our knowledge, oxyl and aminyl radicals that are generated by this strategy have never been applied to cascade C–H bond cleavage.[9] Herein, we report that an aminyl radical generated by the addition of a C-centered radical to a C=N bond undergoes 1,5-hydrogen abstraction followed by iodination under certain limited conditions.

We previously reported a radical acyloxymethylation reaction of imines to give amino alcohols.[10,11] In the reaction of iodomethyl pivalate and *N*-tosyl-*o*-tolualdimine **1a**, however, the expected adduct **2a** was produced only in 33% yield, and dipivalate **3** was obtained in 12% yield (Scheme 1, above).[12] The production of **3** is rationalized by the reaction of pivaloyloxymethyl radical and benzyl radical **II**, formed *via* 1,5-hydrogen abstraction of amidyl radical **I**. This observation led us to initiate the development of radical addition to imines followed by C($sp^3$)–H iodination (Scheme 1, below). The addition of an alkyl radical to the C=N bond of **1** results in the formation of amidyl radical **I'**. If this radical abstracts an intramolecular non-benzylic hydrogen atom, non-benzylic alkyl radical **II'** is generated. Iodine abstraction of **II'** from alkyl iodide produces the iodinated product **4** and alkyl radical R•, which propagates the radical chain.

We began this study using *N*-tosyl-pentanaldimine **1b**, which has γ-hydrogen to be abstracted. To a solution of **1b** (0.2 mmol)

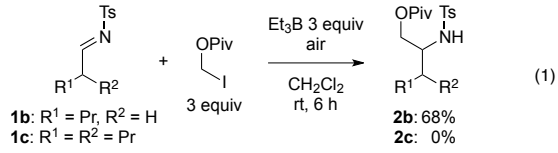
† This paper is dedicated to the memory of the late professor Harry Wasserman.

* Corresponding author. Tel.: +81-75-753-4573; fax: +81-75-753-4604; e-mail: yamak@pharm.kyoto-u.ac.jp



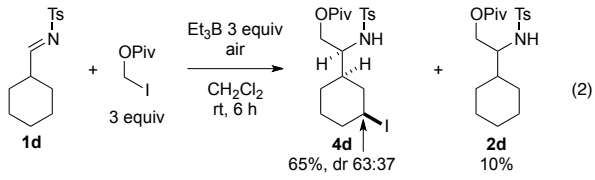

**Scheme 1.** Expected C($sp^3$)–H iodination based on the observed byproduct formation.

and iodomethyl pivalate (0.6 mmol) in dichloromethane (0.4 mL), a 1 M solution of triethylborane in hexane (0.6 mL, 0.6 mmol) was added, and the mixture was stirred for 6 h at rt under ordinary atmosphere. The reaction gave only adduct **2b** in 68% yield, and no iodinated product was produced (eq 1). We speculated that the use of imine **1c**, which was derived from 2-butylpentanal, should increase the possibility that the resulting aminyl radical takes a suitable conformation for the 1,5-hydrogen abstraction. However, the isomerization to the corresponding enamide took place, and no radical addition proceeded.



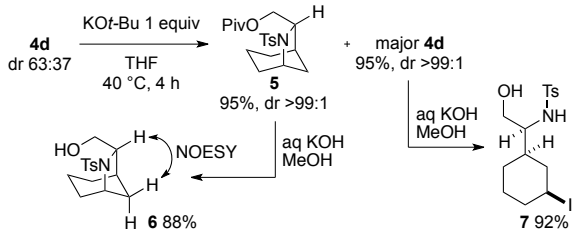

(1)

To our delight, when **1d** was used, the iodinated product **4d** was isolated in 65% yield along with **2d** in 10% yield (eq 2). Although **4d** has four possible diastereomers, it was obtained as a 63:37 mixture of two diastereomers concerning the stereogenic center on the iodinated carbon.



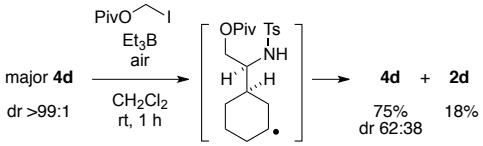

(2)

The stereochemistry of the diastereomers was determined as shown in Scheme 2: When **4d** with 63:37 diastereomer ratio (dr) was treated with potassium *tert*-butoxide in THF at 40 °C, only the minor diastereomer of **4d** underwent the cyclization to give the bicyclo compound **5**, and the major diastereomer was recovered almost quantitatively (95%). The NOESY correlation of alcohol **6**, which was obtained by hydrolysis of **5**, determined the relative configuration of **6**, which, in turn, assigned the stereochemistry of the minor isomer of **4d**. The relative configuration of major **4d** was determined after hydrolysis into alcohol **7** by X-ray crystallography.[13]




**Scheme 2.** Derivatization of **4d** to determine the stereochemistry.

The observed diastereoselectivity is opposite to the reported axial selectivity in halogenation of substituted cyclohexyl radicals.[14] This disagreement and the reported A-value of iodine atom (0.47),[15] corresponding to 68% equatorial population, indicate that the diastereoselectivity was thermodynamically controlled. Indeed, formation of the minor isomer was observed when major **4d** was exposed to the radical reaction conditions, probably through the deiodination–reiodination sequence (Scheme 3).



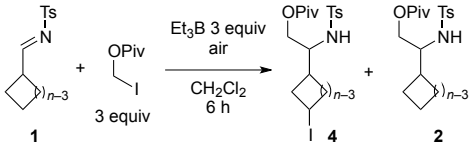

**Scheme 3.** Epimerization of **4d** under the radical reaction conditions.

The use of iodomethyl pivalate was critical. When other radical precursors such as ethyl iodide, isopropyl iodide, and *tert*-butyl iodide were used in the reaction, complex mixtures were produced. Since ethyl and isopropyl radicals undergo addition to *N*-tosyl imines,[16] the results probably suggest inferior iodine donating abilities of ethyl and isopropyl iodides to that of iodomethyl pivalate. *tert*-Butyl radical likely failed to undergo the addition reaction, because no addition product was obtained when *tert*-butyl iodide was used in place of ethyl and isopropyl iodide in the reaction of *N*-tosyl-benzaldimine.

The ring size of aldimines also has a significant effect (Table 1). Although 5-membered ring cyclopentanecarbaldimine **1g** gave the iodinated product **4g** in 75% yield along with **2g** in 15% yield (entry 3), 3-, 4-, and 7-membered imines **1e**, **1f**, and **1h** only produced non-iodinated products **2e**, **2f**, and **2h** in 68%, 72%, and 68% yields, respectively (entries 1, 2, and 5). Interestingly, cyclopentane **4g** was obtained as a mixture of all the possible diastereomers (dr 38:38:18:6; entry 3), while the relative configuration at the two adjacent methine carbons of cyclohexane **4d** was perfectly controlled (eq 2).

Next, we examined the conformational effect of imines. Because the 1,5-hydrogen abstraction requires axial orientation of the aminyl functionality in the transition state, we expected that fixing the orientation of the imine moiety to the equatorial direction might force 1,4-hydrogen abstraction[17] to occur (Scheme 4). The reaction of *trans*-4-*tert*-butylcyclohexanecarbaldimine **1i**, however, gave only adduct **2i** in 63% yield, and no product of 1,4-hydrogen abstraction (**4i**) was observed. Accordingly, it should be important that the ring has conformational flexibility to

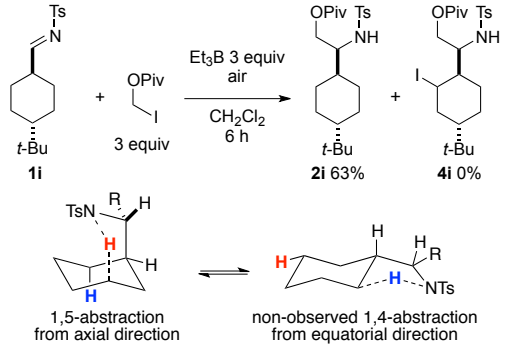
**Table 1.** Effect of the ring size of imines **1**.




**1** **4** **2**

| entry | **1** | *n* | **4** (% yield) | **2** (% yield) |
|---|---|---|---|---|
| 1 | **1e** | 3 | **4e** (0) | **2e** (68) |
| 2 | **1f** | 4 | **4f** (0) | **2f** (72) |
| 3 | **1g** | 5 | **4g** (75)[a] | **2g** (15) |
| 4[b] | **1d** | 6 | **4d** (65)[c] | **2d** (10) |
| 5 | **1h** | 7 | **4h** (0) | **2h** (68) |

[a] A 38:38:18:6 mixture of diastereomers. [b] Data from eq 2 for comparison. [c] A 63:37 mixture of diastereomers.




**Scheme 4.** Non-observed 1,4-hydrogen abstraction.

allow the aminyl functionality to be in the axial position for the hydrogen abstraction to occur. This may also be responsible for the observed ring size effect (Table 1).

As mentioned above, the stereoselectivity was significantly different between the reactions of **1d** and **1g**; only one diastereomer concerning the adjacent stereocenters was produced in the reaction of **1d**, while that of **1g** gave both of the two possible diastereomers. To obtain insight into this difference, the transition states (TS) of the hydrogen abstraction were calculated for model molecules of cyclohexane **A** and cyclopentane **B** (Figure 1).[18] The calculations revealed that the sulfonyl group is required to eclipse either the methyl group or hydrogen on the N-attached carbon in the TS, and the latter conformation minimizes the energy. When the aminyl radical abstracts the non-boldfaced axial

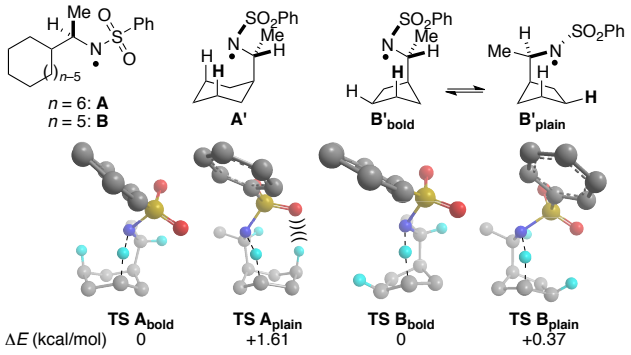



**Figure 1.** Chem 3D perspective view of TS for **A** and **B** calculated at B3LYP/6-31G** (only H atoms in the structural formulas are shown).

hydrogen of **A'**, the sulfonyl group is located over the cyclohexane ring (**TS** $\mathbf{A}_{plain}$). As a result, steric repulsion is caused between the sulfonyl group and the boldfaced axial hydrogen. In the TS to abstract the boldfaced hydrogen, the sulfonyl group is directed out of the ring, and there is no such repulsion (**TS** $\mathbf{A}_{bold}$). The energy difference between **TS** $\mathbf{A}_{bold}$ and **TS** $\mathbf{A}_{plain}$ was 1.61 kcal/mol (94:6 selectivity at 25 °C) at B3LYP/6-31G** level of theory.[19]

Based on calculations, the hydrogen abstraction of **B** occurs *via* envelope conformations $\mathbf{B'}_{bold}$ or $\mathbf{B'}_{plain}$. Although the sulfonyl group is located over the ring in **TS** $\mathbf{B}_{plain}$, the hydrogen nearest the sulfonyl group is not axial but isoclinal (the boldfaced H). Therefore, the steric repulsion in **TS** $\mathbf{B}_{plain}$ is likely smaller than that in **TS** $\mathbf{A}_{plain}$. Indeed, the energy difference between **TS** $\mathbf{B}_{bold}$ and **TS** $\mathbf{B}_{plain}$ was only 0.37 kcal/mol (65:35 selectivity at 25 °C).[20] These results rationalize the observed difference of selectivity in the reactions of **1d** and **1g**. The free energies of the TS for the 1,4-hydride abstraction of **1d** and **1g**, which was not observed, were 2.81 and 2.60 kcal/mol higher than those for the 1,5-hydride abstraction, respectively (99:1 selectivity at 25 °C). This is also in agreement with the observed regioselectivity.

In conclusion, *N*-tosyl-aminyl radicals, resulting from the addition of pivaloyloxymethyl radical to *N*-tosyl-imines, underwent 1,5-hydrogen abstraction when cyclopentane- or cyclohexanecarbaldimines were utilized. Not only the ring size, but also the conformational flexibility of the ring and the choice of the iodine source were crucial factors. The reaction was applicable to the construction of a 6-azabicyclo[3.2.1]octane framework. These findings are informative for designing novel radical reactions, despite the limited scope of the reaction.

## Acknowledgments

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## References and notes

1 (a) Ryabov, A. D. *Synthesis* **1985**, 233. (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (c) *Activation and Functionalization of C–H Bonds;* Goldberg, K. I., Goldman, A. S. Eds.; ACS Symposium Series 885; American Chemical Society: Washington, DC, 2002. (d) *Directed Metallation;* Chatani, N. Ed.; Topics in Organometallic Chemistry 24; Springer-Verlag: Berlin, 2007. (e) *C–H Activation;* Yu, J.-Q., Shi, Z. Eds.; Topics in Current Chemistry 292; Springer-Verlag: Berlin, 2010.

2 Selected recent examples: (a) Chen, K.; Shi, B.-F. *Angew. Chem. Int. Ed.* **2014**, *53*, 11950. (b) Zhu, R.-Y.; He, J.; Wang, X.-C.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 13194. (c) Xiao, K.-J.; Lin, D. W.; Miura, M.; Zhu, R.-Y.; Gong, W.; Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 8138. (d) Al-Amin, M.; Arisawa, M.; Shuto, S.; Ano, Y.; Tobisu, M.; Chatani, N. *Adv. Synth. Catal.* **2014**, 356. 1631. (e) Nadres, E. T.; Santos, G. I. F.; Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2013**, *78*, 9689. (f) Zhang, S.-Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (g) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (h) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

3 (a) Egloff, G.; Schaad R. E.; Lowry, Jr., C. D. *Chem. Rev.* **1930**, *8*, 1. (b) *Free Radicals, Vol. 1 & 2;* Kochi, J. K. Ed.; Wiley: New York, 1973. (c) Hill, C. L. *Activation and Functionalization of Alkanes;* Wiley: New York, 1989.

4 (a) Kamijo, S.; Hirota, M.; Tao, K.; Watanabe, M.; Murafuji, T. *Tetrahedron Lett.* **2014**, *55*, 5551. (b) Amaoka, Y.; Nagatomo, M.; Watanabe, M.; Tao, K.; Kamijo, S.; Inoue, M. *Chem. Sci.* **2014**, *5*, 4339.

(c) Bergonzini, G.; Schindler, C. S.; Wallentin, C.-J.; Jacobsen, E. N. Stephenson, C. R. J. *Chem. Sci.* **2014**, *5*, 112. (d) Amaoka, Y.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2013**, *15*, 2160. (e) Sonobe, T.; Oisaki, K.; Kanai, M. *Chem. Sci.* **2012**, *3*, 3249. (f) Kamon, T.; Irifune, Y.; Tanaka, T.; Yoshimitsu, T. *Org. Lett.* **2011**, *13*, 2674. (g) Chen, M. S.; White, M. C. *J. Am. Chem. Soc.* **2004**, *126*, 1346. (h) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Tomioka, K. *J. Org. Chem.* **2004**, *69*, 1531.

5 (a) Yoshimitsu, T.; Matsuda, K.; Nagaoka, H.; Tsukamoto, K.; Tanaka, T. *Org. Lett.* **2007**, *9*, 5115. (b) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783. (c) Yoshimitsu, T.; Arano, Y.; Nagaoka, H. *J. Am. Chem. Soc.* **2005**, *127*, 11610. (d) Yamada, K.; Fujihara, H.; Yamamoto, Y.; Miwa, Y.; Taga, T.; Tomioka, K. *Org. Lett.* **2002**, *4*, 3509.

6 Selected recent examples: (a) Hashimoto, T.; Hirose, D.; Taniguchi, T. *Angew. Chem. Int. Ed.* **2014**, *53*, 2730. (b) Chen, H.; Chiba, S. *Org. Biomol. Chem.* **2014**, *12*, 42. (c) Hennessy, E. T.; Betley, T. A. *Science* **2013**, *340*, 5911. (d) Motiwala, H. F.; Gülgeze, B.; Aubé, J. *J. Org. Chem.* **2012**, *77*, 7005. (e) Voica, A.-F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P. S. *Nat. Chem.* **2012**, *4*, 629. (f) Kundu, R.; Ball, Z. T. *Org. Lett.* **2010**, *12*, 2460. (g) Kamijo, S.; Hoshikawa, T.; Inoue, M. *Tetrahedron Lett.* **2010**, *51*, 872. (h) Allen, C. P.; Benkovics, T.; Turek, A. K.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 12560.

7 (a) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640. (b) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 4076.

8 (a) Hofmann, A. W. *Ber.* **1883**, *16*, 558. (b) Hofmann, A. W. *Ber.* **1885**, *18*, 5. (c) Hofmann, A. W. *Ber.* **1885**, *18*, 109.

9 Cascade addition to multiple bonds: (a) Bowman, W. R.; Stephenson, P. T.; Young, A. R. *Tetrahedron* **1996**, *52*, 11445. (b) Benati, L.; Bencivenni, G.; Leardini, R.; Minozzi, M.; Nanni, D.; Scialpi, R.; Spagnolo, P.; Zanardi, G.; Rizzoli, C. *Org. Lett.* **2004**, *6*, 417. (c) Jaramillo-Gómez, L. M.; Loaiza, A. E.; Martin, J.; Ríos, L. A.; Wang, P. G. *Tetrahedron Lett.* **2006**, *47*, 3909. (d) Servais, A.; Azzouz, M.; Lopes, D.; Courillon, C.; Malacria, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 576. (e) Beaume, A.; Courillon, C.; Derat, E.; Malacria, M. *Chem. Euro. J.* **2008**, *14*, 1238.

10 Yamada, K.; Nakano, M.; Maekawa, M.; Akindele, T.; Tomioka, K. *Org. Lett.* **2008**, *10*, 3805.

11 Our other related works: (a) Fujii, S.; Konishi, T.; Matsumoto, Y.; Yamaoka, Y.; Takasu, K.; Yamada, K. *J. Org. Chem.* **2014**, *79*, 8128. (b) Yamada, K.; Konishi, T.; Nakano, M.; Fujii, S.; Cadou, R.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2012**, *77*, 5775. (c) Akindele, T.; Yamada, K.; Sejima, T.; Maekawa, M.; Yamamoto, Y.; Nakano, M.; Tomioka, K. *Chem. Pharm. Bull.* **2010**, *58*, 265. (d) Yamada, K.; Maekawa, M.; Yamamoto, Y.; Nakano, M.; Akindele, T.; Tomioka, K. *Tetrahedron Lett.* **2009**, *50*, 6040. (e) Yamada, K.; Maekawa, M.; Akindele, T.; Yamamoto, Y.; Nakano, M.; Tomioka, K. *Tetrahedron* **2009**, *65*, 903. (f) Akindele, T.; Yamada, K.; Tomioka, K. *Acc. Chem. Res.* **2009**, *42*, 345.

12 Yamada, K.; Konishi, T.; Nakano, M.; Fujii, S.; Cadou, R.; Yamamoto, Y.; Tomioka, K. *J. Org. Chem.* **2012**, *77*, 1547.

13 CCDC-1029136 contains the supplementary crystallographic data of **7**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

14 Damm, W.; Giese, B.; Hartung, J.; Hasskerl, T.; Houk, K. N.; Hüter, O.; Zipse, H. *J. Am. Chem. Soc.* **1992**, *114*, 4067.

15 Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.* **1971**, *3*, 139.

16 Miyabe, H.; Ueda, M.; Naito, T. *Chem. Commun.* **2000**, 2059.

17 1,4-Hydrogen abstraction is not common but was reported: (a) Nikishin, G. I.; Troyansky, E. I.; Lazareva, M. I. *Tetrahedron Lett.* **1985**, *26*, 3743. (b) Chen, S.-H.; Huang, S.; Gao, Q.; Golik, J.; Farina, V. *J. Org. Chem.* **1994**, *59*, 1475. (c) Crich, D.; Sun, S.; Brunckova, J. *J. Org. Chem.* **1996**, *61*, 605. (d) Montevecchi, P. C.; Navacchia, M. L. *Tetrahedron Lett.* **1996**, *37*, 6583. (e) Gulea, M.; López-Romero, J. M.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2000**, *2*, 2591. (f) Ryu, I.; Fukuyama, T.; Tojino, M.; Uenoyama, Y.; Yonamine, Y.; Terasoma, N.; Matsubara, H. *Org. Biomol. Chem.* **2011**, *9*, 3780.

18 All the calculations were performed using Gaussian 09W program at B3LYP/6-31G(d,p) level of theory. The TS geometries were verified by vibrational frequency analysis.

19 In **TS $A_{plain}$**, the dihedral angle of C–C–C–N is forced to be smaller (25°), probably to minimize the steric repulsion, than that in **TS $A_{bold}$** (51°). This torsional strain is likely the reason for the elevated energy.

20 The dihedral angles of C–C–C–N are 41° and 56° in **TS $B_{plain}$** and **TS $B_{bold}$**, respectively. The observed correlation between the difference of the dihedral angles and that of the energies supports the above speculation that the torsional strain would be a major factor in the TS energy.

## Supplementary Material

Experimental and computational details, and characterization data and NMR spectra of new compounds are available as a supplementary material.