Heteroatom Chemistry
Volume 19, Number 6, 2008

Bismuth-Catalyzed Cyclization of Amino-1,6-enynes

Kimihiro Komeyama, Motoyoshi Miyagi, and Ken Takaki

Department of Chemistry and Chemical Engineering, Graduate School of Engineering, Hiroshima University, 1-4-1 Kagamiyama, Higahi-Hiroshima, 739-8527, Japan

Received 12 November 2007; revised 6 February 2008, 5 April 2008

ABSTRACT: *$Bi(OTf)_3$ effectively catalyzed the cyclization of amino-1,6-enynes, leading to bicyclic amine and cyclopentadienyl amino compounds. The selectivity of the products depends on the substitution pattern of the olefinic moiety. ^{19}F NMR trace experiment of the reaction and other results indicate a novel alkynophilicity of the bismuth species.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:644–648, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20490

INTRODUCTION

Heterofunctionalization of carbon–carbon multiple bonds is one of the most desirable and elegant tool for the construction of carbon-heteroatom tethers from simple substrate, and the methodology has been widely recognized as a key step in organic chemistry [1–3]. This transformation was rapidly developed by a high alkynophilicity of the noble metal catalysts such as gold, silver, platinum, and mercury, which accomplished a diverse set of nucleophilic addition of *N*- and *C*-nucleophiles to olefins [4,5], alkynes [6–9], allenes [10,11], and enynes [12–14]. Despite excellent results in this field, these complexes are expensive, partially toxic, and not suitable for industrial use. Therefore, the development of more practical catalyst system is highly desired. On the other hand, we have recently reported iron salts-catalyzed intramolecular heterofunctionalization of unactivated olefins with amines, alcohols, and carboxylic acids to provide the corresponding heterocyclic compounds, respectively, in excellent yields [15–17]. In these reports, the iron could activate both donors and acceptors via dual mode. However, the catalyst showed lower activity for intramolecular nucleophilic addition of amino group to alkynes than that to olefins. Thus, we researched other catalysts that can be used for alkyne activation free from environmental problem. Gratifyingly, $Bi(OTf)_3$ was found to reveal a high alkynophilicity. That is, the catalyst promoted cyclization of amino-1,6-enynes to yield aminobicyclic compounds, wherein the reaction mode drastically depended on a stability of the cationic intermediate. In this communication, we would like to report these unprecedented results.

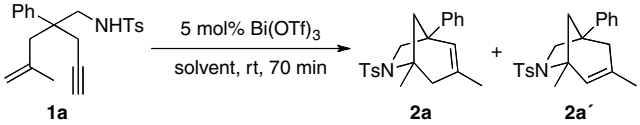
RESULTS AND DISCUSSION

When amino-1,6-enyne **1a** was treated with 5 mol% of $Bi(OTf)_3$ at room temperature for 70 min in acetonitrile, bicyclic materials **2a** and **2a′** were obtained in 93% total yield with a ratio of 86/14 (Table 1, entry 1). Optimization studies revealed that the reaction is sensitive to the solvent. Thus, MeCN, DCE, and toluene were suitable for the transformation, whereas the lower conversion and product selectivity were observed with $MeNO_2$ and 1,4-dioxane.

$Bi(OTf)_3$ was effective catalyst in the transformation to comparison with other representative transition metals as illustrated in Table 2. In the absence of the catalyst, the reaction did not proceed at all under the similar conditions. Hard Lewis acids such as $AlCl_3$ and $Sc(OTf)_3$ were ineffective for the cyclization to give a slight yield of bicyclic product **2** with high **2a**-selectivity (Table 1, entries 1 and 2). Similar low activity and no conversion of **1a** were

Correspondence to: Kimihiro Komeyama; e-mail: kkome@hiroshima-u.ac.jp.

TABLE 1 Solvent Effect for $Bi(OTf)_3$-Catalyzed Cyclization of **1a**

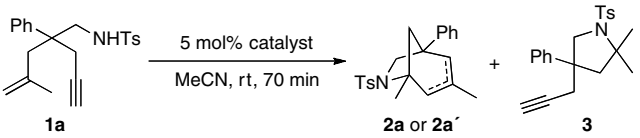


1a **2a** **2a´**

Entry	*Solvent*	*Conversion (%)*[a]	*Total Yield (%)*[a,b]	
1	MeCN	97	93	(86/14)
2	DCE	100	82	(76/24)
3	Toluene	83	75	(74/26)
4	$MeNO_2$	93	53	(79/21)
5	1,4-Dioxane	22	15	(68/32)

[a]Determined by ^{1}H NMR.
[b]Parenthesis value indicates isomeric ratio of **2a** and **2a′**.

TABLE 2 Catalyst Screening for Cyclization of **1a**



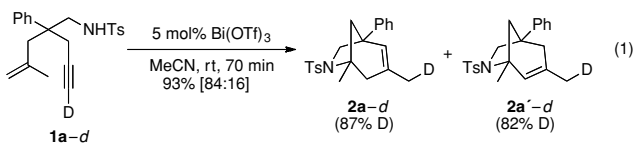
1a **2a** or **2a´** **3**

			Product and Yield (%)[a,b]	
Entry	*Catalyst*	*Conversion (%)*[a]	**2**	**3**
1	$AlCl_3$	4	4 (100:0)	0
2	$Sc(OTf)_3$	12	7 (99 > :1)	4
3[c]	$Fe(OTf)_3$	44	10 (91: 9)	9
4	$Fe(OTf)_2$		No reaction	
5	$Bi(OTf)_3$	97	93 (86:14)	0
6	$Ni(OTf)_2$		No reaction	
7	$Zn(OTf)_2$	4	0	2
8	$PdCl_2$	60	2 (99 > :1)	22
9	$PtCl_2$	100	0	29
10[d]	AgOTf	42	9 (99 > 1)	0

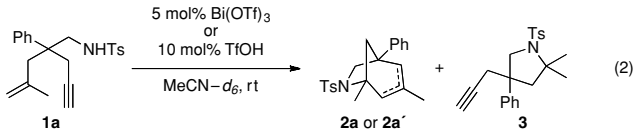
[a]Determined by ^{1}H NMR.
[b]Parenthesis value indicates isomeric ratio of **2a** and **2a′**.
[c]Reaction was carried out at 80°C for 2 h.
[d]Reaction was carried out for 14 h.

observed in the case of borderline acid such as Fe(II), Ni(II), and Zn(II) triflates (entries 4 with 6 and 7), but $Fe(OTf)_3$ catalyst yielded a moderate conversion of the substrate, albeit with low product contribution, wherein any unassailable oligomers were formed (entry 3). Interestingly, although π-acid catalyst, $PdCl_2$ and $PtCl_2$, afforded moderate to high consumption of **1a**, monocyclic amine **3** and the oligomer were mainly produced (entries 8 and 9). In contrast, exposure of **1a** with AgOTf catalyst gave a negligible yield of **2** (9%) by NMR measurement of the complexed reaction mixture. These findings indicate that $Bi(OTf)_3$ plays an individual role in this cyclization.

To get information about the construction of carbon-skeleton of the products **2a** and **2a′**, the reaction of deuterated aminoenyne **1a**-*d* (95% D) was carried out under similar conditions (Eq. (1)). The reaction smoothly proceeded to yield a mixture of isomers, **2a**-*d* and **2a′**-*d*, wherein deuterium was incorporated at an allylic methyl group (**2a**-*d*: 87% D, **2a′**-*d*: 82% D). This result provided the definite evidence for the origin of the product structure: The skeleton was formed by connection of olefin with both alkyne and amine moieties.



1a–*d* (95% D) **2a**–*d* (87% D) **2a′**–*d* (82% D)



1a **2a** or **2a´** **3**

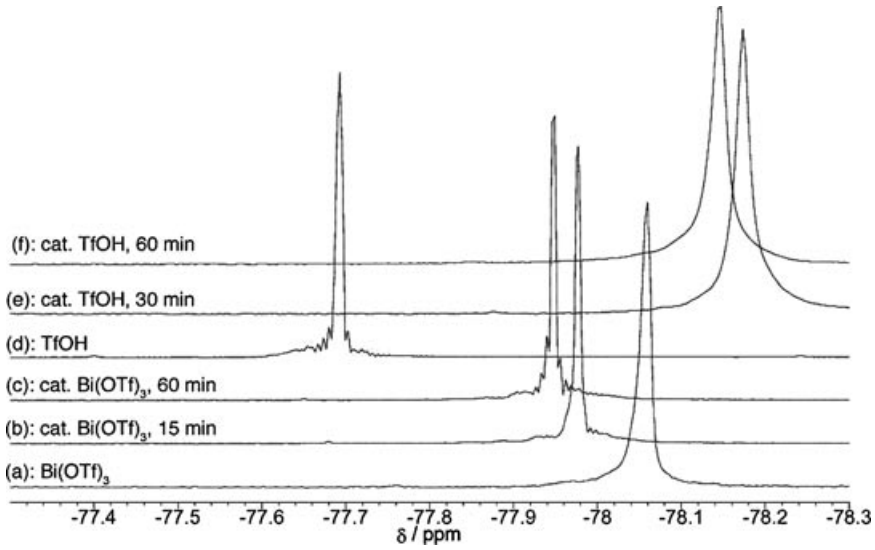
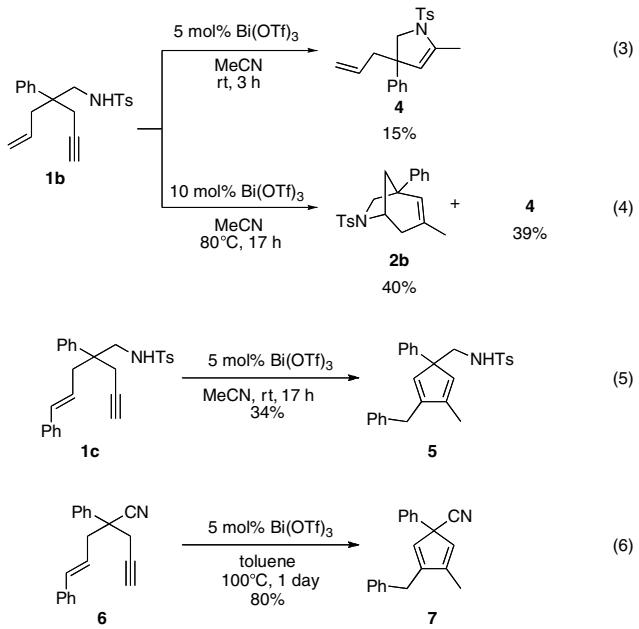
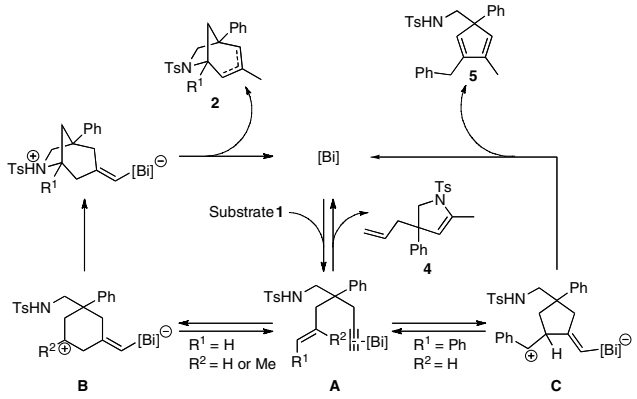


FIGURE 1 ^{19}F NMR monitoring of the reaction of **1a** in acetonitrile-d_3 with $Bi(OTf)_3$ (5 mol%); (b) after 15 min; (c) 60 min, and with TfOH (15 mol%); (e) after 30 min; (f) after 60 min. The spectra (a) and (d) indicate the resonance of $Bi(OTf)_3$ and TfOH in acetonitrile-d_3, respectively.

It remains unclear whether the present cyclization would be caused by Brønsted acid, TfOH, or not, which may be generated from the bismuth catalyst in situ. Because Brønsted acids are known to activate the siloxy alkynes, they may exhibit a similar effect for terminal alkyne moiety of **1a** [18]. To prove this point, the reactions of **1a** with $Bi(OTf)_3$ and TfOH catalysts were compared by ^{19}F NMR monitoring (Eq. (2)). If TfOH was generated in the reaction, signal of the acid or its amine salt should be observed in the spectra. As illustrated in Fig. 1, when aminoenyne **1a** was treated with catalytic amount of $Bi(OTf)_3$ (δ–78.06 ppm, **a**), its signal completely disappeared at once, and then a new signal appeared at from −77.98 to −77.95 ppm in the period of 15–60 min without any other signals (**b** and **c**). In the meantime, most of **1a** has been converted to only **2a** and **2a′**. In contrast, the reaction with TfOH (δ–77.69 ppm, **d**) exhibited a broad signal at from −78.17 to −78.15 ppm in the period of 30–60 min (**e** and **f**), giving rise to the products **2a** and **2a′** in 75% total yield together with pyrrolidine **3a** (8%) as a minor product. However, the conversion of **1a** with TfOH was much slower than that with $Bi(OTf)_3$, even it took 5 h to reach to 95% conversion. Therefore, it is likely that the present reaction is catalyzed by $Bi(OTf)_3$, not by TfOH.

To test the generality of the reaction, we tried out the reaction of differently substituted aminoenynes. The reaction of **1b** gave dihydropyrrole **4** in low yield under standard conditions. It is, however, noteworthy that monocyclic amine **4** was derived from only alkynyl unit of **1b**, not from olefinic moiety, indicating a strong alkynophilicity of $Bi(OTf)_3$ (Eq. (3)). Increase of catalyst lording (10 mol%) and reaction temperature (80°C) changed the product selectivity to provide aminobicyclic alkene **2b** as a single isomer in 40% yield along with **4** (39% yield) (Eq. (4)). In contrast, 1-phenyl substituted aminoenyne **1c** showed different reaction manner. Thus, the enyne cyclization took place to yield cyclopentadiene **5** without participation of amino moiety (Eq. (5)). Interestingly, treatment of enyne **6** with the bismuth catalyst furnished similar cyclopentadiene derivative **7**, even so in different conditions (Eq. (6)).





SCHEME 1 Plausible reaction mechanisms.

Based on these results, the reaction process could be explained as depicted in Scheme 1. Thus, preferential coordination of the bismuth species to the alkyne moiety of **1** would yield a key intermediate **A**. Then, in the case of 1,1-disubstituted olefin **1a** ($R^1 = H$; $R^2 = Me$), **A** would exclusively changed to the tertiary carbocation species **B**, which was followed by nucleophilic addition of the amino group to give the product **2** after protonation and isomerization. In contrast, because the intermediate **B** derived from **1b** ($R^1 = R^2 = H$) was less stable secondary cation than that from **1a**, direct amination of alkyne moiety of the corresponding intermediate **A** could compete with the cyclizations via **B**, leading to both **4** and **2b**, respectively. In addition, substrate **1c** ($R^1 = Ph$; $R^2 = H$) would choice the intermediate **C** due to high stability of benzylic cation. β-Proton elimination of **C** followed by isomerization, instead of intramolecular addition of amino group would yield the cyclopentadienyl derivative **5**.

CONCLUSION

In conclusion, we have demonstrated a novel alkynophilicity of $Bi(OTf)_3$ catalyst in the cyclization of amino-1,6-enynes. The reaction mode depended on the substitution of the olefinic moiety because of the stability of the cationic intermediate at all. In comparison with other transition metal-catalyzed cyclizations, the bismuth catalyst is helpful for organic transformation due to its easy handling and commercial availability. In the demonstrated transformation, we found that the bismuth employs an individual effect to activate amino enynes. The actual role of the bismuth is not yet clear, but the authors believe that the catalyst acts as a dual activator of both amino group and carbon–carbon multiple bonds, because the borderline acid has kept a middle LUMO energy between hard and soft acid ones [19,20]. Studies on the product selectivity and the reaction scope are currently in progress.

EXPERIMENTAL

Representative Procedure for Tandem Hydroamination of **1a**

A solution of aminoenyne **1a** (51.5 mg, 0.14 mol) and $Bi(OTf)_3$ (4.6 mg, 7.0 μmol) in DCE (1.4 mL) was stirred at room temperature for 70 min under N_2 atmosphere. The reaction mixture was passed through a short silica-gel column with ether eluent. Purification of the crude product by column chromatography (hexane/AcOEt = 10:1, SiO_2) gave the product **2a** and **2a′** in 70% and 5% yields, respectively.

*3,5-Dimethyl-1-phenyl-6-tosyl-6-azabicyclo[3.2.1]-oct-2-ene (**2a**).* Isolated as a colorless oil; ^{1}H NMR ($CDCl_3$, 270.05 MHz) δ: 1.46 (3H, s), 1.66, (3H, s), 2.09 (2H, s), 2.12 (1H, d, J = 17.8 Hz), 2.40 (3H, s), 2.65 (1H, d, J = 17.8 Hz), 3.51 (1H, d, J = 8.1 Hz), 4.00 (1H, d, J = 8.1 Hz), 5.53 (1H, s), 7.19–7.35 (7H, m), 7.74 (2H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 21.3, 21.7, 25.4, 44.5, 45.9, 49.0, 62.2, 66.0, 125.8, 126.7, 126.8, 128.5, 129.0, 129.2, 129.6, 133.4, 139.1, 142.5, 143.2; LRMS *m/z*: 367 (M^+, 2), 184 (36), 169 (48), 91 (100), 65 (42); HRMS calcd for $C_{22}H_{25}NO_2S$ (M^+) 367.1606, found 367.1615.

*3,5-Dimethyl-1-phenyl-6-tosyl-6-azabicyclo[3.2.1]-oct-3-ene (**2a′**).* Isolated as a colorless oil; ^{1}H NMR ($CDCl_3$, 395.75 MHz) δ: 1.31 (3H, s), 1.68 (3H, s), 2.03 (1H, d, J = 10.5 Hz), 2.12 (1H, d, J = 17.7 Hz), 2.22 (1H, d, J = 17.7 Hz), 2.29 (1H, d, J = 10.5 Hz), 2.42 (3H, s), 3.70–3.71 (2H, m), 5.36 (1H, s), 7.17–7.34 (7H, m), 7.72 (2H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 14.1, 21.5, 44.1, 48.1, 48.6, 61.5, 63.6, 125.2, 126.6, 127.4, 127.8, 128.3, 128.6, 129.0, 129.1, 134.8, 137.4, 142.7, 145.8; LRMS *m/z*: 367 (M^+, 3.7), 183 (25), 169 (33), 91 (100), 65 (41); HRMS calcd for $C_{22}H_{25}NO_2S$ (M^+) 367.1606, found: 367.1603.

*3-Methyl-1-phenyl-6-tosyl-6-azabicyclo[3.2.1]oct-2-ene (**2b**).* Isolated as a colorless oil; ^{1}H NMR ($CDCl_3$, 270.05 Hz) δ: 1.61 (3H, s), 1.63–1.68 (1H, m), 2.00 (1H, dd, J = 10.5, 1.4 Hz), 2.25–2.42 (2H, m), 2.40 (3H, s), 3.23 (1H, d, J = 8.4 Hz), 3.91 (1H, dd, J = 8.4 Hz, 1.4 Hz), 4.34–4.38 (1H, m), 5.58 (1H, m), 7.16 (2H, d, J = 8.1 Hz), 7.23–7.34 (5H, m), 7.72 (2H, d, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 21.5, 22.3, 39.0, 40.1, 47.7, 57.4, 61.1, 125.8, 126.8, 127.0, 128.6, 129.7, 130.7, 132.7, 135.7, 143.1,

143.4; LRMS *m/z*: 353 (M^+, 6), 198 (75), 169 (70), 91 (100), 65 (50); HRMS calcd for $C_{21}H_{23}NO_2S$ (M^+) 353.1449, found 353.1445.

*2,2-Dimethyl-4-phenyl-4-(prop-2-ynyl)-1-tosylpyrrolidine (**3**).* Isolated as a colorless oil; ^{1}H NMR ($CDCl_3$, 270.05 MHz) δ: 1.32 (3H, s), 1.63 (3H, s), 1.91 (1H, t, J = 2.7 Hz), 2.18 (1H, d, J = 13.0 Hz), 2.42 (3H, s), 2.47 (1H, dd, J = 16.7, 2.7 Hz), 2.48 (1H, d, J = 13.0 Hz), 2.62 (1H, dd, J = 16.7, 2.7 Hz), 3.61 (1H, d, J = 9.9 Hz), 3.75 (1H, d, J = 9.9 Hz), 7.14 (2H, d, J = 8.2 Hz), 7.23–7.30 (5H, m), 7.77 (2H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 21.5, 29.4, 29.8, 30.9, 46.4, 52.2, 56.9, 64.9, 71.3, 80.6, 126.3, 126.8, 127.4, 129.1, 129.4, 137.9, 142.9, 144.0; LRMS *m/z*: 367 (M^+, 0.3), 352 (27), 155 (24), 91 (100), 65 (45); HRMS calcd for $C_{22}H_{25}NO_2S$ (M^+) 367.1606, found 367.1608.

*3-Allyl-5-methyl-3-phenyl-1-tosyl-2,3-dihydro-1H-pyrrole (**4**).* Isolated as a colorless oil; ^{1}H NMR ($CDCl_3$, 270.05 Hz) δ: 2.17 (3H, d, J = 1.4 Hz), 2.23–2.46 (2H, m), 2.37 (3H, s), 3.83 (1H, d, J = 11.1 Hz), 3.95 (1H, d, J = 11.1 Hz), 4.86–4.92 (2H, m), 5.09 (1H, d, J = 1.4 Hz), 5.30–5.43 (1H, m), 7.00 (2H, d, J = 7.9 Hz), 7.13–7.24 (5H, m), 7.58 (2H, d, J = 7.9 Hz);^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 15.5, 21.5, 45.8, 51.0, 62.1, 116.1, 118.1, 126.0, 126.1, 127.3, 128.3, 129.6, 133.7, 134.7, 139.3, 143.4, 146.1; LRMS *m/z*: 353 (M^+, 0.4), 312 (77), 156 (54), 115 (25), 91 (100), 65 (43); HRMS calcd for $C_{18}H_{18}NO_2S$ (M^+ – allyl) 312.1058, found 312.1071.

*2-Methyl-5-phenyl-3-(phenylmethyl)-5-[{(4-toluenesulfonyl)amino}methyl]cyclopenta-1,3-diene (**5**).* Isolated as a white solid; mp 171.5–172.0°C; ^{1}H NMR ($CDCl_3$, 395.75 MHz) δ: 1.97 (3H, s), 2.38 (3H, s), 3.01 (1H, dd, J = 17.1, 2.0 Hz), 3.03 (1H, dd, J = 17.1, 2.0 Hz), 3.18 (1H, dd, J = 11.6, 3.7 Hz), 3.30 (1H, dd, J = 11.6, 3.7 Hz), 4.29 (1H, dd, J = 8.7, 3.5 Hz), 5.95 (1H, s), 6.27 (1H, t, J = 2.0 Hz), 7.16–7.34 (12H, m), 7.63 (2H, d, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 13.2, 21.5, 43.3, 51.8, 54.4, 119.6, 126.2, 126.3, 126.8, 127.1, 128.3, 128.4, 128.8, 129.7, 135.8, 136.4, 137.8, 143.4, 144.5, 144.8, 145.9; HRMS calcd for $C_{27}H_{27}NO_2S$ (M^+) 429.1762, found 429.1770.

*5-Cyano-2-methyl-5-phenyl-3-(phenylmethyl)cyclopenta-1,3-diene (**7**).* Isolated as a colorless oil; ^{1}H NMR ($CDCl_3$, 395.75 MHz) δ: 2.06 (3H, d, J = 1.2 Hz), 3.27 (1H, dd, J = 17.1, 2.2 Hz), 3.83 (1H, dd, J = 17.1, 2.4 Hz), 5.91 (1H, s), 6.44 (1H, t, J = 2.2 Hz), 7.20–7.43 (10H, m); ^{13}C NMR ($CDCl_3$, 67.8 MHz) δ: 19.3, 38.4, 43.7, 112.5, 112.8, 118.3, 125.7, 126.1, 127.3, 127.9, 128.0, 128.6, 129.0, 137.8, 138.9, 139.0; HRMS calcd for $C_{20}H_{17}N$ (M^+) 271.1361, found 271.1367.

ACKNOWLEDGMENTS

This work has been supported financially by the Grant-in Aid for Scientific Research on Priority Areas No. 18850015 from the Ministry of Education, Science, Sports, Culture, and Technology, Japan. We are gratefully acknowledged to professors Yohsuke Yamamoto and Atsushi Kawachi for ^{19}F NMR measurement.

REFERENCES

[1] Muller, T. E.; Beller, M. Chem Rev 1998, 98, 675.
[2] Pohlki, F.; Doye, S. Chem Soc Rev 2003, 32, 104.
[3] Alonso, F.; Beletskaya, I. P.; Yus, M. Chem Rev 2004, 104, 3079.
[4] Bender, C. F.; Widenhoefer, R. A. J Am Chem Soc 2005, 127, 1070.
[5] Bender, C. F.; Widenhoefer, R. A. Chem Commun 2006, 4143.
[6] Fukuda, Y.; Utimoto, K.; Nozaki, H. Heterocycles 1987, 25, 297.
[7] Staben, S. T.; Kennedy-Smith, J. J.; Huangm, D. B.; Corkey, K.; LaLonde, R. L.; Toste, F. D. Angew Chem, Int Ed 2006, 45, 5991.
[8] Sun, J.; Kozmin, S. A. Angew Chem, Int Ed 2006, 45, 4991.
[9] Jiménez-Núñez, E.; Echavarren, A. M. Chem Commun 2007, 333.
[10] Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. J Am Chem Soc 2006, 128, 9066.
[11] LaLonde, R. L.; Sherry, B. S.; Kang, E. J.; Toste, F. D. J Am Chem Soc 2007, 129, 2452.
[12] Zhang, L.; Sun, J.; Kozmin, S. A. Adv Synth Catal 2006, 348, 2271.
[13] Genin, E.; Toullec, P. Y.; Antoniotti, S.; Brancour, C.; Genêt, J.-P.; Michelet, V. J Am Chem Soc 2006, 128, 3112.
[14] Buzas, A. K.; Intrate, F. M.; Gagosz, F. Angew Chem, Int Ed 2007, 46, 1141.
[15] Komeyama, K.; Morimoto, T.; Takaki, K. Angew Chem, Int Ed 2006, 45, 2938.
[16] Komeyama, K.; Mieno, Y.; Yukawa, S.; Morimoto, T.; Takaki, K. Chem Lett 2007, 36, 752.
[17] Komeyama, K.; Morimoto, T.; Nakayama, Y.; Takaki, K. Tetrahedron Lett 2007, 48, 3259.
[18] Zhang, L.; Kozmin, S. A. J Am Chem Soc 2004, 126, 10204.
[19] Fleming, I. Frontier Orbital and Organic Chemical Reactions; Wiley: London, 1976.
[20] Ho, T.-L. Hard and Soft Acids and Bases Principle in Organic Chemistry; Academic Press: New York, 1977.