CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200901103

Atropisomerism of α,β-Unsaturated Amidines: Stereoselective Synthesis by Catalytic Cascade Reaction and Optical Resolution

Naoya Shindoh, Yoshiji Takemoto,* and Kiyosei Takasu*[a]

Atropisomerism, a stereochemical property resulting from restricted rotation around a single bond where the steric strain barrier is high enough, has been the subject of much attention in organic chemistry. Well-studied biaryls, along with several classes of atropisomeric compounds including *ortho*-substituted anilides, *N*-arylimides, and diaryl ethers have been identified and their stereoselective synthesis has been explored.[1,2] In particular, axially chiral biaryls have been well studied because they provide an effective chiral environment for asymmetric reaction when they act as chiral ligands of metal catalysts or organocatalysts. Moreover, axially chiral anilides are utilized as useful chiral building blocks for *N*-heterocycles with axial-to-center chirality transfer.[3] In contrast to the above atropisomers whose rotationally-restricted single bond is directly connected to one or two aryl group(s), atropisomerism in acyclic π-systems such as 1,3-dienes[4] and α,β-unsaturated carbonyl derivatives have rarely been studied. To the best of our knowledge, there is only one example of the optical resolution of α,β-unsaturated carboxylic acid derivatives. Mannschreck and his co-workers reported the optical property of atropoisomeric thioamide derivatives of acrylic acid.[5] However, atropisomerism of α,β-unsaturated amidine derivatives, which would be potential synthetic precursors for heterocyclic compounds, is unexplored. We envisioned that highly substituted amidines **1** would provide a comparable stable atropisomer on axial chirality around a C2−C3 single bond (Figure 1). Herein, we report the optical resolution of atropisomeric α,β-unsaturated amidines and a novel stereoselective synthetic method of α,β-unsaturated amidines with bulky substituents.

[a] N. Shindoh, Prof. Dr. Y. Takemoto, Prof. K. Takasu
Graduate School of Pharmaceutical Sciences
Kyoto University
Yoshida, Sakyo-ku, Kyoto 606-8578 (Japan)
Fax: (+81) 75-753-4610
E-mail: kay-t@pharm.kyoto-u.ac.jp
takemoto@pharm.kyoto-u.ac.jp

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200901103.

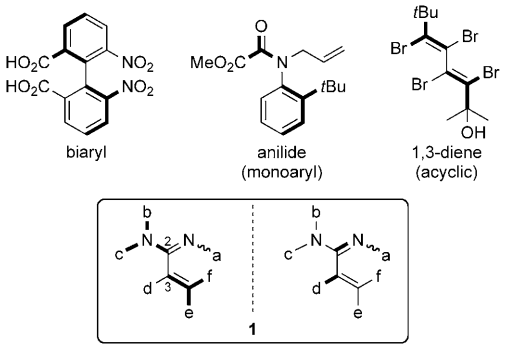
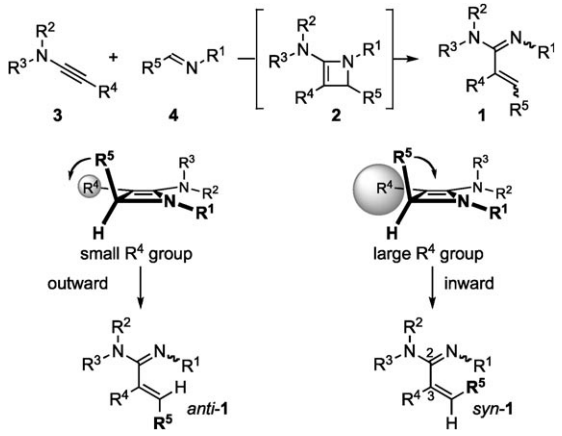


Figure 1. Representative atropisomers (biaryls, anilides and 1,3-dienes) and putative atoropisomeric α,β-unsaturated amidines **1**.

At the outset of this study, we considered the preparation of steric hindered α,β-unsaturated amidines. We thought that efficient synthesis of **1** by a coupling reaction to make a C2−C3 single bond or direct addition or substitution reaction to introduce a bulky substituent would be difficult. To achieve stereoselective synthesis of α,β-unsaturated amidines, we focused on the cascade reaction, consisting of [2+2] cycloaddition and successive electrocyclic ring-opening reaction (cycloreversion) of nitrogen-substituted alkynes and imines (Scheme 1).[6] The cascade reaction corresponds to formal aza–enyne metathesis. In the [2+2] cycloaddition, the repulsive steric interaction of bulky substituents on both substrates would decrease owing to the linear geometry of the alkyne substrate. We expected that cycloreversion of the resulting azetine intermediate **2** would proceed in a geometrical selective manner. As a related study, cycloreversion of cyclobutenes has been well explored to give the corresponding 1,3-butadienes.[7,8] In the thermal cycloreversion of four-membered rings, the geometry of the product is ruled out by conrotatory rotation of the σ-orbital of the central single bond and torquoselectivity (inward vs outward rotation in the conrotatory rotation). The torquoselectivity of 2-amino-2-azetines **2** can be controlled by the bulkiness of the substituent at the 3-position (Scheme 1). That is, when the R^4 group at the C(3) position is comparatively small, outward

rotation would favorably result in *anti*-**1** (relative configuration of amidine against R^5 group) to avoid steric repulsion between the R^5 group and the resulting produced amidine moiety. By contrast, when the R^4 group is sufficiently large, a steric repulsion between the R^4 and the R^5 groups would result in inward selective cycloreversion to afford *syn*-**1**. The R^5 group directed toward the amidine moiety would significantly increase the rotation barrier around the C2–C3 axis.



Scheme 1. Our synthetic strategy toward α,β-unsaturated amidine **1**: A proposed torquoselectivity in thermal cycloreversion of **2**.

Our initial exploration of the formal aza–enyne metathesis of nitrogen-substituted alkynes with imines indicated that ynamides **3** bearing a sulfonyl moiety and *N,C*-diarylaldimines **4** are suitable substrates, owing to the chemical yields of the products and easy handling of both substrates.[9] Moreover, the reaction was effectively catalyzed by triflic imide (Tf_2NH).[10] The results of the reaction are summarized in Table 1. The reaction proceeded smoothly at ambient temperature to 60 °C to give α,β-unsaturated amidines in moderate to excellent yield. In all cases, no azetine **2**, a reaction intermediate, was detected. This result indicates that the electrocyclic ring-opening step is much faster than the initial [2+2] cycloaddition.

Compounds **1aa** and **1ba**, which were synthesized from terminal alkyne **3a** and phenylalkyne **3b**, respectively, were obtained as a single geometrical isomer in which the *p*-tolyl substituent on the C(3) position and the amidine moiety are on opposite sides of the double bond (entries 1 and 2 in Table 1). Their configuration was assigned by ^{1}H NMR and X-ray crystallography (see Supporting Information). On the other hand, to our delight, when the terminal ynamide was substituted with the bulky triisopropylsilyl (TIPS) group, we found that the geometrical selectivity was completely reversed. Thus, the reaction of ynamide **3c** with **4a** gave exclusively *syn*-**1ca**; its configuration was confirmed by X-ray analysis (entry 3). Only the *E* configuration of the amidine C=N double bond was observed in all cases. The 1,3-allylic strain of the amidine moiety (N=C–N) caused the stereoselection.

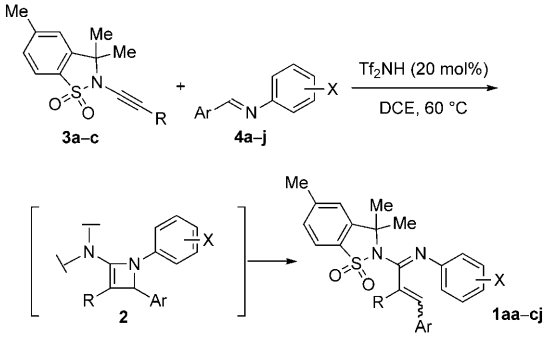
The ^{1}H NMR spectrum of **1ca** in [D_6]DMSO at 30 °C revealed that protons of two methyl substituents on the benzosultam are observed as two independent singlet signals. Thus, the two methyl substituents are diastereotopic and a significant chirality on the NMR time scale exists at this temperature (Figure 2). The observed chirality would, as expected, be derived from the rotation barrier around the C2–C3 bond, since the crystal structure[11] of **1cb** indicates a highly hindered environment around this axis (Figure 3) and the dihedral angle of two double bonds is 90.2°. Dynamic NMR study revealed the coalescence temperature (T_c) of two methyl peaks to be 74 °C, and $\Delta G^{\ddagger}_{74\,^\circ C}$ was calculated to be 17.6 kcal mol^{-1} (entry 3). In contrast, no atropisomers of *anti*-**1aa** and *anti*-**1ba** were detected even at −90 °C.

Next, we investigated the effects of the Ar^1 and the Ar^2 groups, which are substituents on amidine nitrogen and β-carbon, respectively, on the rotation barrier (Table 1, entries 3–12). Steric bulkiness of the Ar^1 group affects the atropisomerism. Namely, the coalescence temperature increased 7 °C when the *para*-CF_3 group was moved to the *meta*-position (entries 4 and 5). Furthermore, introduction of a substituent on the *ortho*-position of Ar^1 significantly influences the rotational barrier of α,β-unsaturated amidine (entries 6 and 7). In contrast, the substituent effect of Ar^2 is not so simple. Introduction of a bulky substituent on the *ortho*-position apparently decreases the rotational barrier; replacement of the phenyl group in **1cb** with 1-naphthyl group lowers T_c as much as 20 °C (entry 8). Comparison of the X-ray structures of **1cb** and **1cf** revealed that, while the phenyl ring seems to conjugate olefin and both π-systems appear planar in **1cb**, the naphthyl ring is skewed from the olefin plane in **1cf** (Figure 3). Interestingly, the electron density of the Ar^2 group is rather important. Introduction of an electron-donating substituent on the Ar^2 group afforded higher T_c than that of an electron withdrawing CF_3 or NO_2 substituent (entries 3 vs 4, 9 vs 10). These observations indicate that conjugation of olefin with the Ar^2 group would be important. Finally, we found that the five- membered heteroaromatic ring as a R^2 group significantly hindered the rotation of the axis (entries 11 and 12).

Although α,β-unsaturated amidines **1ca–cj** (Table 1) display axial chirality within the NMR time scale, it was impossible to separate their enantiomers by chiral HPLC under any conditions tested. As far as molecular modeling based on the obtained conformation from the X-ray crystallography, the rotation of the C2–C3 axis might be completely suppressed owing to the bulky substituents. We considered that rapid racemization of **1** would be caused by the *E*/*Z* isomerization about the amidine C=N double bond. In the ground state *E* configuration of the C=N double bond, the C2-C3 axis seems to be "locked" by the *E*-oriented N2-aryl group. However, the N2-aryl group can be partially "unlocked" by isomerization of the amidine moiety (Scheme 2).

We considered that large *ortho*-substituents on the N2-aryl group would prevent this "unlocking" by steric repulsion between the N1-benzosultam group. To synthesize more atropisomerically stable α,β-unsaturated amidines,

Table 1. Formal aza–enyne metathesis of ynamides **3** and imines **4**.[a]



Entry	Ynamide (R)	Imine (X, Ar)	Product	Yield [%][b]	T_c [°C][c,d]	$\Delta G_c^{\neq}$ [kcal mol^{-1}][e]
1[f]	**3a** (H)	**4a** (*p*-CF_3, *p*-MeC_6H_4)	**1aa**	78	< -90[g]	–
2[f]	**3b** (C_6H_5)	**4a**	**1ba**	93	< -90[g]	–
3	**3c** (TIPS)	**4a**	**1ca**	77	74	17.6
4	**3c**	**4b** (*p*-CF_3, C_6H_5)	**1cb**	71	70	17.4
5	**3c**	**4c** (*m*-CF_3, C_6H_5)	**1cc**	75	77	17.9
6	**3c**	**4d** (*o*-OH, *p*-MeC_6H_4)	**1cd**	49	100	18.1
7	**3c**	**4e** (*o*-I, *p*-MeC_6H_4)	**1ce**	73	130	19.3
8	**3c**	**4f** (*p*-CF_3, 1-naphthyl)	**1cf**	57	50	15.9
9	**3c**	**4g** (*p*-CF_3, *p*-$NO_2C_6H_4$)	**1cg**	41	62	17.2
10	**3c**	**4h** (*p*-CF_3, *p*-$MeOC_6H_4$)	**1ch**	81	76	17.9
11	**3c**	**4i** (*p*-CF_3, 2-furyl)	**1ci**	76	86	18.2
12	**3c**	**4j** (*p*-CF_3, 2-benzofuryl)	**1cj**	98	92	18.8

[a] All reactions were performed using 0.24 mmol of **3** and 0.2 mmol of **4**. [b] Isolated yield. [c] T_c means coalescence temperature. [d] T_c was measured in [D_6]DMSO. [e] $\Delta G^{\neq}_c$ means racemisation energy at the coalescence temperature. [f] Reaction was performed at ambient temperature. [g] T_c was measured in $CDCl_3$.

protection of the *ortho*-hydroxyl group of **1cd** by a bulky group was investigated. After several attempts, we found deprotonation of the hydroxyl group with NaH followed by treatment with TIPSOTf smoothly afforded amidine **6** (Scheme 3). Amidines **7** and **8** were also synthesized from the corresponding hydroxy-substituted amidines. Dynamic NMR study of **6–8** revealed that two methyl substituents on the benzosultam moiety were observed as two independent singlet peaks even at 150 °C in [D_6]DMSO ($T_c > 150$ °C).

Finally, we successfully separated each atropisomer of **6–8** by chiral HPLC using a CHIRALPAK AD-H column at 10 °C (see Supporting Information). The CD spectra clearly demonstrate that two separated fractions contain pure enantiomers (Figure 4). Time-course CD measurement of **7a** (90 % *ee*) at −10 °C revealed that the racemization half-life of **7** at this temperature was 3 h, and $\Delta G^{\neq}_{-10\,°C}$ was calculated to be 20.8 kcal mol^{-1}.

In conclusion, we prepared enantiomers of axially chiral α,β-unsaturated amidines and examined their dynamic chirality. We also developed a novel synthetic method of α,β-unsaturated amidines by catalytic cascade reaction of ynamides and imines, consisting of [2+2] cycloaddition and thermal cycloreversion, in a stereoselective manner. α,β-Unsaturated amidines would be a useful building block for biologically active heterocyclic compounds via intramolecular cyclization.[10] The atropisomers would be applicable in asymmetric synthesis with axial-to-center chirality transfer. Further studies on asymmetric synthesis of α,β-unsaturated amidines and their

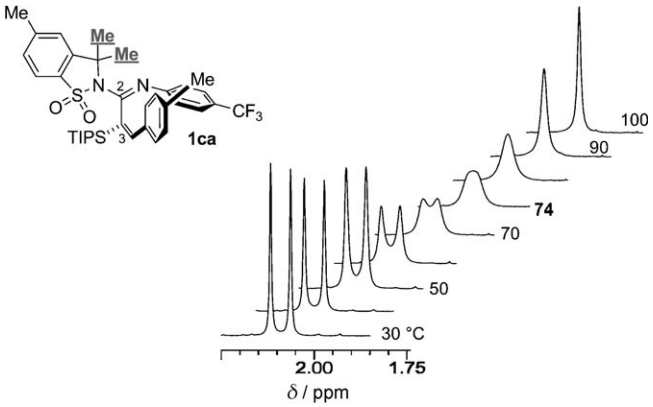


Figure 2. Dynamic ^{1}H NMR (highlighted methyl peaks) of **1ca** in [D$_6$]DMSO.

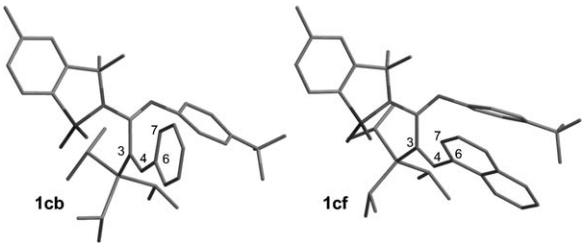
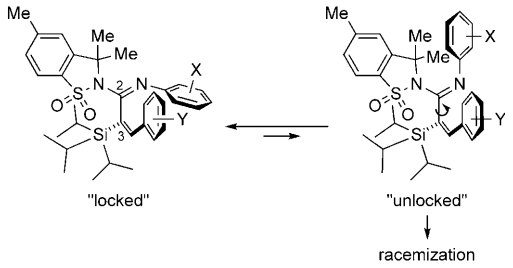
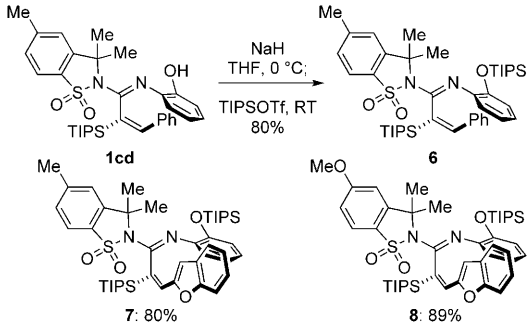


Figure 3. X-ray structures of **1cb** and **1cf**. Dihedral angles of olefin and aromatic planes ϕ C(3)-C(4)-C(6)-C(7) are 1.4 and 39.7° for **1cb** and **1cf**, respectively.



Scheme 2. A possible racemization pathway of α,β-unsaturated amidines.



Scheme 3. Preparation of *ortho*-silyloxy substituted amidines **6**–**8**.

synthetic utilization as a chiral building block are ongoing in our laboratory.

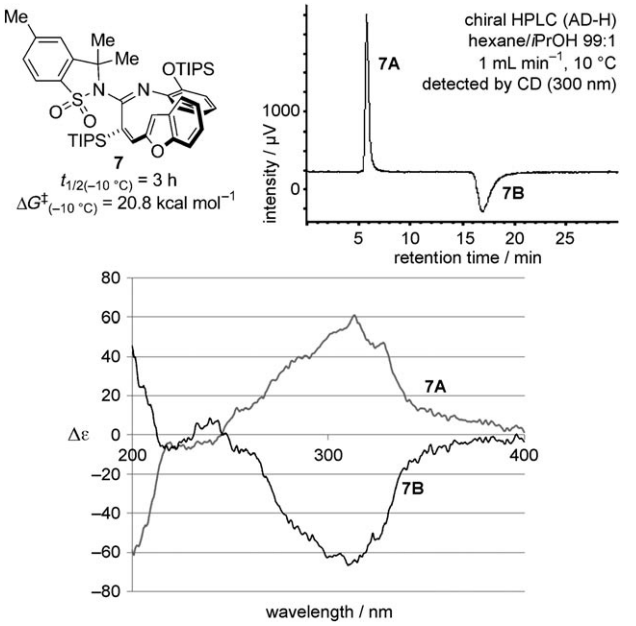


Figure 4. Chiral HPLC using AD-H (detected by CD) and CD spectra of **7** at −10°C.

Experimental Section

Typical procedure for Tf_2NH-catalyzed formal aza–eneyne metathesis (reaction of 3b and 4a): To a stirred solution of imine **4a** (52.9 mg, 0.201 mmol) and ynamide **3b** (76.9 mg, 0.247 mmol) in 1,2-dichloroethane (0.4 mL) was added Tf_2NH (0.4 M solution in 1,2-dichloroethane, 50 μL, 20 μmol, 10 mol%) at ambient temperature. After being stirred for 15 min, the mixture was diluted with $CHCl_3$, quenched with saturated aqueous solution of $NaHCO_3$, and the aqueous phase was extracted twice with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude mixture was purified by flash column chromatography (AcOEt/hexane 1:8) to afford amidine **1ba** (108 mg, 93%) as a white solid. M.p. 217–218°C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.65 (d, J = 8.1 Hz, 1H), 7.36 (dd, J = 8.1, 0.7 Hz, 1H), 7.31–7.27 (m, 2H), 7.08–7.03 (m, 4H), 6.99, (d, J = 8.1 Hz, 2H), 6.98–6.92 (m, 4H), 6.59 (d, J = 8.3 Hz, 2H), 2.52 (s, 3H), 2.25 (s, 3H), 2.09 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, TMS): δ = 154.8, 151.4, 144.9, 143.7, 138.0, 136.8, 136.3, 132.0, 130.7, 130.3, 129.9, 129.8, 129.4, 128.9, 127.8, 127.3, 125.2 (q, $^3J_{C,F}$ = 3.6 Hz), 124.5 (q, $^2J_{C,F}$ = 32.4 Hz), 124.4 (q, $^1J_{C,F}$ = 271.1 Hz), 122.9, 121.1, 121.0, 67.1, 27.0, 22.0, 21.2 ppm; IR (KBr): $\tilde{\nu}$ = 1642, 1608, 1323, 1170, 1114 cm^{-1}; LRMS (FAB): m/z: 575 [M+H$^+$]. An analytical sample for X-ray crystallography was prepared by recrystallization from methanol as pillars. Crystal data for **1ba**.[11] $C_{33}H_{29}F_3N_2O_2S$, monoclinic, space group $P2_1/c$, a = 10.5560(2), b = 15.3653(3), c = 36.3764(7) Å, β = 90.288(1)°, V = 5900.0(2) Å^3, Z = 8, ρ_{calcd} = 1.294 g cm^{-3}, R = 0.068, R_w = 0.103, GOF = 0.995.

Acknowledgements

The work was supported by a Grant-in-Aid for Scientific Research and Targeted Proteins Research Program from Ministry of Education, Culture, Sports, Science, and Technology, Japan, and the Research Foundation for Pharmaceutical Sciences.

Keywords: amidines · atropisomerism · cascade reaction · cycloaddition · electrocyclic reactions

[1] For recent reviews, see: a) G. Bringmann, A. J. P. Mortimer, P. A. Keller, M. J. Gresser, J. Garner, M. Breuning, *Angew. Chem.* **2005**, *117*, 5518–5563; *Angew. Chem. Int. Ed.* **2005**, *44*, 5384–5427; b) J. Clayden, *Chem. Commun.* **2004**, 127–135.

[2] For recent selected examples of atropisomerism, see: a) O. Kitagawa, M. Yoshikawa, H. Tanabe, T. Morita, M. Takahashi, Y. Dobashi, T. Taguchi, *J. Am. Chem. Soc.* **2006**, *128*, 12923–12931; b) M. S. Betson, J. Clayden, C. P. Worrall, S. Peace, *Angew. Chem.* **2006**, *118*, 5935–5939; *Angew. Chem. Int. Ed.* **2006**, *45*, 5803–5807; c) J. Clayden, C. P. Worrall, W. J. Moran, M. Helliwell, *Angew. Chem.* **2008**, *120*, 3278–3281; *Angew. Chem. Int. Ed.* **2008**, *47*, 3234–3237; d) T. Kawabata, C. Jiang, K. Hayashi, K. Tsubaki, T. Yoshimura, S. Majumdar, T. Sasamori, N. Tokitoh, *J. Am. Chem. Soc.* **2009**, *131*, 54–55; e) J. Clayden, H. Turner, M. Helliwell, E. Moir, *J. Org. Chem.* **2008**, *73*, 4415–4423; f) F. Faigl, G. Tárkányi, K. Fogassy, D. Tepfenhardt, A. Thurner, *Tetrahedron* **2008**, *64*, 1371–1377.

[3] For recent examples, see: a) M. Petit, S. J. Geib, D. P. Curran, *Tetrahedron* **2004**, *60*, 7543–7552; b) Y. Zhang, Y. Wang, W-M. Dai, *J. Org. Chem.* **2006**, *71*, 2445–2455; c) A. J. B. Lapierre, S. J. Geib, D. P. Curran, *J. Am. Chem. Soc.* **2007**, *129*, 494–495; d) T. Kawabata, K. Moriyama, S. Kawakami, K. Tsubaki, *J. Am. Chem. Soc.* **2008**, *130*, 4153–4157; e) D. B. Guthrie, D. P. Curran, *Org. Lett.* **2009**, *11*, 249–251.

[4] Some reports on optical resolution of atropisomeric 1,3-dienes were found in literature; a) E. F. Kiefer, T. J. Levek, T. T. Bopp, *J. Am. Chem. Soc.* **1972**, *94*, 4751–4753; b) M. Rösner, G. Köbrich, *Angew. Chem.* **1974**, *86*, 775–776; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 741–742; c) D. J. Pasto, J. K. Borchardt, *J. Am. Chem. Soc.* **1974**, *96*, 6220–6221.

[5] M. Kuttenberger, M. Frieser, M. Hofweber, A. Mannschreck, *Tetrahedron: Asymmetry* **1998**, *9*, 3629–3645.

[6] a) R. Fuks, R. Buijle, H. G. Viehe, *Angew. Chem.* **1966**, *78*, 594–595; *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 585; b) R. Fuks, H. G. Viehe, *Chem. Ber.* **1970**, *103*, 573–582; c) R. A. Abramovitch, B. Mavunkel, J. R. Stowers, M. Wegrzyn, C. Riche, *J. Chem. Soc. Chem. Commun.* **1985**, 845–846.

[7] a) T. Durst, L. Breau in *Comprehensive Organic Synthesis, Vol. 5* (Eds.: B. M. Trost, I. Fleming, L. A. Paquette), Pergamon, New York, **1991**, pp. 675–697; b) W. R. Dolbier, Jr., H. Koroniak, K. N. Houk, C. Sheu, *Acc. Chem. Res.* **1996**, *29*, 471–477.

[8] For reactions involving ring-opening of 2-oxetenes or 2-azetines, see: a) H. Ishitani, S. Nagayama, S. Kobayashi, *J. Org. Chem.* **1996**, *61*, 1902–1903; b) Y. Ma, C. Qian, *Tetrahedron Lett.* **2000**, *41*, 945–947; c) M. Shindo, S. Oya, Y. Sato, K. Shishido, *Heterocycles* **2000**, *52*, 545–548; d) M. Shindo, K. Matsumoto, S. Mori, K. Shishido, *J. Am. Chem. Soc.* **2002**, *124*, 6840–6841; e) T. Yoshikawa, S. Mori, M. Shindo, *J. Am. Chem. Soc.* **2009**, *131*, 2092–2093.

[9] Hsung et al reported practical synthesis of ynamides: a) M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen, C. J. Douglas, *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369; b) I. K. Sagamanova, K. C. M. Kurtz, R. P. Hsung, *Org. Synth.* **2007**, *84*, 359–367.

[10] Tf_2NH-catalyzed reactions employing ynamides or imines as substrate can be found in literature. Ynamides in Tf_2NH-catalyzed reactions: a) Y. Zhang, *Tetrahedron Lett.* **2005**, *46*, 6483–6486; b) K. C. M. Kurtz, R. P. Hsung, Y. Zhang, *Org. Lett.* **2006**, *8*, 231–234. Aldimines in Tf_2NH-catalyzed reactions: a) K. Takasu, N. Shindoh, H. Tokuyama, M. Ihara, *Tetrahedron* **2006**, *62*, 11900–11907; b) N. Shindoh, H. Tokuyama, Y. Takemoto, K. Takasu, *J. Org. Chem.* **2008**, *73*, 7451–7456; c) N. Shindoh, H. Tokuyama, Y. Takemoto, K. Takasu, *Heterocycles* **2009**, *77*, 187–192.

[11] CCDC 724921 (**1cb**) and 724922 (**1cf**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Received: April 27, 2009
Published online: June 19, 2009

