Organic LETTERS

Letter

pubs.acs.org/OrgLett

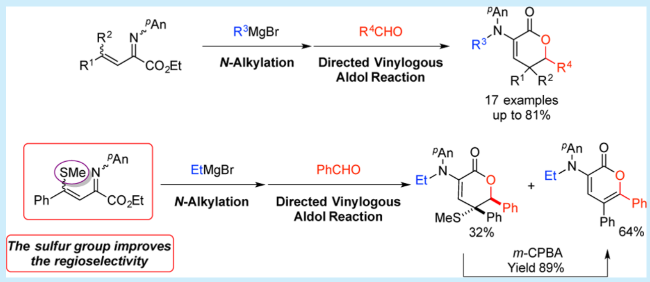
Tandem *N*-Alkylation/Vinylogous Aldol Reaction of *β*,*γ*-Alkenyl *α*-Iminoester

Hirotaka Tanaka, Isao Mizota, and Makoto Shimizu*

Department of Chemistry for Materials, Graduate School of Engineering, Mie University, Tsu, Mie 514-8507, Japan

Ⓢ *Supporting Information*

ABSTRACT: This report describes a highly regioselective tandem *N*-alkylation/vinylogous aldol reaction of *β*,*γ*-alkenyl *α*-iminoesters. The sulfur group improves the regioselectivity of the directed vinylogous aldol reaction, providing a new synthetic method of 3-amino-2-pyrones.



Aldol reactions using metal enolates formed from the 1,4-addition of organometallic reagents to *α*,*β*-unsaturated carbonyl compounds are very useful in organic chemistry because they facilitate three-component assembly reactions that can build complex molecules.[1] However, the reported examples of the vinylogous aldol reactions[2] have used allenic esters as starting materials.[3d] The directed vinylogous aldol reaction,[3] via in situ formation of the enolate, benefits from atom economy compared to the Mukaiyama vinylogous aldol reaction.[4] However, steric factors related to the substrates have affected its regioselectivity[3b,c] and the use of excess amounts of bulky Lewis acids has often been required.[3a,f,g]

An umpolung reaction of an *α*-iminoester involving nucleophilic addition to the nitrogen atom is difficult due to the electronegativity of the imino group.[5] We have developed umpolung reactions of *α*-iminoesters followed by C−C bond formation using the metal enolate produced by *N*-alkylation.[6] Nonetheless, constructing C−C bonds via subsequent reactions of the resulting enolates remains of interest. Recently, we reported the *N*-alkylation of *β*,*γ*-alkynyl *α*-iminoesters followed by regioselective acylation through the formation of magnesium yne-enolates.[6a] This report focuses on the synthesis of dienolates by *N*-alkylation of *β*,*γ*-alkenyl *α*-iminoesters[7] and describes a new tandem *N*-alkylation/vinylogous aldol reaction via in situ formation of these dienolates. In particular, the sulfur moiety on the alkene portion of the substrate controls the regioselectivity of the directed vinylogous aldol reaction.

In the initial *N*-alkylation step, the *β*,*γ*-alkenyl *α*-iminoester **1a** underwent reaction under the *N*-alkylation conditions optimized for the *β*,*γ*-alkynyl *α*-iminoester (1.1 equiv of EtMgBr, THF, −78 °C to rt, 30 min), to give the desired *N*-adduct isomers **2** and **3** in a low combined yield of 24% (Table 1, entry 1). Other organometallic reagents and reaction conditions were examined to improve this step, but the yields could not be improved (see Tables S1 and S2 in Supporting Information (SI)). All the reaction byproducts could not be

Table 1. Optimization of *N*-Alkylation of *β*,*γ*-Alkenyl *α*-Iminoester[a]

1a : R^1 = Ph, R^2 = H
1b : R^1 = 2,6-$Me_2C_6H_3$, R^2 = H
1c : R^1 = R^2 = Ph

entry	1	temp (°C)	time (min)	yield (%)[b]		2:3	smr (%)[c]
1	**1a**	−78 to rt	30	**2a, 3a**	24	83:17	0
2	**1a**	−78	30	**2a, 3a**	33	67:33	50
3	**1b**	−78	30	**2b**	32	100:0	49
4	**1b**	−78 to rt	2.5 h	**2b**	61	100:0	0
5	**1b**	−78 to 40	30	**2b**	85	100:0	0
6	**1b**	−78 to 40	10	**2b**	58	100:0	15
7	**1c**	−78 to 40	30	**2c**	91	100:0	0

[a]The reaction was carried out according to the typical procedure. [b]Isolated yield. [c]Recovery of the starting material.

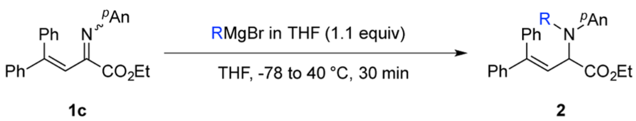
isolated, but 1,4-addition to the conjugate imine might be occurring as a side reaction, explaining the low yields. Substrates containing a bulky substituent, such as 2,6-$Me_2C_6H_3$, on their alkene portion **1b** provided the desired, *N*-adducts with almost the same yields as in the case of **1a** at low temperature (entries 2 and 3). When the reaction was performed from −78 °C to rt, the starting material was completely consumed without noticeable side reactions, and the desired product **2b** was obtained as the sole product in 61% yield (entry 4). Furthermore, when the reaction temperature rose from −78 to 40 °C, the reaction proceeded more rapidly to produce the *N*-adduct in the best yield (85%) (entry 5). The use of substrates bearing three substituents on their alkene

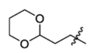
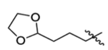
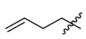
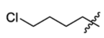
Received: March 17, 2014
Published: April 10, 2014

portion completely prevented side reactions, giving the desired product in 91% yield (entry 7). The *N*-alkylation hinges on the geometry of the imine (Table S3 in SI) and is assumed to proceed through reaction of the more reactive isomer (*E*)-**1**, which is obtained by isomerization of the (*Z*)-isomer by heating above room temperature. Optimization of reaction solvents showed that THF resulted in the best yield (Table S5 in SI).

Under these optimized conditions (Table 1, entry 7), the scope of Grignard reagents was examined (Table 2). Linear

Table 2. Scope of Grignard Reagents for *N*-Alkylation[a]



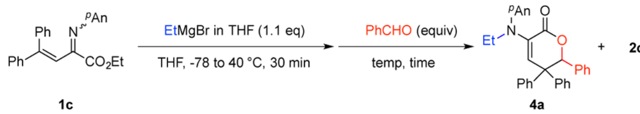
entry	R	2	yield (%)[b]	entry	R	2	yield (%)[b]
1	Et	**2c**	91	10	Allyl	-	0
2	^{n}Pr	**2d**	92	11		**2k**	96
3	^{n}Bu	**2e**	90				
4	^{n}Hex	**2f**	88	12		**2l**	83
5	^{n}Oct	**2g**	92				
6	^{i}Bu	**2h**	68	13		**2m**	77
7	Me	**2i**	10				
8	^{i}Pr	**2j**	10	14		**2n**	54
9	Ph	-	0				

[a]The reaction was carried out according to the typical procedure. [b]Isolated yield.

primary alkyl Grignard reagents gave the desired *N*-adducts in excellent yields (Table 2, entries 1−5), while a branched counterpart afforded the desired product in good yield (entry 6). In contrast, methyl and secondary alkyl Grignard reagents produced the desired compounds in low yields (entries 7 and 8) and the phenyl and allyl derivatives did not produce the *N*-alkylation products (entries 9 and 10). However, primary Grignard reagents with functional groups, such as cyclic acetals (entries 11 and 12), terminal alkene (entry 13), and halogen (entry 14), did not affect this reaction. In most cases where low yields were observed, nucleophilic addition to the ethoxycarbonyl group occurred as the side reaction.

Next, the tandem *N*-alkylation/vinylogous aldol reaction was investigated (Table 3). After *N*-alkylation under the optimized conditions, 5.0 equiv of benzaldehyde were added to the reaction mixture for the subsequent vinylogous aldol reaction. In this case, the intramolecular cyclization proceeded to give δ-lactone **4a**. Examination of reaction temperature effects demonstrated that reactions run at higher temperatures gave the desired products in better yields (entries 1−5). Further optimization of the reaction conditions indicated that the best yield was obtained in reactions conducted with 5.0 equiv of benzaldehyde for 1.5 h (entries 5−9). Although the *N*-alkylation followed by hydrolysis of the resulting enamine provided **2c** as a byproduct, this compound may also result from the retro aldol reaction of the unstable aldol product formed by α-addition. Based on this hypothesis, we studied the ester portion of the substrates, the addition of a Lewis acid to improve aldehyde reactivity, and the effect of a Lewis base[3d] on the retro aldol reaction of the α-aldolate that can reproduce the

Table 3. Optimization of Tandem *N*-Alkylation/Vinylogous Aldol Reaction[a]



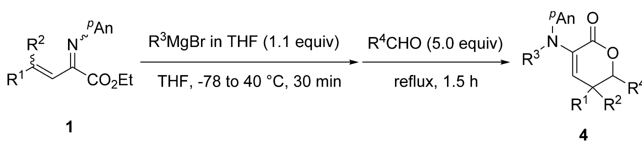
entry	equiv	temp	time	4a (%)[b]	2c (%)[b]
1	5.0	0 °C	15 min	0	79
2	5.0	rt	15 min	19	73
3	5.0	40 °C	15 min	46	49
4	5.0	50 °C	15 min	58	20
5	5.0	reflux	15 min	73	20
6	5.0	reflux	1.5 h	77	22
7	5.0	reflux	9.0 h	63	20
8	2.5	reflux	1.5 h	69	23
9	10.0	reflux	1.5 h	56	29

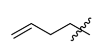
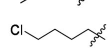
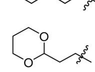
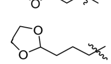
[a]The reaction was carried out according to the typical procedure. [b]Isolated yield.

γ-adduct. However, the yield of **4a** did not increase (Tables S7 and S8 in SI), suggesting that the magnesium α-aldolate may be stabilized by a strong chelation between the magnesium and the nitrogen atoms.

The scope of substrates, Grignard reagents, and aldehydes was evaluated under the optimized conditions (Table 4). When 2-thienyl, an electron-donating substituent such as 4-MeO-

Table 4. Scope of Substrates[a]

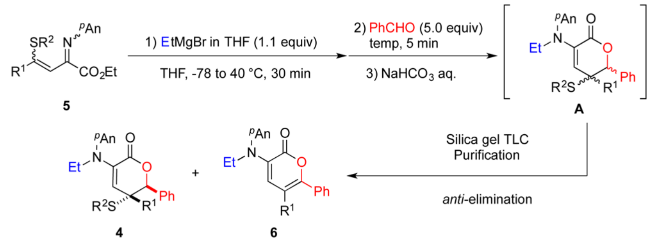


entry	R[1]	R[2]	R[3]	R[4]	yield(%)[b]
1	2-thienyl	2-thienyl	Et	Ph	**4b** 64(6)
2	2-thienyl	4-MeOC$_6$H$_4$	Et	Ph	**4c** 43[c](33)
3	2-thienyl	4-FC$_6$H$_4$	Et	Ph	**4d** 40[d](18)
4	2,6-Me$_2$C$_6$H$_3$	H	Et	Ph	**4e** 56[e](7)
5	Ph	Ph	^{n}Oct	Ph	**4f** 35(37)
6	Ph	Ph	^{i}Bu	Ph	**4g** 51(35)
7	Ph	Ph		Ph	**4h** 74(22)
8	Ph	Ph		Ph	**4i** 55(12)
9	Ph	Ph		Ph	**4j** 51(30)
10	Ph	Ph		Ph	**4k** 60(20)
11	Ph	Ph	Et	2-thienyl	**4l** 74(12)
12	Ph	Ph	Et	4-MeOC$_6$H$_4$	**4m** 58(29)
13	Ph	Ph	Et	4-ClC$_6$H$_4$	**4n** 56(37)
14	Ph	Ph	Et	2-Py	**4o** 81(5)
15	Ph	Ph	Et	PhCH=CH	**4p** 79(0)
16	Ph	Ph	Et	PhC≡C	**4q** 25(32)

[a]The reaction was carried out according to the typical procedure. [b]Yields refer to pure isolated compounds, and yields of **2** are in the parentheses. [c]The diastereomer ratio is 54:46. [d]The diastereomer ratio is 62:38. [e]The diastereomer ratio is 56:44.

dx.doi.org/10.1021/ol5007983 | *Org. Lett.* 2014, 16, 2276−2279

Table 5. Tandem Reaction of β,γ-Alkenyl α-Iminoesters Bearing Sulfenyl Groups[a]



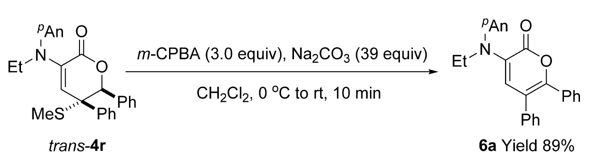
entry	R^1	R^2	temp[b]	**A** (*cis*/*trans*)	yield (%)[c] **4** + **6** (**4**:**6**)		
1	Ph	Me	refl	nd[d]	**4r**, **6a**	98	(86[e]:14)
2	Ph	Me	40 °C	71:29	**4r**, **6a**	96	(33:67)
3	2-thienyl	Me	refl	76:24	**4s**, **6b**	89	(26:74)
4	Ph	^{t}Bu	refl	nd[d]	**4t**, **6a**	85	(56:44)

[a]The reaction was carried out according to the typical procedure. [b]Temperature for the addition of the aldehyde. [c]Isolated yield. [d]Not determined. [e]A 67:33 mixture of *cis*- and *trans*-isomers. Purification of the compund **A** was carried out by deactivated silica gel TLC.

C_6H_4, an electron-withdrawing substituent such as 4-F-C_6H_4, and 2,6-$Me_2C_6H_3$ (R^1 and R^2) were introduced on the alkene portion of β,γ-alkenyl α-iminoesters, the desired δ-lactones **4** were obtained in moderate-to-good yields. The use of primary Grignard reagents (R^3) that readily underwent *N*-alkylation allowed the desired tandem reaction to proceed in moderate-to-good yield. Aromatic and heteroaromatic aldehydes afforded the desired products in moderate-to-high yields. On the other hand, aliphatic aldehydes produced only *N*-adducts **2** instead of the desired products. The unsaturated aldehyde, cinnamaldehyde, was effective in this reaction, and alkynyl aldehyde afforded the desired product, albeit in low yield.

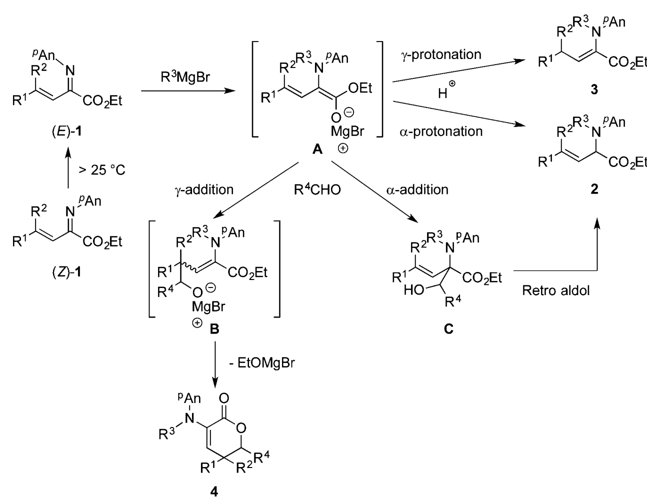
Higher temperatures enhanced the γ-selectivity of the tandem reaction. Nonetheless small amounts of *N*-adducts **2** were still obtained. The use of substrates bearing sulfenyl groups on the alkene part may improve γ-selectivity (Table 5). In fact, substrates containing *t*-BuS or MeS effectively underwent *N*-alkylation (see also Table S6 in SI), and the subsequent vinylogous aldol reaction was more selective in producing δ-lactones **4** in excellent yields (Table 5, entries 1–4).[8] Remarkably, the crude products only consisted of δ-lactone **4** but silica gel TLC chromatography purification produced 2-pyrone **6**. The ratios between δ-lactones **4** and 2-pyrones **6** matched the diastereomeric ratios of the δ-lactones in the crude products. In addition, the stereochemistry of isolated δ-lactone **4s** was determined to be *trans* by nuclear Overhauser effect (NOE) measurements. This suggests that 2-pyrones **6** may arise from the *anti*-elimination of the thiols. 3-Amino-2-pyrones are valuable in organic synthesis because of their biological activity such as selective cyclooxygenase-1 (COX-1) inhibitors.[9] Furthermore, 2-pyrone can be readily transformed into other heterocyclic compounds such as pyridine and 2-pyridone.[10] The isolated *anti*-isomer **4r** could also be converted into 3-amino-2-pyrone **6a** via *syn*-elimination of the sulfoxide (Scheme 1). Notably, the sulfenyl groups impact this tandem reaction in several ways. (1) The first *N*-alkylation step proceeds selectively because of steric hindrance. (2) Anion stability allows the second aldol reaction with the dienolate to occur via γ-addition. (3) The 3-amino-2-pyrone is produced via *anti*-elimination of the thiolate. To the best of our knowledge, this example is the first directed vinylogous aldol reaction promoted by sulfur-containing groups.

Scheme 1. Transformation of the *trans*-Isomer 4r



A proposed reaction mechanism is shown in Scheme 2. β,γ-Alkenyl α-iminoester **1** is a mixture of *Z* and *E* diastereomers.

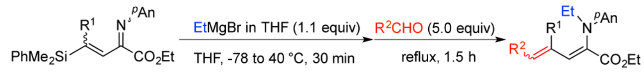
Scheme 2. Assumable Reaction Mechanism



The inert (*Z*)-**1** isomerizes into its reactive form (*E*)-**1** by heating above room temperature. The *N*-alkylation proceeds with the Grignard reagent to give magnesium dienolate **A** through formation of a five-membered intermediate composed of the imino nitrogen, the carbonyl oxygen, and the magnesium atom.[6m] The α- and γ-protonations of dienolate **A** afford the *N*-adducts **2** and **3**, respectively. After γ-addition of dienolate **A** to the aldehyde to form magnesium aldolate **B**, an intramolecular cyclization proceeds with a concomitant formation of MgOEt to provide δ-lactone **4**. The α-adduct **C** may undergo a retro aldol reaction followed by protonation to produce *N*-adduct **2**.

Finally, we studied a tandem reaction of β,γ-alkenyl α-iminoester bearing a phenyldimethylsilyl group on its alkene part (Table 6). After the vinylogous aldol reaction, the Peterson

Table 6. Tandem Reaction of β,γ-Alkenyl α-Iminoesters Bearing a Silyl Group[a]



7 8

entry	R[1]	R[2]	yield (%)[b]				
			8 (*dr*)			2	
1	Ph	Ph	**8a**	61	(87:13)	**2y**	14
2	2-thienyl	Ph	**8b**	49	(93:7)	**2z**	4
3	Ph	(*E*)-PhCH═CH	**8c**	71	(64:36)	**2y**	trace

[a]The reaction was carried out according to the typical procedure. [b]Isolated yield.

olefination[11] proceeded faster than the intramolecular cyclization to provide dienamines **8** in moderate yields (entries 1 and 2). Cinnamaldehyde also produced trienamine **8c** (entry 3).

Hence, we have developed a highly regioselective tandem *N*-alkylation using the umpolung/directed vinylogous aldol reaction of β,γ-alkenyl α-iminoesters. Sulfenyl substituents on the alkene part of the substrates notably enhanced the selectivities of both steps and induced the formation of 3-amino-2-pyrones via *anti*-elimination.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mshimizu@chem.mie-u.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Grants-in-Aid for Scientific Research (B) and Scientific Research on Innovative Areas "Organic Synthesis Based on Reaction Integration. Development of New Methods and Creation of New Substances" from JSPS and MEXT.

■ REFERENCES

(1) For the tandem 1,4-addition/aldol reaction: (a) Howell, G. P.; Fletcher, S. P.; Geurts, K.; ter Horst, B.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 14977. (b) Brown, M. K.; Degrado, S. J.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2005**, *44*, 5306. (c) Nicolaou, K. C.; Tang, W.; Dagneau, P.; Faraoni, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3874. (d) Subburaj, K.; Montgomery, J. *J. Am. Chem. Soc.* **2003**, *125*, 11210. (e) Yoshida, K.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **2002**, *124*, 10984. (f) Heng, K. K.; Smith, R. A. J. *Tetrahedron* **1979**, *35*, 425.

(2) For reviews of the vinylogous aldol reaction: (a) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076. (b) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929. For catalytic vinilogous aldol reaction: (c) Hassan, A.; Zbieg, J. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3493 and references cited therein.

(3) For the directed vinylogous aldol reaction: (a) Gazaille, J. A.; Sammakia, T. *Org. Lett.* **2012**, *14*, 2678. (b) Zhang, J.; Gu, L.; Gong, Y. *Synlett* **2012**, *23*, 468. (c) Aponte, J. C.; Hammond, G. B.; Xu, B. *J. Org. Chem.* **2009**, *74*, 4623. (d) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2007**, *129*, 7439. (e) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440. (f) Saito, S.; Shiozawa, M.; Yamamoto, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1769. (g) Saito, S.; Shiozawa, M.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1998**, *120*, 813.

(4) For a general review of the Mukaiyama vinylogous aldol reaction: Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2005**, *44*, 4682.

(5) For the *N*-alkylation to α-imino esters: (a) Dickstein, J. S.; Kozlowski, M. C. *Chem. Soc. Rev.* **2008**, *37*, 1166. (b) Dickstein, J. S.; Fennie, M. W.; Norman, A. L.; Paulose, B. J.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 15794. (c) Chiev, K. P.; Roland, S.; Mangeney, P. *Tetrahedron: Asymmetry* **2002**, *13*, 2205. (d) Mae, M.; Amii, H.; Uneyama, K. *Tetrahedron Lett.* **2000**, *41*, 7893. (e) Bertrand, M. P.; Feray, L.; Nouguier, R.; Perfetti, P. *Synlett* **1999**, 1148. (f) Yoo, S.-e.; Gong, Y.-d. *Heterocycles* **1997**, *45*, 1251. (g) Uneyama, K.; Yan, F.; Hirama, S.; Katagiri, T. *Tetrahedron Lett.* **1996**, *37*, 2045. (h) Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415. (i) Fiaud, J.-C.; Kagan, H. B. *Tetrahedron Lett.* **1971**, *12*, 1019.

(6) For *N*-alkylation to α-imino esters in our laboratory: (a) Mizota, I.; Matsuda, Y.; Kamimura, S.; Tanaka, H.; Shimizu, M. *Org. Lett.* **2013**, *15*, 4206. (b) Sano, T.; Mizota, I.; Shimizu, M. *Chem. Lett.* **2013**, *42*, 995. (c) Shimizu, M.; Kurita, D.; Mizota, I. *Asian J. Org. Chem.* **2013**, *2*, 208. (d) Shimizu, M.; Takao, Y.; Katsurayama, H.; Mizota, I. *Asian J. Org. Chem.* **2013**, *2*, 130. (e) Nishi, T.; Mizota, I.; Shimizu, M. *Pure Appl. Chem.* **2012**, *84*, 2609. (f) Mizota, I.; Tanaka, K.; Shimizu, M. *Tetrahedron Lett.* **2012**, *53*, 1847. (g) Shimizu, M.; Hachiya, I.; Mizota, I. *Chem. Commun.* **2009**, 874. (h) Shimizu, M. *Pure Appl. Chem.* **2006**, *78*, 1867. (i) Shimizu, M.; Itou, H.; Miura, M. *J. Am. Chem. Soc.* **2005**, *127*, 3296. (j) Niwa, Y.; Shimizu, M. *J. Am. Chem. Soc.* **2003**, *125*, 3720. (k) Niwa, Y.; Takayama, K.; Shimizu, M. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1819. (l) Niwa, Y.; Takayama, K.; Shimizu, M. *Tetrahedron Lett.* **2001**, *42*, 5473. (m) Shimizu, M.; Niwa, Y. *Tetrahedron Lett.* **2001**, *42*, 2829.

(7) (a) Vicario, J.; Aparicio, D.; Palacios, F. *Tetrahedron Lett.* **2011**, *52*, 4109. (b) Palacios, F.; Vicario, J.; Aparicio, D. *J. Org. Chem.* **2006**, *71*, 7690. (c) Palacios, F.; Vicario, J.; Aparicio, D. *Eur. J. Org. Chem.* **2006**, 2843. (d) Palacios, F.; Vicario, J. *Org. Lett.* **2006**, *8*, 5405.

(8) When the substrate (R^1 = 2-thienyl, R^2 = *tert*-butyl) was used, a crude cyclized product **A** was obtained in ca. 59% yield. However, this starting material was unstable upon purification by silica gel TLC, and the product **A** could not be separated from the decomposed starting material.

(9) (a) Chu, X.-P.; Zhou, Q.-F.; Zhao, S.; Ge, F.-F.; Fu, M.; Chen, J.-P.; Lu, T. *Chin. Chem. Lett.* **2013**, *24*, 120. (b) Zhou, Q.-F.; Zhu, Y.; Tang, W.-F.; Lu, T. *Synthesis* **2010**, *2*, 211.

(10) Yeh, P.-P.; Daniels, D. S. B.; Cordes, D. B.; Slawin, A. M. Z.; Smith, A. D. *Org. Lett.* **2014**, *16*, 964.

(11) (a) van Staden, L. F.; Gravestock, D.; Ager, D. J. *Chem. Soc. Rev.* **2002**, *31*, 195. (b) Peterson, D. J. *J. Org. Chem.* **1968**, *33*, 780.