JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

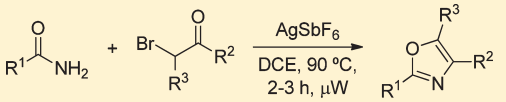
A Silver-Mediated One-Step Synthesis of Oxazoles

Dougal J. Ritson, Christian Spiteri, and John E. Moses*

School of Chemistry, University of Nottingham, University Park, NG7 2RD, United Kingdom

Supporting Information

ABSTRACT: A silver-mediated one-step procedure to 2,4-disubstituted and 2,4,5-trisubstituted oxazoles has been developed. The method is complementary to existing technologies, yet provides advantages with regard to simplicity, efficiency, and performance. The silver product can be readily recycled, thus minimizing waste.



Oxazoles are an important class of heterocycle with application in the pharmaceutical industry and natural products chemistry.[1,2] Their useful properties and common occurrence render them attractive targets for methodology development. It is therefore no surprise that many useful syntheses of oxazoles have been developed over the years.[3−5]

The well-known Robinson−Gabriel[6,7] oxazole synthesis involves intramolecular cyclization (in an *N*-acyl α-aminoketone) of an amide carbonyl onto a ketone group with ensuing elimination of water. Wipf et al. developed a useful modification of the cyclodehydration step, and this method has become one of the premier routes for constructing oxazoles.[8] Another common approach involves the cyclodehydration of *β*-hydroxy amides to form 2-oxazolines, followed by oxidation to the corresponding oxazole.[9] Both strategies are similar overall differing only in the order of oxidation and cyclodehydration steps.

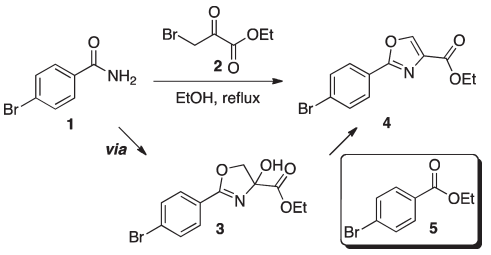
Despite the number of methods available for oxazole synthesis, there remains much scope for the development of single-step protocols, which are desirable in terms of efficiency and step economy. Moody et al. have made advances in this respect, developing a one-step synthesis of oxazoles using Rh catalyzed carbene chemistry.[4b] This method, however, requires the availability of α-diazo-*β*-keto-carboxylate starting materials, which may not always be convenient or practical. Jiang et al. have recently reported an elegant one-pot protocol from alkenes involving a TBHP/I_2-mediated oxidative cyclization.[10]

We became interested in the "one-step" Blümlein−Lewy (BL) oxazole method. This procedure was attractive due to the ready availability of starting materials and straightforward experimental procedure.

The reaction involves a primary amide **1**, with a bromopyruvate ester **2** in alcoholic solvent,[11] which leads to the corresponding oxazoline **3**, before undergoing cyclodehydration to the oxazole **4** (Scheme 1). However, this method has been scarcely used compared to others, mainly due to low conversions and unwanted side product formation of **5**.[12,13]

We believed an improvement to this methodology could be achieved by the addition of silver salts for a number of reasons: (i) their halophilicity would activate bromopyruvate for nucleophilic attack, thus driving the reaction by formation of AgBr; (ii) the subsequent formation of a conjugate acid could facilitate conversion of **3** to **4** (vide supra); (iv) their tolerance to amides;[14] (v) their Lewis acidity, thus assisting the formation of **4** from **3**; and (vi) their low toxicity and reasonable cost.[15]

Scheme 1. The Blümlein−Lewy Oxazole Synthesis



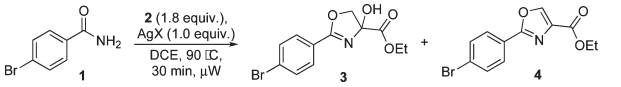
To test our hypothesis a screen of silver salts was performed. Thus, model substrates **1** and **2** were heated in a microwave reactor (90 °C for 0.5 h in DCE), using 1 equiv of a given silver salt. Table 1 illustrates our initial findings.[16] Gratifyingly, the target product **4** was formed in significant amount in most of the reactions with silver salts (entries 2−11), as compared to the control reaction (entry 1). Entries 5, 7, and 9 gave only moderate conversion of **1** to **3** and poor conversion of **3** to **4**. On the other hand, $Ag(O_2CCF_3)$ (entry 8) gave an improved conversion of **1** into **4**, while further increasing the Lewis acidity gave even better results (entries 2, 6, 10, and 11). Interestingly, the common silver salts AgF and $AgNO_3$ gave a complex reaction mixture and poor conversion into **3** and **4** (entries 3 and 4). The best results were obtained with $AgSbF_6$ and $AgClO_4$ (entries 6 and 11). In each case, silver bromide precipitated out of solution and was easily recovered by filtration.

Optimization was initially performed with $AgClO_4$, but it soon emerged that this salt led to some product degradation upon prolonged heating (cf. Table S1 and S2 in the Supporting Information). Therefore, $AgSbF_6$ became the preferred reagent

Received: December 23, 2010
Published: March 25, 2011

dx.doi.org/10.1021/jo1025332 | *J. Org. Chem.* 2011, 76, 3519–3522

Table 1. Examination of the Effect of Silver Salts on the Conversion of 1 and 2 into 3 and 4



entry	AgX	ratio [**1**:**3**:**4**][a]
1	-	1:<0.05:<0.05
2	AgOTf	0.50:1:1
3	$AgNO_3$	1:0.13:<0.05
4	AgF	1:0.12:<0.05
5	Ag_2CO_3	1:1.6:<0.05
6	$AgSbF_6$	0.23:1:1
7	AgOAc	1:1:<0.05
8	$Ag(O_2CCF_3)$	1.9:2.0:1
9	$AgNO_2$	1:2:<0.05
10	$AgBF_4$	0.73:0.67:1
11	$AgClO_4$	0.32:0.30:1

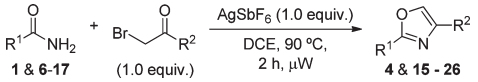
[a] Ratio determined from crude ^{1}H NMR.[16] Conditions: To **1** (0.15 mmol) and **2** (1.8 equiv) in anhydrous DCE (0.5 mL) was added the AgX species; heating at 90 °C for 0.5 h in a sealed tube in a microwave.

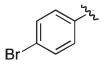
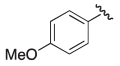
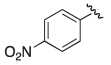
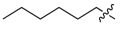
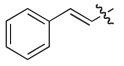
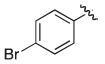
of choice. Thus, optimal conditions were found to be as follows: **1** (1.0 equiv), **2** (1.0 equiv), and $AgSbF_6$ (1.0 equiv) in DCE and irradiated at 90 °C for 2 h in a microwave reactor, affording **4** in quantitative yield (Table 2, entry 1). The use of $AgSbF_6$ was found essential for optimal oxazole formation as the reaction without silver salt gave **4** in only 10% yield.

We next investigated the substrate scope of the reaction under our optimized conditions (Table 2).[17] Electron-rich aromatic amides generally gave better results than electron-poor aromaric amides, cf. entries 2, 3, and 4 vs entries 5 and 6. Changing the position of the substituents led to minor differences in yield (entry 3 vs 4). The deactivated *p*- and *m*-nitro-substituted amides **9** and **10** gave the oxazoles **18** and **19** in very high yield, and this was unaffected by the positioning of the nitro substituent (entries 5 and 6). The heterocyclic amides thiophene-2-carboxamide (**11**) and 2-furamide (**12**) were also excellent substrates for the reaction, giving **20** and **21** in 90% and 81% yield, respectively (entries 7 and 8). 4-Amidopyridine, however, gave no oxazole product (entry 9), a problem we can only ascribe to the basicity of the pyridino nitrogen. Unfortunately, aliphatic amides were poor substrates, giving complex reaction mixtures (entries 10 and 11). This is perhaps due to the ability of the oxazoline intermediate to tautomerize to an enamine-type species, which can then undergo degradation pathways. Tautomerizations of this kind have been reported in similar systems.[18]

Our methodology can, however, be extended to amides which are flanked by double bonds. Thus, cinnamamide (**16**) gave **25** in good yield, which goes someway to substantiate our hypothesis that enolizable amides pose problems for the current protocol. Panek et al. have already demonstrated the utility of **25** in terms of providing a handle at the 2-position for further manipulation, making **25** an attractive intermediate, as the 2- or 4-position can be easily elaborated.[13] We then considered that other activating groups could be used in place of the ester carbonyl in pyruvate. Hence, we subjected 2-bromoacetophenone (**17**) and **4** to our optimized reaction conditions and were delighted to obtain **26** in 81% yield. This method then can provide very convenient access to contiguously linked aromatic molecules.

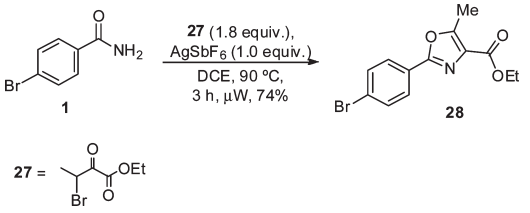
Table 2. Compatibility of Substrates with the Reaction Condition



entry	amide/ oxazole	R^1	R^2	yield (%)[a]
1	**1/4**		COOEt	100
2	**6/15**		COOEt	89
3	**7/16**		COOEt	97
4	**8/17**		COOEt	90
5	**9/18**		COOEt	80
6	**10/19**		COOEt	81
7	**11/20**		COOEt	90
8	**12/21**		COOEt	81
9	**13/22**		COOEt	0
10	**14/23**		COOEt	[b]
11	**15/24**		COOEt	[b]
12	**16/25**		COOEt	60
13	**17/26**		Ph	81

[a] Isolated yield. [b] Complex reaction mixture from which the oxazole could not be fully purified. From ^{1}H NMR we estimate ca. 20% yield.

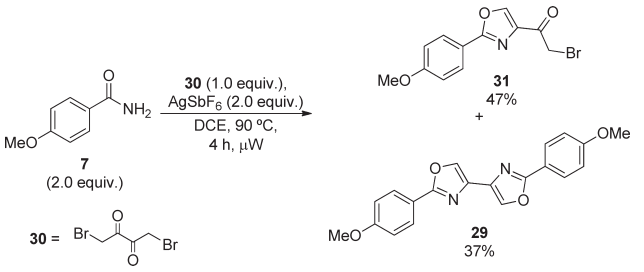
Scheme 2. Access to Trisubstituted Oxazoles



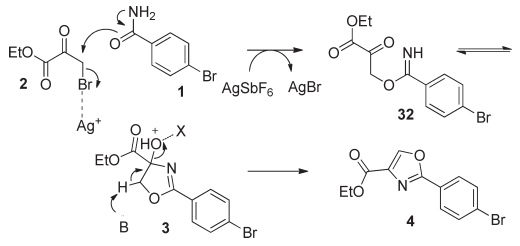
We were curious to learn if the conditions would also allow the synthesis of 2,4,5-substituted oxazoles. When ethyl 3-bromo-2-oxobutanoate (**27**) was used in place of ethyl bromopyruvate (Scheme 2), the trisubstituted oxazole **28** was formed cleanly after 3 h in 74% yield. This extension of the methodology was significant, as other methods[3b,13] for the synthesis of 2-substituted-oxazole-4-carboxylates generally cannot be employed to access trisubstituted oxazoles, or are limited to aliphatic substrates,[3c] or use lengthy procedures.[4c-4j,5]

dx.doi.org/10.1021/jo1025332 |*J. Org. Chem.* 2011, 76, 3519–3522

Scheme 3. Synthesis of Bis-Oxazole 29



Scheme 4. Possible Mechanism for Silver-Mediated Oxazole Formation



Bis- and polyoxazoles are common motifs in many natural products, for example diazonamide A[19] and telomestatin,[20] and we were keen to establish if our methodology could be extended to the synthesis of simple bis-oxazoles. In a test experiment, when 1,4-dibromo-2,3-butanedione (**30**) was reacted with 4-methoxybenzamide (**7**), a separable mixture of mono-oxazole **31** and bis-oxazole **29** were recovered in 47% and 37% isolated yield, respectively (Scheme 3). This preliminary result was encouraging for more detailed studies.

Mechanistically, we suppose that the silver salt activates the α-bromo-group in **2** to nucleophilic attack by the amide **1**, driven by the formation of a strong silver bromide bond.

Dehydration of the oxazoline intermediate **3** may be assisted by protonation of the tertiary alcohol by the conjugate acid $HSbF_6$, or perhaps by coordination to silver (Scheme 4). Detailed investigations are underway and will be reported in due course.

In conclusion, we have developed a silver-mediated one-step synthesis of di- and trisubstituted oxazoles from primary amides and activated β-bromo-α-ketones. The method is simple to perform under mild conditions. The silver salt (AgBr) can be readily recovered at the end of the reaction by simple filtration. The yields obtained are superior compared to many other methods.[3−5] We believe that our method complements related technologies, providing an alternative to known syntheses of oxazoles, especially those pertaining to the synthesis of oxazole-4-carboxylates.[3b,c,8,9,13]

EXPERIMENTAL SECTION

General Microwave Procedure for Optimized Conditions. To a dry tube under Ar atmosphere were added the amide (0.30 mmol), β-bromo-α-oxoester (0.30 mmol), anhydrous 1,2-dichloroethane (0.45 mL), and $AgSbF_6$ (0.30 mmol, 103 mg). The mixture was stirred for 1 min then heated to 90 °C in a sealed tube in a microwave reactor for 2 h (3 h in the case of **27**) with stirring. After this time the reaction was cooled to room temperature and a saturated solution of $NaHCO_3$ (5 mL) was added and the product was extracted with EtOAc (2 × 7 mL). The combined organics were washed with a saturated solution of brine (4 mL), dried (Na_2SO_4), filtered, and purified by flash chromatography or preparative TLC.

Ethyl 2-(4-bromophenyl)oxazole-4-carboxylate (4): colorless solid, 100%; mp 97−99 °C; R_f 0.31 (4:1, petrol−EtOAc); ν_{max}/cm^{-1} 3171, 3011, 1736; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 8.01 (d, J = 8.5 Hz, 2 H), 7.65 (d, J = 8.5 Hz, 2 H), 4.46 (q, J = 7.1 Hz, 2 H), 1.44 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 161.2, 143.8, 134.8, 132.1, 128.3, 125.8, 125.3, 61.4, 14.3; HRMS (ESI) calcd for $C_{12}H_{10}BrNNaO_3$ $[M + Na]^+$ 317.9742, found 317.9726.

Ethyl 2-(4-nitrophenyl)oxazole-4-carboxylate (18): pale yellow solid, 80%; mp 120−122 °C; R_f 0.18 (4:1, petrol−EtOAc); ν_{max}/cm^{-1} 2927, 2855, 1738, 1526; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (m, 5 H), 4.47 (q, J = 7.1 Hz, 2 H), 1.44 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.3, 149.2, 144.7, 135.5, 131.8, 127.8, 124.2, 61.6, 14.3; HRMS (ESI) calcd for $C_{12}H_{10}N_2NaO_5$ $[M + Na]^+$ 285.0487, found 285.0469.

Ethyl 2-(3-nitrophenyl)oxazole-4-carboxylate (19). colorless solid, 81%; mp 124−126 °C; R_f 0.15 (4:1, petrol−EtOAc); ν_{max}/cm^{-1} 2959, 1738, 1521; ^1H NMR (400 MHz, $CDCl_3$) δ 8.97 (app t, J = 1.8 Hz, 1 H), 8.49 (m, 1 H), 8.38 (ddd, J = 8.4, 2.3, 1.1 Hz, 1 H), 8.37 (s, 1 H), 7.72 (t, J = 8.2 Hz, 1 H), 4.47 (q, J = 7.1 Hz, 2 H), 1.45 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 160.1, 148.6, 144.4, 135.1, 132.4, 130.2, 128.0, 125.6, 121.7, 61.6, 14.1; HRMS (ESI) calcd for $C_{12}H_{10}N_2NaO_5$ $[M + Na]^+$ 285.0487, found 285.0469.

Ethyl 2-(furan-2-yl)oxazole-4-carboxylate (21): colorless solid, 81%; mp 46−48 °C; R_f 0.20 (4:1, petrol−EtOAc); ν_{max}/cm^{-1} 3172, 3010, 1737; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 (s, 1 H), 7.61 (dd, J = 1.7, 0.7 Hz, 1 H), 7.19 (dd, J = 3.5, 0.6 Hz, 1 H), 6.58 (dd, J = 3.5, 1.8 Hz, 1 H), 4.44 (q, J = 7.1 Hz, 2 H), 1.42 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.0, 154.9, 145.1, 143.1, 141.9, 134.6, 113.2, 112.0, 61.4, 14.3; HRMS (ESI) calcd for $C_{10}H_9NNaO_4$ $[M + Na]^+$ 230.0429, found 230.0423.

2-Bromo-1-[2-(4-methoxyphenyl)oxazol-4-yl]ethanone (31): white solid, 47%; mp 147−148 °C; ν_{max}/cm^{-1} (neat) 3124, 3072, 2956, 1697, 1462; ^1H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1 H), 8.01−8.03 (m, 2 H), 6.99−7.01 (m, 2 H), 4.53 (s, 2 H), 3.89 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.3, 162.3, 162.1, 142.5, 139.2, 128.6, 118.9, 114.3, 55.4, 32.1; HRMS (ESI) calcd for $C_{12}H_{10}BrNNaO_3$ $[M + Na]^+$ 317.9736, found 317.9728.

ASSOCIATED CONTENT

Supporting Information. Full experimental details and analytical data (NMR, HRMS, IR) for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: john.moses@nottingham.ac.uk.

ACKNOWLEDGMENT

The authors would like to thank the EPSRC, AICR, GSK, and the University of Nottingham for support. We also would like to thank Dr. Pallavi Sharma for fruitful discussion.

REFERENCES

(1) Palmer, D. C.; Taylor, E. C. The Chemistry of Heterocyclic Compounds. *Oxazoles: Synthesis, Reactions and Spectroscopy, Parts A & B*; Wiley: Hoboken, NJ, 2004; Vol. 60.

(2) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995–12042.
(3) (a) For a review see: Grant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297–2360. (b) Graham, T. H. *Org. Lett.* **2010**, *12*, 3614–3617. (c) Murai, K.; Takahara, Y.; Matsushita, T.; Komatsu, H.; Fujioka, H. *Org. Lett.* **2010**, *12*, 3456–3459. (d) Sakakura, A.; Kondo, R.; Ishihara, K. *Org. Lett.* **2005**, *7*, 1971–1974. (e) Davies, J. R.; Kane, P. D.; Moody, C. J. *Tetrahedron* **2004**, *60*, 3967–3977. (f) Kreisberg, J. D.; Magnus, P.; Shinde, S. *Tetrahedron Lett.* **2002**, *43*, 7393–7396. (g) Brain, C. T.; Paul, J. M. *Synlett* **1999**, 1642–1644. (h) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207–8215. (i) Shapiro, R. *J. Org. Chem.* **1993**, *58*, 5759–5764.
(4) (a) Wan, C.; Zhang, J.; Wang, S.; Fan, J.; Wang, Z. *Org. Lett.* **2010**, *12*, 2338–2341. (b) Shi, B.; Blake, A. J.; Lewis, W.; Campbell, I. B.; Judkins, B. D.; Moody, C. J. *J. Org. Chem.* **2010**, *75*, 152–161. (c) dos Santos, A.; El Kaïm, L.; Grimaud, L.; Ronsseray, C. *Chem. Commun.* **2009**, 3907–3909. (d) Bonne, D.; Dekhane, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2485–2488. (e) Kumar, M. P.; Liu, R.-S. *J. Org. Chem.* **2006**, *71*, 4951–4955. (f) Merkul, E.; Müller, T. J. J. *Chem. Commun.* **2006**, 4817–4819. (g) Barrett, A. G. M.; Cramp, S. M.; Hennessy, A. J.; Procopiou, P. A.; Roberts, R. S. *Org. Lett.* **2001**, *3*, 271–273.
(5) (a) Lechel, T.; Lentz, D.; Reissig, H.-U. *Chem.—Eur. J.* **2009**, *15*, 5432–5435. (b) Kison, C.; Opatz, T. *Chem.—Eur. J.* **2009**, *15*, 843–845. (c) Araki, H.; Katoh, T.; Inoue, M. *Tetrahedron Lett.* **2007**, *48*, 3713–3717. (d) Keni, M.; Tepe, J. J. *J. Org. Chem.* **2005**, *70*, 4211–4213.(e) Wipf, P.; Aoyama, Y.; Benedum, T. E. *Org. Lett.* **2004**, *6*, 3593−3595. (f) Coqueron, P.-Y.; Didier, C.; Ciufolini, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 1411–1414. (g) Wipf, P.; Methot, J.-L. *Org. Lett.* **2001**, *3*, 1261–1264. (h) Eastwood, F. W.; Perlmutter, P.; Yang, Q. *J. Chem. Soc., Perkin Trans. 1* **1997**, 35–42. (i) Ang, K. H.; Prager, R. H.; Smith, J. A.; Weber, B.; Williams, C. M. *Tetrahedron Lett.* **1996**, *37*, 675–678. (j) Yoo, S.-K. *Tetrahedron Lett.* **1992**, *33*, 2159–2162.
(6) Robinson, R. *J. Chem. Soc., Trans.* **1909**, *95*, 2167–2174.
(7) Gabriel, S. *Ber.* **1910**, *43*, 134–138.
(8) Wipf, P.; Miller, C. P. *J. Org. Chem.* **1993**, *56*, 3604–3606.
(9) For leading references see: Philips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165–1168.
(10) Jiang, H.; Huang, H.; Cao, H.; Qi, C. *Org. Lett.* **2010**, *12*, 5561–5563.
(11) (a) Blümlein, F. O. *Ber.* **1884**, *17*, 2578–2581. (b) Lewy, M. *Ber.* **1887**, *20*, 2576–2580.
(12) Moody., C. J.; Swann., E. *J. Med. Chem.* **1995**, *38*, 1039–1043.
(13) Panek, J. S.; Beresis, R. T. *J. Org. Chem.* **1996**, *61*, 6496–6497.
(14) Ramón, R. S.; Bosson, J.; Díez-Gonzàlez, S.; Marion, N.; Nolan, S. P. *J. Org. Chem.* **2010**, *75*, 1197–1202.
(15) Many silver salts are comparable in price to DAST, for example. AgBr can be recovered by simple filtration and recycled.
(16) Ratios were estimated from the oxazole CH (δ 8.30) of **4**, 1 diastereotopic CH_2 of the oxazoline ring of **3** (δ 4.72) and the NH_2 (δ 6.10) of **1**. Other by-products were negligible.
(17) $AgSbF_6$ followed the same trends as $AgClO_4$, e.g., when the reaction time was decreased to 1 h the yield dropped to 76%, when THF was used as solvent only 19% of **3** was recovered.
(18) (a) Aguilar, E.; Meyers, A. I. *Tetrahedron Lett.* **1994**, *35*, 2473–2476. (b) Holzapfel, C. W.; Pettit, G. R. *J. Org. Chem.* **1985**, *50*, 2323–2327.
(19) Cheung, C.-M.; Goldberg, F. W.; Magnus, P.; Russell, C. J.; Turnbull, R.; Vince Lynch, V. *J. Am. Chem. Soc.* **2007**, *129*, 12320–12327.
(20) Doi, T.; Yoshida, M.; Shin-ya, K.; Takahashi, T. *Org. Lett.* **2006**, *8*, 4165–4167.