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Studies of multicomponent Kinugasa reactions in aqueous media

Craig S. McKay [a,b], David C. Kennedy [a], John Paul Pezacki [a,b,*]

[a] Steacie Institute for Molecular Sciences, National Research Council, 100 Sussex Drive, Ottawa, Canada K1A 0R6
[b] Department of Chemistry, University of Ottawa, 10 Marie Curie, Ottawa, Canada K1N 6N5

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ABSTRACT

Micelle-promoted, copper-catalyzed multicomponent Kinugasa reactions were studied in aqueous media. Reactions were performed in a 'single pot' for a series of in situ generated *C,N*-diphenylnitrones with Cu(I) phenylacetylide providing β-lactams in yields of 45–85%. Substituents affect the reaction by either accelerating cycloaddition or minimizing side reactions.

Multicomponent reactions enable multiple reactions to be combined in a single procedural step. Multicomponent reactions have been applied to the construction of a number of complex molecular structures.[1,2] These reactions avoid potentially difficult purification steps and conserve both solvents and reagents. The use of water as a solvent has further advantages in that it is economical and enables reactions to be performed on water-soluble biomolecular substrates.[3] Organic reactions in water are often limited in scope due to poor solubility of the organic compounds. Nevertheless, a number of heterocyclic compounds including acridines,[4] furans,[5] indoles,[6] pyrazines,[7] pyridines,[8] pyrimidines,[9] and pyrazolines[10] have been successfully synthesized in aqueous media. The development of new multicomponent reactions in aqueous media to form complex organic molecules remains an important challenge.

β-Lactams represent one of the best known and extensively studied class of heterocycles, primarily as a result of their powerful antibiotic activities.[11,12] β-lactams were first synthesized by Staudinger in 1907 via the cycloaddition of ketenes with imines.[13] Since then there have been a number of methodologies for the construction of the β-lactam ring.[14] A convergent route to β-lactams was reported by Kinugasa et al. in 1972, whereby *C,N*-diphenylnitrones were reacted with in situ-generated Cu(I) phenylacetylide in anhydrous pyridine,[15] and a generally accepted mechanism of β-lactam formation has been established.[16] Asymmetric variants of the Kinugasa reaction use chiral ligands for chelation to copper such as bis(oxazoline)-type ligands,[17] Evans' oxazolidinone ligand,[18] planar chiral bis(azaferrocene) ligands,[19] tris(oxazoline) ligands,[20] and HETPHOX ligands.[21]

Previously, Chatterjee et al. reported a convenient 'single pot' synthesis of isoxazolines which involved micelle-catalyzed nitrone formation followed by cycloaddition in aqueous media.[22] We have recently utilized this methodology to functionalize an unnatural amino acid containing a cyclic α,β-unsaturated ketone with in situ-generated *C,N*-diphenylnitrone in aqueous media.[23] Also click conditions for the Kinugasa reaction have been successfully reported.[24] Herein, we report studies of simultaneous micelle and copper-catalyzed multicomponent Kinugasa reactions in water. The multicomponent process proceeds by a two-step reaction sequence involving the micelle-promoted nitrone formation from substituted benzaldehydes and *N*-phenylhydroxyl amine followed by the in situ 1,3-dipolar cycloaddition and rearrangement reaction with Cu(I) phenylacetylide (Fig. 1).

A key step to establishing optimal reaction conditions for the multicomponent Kinugasa reaction is the optimization of the in situ generation of the nitrone. To accomplish this, we employed similar conditions to those used by Chatterjee et al.[22] Dehydrative nitrone formation from benzaldehyde (**1a**) (0.4 mmol) and phenyl hydroxylamine (**2**) (0.5 mmol) in the presence of SDS micelles (0.4 mmol) in degassed water at room temperature (rt) proceeded in 30 min. to form *C,N*-diphenylnitrone. It was found that sonication of the reaction mixture for 5 min decreased the time of nitrone

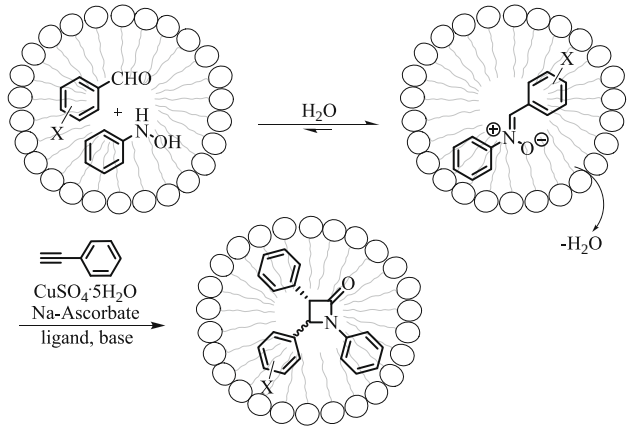

Figure 1. Micelle-promoted multicomponent β-lactam synthesis by the Kinugasa reaction.

* Corresponding author. Tel.: +1 613 993 7253; fax: +1 613 941 8447.
E-mail address: John.Pezacki@nrc.ca (J.P. Pezacki).

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formation, presumably by helping to effectively solubilize the reagents by the surfactant. This method of nitrone formation complements traditional approaches using organic solvents,[18] which often require anhydrous conditions and/or the use of dehydrating agents.

We found that cooling the in situ-generated *C*,*N*-diphenylnitrone to 0 °C led to better yields of β-lactam **4a**, Scheme 1. The cooled solution was then reacted with phenylacetylene (0.2 mmol), (+)-sodium-L-ascorbate (0.08 mmol), and $Cu(SO)_4$ (0.04 mmol) in the dark. The latter reaction also contained an excess of pyridine (1.6 mmol) and 0.1 M ethanolamine (ETA) buffered at pH 10. This mixture was allowed to react for 30 min at 0 °C and was then stirred at room temperature for 10 h. The reaction mixture consisted of essentially three products (Scheme 1), the *cis*- and *trans*-β-lactams (**4a**) in 46% overall yield and an amide product (**5**) in 36% yield, the structure of which was confirmed by X-ray crystallography. As far as we are aware, amide **5** is not a typical by-product of the Kinugasa reaction or a common decomposition product of β-lactams.

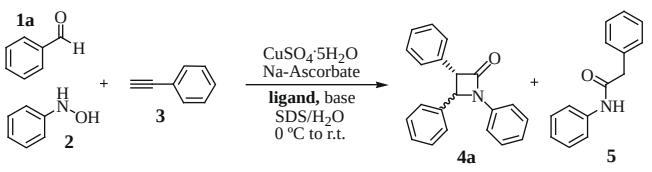
To investigate the origins of the side product **5**, we performed a series of reactions systematically removing each component of the multicomponent reaction. None of these control reactions led to the formation of **5**. Also, we placed product **4a** into solutions containing copper, ascorbate, and SDS, to determine if **5** is a decomposition product of **4a**. We did not see any reaction of **4a** under these conditions, therefore side product **5** clearly does not arise from the decomposition of **4a**. Previously, Tang and co-workers[20b] observed a different side product in the Kinugasa reaction and proposed a ketene intermediate for it's formation.[20b] Here, we propose that an analogous ketene is formed and that in water it gives rise to **5**, according to the pathway given in Scheme 2.

Na-ascorbate reduces Cu(II) to Cu(I) under aqueous conditions, and allows for the in situ generation of the Cu(I) phenylacetylide. This intermediate then reacts with the in situ-generated nitrone in a formal [3+2] cycloaddition forming an isoxazoline intermediate. Protonation and subsequent rearrangement of the oxaziridine produce a mixture of *cis*- and *trans*-β-lactams. The diastereoselectivity depends on the ease of isomerization at C-3, as shown previously.[16,20,25]

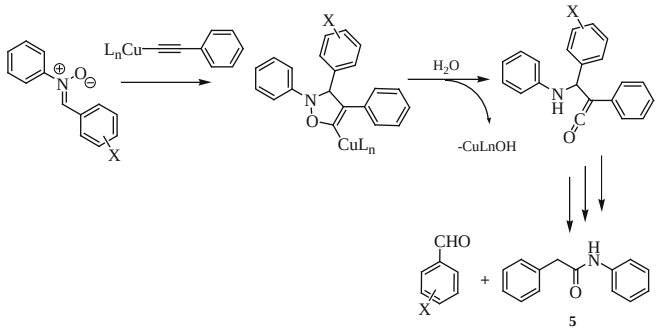
Under the conditions used in Table 1, Cu(I) loading did not significantly affect the product composition; however, lower Cu loading resulted in longer reaction times. Catalyst loading below 20 mol % caused the reaction to be very sluggish and gave poor yields of *cis*- and *trans*-**4a**. A proposed catalytic cycle for the copper-catalyzed Kinugasa reaction in water is shown in Figure 2.

In a screen of three nitrogen-containing ligands, it was found that conducting the reaction with excess pyridine yielded *cis*- and *trans*-**4a** in 46% yield (Table 2). In contrast, decreasing the amount of pyridine below 2 equiv resulted in a very slow reaction and trace amounts of *cis*- and *trans*-**4a** were detected. Presumably, excess pyridine facilitates regeneration of the active Cu catalyst.

Alternatively, 2,2′-bipyridyl was found to be a more efficient ligand in the reaction and provided *cis*- and *trans*-**4a** and **5** in yields of 42% and 29%, respectively, with the addition of only one equivalent. This is likely attributed to stronger Cu(I) binding of this bidentate ligand in solution. Next, tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (TBTA), a ligand commonly used in azide–alkyne cycloadditions,[26] was examined. The reaction was slower and provided **4a** and **5** in 31% and 22% yields after an extended reaction time.



Scheme 1.



Scheme 2.

Table 1
Effect of Cu catalyst loading on the multicomponent Kinugasa reaction in water[a]

Entry	Cu catalyst[b] (mol %)	Time (h)	% Yield[c]	
			4a (cis/trans)	**5**
1	100	6	46 (1.2:1)	36
2	80	7	46 (1.2:1)	36
3	20	10	46 (1.2:1)	36

[a] Reaction conditions; [**1a**]:[**2**]:[**3**]:ETA:py = 2:2.4:1:2:8 in degassed SDS/H_2O (0.05 M) in dark from 0 °C to rt under argon.
[b] Na-ascorbate:$CuSO_4$ = 2:1.
[c] Determined by HPLC analysis. ETA = 0.1 M ethanolamine buffer at pH 10.

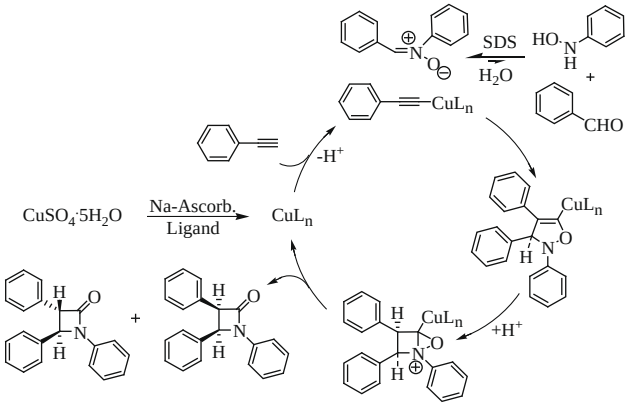


Figure 2. Proposed catalytic cycle for Cu(I)-catalyzed Kinugasa reaction in water.

Table 2
Effect of ligand on the micelle-catalyzed Kinugasa reaction in water[a]

Entry	Ligand[c] (equiv)	Time (h)	Yield[b] (%)	
			4a (cis/trans)	**5**
1	py (10)	9	46 (1.2:1)	36
2	py (8)	10	46 (1.2:1)	36
3	py (2)	20	15(1:1)	18
4	bpy (1)	10	42 (1.4:1)	29
5	TBTA[d] (0.2)	24	31 (1:1)	22

[a] Reaction conditions; [**1a**]:[**2**]:[**3**]:Na-ascorbate:$CuSO_4$:ETA = 2:2.4:1:0.4:0.2:2 in degassed SDS/H_2O (0.05 M) in dark from 0 °C to rt under argon.
[b] Determined by HPLC analysis.
[c] py = pyridine, bpy = 2,2′-bipyridyl, TBTA = tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine.
[d] TBTA was dissolved in 0.05 M SDS prior to adding to the reaction.

Table 3
Effect of stoichiometry on the multicomponent Kinugasa reaction in aqueous media[a]

Entry	**1a**:**3**	Base	Yield[b] (%)	
			4a (cis/trans)	**5**
1	4:1	ETA	44 (1.1:1)	35
2	2:1	ETA	46 (1.2:1)	36
3	2:1	Tris	39 (1:1)	41
4	2:1	—	40 (2:1)	47
5	1:2	ETA	24 (1:1)	24
6	1:2	Tris	37 (1:1)	39
7	1:2	—	33 (1.5:1)	37

[a] Reaction conditions; Na-ascorbate:$CuSO_4$:base:py = 0.4:0.2:2:8 in degassed SDS/H_2O (0.05 M) in dark from 0 °C to rt under argon.
[b] Determined by HPLC analysis. ETA = ethanolamine buffer (0.1 M pH 10), Tris = tris(hydroxymethyl)aminomethane buffer (0.1 M pH 8).

The stoichiometry of **1a**:**3** was also varied (Table 3). We found that the yield of **4a** was consistently higher when using an excess of **1a** relative to **3.** Interestingly, the multicomponent Kinugasa reaction proceeds when buffered to pH 8 using a 0.1 M Tris buffer, providing *cis*- and *trans*-**4a** and **5** in 39% and 41% yields. The use of a buffer maintained a constant pH throughout the course of the reaction, and it was found that the highest yields of *cis*- and *trans*-**4a** and **5** were 46% and 36%, respectively, when an ETA solution buffered to pH 10 was used.

We next examined if the base employed affects the yield and selectivity of the reaction. As shown in Table 4, two inorganic salts, primary amines, secondary amines, and a tertiary amine could all effectively promote the reaction. Compared with primary and tertiary amines, secondary amines afforded the β-lactam products with better *cis*-diastereoselectivity. Bulkier amines also favored the formation of the *cis*-**4a** diastereomer. This suggests that the amine may coordinate to Cu(I).

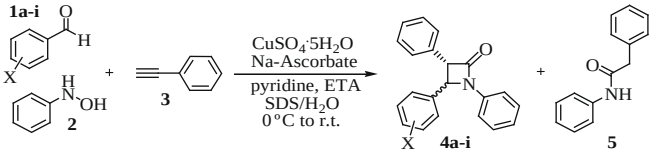
Next, we examined the generality of the micelle-promoted and copper-catalyzed multicomponent Kinugasa reaction by applying a series of substituted benzaldehydes[27,28] at the *para*- and *meta*-positions (Table 5). The presence of electron-donating groups (EDGs) resulted in lower yields of the corresponding *cis*- and *trans*-β-lactams (**4b–d)** in slightly shorter reaction times relative to when electron-withdrawing groups (EWGs) were employed (Table 5, entries 2–4). The yield of **5** was consistently lower when the electron-withdrawing groups were present on the benzaldehyde. There are three competing reactions that affect the product composition; formation of β-lactams, formation of **5,** and hydrolytic decomposition of the in situ-generated nitrone. Reactions of nitrones bearing EWGs resulted in a lower yield of **5** and less decomposition (higher overall yield of **4**+**5**) relative to those containing EDGs. While the reactions take slightly longer to reach completion using EWGs (Table 5, entries 6–9), the lack of competing pathways results in increased yields of *cis*- and *trans*-β-lactams, **4e–i**, respectively. The longer reaction times likely result from a modest substituent effect on the rate constant for cycloaddition between the in situ-generated Cu(I) phenylacetylide and the in situ-generated nitrone. Also, less decomposition over the first 10 h contributes to the much higher yields for the latter reactions. The ratio of cis/trans for all substituted β-lactams (**4b–i**) did not change with respect to **4a**.

Table 4
Effect of base on the multicomponent Kinugasa reaction in water[a]

Entry	Base	Time (h)	Yield[b] (%)	
			4a (cis/trans)	**5**
1	Na_2CO_3	10	38 (1.2:1)	46
2	$NaHCO_3$	8	44 (1.1:1)	43
3	DIPA	11	42 (2.5:1)	45
4	Cy_2NH	12	31 (2.8:1)	39
5	Et_3N	10	45 (1.6:1)	43
6	Tris	12	38 (1:1)	45
7	ETA	10	46 (1.2:1)	36

[a] Reaction conditions; [**1a**]:[**2**]:[**3**]:Na-ascorbate:$CuSO_4$:py:ETA = 2:2.4:1:0.4:0.2:8:2 in degassed SDS/H_2O (50 mM) in dark from 0 °C to rt under argon.
[b] Determined by HPLC analysis.

Table 5
Multicomponent Kinugasa reaction scope with respect to the α-aryl nitrone substituent[a]



Entry	Substituent (X=)	Time (h)	Yield[b] (%)	
			4 (cis/trans)	**5**
1	H, **4a**	10	46 (1.2:1)	36
2	*p*-Me, **4b**	13	45 (1.3:1)	24
3	*p*-OMe, **4c**	8	62 (1.2:1)	26
4	*m*-OMe, **4d**	9	60 (1.2:1)	15
5	*p*-Br, **4e**	18	73 (1.6:1)	22
6	*p*-CO_2Me, **4f**	18	85 (1:1)	13
7	*p*-CN, **4g**	18	67 (1.2:1)	18
8	*m*-NO_2, **4h**	18	79 (1.3:1)	11
9	*p*-NO_2, **4i**	18	82 (1.1:1)	15

[a] Reaction conditions; [**1a–i**]:[**2**]:[**3**]:Na-ascorbate:$CuSO_4$:py:ETA = 2:2.4:1:0.4:0.2:8:2 in degassed SDS/H_2O (50 mM) in dark from 0 °C to rt under argon.
[b] Determined by HPLC analysis.

In conclusion, we have studied multicomponent Kinugasa reactions for the simultaneous micelle-promoted and Cu(I)-catalyzed coupling of alkynes with in situ-generated nitrones to form β-lactams. The reaction is tolerant to substituents at the α-aryl position of the nitrone, and the highest yields of β-lactams were obtained when electron-withdrawing substituents are employed. This reaction provides a convenient method for the construction of the β-lactam ring in aqueous media.

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Supplementary data

Detailed experimental procedures, characterization data, and representative HPLC chromatograms are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.035.

References and notes

1. Zhu, J.; Bienaymé, H. *Multicomponent Reactions*; Wiley-VCH: Weinheim, 2005. and references therein.
2. (a) Pan, S. C.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 3622; (b) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *117*, 1628; (c). *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (d) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957; (e) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133; (f) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471; (g) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Sreekanth, A. R.; Mathen, J. S.; Balagopal, L. *Acc. Chem. Res.* **2003**, *36*, 899; (h) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321; (i) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168; (j) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304.
3. (a) Li, C. J.; Chan, T. H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997; (b) Grieco, P. A. *Organic Synthesis in Water*; Blackie Academic & Professional: London, 1998; (c) Lubineau, A.; Auge, J. In *Modern Solvents in Organic Synthesis*; Knochel, P., Ed.; Springer: Berlin, Heidelberg, 1999.

4. Wang, X. S.; Zhang, M. M.; Zeng, Z. S.; Shi, D. Q.; Tu, S. T.; Wei, X. Y.; Zong, Z. M. *Tetrahedron Lett.* **2005**, *46*, 7169.
5. Wnorowski, A.; Yaylayan, V. A. *J. Agric. Food Chem.* **2000**, *48*, 3549.
6. Cho, C. S.; Kim, J. H.; Shim, S. C. *Tetrahedron Lett.* **2000**, *41*, 1811.
7. Totlani, V. M.; Peterson, D. G. *J. Agric. Food Chem.* **2005**, *53*, 4130.
8. Khadilkar, B. M.; Gaikar, V. G.; Chitnavis, A. A. *Tetrahedron Lett.* **1995**, *36*, 8083.
9. Bose, D. S.; Fatima, L.; Mereyala, H. B. *J. Org. Chem.* **2003**, *68*, 587.
10. Wang, Y.; Vera, C. I.; Lin, Q. *Org. Lett.* **2007**, *9*, 4155.
11. (a)*Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic Press: New York, 1982; (b)*The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; Wiley VCH: New York, 1993; (c) Katritzky, A. R.; Rees, C. W.. In *Comprehensive Heterocyclic Chemistry II*; Scriven, E. F. V., Ed.; Pergamon: New York, 1996; Vol. 1B,. Chapter 1.18–1.20 (d) Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383.
12. (a)*Synthesis of β-Lactam Antibiotics Chemistry, Biocatalysis and Process Integration*; Bruggink, A., Ed.; Kluwer: Dordrecht, Netherlands, 2001; (b)*Enantioselective Synthesis of B-Amino Acids*; Palomo, C., Aizpurua, J. M., Ganoba, I., Juaristi, E., Eds.; Wiley-VCH: New York, 1997; p 279; (c) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377.
13. Staudinger, H. *Ann. Chem.* **1907**, *356*, 51.
14. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Pure Appl. Chem.* **2000**, *72*, 1763.
15. (a) Kinugasa, M.; Hashimoto, S. *J. Chem. Soc., Chem. Commun.* **1972**, 466; For a recent review, see: (b) Marco-Contelles, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2198.
16. Ding, L. K.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 2382.
17. Muira, M.; Enna, M.; Okura, K.; Nomura, M. *J. Org. Chem.* **1995**, *60*, 4999.
18. Basak, A.; Gosh, S. C.; Bhowmick, T.; Das, A. K.; Bertolasi, V. *Tetrahedron Lett.* **2002**, *43*, 5499.
19. (a) Lo, M.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 4572; (b) Shintani, R.; Fu, G. C. *Angew. Chem., Int. Ed.* **2003**, *42*, 4082.
20. (a) Ye, M.-C.; Zhou, J.; Huang, Z.-Z.; Tang, Y. *Chem. Commun.* **2003**, 2554; (b) Ye, M.-C.; Zhou, J.; Tang, Y. *J. Org. Chem.* **2006**, *71*, 3576.
21. Coyne, A.; Muller-Bunz, H.; Guiry, P. J. *Tetrahedron: Asymmetry* **2007**, *18*, 199.
22. Chatterjee, A.; Maiti, D. K.; Bhattacharya, P. K. *Org. Lett.* **2003**, *5*, 3967.
23. Lorello, G.; Legault, M. C. B.; Rakic, B.; Bisgaard, K.; Pezacki, J. P. *Bioorg. Chem.* **2008**, *36*, 91.
24. Basak, A.; Chandra, K.; Pal, R.; Ghosh, S. C. *Synlett* **2007**, 1585.
25. (a) Fugisawa, T.; Ichikawa, M.; Ukaji, Y.; Shimizu, M. *Tetrahedron Lett.* **1993**, *34*, 1307; (b) Shimizu, M.; Kume, K.; Fugisawa, T. *Chem. Lett.* **1996**, 545.
26. Chan, T. R.; Hilgraf, R.; Sharpless, K. B.; Fokin, V. V. *Org. Lett.* **2004**, *6*, 2853.
27. Pfleger, R.; Jager, A. *Chem. Ber.* **1957**, *90*, 2460.
28. Bolognese, A.; Diurno, V. M.; Mazzoni, O. *Tetrahedron* **1991**, *47*, 7417.