Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient Synthesis of Isoquinoline Derivatives via AgOTf/$Cu(OTf)_2$-Cocatalyzed Cyclization of 2-Alkynyl Benzaldoxime

Xiaona Zhao [a], Weidong Fan [a], Zhiwei Miao [a b] & Ruyu Chen [a]
[a] State Key Laboratory of Elemento-organic Chemistry, Research Institute of Elemento-organic Chemistry, Nankai University, Tianjin, China
[b] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Tsinghua University, Beijing, China
Accepted author version posted online: 08 Aug 2012.Version of record first published: 06 Mar 2013.

To cite this article: Xiaona Zhao , Weidong Fan , Zhiwei Miao & Ruyu Chen (2013): Efficient Synthesis of Isoquinoline Derivatives via AgOTf/$Cu(OTf)_2$-Cocatalyzed Cyclization of 2-Alkynyl Benzaldoxime, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:12, 1714-1720

To link to this article: http://dx.doi.org/10.1080/00397911.2012.666314

Synthetic Communications®, 43: 1714–1720, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2012.666314

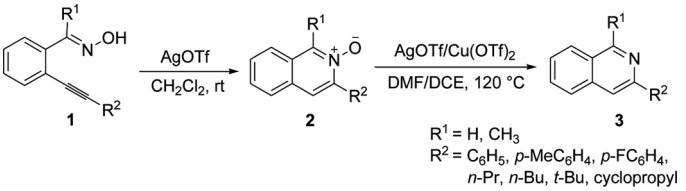
EFFICIENT SYNTHESIS OF ISOQUINOLINE DERIVATIVES VIA AgOTf/Cu(OTf)$_2$-COCATALYZED CYCLIZATION OF 2-ALKYNYL BENZALDOXIME

Xiaona Zhao,[1] Weidong Fan,[1] Zhiwei Miao,[1,2] and Ruyu Chen[1]

[1]*State Key Laboratory of Elemento-organic Chemistry, Research Institute of Elemento-organic Chemistry, Nankai University, Tianjin, China*

[2]*Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology (Ministry of Education), Tsinghua University, Beijing, China*

GRAPHICAL ABSTRACT



Abstract *An efficient, AgOTf and Cu(OTf)$_2$ multicatalytic intramolecular cycloisomerization of 2-alkynylbenzaldoxime is reported. Isoquinoline* N*-oxides have been found to be deoxygenated to the corresponding quinolines in good yields in dimethylformamide/dichloroethane (v/v 5:1) as solvent at 120°C.*

Keywords Intramolecular cycloisomerization; isoquinoline; isoquinoline N-oxide; multicatalytic deoxygenation

INTRODUCTION

Isoquinoline derivatives are an important class of heterocycles and are found in many naturally occurring compounds that exhibit a variety of biological activities such as antitumor, analgesic, antihistaminic, and antifertility activities.[1] Isoquinoline species are not only key structural units in many natural products but are also known as chiral ligands for transition-metal catalysts.[2] For these reasons, the efficient synthesis of the isoquinoline ring system continues to attract the interest of synthetic chemists.[3] A number of classical methods are available for the synthesis of isoquinoline derivatives, including the Bischler–Napieralski,[4] the Pictet–Spengler,[5] and the Pomeranz–Fritsch[6] reactions. However, these methods often suffer from tedious reaction procedures and harsh reaction conditions.

Received September 27, 2011.

Address correspondence to Zhiwei Miao, State Key Laboratory of Elemento-organic Chemistry, Research Institute of Elemento-organic Chemistry, Nankai University, Tianjin 300071, China. E-mail: miaozhiwei@nankai.edu.cn

Over the past two decades, the transition-metal chemistry focusing on isoquinoline synthesis has been developed. Zhu and coworkers developed a novel palladium-catalyzed domino annulation process for the formation of biologically relevant phenanthridines and isoquinolines.[7] Miura reported the rhodium-catalyzed oxidative coupling of aromatic imines with internal alkynes to produce indenone imine and isoquinoline derivatives.[8] In particular, a very recent report by Wu and coworkers has shown that silver triflate could catalyze a novel reaction of 2-alkynylbenzaldoxime with *O*-(trimethylsilyl)aryl triflate to produce the isoquinoline derivatives of 2-oxa-6-aza-bicyclo[3.2.2]nona-6,8-diene.[9] Recent studies have shown that silver species exhibited interesting catalytic activities functioning as a transition-metal catalyst.[10] In 2009, Liang and coworkers have demonstrated that Ag^+-catalyzed cyclization of 2-alkynyl benzyl azides can produce 3-substituted or 1,3-disubstituted isoquinolines.[11]

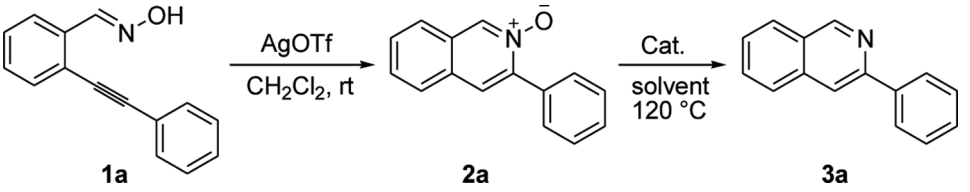
Oximes often function as stable precursors of amino compounds through the reductive cleavage of the N-O bond.[12] A variety of redox processes of the cleavage N-O bond induce the conversions of oximes into amides,[13] nitriles,[14] and enamides.[15] Recently, 2-alkynylbenzaldoximes have been reported as a versatile building block for the synthesis of nitrogen-containing heterocycles.[16] Wu and others discovered that in the presence of Lewis acids, 2-alkynylbenzaldoxime could be transferred to isoquinoline-*N*-oxide.[17] As part of a continuing effort in our laboratory to synthesize biologically relevant heterocyclic compounds,[18] we report that ortho-alkynylaryl aldehyde oxime derivatives catalyzed by transition-metal complexes would afford an intermediate isoquinolinium salt and subsequently transfer into isoquinoline derivatives.

RESULTS AND DISCUSSION

The required 2-alkynylbenzaldoximes **1** were prepared by the condensation of hydroxylamine with the corresponding aldehydes.[19] When **1a** was heated with AgOTf (10 mol%) in CH_2Cl_2 at room temperature, the corresponding cyclized product **2a** was obtained in 94% isolated yield after 3 h. The reaction proceeds through 6-*endo-dig* addition of the oxime *N*-atom on Ag^+-activated alkyne to afford isoquinolinium salt **2a**. The deoxygenation of amine-*N*-oxide to amines has been developed in the synthesis of heterocycles in many procedures.[20] We studied various catalysts for the deoxygenation of amine-*N*-oxide reaction using **2a** as substrate. The results revealed that there was no product formed without the aid of a Lewis acid (entry 1, Table 1). When **2a** was reacted with AgOTf (10 mol%) in dimethylformamide (DMF) at 120 °C, isoquinoline **3a** was obtained in 38% isolated yield after 48 h (entry 2, Table 1). Other silver salts screened (e.g., $AgSbF_6$, Ag_2O, and $AgClO_4$) were also able to promote the deoxygenation reaction in dimethylformamide (DMF) (entries 3–5, Table 1). The use of $Cu(OTf)_2$ cocatalyst (10 mol%) along with AgOTf (10 mol%) further boosted the reactivity, giving **3a** in 82% yield in 24 h. Use of $Cu(OTf)_2$ in less than 5 mol% led to a poor yield, due to the decomposition. Change of cocatalyst to $Zn(OTf)_2$ also led to a lower yield of **3a** (entries 6–8, Table 1).

With the best multicatalytic system [$AgOTf/Cu(OTf)_2$] being identified, we next carried out the reaction in different solvents. Among the solvents screened, toluene and MeCN were providing **3a** in lower yields, while more polar solvent mixtures

Table 1. Screening of the reactions of (*E*)-2-(2-phenylethynyl)benzaldehyde oxime **1a** under different conditions[a]



1a **2a** **3a**

Entry[a]	Catalyst (equiv.)	Solvent	Time (h)	Yield (**3a**)[e]
1	—	DMF	24	—
2	AgOTf (0.1)	DMF	48	38
3	$AgSbF_6$ (0.1)	DMF	48	42
4	Ag_2O (0.1)	DMF	36	41
5	$AgClO_4$ (0.1)	DMF	36	48
6	AgOTf (0.1) / $Cu(OTf)_2$ (0.1)	DMF	24	82
7	AgOTf (0.1) / $Cu(OTf)_2$ (0.05)	DMF	24	69
8	AgOTf (0.1) / $Zn(OTf)_2$ (0.1)	DMF	24	62
9	AgOTf (0.1) / $Cu(OTf)_2$ (0.1)	Toluene	24	44
10	AgOTf (0.1) / $Cu(OTf)_2$ (0.1)	MeCN	36	32
11[b]	AgOTf (0.1) / $Cu(OTf)_2$ (0.1)	DMF/DCE	24	82
12[c]	AgOTf (0.1) / $Cu(OTf)_2$ (0.1)	DMF/DCE	24	85
13[d]	AgOTf (0.1) / $Cu(OTf)_2$ (0.1)	DMF/DCE	24	90

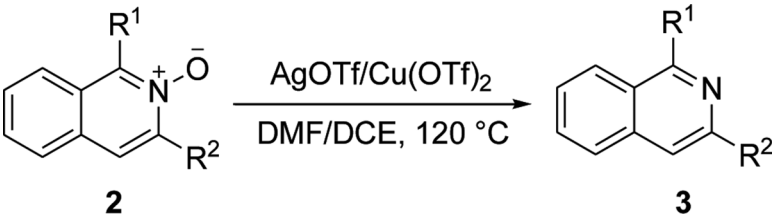
[a]Unless otherwise noted all the reactions were performed with 0.5 mmol of **2a** and 10 mol% catalyst in 5 ml solvent at 120 °C.
[b]DMF/DCE (v/v = 1:1).
[c]DMF/DCE (v/v = 1:3).
[d]DMF/DCE (v/v = 1:5).
[e]Isolated yields.

[DMF/dichloroethane (DCE)] with diffenent ratios displayed steady and the greatest conversion (entries 9–13, Table 1). Therefore, the tentatively optimized reaction conditions were determined as DMF/DCE (v/v = 5:1) as the solvent in further investigations.

Under these optimum conditions, we next examine the generality of the reaction in the synthesis of various isoquinoline skeletons (Table 2). It was found that all the reactions of substrates bearing no further substituent at the benzylic position ($R^1 = H$) went to completion in the presence of catalytic amounts of AgOTf/$Cu(OTf)_2$ in DMF/DCE (v/v = 5:1) at 120 °C within 24 h and the desired products **3** were obtained in good to excellent yields. When R^2 was replaced by 4-methylphenyl or 4-fluorophenyl, the reaction was still going very well and the desired products were isolated (**3a–g**, Table 2). The results indicated that the electron-donating or electron-withdrawing group attached on the aromatic ring of isoquinolinium salt **2** was not influencing this deoxygenation reaction. When R^2 was replaced by an alkyl group, the reaction was performed smoothly but with lower yields (**3d–g**, Table 2). We also explored ketoxime derivatives and the reactions of ketoximes occurred with lower yields than those of aldoximes (**3h–k**, Table 2).

A plausible mechanism for the reductive N-O bond cleavage of amine-*N*-oxide is outlined in Scheme 1. In the first step, the reaction was assumed to proceed by the

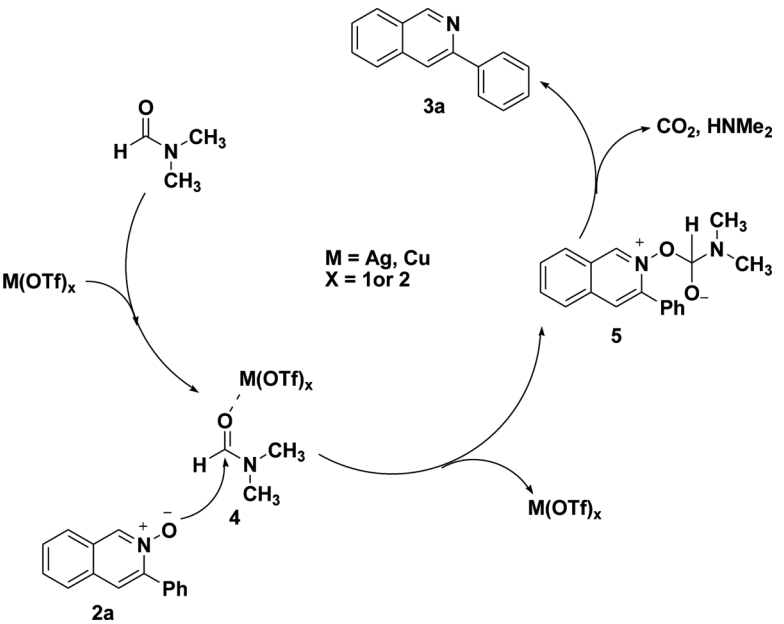
Table 2. AgOTf/$Cu(OTf)_2$-catalyzed reactions of isoquinoline-*N*-oxides **2**



2 **3**

Product[a]	R^1	R^2	Yield (%)[b]
3a	H	C_6H_5	90
3b	H	4-MeC_6H_4	83
3c	H	4-FC_6H_4	70
3d	H	*n*-Pr	76
3e	H	*n*-Bu	75
3f	H	*t*-Bu	68
3g	H	Cyclopropyl	80
3h	CH_3	C_6H_5	78
3i	CH_3	4-MeC_6H_4	73
3j	CH_3	4-FC_6H_4	68
3k	CH_3	*n*-Bu	64

[a]Unless otherwise noted all the reactions were performed with 0.5 mmol of **2** and 10 mol% AgOTf along with 10 mol% $Cu(OTf)_2$ in 2 ml DMF and DCE (v/v = 5:1) at 120 °C for 24 h.
[b]Isolated yields.



Scheme 1. Plausible reaction mechanism.

DMF coordinate to $M(OTf)_x$ (M = Ag or Cu, x = 1 or 2) to give complex **4**. Then, isoquinoline-*N*-oxide **2** attacked the carbonyl group of complex **4** and removed the $M(OTf)_x$ to get a intermediate **5**. In a subsequent step, removal of CO_2 and $HNMe_2$ and cleavage of the N-O bond led to the formation of the corresponding amine **3a**. The notable advantages of the present procedure are the ease of manipulation, the good yields, the mild reaction conditions, and the tolerance of the reaction substrates.

EXPERIMENTAL

All reactions were carried out under an inert atmosphere and in heat-dried glassware. Column chromatography was performed on silica gel (particle size 10–40 μm, Ocean Chemical Factory of Qingdao, Qingdao, China). ^1H and ^{13}C NMR spectra were recorded on Brucker 400 (400 MHz for ^1H, 162 MHz for ^{13}C) and Brucker 300 (300 MHz for ^1H, 75 MHz for ^{13}C) spectrometers. Chemical shifts were reported in parts per million (ppm) downfield from internal tetramethylsilane (TMS). Mass spectra were recorded on a LCQ advantage spectrometer with electrospray ionization (ESI) resource. HR-MS were recorded on APEXII and ZAB-HS spectrometers.

General Procedure for Preparation of 2-Alkynylbenzaldoxime 1

A solution of 2-alkynylbenzaldehyde (3.0 mmol), hydroxylamine hydrochloride (6 mmol, 2.0 equiv), and pyridine (6.0 mmol, 2.0 equiv) in C_2H_5OH (15 mL) was stirred under reflux for 2 h. After completion of the reaction as indicated by thin-layer chromatography (TLC), the solvent was evaporated, and the reaction was quenched with water (10 mL), extracted with AcOEt (2 × 30 mL), and dried by anhydrate Na_2SO_4. Evaporation of the solvent followed by purification on silica gel [AcOEt/petroleum ether (bp 60–90 °C) 1:3] provided the corresponding 2-alkynylbenzaldoxime **1**.

General Procedure for the Synthesis of Isoquinoline-N-oxide 2

AgOTf (7 mg, 10 mmol%) was added to a solution of oxime **1** (0.27 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at rt for 30 min. The solvent was removed, and the residue was purified by silica-gel chromatography (CH_2Cl_2/MeOH, 10:1) to give product **2** as a white solid.

General Procedure for the Synthesis of Isoquinoline 3

Isoquinoline-*N*-oxide **2** (0.5 mmol) in DMF/DCE (v/v = 5:1) was stirred at room temperature for 10 min. AgOTf (13 mg, 10 mol%) and $Cu(OTf)_2$ (18 mg, 10 mol%) were added to the mixture subsequently, and the mixture was kept stirring for 24 h [TLC (silica gel) monitoring] at 120 °C. The resulting mixture was filtered through a silica-gel column and concentrated. The residue was purified by flash column chormatography [silica gel, AcOEt/petroleum ether (bp 60–90 °C) 1:20] to afford the product **3.**

CONCLUSION

In conclusion, we have described an efficient method for the synthesis of isoquinoline derivatives via multicatalytic deoxygenation of amine-*N*-oxides to the

corresponding amines. The feature of this procedure is its simplicity, mild reaction conditions, and its generality with regard to aromatic substrates. Further studies to elucidate the mechanism of this novel reaction and to extend the scope of its synthetic utility are in progress in our laboratory.

ACKNOWLEDGMENTS

We thank the National Natural Science Foundation of China (21072102), the Committee of Science and Technology of Tianjin (11JCYBJC04200), and State Key Laboratory of Elemento-organic Chemistry in Nankai University for financial support.

REFERENCES

1. (a) *The Chemistry of Heterocyclic Compounds: Isoquinolines*; G. M. Coppola, H. F. Schuster (Eds.); John Wiley & Sons: New York, 1981; vol. 38, part 3; (b) Timari, G.; Soos, T.; Hajos, G.; Messmer, A.; Nacsa, J.; Molnar, J. *Biol. Org. Med. Chem. Lett.* **1996**, *23*, 2831; (c) Bentley, K. W. *The Isoquinoline Alkaloids*; Hardwood Academic: Amsterdam, the Netherlands, 1998; vol. 1.
2. (a) Selected papers: Durola, F.; Sauvage, J.-P.; Wenger, O. S. *Chem. Commun.* **2006**, *171*; (b) Sweetman, B. A.; Müller-Bunz, H.; Guiry, P. J. *Tetrahedron Lett.* **2005**, *46*, 4643; (c) Lim, C. W.; Tissot, O.; Mattison, A.; Hooper, M. W.; Brown, J. M.; Cowley, A. R.; Hulmes, D. I.; Blacker, A. *J. Org. Process Res. Dev.* **2003**, *7*, 379; (d) Alcock, N. W.; Brown, J. M.; Hulmes, G. I. *Tetrahedron: Asymmetry* **1993**, *4*, 743.
3. For selected examples, see (a) Yang, Y.-Y.; Shou, W.-G.; Chen, Z.-B.; Hong, D.; Wang, Y.-G. *J. Org. Chem.* **2008**, *73*, 3928; (b) Pandy, G.; Balakrishnan, M. *J. Org. Chem.* **2008**, *73*, 8128; (c) Hashmi, A. S. K.; Schaefer, S.; Woelfe, M.; DiezGil, C.; Fischer, P.; Laguna, A.; Blanco, M. C.; Gimeno, M. C. *Angew. Chem. Int. Ed.* **2007**, *46*, 6184; (d) Konno, T.; Chae, J.; Miyabe, T.; Ishihara, T. *J. Org. Chem.* **2005**, *70*, 10172; (e) Palacios, F.; Alonso, C.; Rodríguez, M.; de Marigorta, E. M.; Rubiales, G. *Eur. J. Org. Chem.* **2005**, 1795; (f) Dai, G. X.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920; (g) Ichikawa, J.; Wada, Y.; Miyazaki, H.; Mori, T.; Kuroki, H. *Org. Lett.* **2003**, *5*, 1455; (h) Huo, Z. B.; Yamamoto, Y. *Tetrahedron Lett.* **2009**, *50*, 3651.
4. (a) Ishikawa, T.; Shimooka, K.; Narioka, T.; Noguchi, S.; Saito, T.; Ishikawa, A.; Yamazaki, E.; Harayama, T.; Seki, H.; Yamaguchi, K. *J. Org. Chem.* **2000**, *65*, 9143; (b) Sotomayor, N.; Dominguez, E. *J. Org. Chem.* **1996**, *61*, 4062.
5. (a) Youn, S. W. *J. Org. Chem.* **2006**, *71*, 2521; (b) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev.* **2004**, *104*, 3341; (c) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.
6. (a) Boudou, M.; Enders, D. *J. Org. Chem.* **2005**, *70*, 9486; (b) Walker, E. R.; Leung, S. Y.; Barrett, A. G. M. *Tetrahedron Lett.* **2005**, *46*, 6537.
7. Gerfaud, T.; Neuville, L.; Zhu, J. P. *Angew. Chem. In. Ed.* **2009**, *48*, 572.
8. Fukutani, T.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Commun.* **2009**, 5141.
9. Ren, H.; Luo, Y.; Ye, S. Q.; Wu, J. *Org. Lett.* **2011**, *13*, 2552.
10. For selected recent reviews of Ag-catalyzed reactions, see (a) Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3199; (b) Weibel, J.-M.; Blanc, A.; Pale, P. *Chem. Rev.* **2008**, *108*, 3149; (c) Álvarez-Corral, M.; Muñoz-Dorado, M.; Rodríguez-Garcìa, I. *Chem. Rev.* **2008**, *108*, 3174; (d) Li, Z.; He, C. *Eur. J. Org. Chem.* **2006**, 4313.
11. Niu, Y. N.; Yan, Z. Y.; Gao, G. L.; Wang, H. L.; Shu, X. Z.; Ji, K. G.; Liang, Y. M. *J. Org. Chem.* **2009**, *74*, 2893.

12. Barton, D. H. R.; Motherwell, W. B.; Simon, E. S.; Zard, S. Z. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2243.
13. (a) Fujiwara, H.; Ogasawara, Y.; Yamaguchi, K.; Mizuno, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 5202; (b) Ramalingan, C.; Park, Y.-T. *J. Org. Chem.* **2007**, *72*, 4536; (c) Owston, N. A.; Parker, A. J.; Williams, M. J. *Org. Lett.* **2007**, *9*, 3599.
14. (a) Yang, S. H.; Chang, S. *Org. Lett.* **2001**, *3*, 4209 (b) Yamaguchi, K.; Fujiwara, H.; Ogasawara, Y.; Kotani, M.; Mizuno, N. *Angew. Chem. Int. Ed.* **2007**, *46*, 3922.
15. Zhao, H.; Wandenbossche, C. P.; Koenig, S. G.; Singh, S. P.; Bakale, R. P. *Org. Lett.* **2008**, *10*, 505.
16. Chen, Z. Y.; Yu, X. X.; Su, M. C.; Yang, X. D.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702.
17. (a) Chen, Z. Y.; Yu, X. X.; Su, M. C.; Yang, X. D.; Wu, J. *Adv. Synth. Catal.* **2009**, *351*, 2702; (b) Huo, Z.; Tomeba, H.; Yamamoto, Y. *Tetrahedron Lett.* **2008**, *49*, 5531; (c) Yeom, H.-S.; Kim, S.; Shin, S. *Synlett* **2008**, 924.
18. (a) Wang, F.; Wang, Y. D.; Cai, L. C.; Miao, Z. W.; Chen, R. Y. *Adv. Synth. Catal.* **2008**, *350*, 2733; (b) Wang, F.; Miao, Z. W.; Chen, R. Y. *Org. Biomol. Chem.* **2009**, *7*, 2848.
19. Ding, Q. P.; Wu, J. *Adv. Synth. Catal.* **2008**, *350*, 1850.
20. Yoo, B. W.; Choi, J. W.; Yoon, C. M. *Tetrahedron Lett.* **2006**, *47*, 125.