Pyrrole Functionalization

DOI: 10.1002/ange.200705940

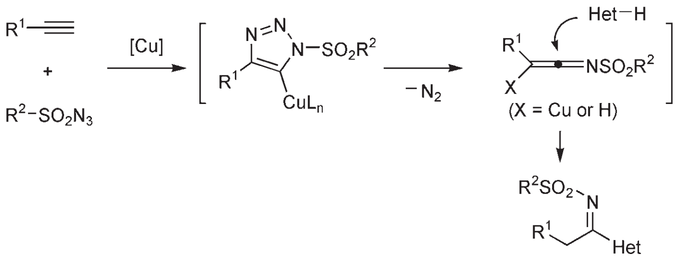
Room Temperature Copper-Catalyzed 2-Functionalization of Pyrrole Rings by a Three-Component Coupling Reaction**

*Seung Hwan Cho and Sukbok Chang**

Dedicated to Professor Sang Chul Shim

The efficient construction of a C–C bond is an important process in modern synthetic chemistry.[1] In particular, the functionalization of heterocycles such as pyrrole units, which have utility in organic synthesis and medicinal chemistry,[2] relies on the C–C bond forming strategies. A wide range of synthetic strategies involving Friedel–Crafts reactions have been devised.[3]

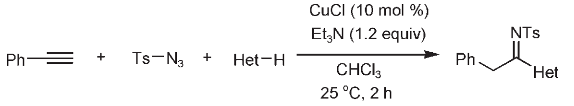
Recently, we developed a Cu-catalyzed three-component coupling reaction of terminal alkynes and sulfonyl azides with amines, alcohols, or water to afford amidines, imidates, and amides, respectively.[4] The reaction was versatile with regard to the substrate scope and the synthetic applicability. The reaction is proposed to proceed through a ketenimine intermediate, which is generated in situ from the triazole cycloadduct upon release of N_2 gas.[5] Our ongoing work in this area led us to propose that the construction of a C–C bond would be feasible by employing aromatic heterocycles in our multicomponent protocol (Scheme 1).[6]

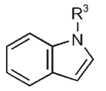
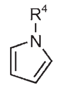


Scheme 1. Proposed route to substituted aromatic heterocycles by using the three-component reaction.

At the outset of these studies we treated a mixture of phenylacetylene (1.2 equiv), *p*-toluenesulfonyl azide, and triethylamine (1.2 equiv) in chloroform with indole (3.0 equiv). However, no reaction was observed in the presence of a copper catalyst (Table 1, entry 1). The same result was obtained with an *N*-methylindole derivative (Table 1, entry 2).[7] In contrast, when we employed a pyrrole unit as the heterocyclic substrate, the reaction proceeded to afford the anticipated product in good yield (78%) under mild conditions (Table 1, entry 3).[8] The structure of the isolated pyrrole derivative was confirmed by X-ray crystallographic analysis.[9]

Table 1: Survey of aromatic heterocycles in the Cu-catalyzed three-component coupling reaction.[a]



Entry	Heterocycles	(Het-H)	Yield [%][b]
1		$R^3 = H$	< 1
2		Me	< 1
3		$R^4 = H$	78
4[c]		H	70
5[d]		H	43
6		Me	28
7		CH_2Ph	20
8		*t*BuOC(O)	< 1

[a] Alkyne (0.6 mmol), sulfonyl azide (0.5 mmol), Et_3N (0.6 mmol), heterocycle (1.5 mmol), and CuCl (10 mol%) in chloroform (1.0 mL). [b] Yield was determined by ^1H NMR spectroscopy by using an internal standard (1,1,2,2-tetrachloroethane). [c] CuI (10 mol%) was employed as a catalyst. [d] Used 1.2 equiv of azide (to phenylacetylene).

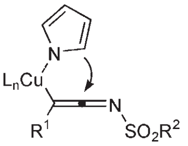
Interestingly, the use of CuI as the catalyst, which was most successfully employed in our previous studies,[4] resulted in a slightly lower product yield (Table 1, entry 4). The ratio of the three components was found to be important as it affected the product yields. In fact, whereas the product was obtained in 78% with a slight excess of alkyne (1.2 equiv) relative to sulfonyl azide (Table 1, entry 3), a notably lower yield was obtained with a reversed ratio of the two reactants (Table 1, entry 5). More interestingly, when N-substituted pyrrole derivatives were used, the reaction was sluggish and afforded poor yields compared to the parent pyrrole unit (Table 1, entries 6–8). The electronic variation of the N-substituents on the pyrrole ring did not alter the reactivity. Different types of heterocycles such as furan, thiophene, or imidazole rings do not participate in the reaction under the optimized conditions.[8]

---

[*] S. H. Cho, Prof. Dr. S. Chang
Center for Molecular Design and Synthesis (CMDS)
Department of Chemistry and
School of Molecular Science (BK21)
Korea Advanced Institute of Science and Technology (KAIST)
Daejeon, 305-701 (Republic of Korea)
Fax: (+82) 42-869-2810
E-mail: sbchang@kaist.ac.kr

[**] This research was supported by CMDS at KAIST and the KOSEF grant (No. R01-2007-000-10618-0).

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Proposed Cu-chelated ketenimine intermediate for accessing 2-functionalized pyrrole rings.

The results obtained above and the inability of the indole substrates participate in the reaction led us to propose that the pyrrole nitrogen atom coordinates to the copper center as the pyrrole attacks the ketenimine intermediate, thereby facilitating the progress of the reaction (Scheme 2). In fact, a similar chelation assisted pathway was recently proposed by Baran et al. in the addition of a pyrrole unit to the α-carbon of enolizable carbonyl compounds (e.g. ketones, esters, amides, latones, or lactams) in the presence of a stoichiometric Cu^{II} species.[10] However, the possibility that the unbound pyrrole unit (no coordination to copper) directly attacks the ketenimine intermediate cannot be ruled out at the moment.

The substrate scope of the present three-component coupling reaction with the parent pyrrole substrate was investigated next (Table 2). A wide range of 1-alkynes and sufonyl azides readily participated in the reaction with the pyrrole reactant at ambient temperatures. Reactions with either aromatic or aliphatic alkynes were complete within a few hours irrespective of their electronic or steric variations (Table 2, entries 1–5).

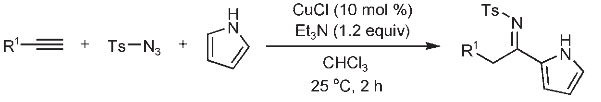
The presence of various functional groups such as halides, conjugated double bonds, or alkoxy moieties did not inhibit the catalytic reactions (Table 2, entries 6, 7, and 8, respectively). Notably, the Boc-protected (Boc = *tert*-butylcarboxy)-amino group was also tolerated (Table 2, entry 9).

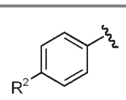
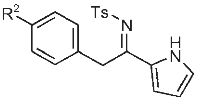
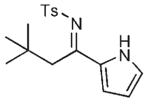
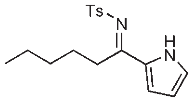
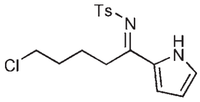
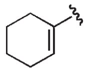
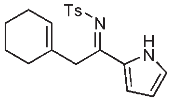
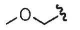
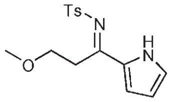
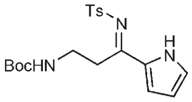
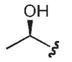
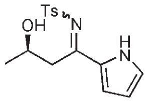
A reaction employing an optically active unprotected propargyl alcohol furnished an interesting product, 2-(1-imino-3-3-hydroxyl)-pyrrole, in a respectable yield with complete retention of the stereochemistry at the stereogenic center (Table 2, entry 10). Such compounds can be versatile in that they are attractive precursors for the formation of 2-(1,3-aminohydroxyl)pyrroles by undergoing selective reduction of the sulfonylimino group.[11]

The scope of the sulfonyl azides was also examined and revealed that azido compounds such as 4-acetamido benzenesulfonyl- or methanesulfonyl azide can be used. In each case, satisfactory product yields were obtained from the catalytic reactions (see the Supporting Information for details).

Next we employed pyrrole derivatives, bearing various substituents, as reactants under the optimized conditions and found that the reactions proceeded smoothly (Table 3). Pyrrole rings susbtituted at the 2-position or at both the 2- and 4-positions were viable components (Table 3, entries 1–2), and the reaction of a 3-substituted pyrrole substrate afforded a product bearing the sulfoniminoalkyl moiety at the 2-position with excellent selectivity (Table 3, entry 3). When 2,2′-bispyrrole (**1a**) was subjected to the reaction conditions a monosusbtituted product **2d** was provided in good yield (Table 3, entry 4).[12] Remarkably, we found that the progress of the reaction can be controlled by the stoichiometry of reactants. For example, with 2,2′-dipyrrolomethane (**1b**) either the monosubstituted product **2e** or the disubstituted product **2f** could be obtained depending upon the number of equivalents of alkyne and azide used (Table 3, entries 5 and 6, respectively). As a result, the disubstituted product **2g**, having two different sulfoniminoalkyl groups, could be obtained in excellent yield by a sequential reaction procedure (Table 3, entry 7). The bipyrrole or dipyrrolomethane derivatives obtained are potentially useful as synthetic building blocks in the areas of corrole or porphyrin chemistry.[13]

Table 2: 2-Functionalization of pyrrole rings by the Cu-catalyzed three-component coupling reaction.[a]



Entry	R^1	Product		Yield [%][b]
1			R^2 = H	78
2			CF_3	70
3			CH_3	71
4				89
5				85
6				86
7				75
8[c]				77
9				82
10				54[d]

[a] Alkyne (0.6 mmol), sulfonyl azide (0.5 mmol), Et_3N (0.6 mmol), pyrrole (1.5 mmol), and CuCl (10 mol%) in chloroform (1.0 mL). [b] Yield of isolated product. [c] Run with alkyne (1.0 mmol for 8 h at the same temperature. [d] A mixture of inseparable stereoisomers (imino group) with a 4.3:1 ratio determined from ^1H NMR spectroscopy.

An optically active propargylsilylether was used in the three-component coupling with subsequent hydrolysis to deliver a pyrrole derivative substituted with a 3-hydroxycarbonyl group [Eq. (1)].[14] The stereochemisty of the

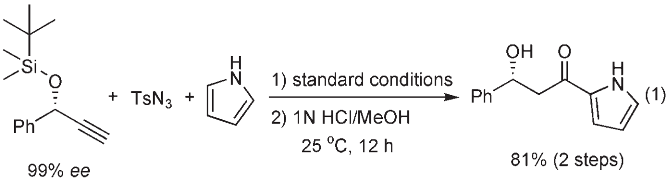
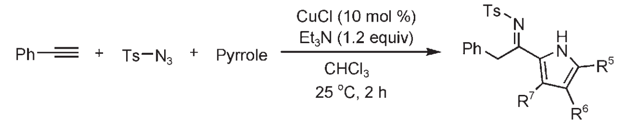
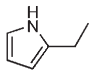
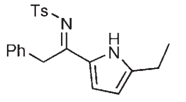
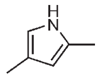
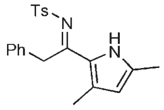
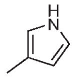
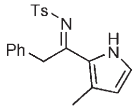
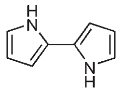
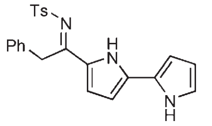
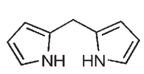
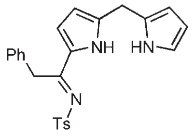
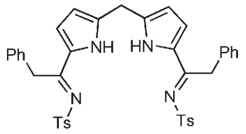
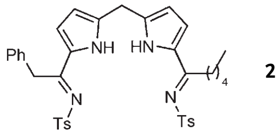


Table 3: 2-Functionalization of various pyrrole derivatives.

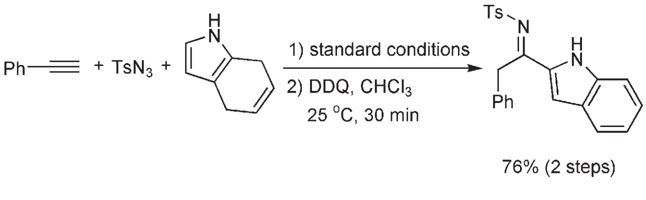


Entry	Pyrrole		Product		Yield [%][a]
1				**2a**	75
2[b]				**2b**	67
3				**2c**	71
4[c]		**1a**		**2d**	79
5[c]		**1b**		**2e**	80
6[d]	**1b**			**2f**	84
7[e]	**2e**			**2g**	91

[a] Yield of isolated product. [b] CuI (10 mol%) was used as a catalyst. [c] Used 1.0 eqiuv phenylacetylene and sulfonyl azide. [d] Used 2.1 eqiuv phenylacetylene and sulfonyl azide. [e] Used 1.0 equiv 1-hexyne (relative to **2e**).

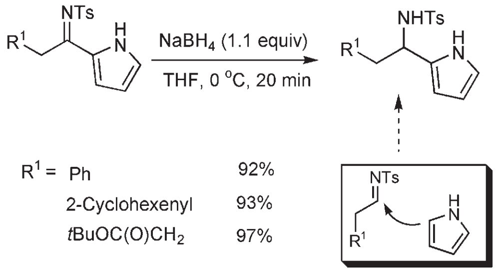
stereogenic center in the 1,3-difunctionalzed pyrrole product was completely retained during the course of the transformations.

The synthetic utility of the present protocol was demonstrated by employing 4,7-dihydroindole as a substrate [Eq. (2)].[15] The Cu-catalyzed three-component reaction between phenylacetylene, *p*-toluenesulfonyl azide, and 4,7-dihydroindole proceeded smoothly under the optimized conditions to afford the desired compound (82%). Aromatization of the 4,7-dihydroxyindole product bearing an imino group was achieved by using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in chloroform to provide 2-substituted indole derivative (93%). Indole rings are usually funtionalized at the 3-position under Friedel–Crafts conditions,[16] whereas our approach may be developed as a complementary method to prepare 2-substituted indole compounds.[3c,17]



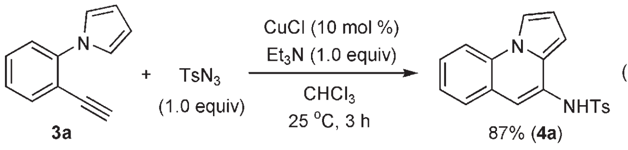
(2)

After optimizing the protocol for generating 2-functionalized pyrroles we turned to the development of a tandem procedure for the synthesis of 2-(α-aminoalkyl)pyrrole derivatives.[18] Such a procedure would be valuable as an efficient alternative to the conventional routes to aminoalkylated pyrrole derivatives by using *N*-sulfonyl imines. The known protocols sometimes involve double Fridel–Crafts reactions that give dipyrrolomethane as an undesired side product, which consequently lowers the yields of the desired products.[19] With regard to the above consideration,[20] the successful synthesis of 2-(α-aminoalkyl)pyrrole compounds from the hydride reduction of preformed 2-iminopyrroles would be noteworthy (Scheme 3). We successfully made three examples of the 2-(α-aminoalkyl)pyrrole derivatives and they were obtained in excellent yields under mild conditions.



Scheme 3. Examples of the reduction of 2-iminopyrrole compounds.

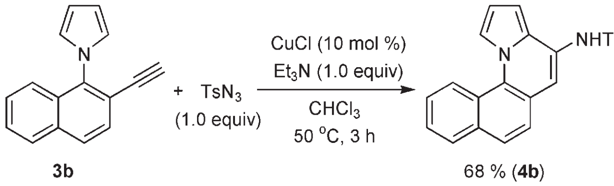
We were also pleased to observe that the present protocol can be readily used in an intramolecular reaction [Eq. (3)].



(3)

For example, 1-(2-ethynylphenyl)pyrrole (**3a**) reacted with a sulfonyl azide in the presence of a CuCl catalyst to afford an isomeric pyrrolo[1,2-*a*]quinoline derivative **4a**[21] in high yield under mild conditions. Furthermore, 1-(2-ethynylnaphthalen-1-yl)-pyrrole (**3b**) was transformed to the benzo[h]pyrrolo-[1,2-*a*]qunoline derivative **4b** in reasonable yield at slightly higher temperatures. To the best of our knowledge, this represents the first preparative example for multiply functionalized pyrrolo[1,2-*a*]quinoline derivatives by the action of Cu catalyst.

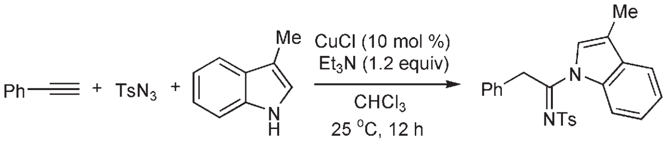
In summary, we have developed a preparative protocol for 2-functionalized pyrroles by using the Cu-catalyzed three-component reactions between 1-alkynes, sulfonyl azides, and pyrrole derivatives. This new procedure for C–C bond



3b

68 % (4b)

(4)



20%

formation appears to offer high selectivity, mild conditions, and a wide substrate scope. A diverse range of studies on the biological activity of the compound library we have accessed is in progress.

Received: December 24, 2007

Keywords: alkynes · azides · C–C bond formation · copper · pyrrole rings

---

[1] a) W. W. Leong, R. C. Larock in *Comprehensive Organometallic Chemistry II*, *Vol. 12* (Eds.: E. W. Abel, F. G. A. Stone, G. Wilkinson), Pergamon, Oxford, UK, **1995**; b) B. Cornils, W. A. Hermann, *Applied Homogeneous Catalysis with Organometallic Compounds*, Wiley, Weinheim, **1999**; c) T.-Y. Luh, M.-k. Leung, K.-T. Wong, *Chem. Rev.* **2000**, *100*, 3187.

[2] a) G. A. Olah, *Friedel–Crafts and Related Reactions*, *Vol. 2*, Part 1, Wiley-Interscience, New York, **1964**; b) G. A. Olah, R. Krishnamurit, G. K. S. Prakash in *Comprehensive Organic Synthesis*, *Vol. 3* (Ed.: B. M. Trost, I. Fleming), Pergamon, Oxford, **1991**, pp. 293–339.

[3] For recent selected examples of asymmetric pyrrole alkylations, see: a) N. A. Paras, D. W. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; b) C. Palomo, M, Oiarbide, B. G. Kardak, J. M. Garcia, A. Linden, *J. Am. Chem. Soc.* **2005**, *127*, 4154; c) D. A. Evans, K. R. Fandrick, *Org. Lett.* **2006**, *8*, 2249.

[4] a) I. Bae, H. Han, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 2038; b) S. H. Cho, E. J. Yoo, I. Bae, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 16046; c) E. J. Yoo, I. Bae, S. H. Cho, H. Han, S. Chang, *Org. Lett.* **2006**, *8*, 1347; d) S. Chang, M. Lee, D. Y. Jung, E. J. Yoo, S. H. Cho, S. K. Han, *J. Am. Chem. Soc.* **2006**, *128*, 12366; e) S. H. Cho, S. Chang, *Angew. Chem.* **2007**, *119*, 1929; *Angew. Chem. Int. Ed.* **2007**, *46*, 1897; f) S. H. Kim, D. Y. Jung, S. Chang, *J. Org. Chem.* **2007**, *72*, 9769.

[5] a) M. Whiting, V. V. Fokin, *Angew. Chem.* **2006**, *118*, 3229; *Angew. Chem. Int. Ed.* **2006**, *45*, 3157; b) M. P. Cassidy, J. Raushel, V. V. Fokin, *Angew. Chem.* **2006**, *118*, 3226; *Angew. Chem. Int. Ed.* **2006**, *45*, 3154; c) S.-L. Cui, X.-F. Lin, Y.-G. Wang, *Org. Lett.* **2006**, *8*, 4517; d) E. J. Yoo, M. Alquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless, S. Chang, *Angew. Chem.* **2007**, *119*, 1760; *Angew. Chem. Int. Ed.* **2007**, *46*, 1730.

[6] For recent examples of the selective addition of indoles to in situ generated ketene iminium species from ynamides, see: a) Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer, A. Davis, *Org. Lett.* **2005**, *7*, 1047; b) Y. Zhang, *Tetrahedron Lett.* **2005**, *46*, 6483.

[7] When 3-methylindole was employed as a coupling partner, an *N*-indoylamidine species was obtained in 20 % yield under the present conditions..

[8] For details, see the Supporting Information.

[9] For details of X-ray crystallographic data, see the Supporting Information.

[10] P. S. Baran, J. M. Richter, D. W. Lin, *Angew. Chem.* **2005**, *117*, 615; *Angew. Chem. Int. Ed.* **2005**, *44*, 609.

[11] For selected examples of the preparation of 1,3-aminoalcohols by selective chelation-assisted reduction, see: a) T. Kochi, T. P. Tang, J. A. Ellman, *J. Am. Chem. Soc.* **2002**, *124*, 6518; b) R. Matsubara, T. Doko, R. Uetake, S. Kobayashi, *Angew. Chem.* **2007**, *119*, 3107; *Angew. Chem. Int. Ed.* **2007**, *46*, 3047.

[12] For selected examples on the synthesis of corroles and their utility, see: a) R. A. Decréau, J. P. Collman, *Tetrahedron Lett.* **2003**, *44*, 3323; b) G. R. Geier III, S. C. Grindrod, *J. Org. Chem.* **2004**, *69*, 6404; c) T. Dohi, K, Morimoto, A. Maruyama, Y. Kita, *Org. Lett.* **2006**, *8*, 2007.

[13] For the preparation of 2,2′-dipyrrolomethane compounds and their synthetic utility, see: a) *The Porphyrin Handbook*, Academic Press, San Diego, **2000**; b) J. L. Sessler, D. Seidel, *Angew. Chem.* **2003**, *115*, 5292; *Angew. Chem. Int. Ed.* **2003**, *42*, 5134.

[14] For synthetic utility of 1,3-hydroxyketone compounds, see: a) L Matoba, Y. Miyama, T. Yamazaki, *Chem. Pharm. Bull.* **1983**, *31*, 476; b) R. Mahrwald, *Chem. Rev.* **1999**, *99*, 1095.

[15] 4,7-Dihydroindole was prepared from indole by the Birch reduction: H. Çavdar, N. Saraçoğlu, *Tetrahedron* **2005**, *61*, 2401.

[16] a) *Friedel–Crafts Alkylation Chemistry: A Century of Discovery* (Eds.: R. M. Roberts, A. A. Khalaf), Dekker, New York, **1984**; b) K. A. Jørgensen, *Synthesis* **2003**, 1117; c) M. Bandini, A. Melloni, A. Umani-Ronchi, *Angew. Chem.* **2004**, *116*, 560; *Angew. Chem. Int. Ed.* **2004**, *43*, 550.

[17] H. Çavdar, N. Saraçoğlu, *J. Org. Chem.* **2006**, *71*, 7793.

[18] a) A. D. Abell, D. A. Hoult, E. J. Jamieson, *Tetrahedron Lett.* **1992**, *33*, 5831; b) M. Johannsen, *Chem. Commun.* **1999**, 2233; c) S. Saaby, P. Bayon, P. S. Aburel, K. A. Jørgensen, *J. Org. Chem.* **2002**, *67*, 4352.

[19] a) S. Kobayashi, M. Sugiura, H. Kitagawa, W. W.-L. Lam, *Chem. Rev.* **2002**, *102*, 2227; b) B. Temelli, C. Unaleroglu, *Tetrahedron* **2006**, *62*, 10130.

[20] Recently, Carretero and co-workers reported a selective Cu-catalyzed aza Friedel–Crafts reaction of *N*-(2-pyridyl)sulfonyl aldimines with indoles and *N*-methylpyrrole; J. Esquivias, R. G. Arrayas, J. C. Carretero, *Angew. Chem.* **2006**, *118*, 645; *Angew. Chem. Int. Ed.* **2006**, *45*, 629.

[21] For selected examples of recent preparative methods for the pyrrolo[1,2-*a*]quinoline skeleton, see: a) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556; b) K. Kanno, Y. Liu, A. Iesato, K. Nakajima, T. Takahashi, *Org. Lett.* **2005**, *7*, 5453; c) K. Kobayashi, A. Takanohashi, K, Hashimoto, O. Morikawa, H. Konishi, *Tetrahedron* **2006**, *62*, 10379; d) D. G. Hulcoop, M. Lautens, *Org. Lett.* **2007**, *9*, 1761.