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Base-Mediated Regio- and Stereoselective Intermolecular Addition of Alkynes to *N*-Heterocycles

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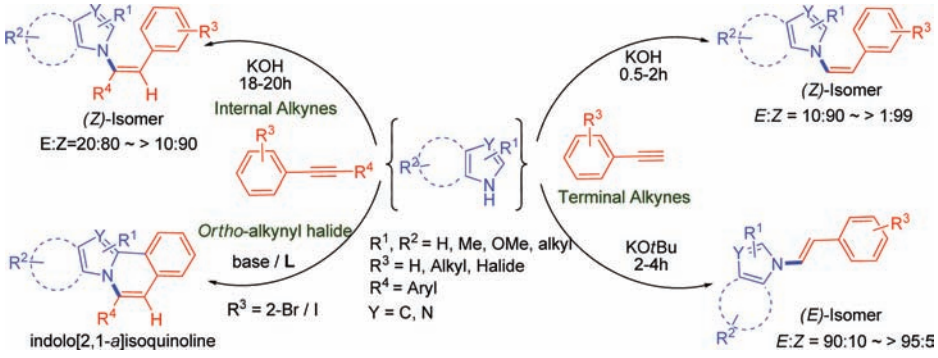
ABSTRACT



The regio- and stereoselective addition of *N*-heterocycles to alkynes using KOH is reported. Formation of (*Z*)-isomers and their conversion to (*E*)-products were found to be dependent upon time as well as the choice of base. Selective attack of *N*-heterocycles on a more electrophilic alkynyl carbon was supported by DFT calculations, and the stereochemistry of the products was established by X-ray crystallographic studies and intramolecular cyclization of *ortho*-haloalkynes in indolo-[2,1-*a*]isoquinolines.

Hydroamination of alkenes, alkynes, and related unsaturated substrates represents an attractive strategy for the preparation of nitrogen heterocycles, enamines and imines.[1] Enamines occupy a prominent place in organic synthesis,[2] and a variety of methods have been reported in the literature for their synthesis.[1,3] The intermolecular addition of alkynes to primary[4] and secondary amines[5] have been well studied; however, the addition of *N*-heterocycles onto internal alkynes remains elusive.

A notable work was reported by Knochel in 1999 for the addition of heterocyclic amines to phenylacetylene using $CsOH \cdot H_2O$ in NMP.[6] Later Kondo reported the addition of *O*- and *N*-nucleophiles to alkynes using phosphazene base *t*-Bu-P4.[7] Moreover, only one example of the addition of pyrrole on diphenylacetylene was reported using *t*-Bu-P4 with poor stereoselectivity.[7] In this regard, the stereo- and

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(1) For recent reviews: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Severin, R.; Doye, S. *Chem. Soc. Rev.* **2007**, *36*, 1407. (c) Pohlki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (d) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.*, 2008, *108*, 3795 and references cited therein.

(2) (a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207. (b) Stork, G. *Med. Res. Rev.* **1999**, *19*, 370. (d) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (e) Trofimov, B. A.; Mikhaleva, A. I.; Morozova, L. V. *Russ. Chem. Rev.* **1985**, *54*, 1034. (f) Cossy, J.; Belotti, D.; Bellosta, V.; Boggio, C. *Tetrahedron Lett.* **1997**, *38*, 2677.

(3) (a) Dash, C.; Shaikh, M.; Butcher, R. J.; Ghosh, P. *Inorg. Chem.* **2010**, *49*, 4972. (b) Cui, D.; Zheng, J.; Yang, L.; Zhang, C. *Synlett* **2010**, 809. (c) Widenhoefer, R. A. *Chem.—Eur. J.* **2008**, *14*, 5382. (d) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (e) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (f) Duncan, A. P.; Bergman, R. G. *Chem. Rec.* **2002**, *2*, 431. (g) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (h) Sandmann, R.; Kaspar, L.; Ackermann, L. *Org. Lett.* 2009, *7*, 2031 and references cited therein. (i) Klein, D. P.; Ellern, A.; Angelici, R. J. *Organometallics* **2004**, *23*, 5662. (j) Brunet, J. J.; Chu, N. C.; Diallo, O.; Vincendeau, S. *J. Mol. Catal. A: Chem.* **2005**, *240*, 245. (k) Castro, I. G.; Tillack, A.; Hartung, C. G.; Beller, M. *Tetrahedron Lett.* **2003**, *44*, 3217. (l) Shanbhag, G. V.; Kumbar, S. M.; Joseph, T.; Halligudi, S. B. *Tetrahedron Lett.* **2006**, *47*, 141. (m) Tillack, A.; Jiao, H. J.; Castro, I. G.; Hartung, C. G.; Beller, M. *Chem.—Eur. J.* **2004**, *10*, 2409. (n) Yi, C. S.; Yun, S. Y. *J. Am. Chem. Soc.* **2005**, *127*, 17000. (o) Zhang, Y. H.; Donahue, J. P.; Li, C. J. *Org. Lett.* **2007**, *9*, 627.

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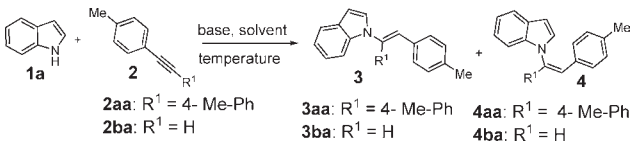
Table 1. Optimization of the Reaction Conditions[a]



entry	alkyne	base	solvent	time (h)/ t °C	yield (%)[b] (**3**:**4**)[c]
1[d]	**2aa**	KO*t*Bu	DMSO	24/110	68 (40:60)
2[e]	**2aa**	KO*t*Bu	DMSO	24/110	45 (20:80)
3[f]	**2aa**	KO*t*Bu	DMSO	24/120	55 (30:70)
4[g]	**2aa**	KO*t*Bu	DMSO	24/120	62 (20:80)
5	**2aa**	**KOH**	**DMSO**	**24/120**	**76 (5:95)**
6	**2aa**	Cs_2CO_3	DMSO	24/120	-
7	**2aa**	TEA	DMSO	24/120	-
8	**2aa**	K_2CO_3	DMSO	24/120	-
9	**2aa**	KOH	DMSO	24/30	-
10	**2aa**	KOH	DMSO	24/80	-
11	**2aa**	KOH	DMSO	05/120	10 (0:100)
12	**2aa**	KOH	DMSO	12/120	50 (2:98)
13	**2aa**	KOH	DMSO	48/120	60 (50:50)
14	**2aa**	KOH	DMF	24/120	35 (10:90)
15	**2aa**	KOH	Toluene	24/110	-
16	**2aa**	KOH	DMA	24/120	-
17	**2ba**	KOH	DMSO	24/120	85 (50:50)
18	**2ba**	Cs_2CO_3	DMSO	24/120	80 (0:100)
19	**2ba**	KO*t*Bu	DMSO	24/120	77 (90:10)
20	**2ba**	KOH	DMSO	24/30	-
21	**2ba**	KOH	DMSO	12/80	60 (20:80)
22	**2ba**	**KOH**	**DMSO**	**0.5/120**	**90 (0:100)**
23	**2ba**	KOH	DMSO	2/120	92 (10:90)
24[h]	**2ba**	KOH	DMSO	04/120	90 (20:80)

[a] Reactions were carried out using **1a** (2.0 equiv), **2aa/2ba** (1.0 equiv), and base (2.5 equiv) in solvent (2.0 mL). [b] Total yield of two isomers. [c] Stereoisomeric ratio. [d] **1** (1.0 equiv), **2** (1.0 equiv), CuI (5 mol %), $BtCH_2OH$ (10 mol %), and base (1.4 equiv) were added. [e] **1a** (1.0 equiv), **2** (1.0 equiv). [f] **1a** (2.0 equiv), **2** (1.0 equiv). [g] Base (2.5 equiv). [h] Base (0.20 equiv) was taken.

regioselective addition of *N*-heterocycles on internal alkynes is important and challenging.

Recently, we reported the copper-catalyzed tandem synthesis of indolo- and pyrrolo[2,1-*a*]isoquinolines, which was believed to occur via a hydroamination reaction.[8]

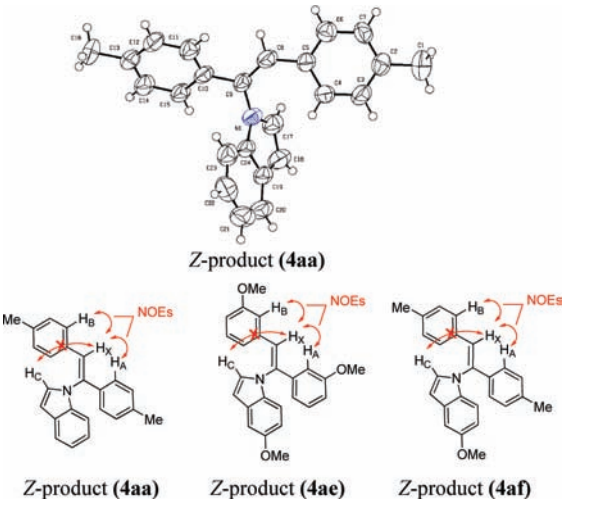


Figure 1. X-ray crystallographic ORTEP drawing of compound **4aa** drawn at the 50% probability level and NOESY studies of compounds **4aa**, **4ae**, and **4af**. See Supporting Information.[9]

Herein, we report the base-mediated regio- and stereoselective addition of *N*-heterocycles onto internal and terminal alkynes and confirmation of the products by X-ray crystallography, NOESY, and intramolecular cyclization of *ortho*-haloalkynes to form indolo[2,1-*a*]isoquinolines.

We followed reaction conditions used for the synthesis of indolo-and pyrrolo[2,1-*a*]isoquinolines.[8] Thus when indole **1a** and alkyne 1,2-di-*p*-tolylethyne **2aa** were treated with CuI (5.0 mol %), ligand $BtCH_2OH$ (10 mol %), and KO*t*Bu (1.4 equiv) in DMSO at 110 °C for 24 h, a mixture of *E*/*Z* isomers of (*E*)-1-(1,2-di-*p*-tolylvinyl)-1*H*-indole **3aa** and (*Z*)-1-(1,2-di-*p*-tolylvinyl)-1*H*-indole **4aa** was obtained in 68% yield with 40:60 stereoselectivity (Table 1, entry 1). When the reaction occurred without CuI and the ligand, **3aa** and **4aa** were obtained in 45% yield and 20:80 stereoselectivity (entry 2). An increase in the amount of **1a** from 1.0 to 2.0 equiv and base from 1.4 to 2.5 equiv afforded the hydroaminated product in 55 and 62% yields respectively (entries 3 and 4). When different bases were tested in this reaction, KOH proved to be the most effective and provided the hydroaminated product **4aa** in 76% yield in high stereoselectivity and the structure of the product formed was confirmed by X-ray (Figure 1;[9] Table 1, entry 5), other bases like Cs_2CO_3, Et_3N, and K_2CO_3 were found to be ineffective (entries 6−8). With a selective base in hand, other parameters such as temperature and solvent were investigated. At lower temperatures, 30 and 80 °C, hydroaminated product **3aa/4aa** was not observed (entries 9 and 10). The reaction was found to proceed smoothly at elevated temperature, and it is worth noting that longer reaction times led to the conversion of the *Z*-isomer

(4) (a) Zhang, Z.; Leitch, D. C.; Lu, M.; Patrick, B. O.; Schafer, L. L. *Chem.—Eur. J.* **2007**, *13*, 2012. (b) Heutling, A.; Pohlki, F.; Doye, S. *Chem.—Eur. J.* **2004**, *10*, 3059. (c) Ackermann, L. *Organometallics* **2003**, *22*, 4367. (d) Tillack, A.; Garcia Castro, I.; Hartung, C. G.; Beller, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 2541. (e) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708. (f) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246.

(5) Hesp, K. D.; Stradiotto, M. *J. Am. Chem. Soc.* 2010, *132*, 18026 and references cited therein.

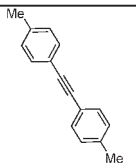
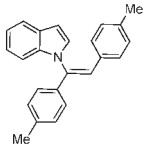
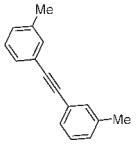
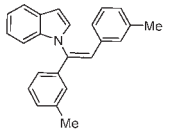
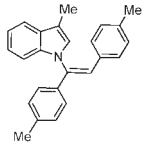
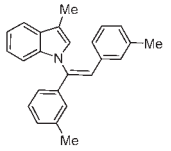
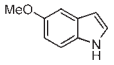
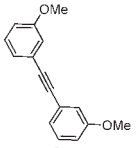
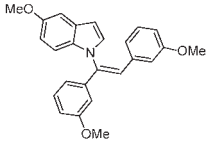
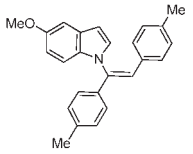
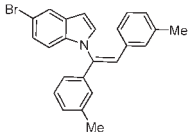
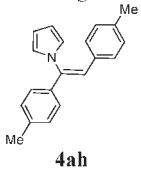
(6) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193. (b) Rodriguez, A.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488. (c) Koradin, C.; Dohle, W.; Rodriguez, A.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571.

(7) Imahori, T.; Hori, C.; Kondo, Y. *Adv. Synth. Catal.* **2004**, *346*, 1090.

(8) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138.

(9) CCDC 802285 (**4aa**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/request/cif.

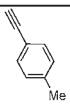
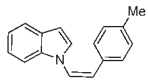
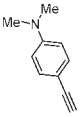
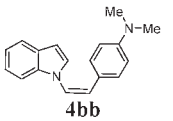
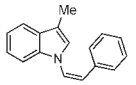
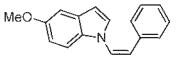
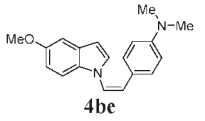
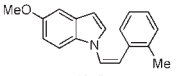
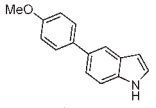
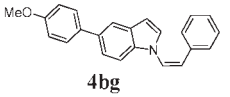
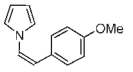
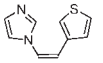
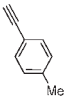
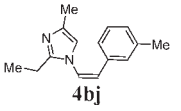
Table 2. Hydroamination of Symmetrical Internal Alkynes[a]

entry	*N*-heterocycle	alkyne	product	yield (%)[b]
1	 **1a**	 **2aa**	 **4aa**	70
2	**1a**	 **2ab**	 **4ab**	69
3	 **1b**	**2aa**	 **4ac**	76
4	**1b**	**2ab**	 **4ad**	74
5	 **1c**	 **2ac**	 **4ae**	75
6	**1c**	**2aa**	 **4af**	77
7	 **1d**	**2ab**	 **4ag**	68
8	 **1e**	**2aa**	 **4ah**	75[c]
9	 **1f**	**2aa**	**nr**	-
10	 **1g**	**2aa**	**nr**	-

[a] The reactions were performed using *N*-heterocycle **1** (2.0 equiv), 1.0 equiv of the alkyne **2**, and 2.5 equiv of KOH in 1.5 mL of DMSO at 120 °C for 24 h unless otherwise noted. [b] Yield of isolated product. [c] Time = 18 h .

to an *E*-isomer (entries 11−13). Among different solvents such as DMSO, DMF, toluene, and dimethylacetamide, DMSO was found to be most effective (entries 14−16).

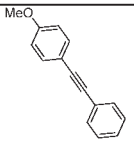
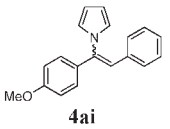
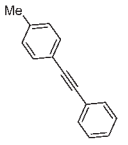
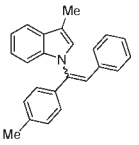
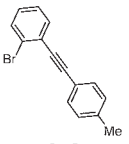
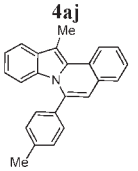
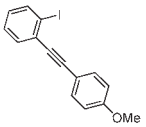
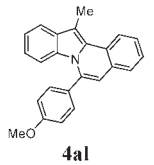
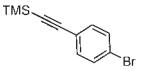
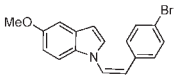
Table 3. Hydroamination of Terminal Alkynes[a]

entry	*N*-heterocycle	alkyne	product	yield (%)[b]
1	**1a**	 **2ba**	 **4ba**	90
2	**1a**	 **2bb**	 **4bb**	70[c]
3	**1b**	 **2bc**	 **4bc**	96
4	**1c**	**2bc**	 **4bd**	94
5	**1c**	**2bb**	 **4be**	95[c]
6	**1c**	 **2bd**	 **4bf**	96
7	 **1h**	**2bc**	 **4bg**	94
8	**1e**	 **2be**	 **4bh**	99[d]
9	**1f**	 **2bf**	 **4bi**	86
10	**1g**	 **2ba**	 **4bj**	89
11	**1a**	 **2bf**	**nr**	-

[a] The reactions were performed using *N*-heterocycle **1** (2.0 equiv), 1.0 equiv of the alkyne **2**, and 0.2 equiv of KOH in 1.5 mL of DMSO at 120 °C for 0.5−1 h unless otherwise noted. [b] Yield of isolated product. [c] Time = 2 h . [d] Time = 15 min.

The addition of **1a** onto 1-ethynyl-4-methylbenzene (**2ba**) using optimized conditions afforded a mixture of *E*/*Z* isomers (*E*)-1-(4-methylstyryl)-1*H*-indole **3ba** and (*Z*)-1-(4-methylstyryl)-1*H*-indole **4ba** in 85% yield and 50:50 stereoselectivity (entry 17). The effective addition of heterocyclic amines followed the anti-Markovnikov rule, and the stereoselectivity of product was found to be dependent on the nature of the base, reaction time, and temperature.[1] Cs_2CO_3 afforded only the *Z*-isomer (**4ba**) in 80% yield (entry 18); however KO*t*Bu provided the

Table 4. Hydroamination of Unsymmetrical Internal Alkynes[a]

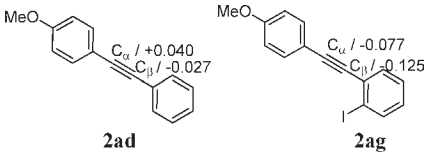
entry	*N*-heterocycle	alkyne	product	yield (%)[b]
1	**1e**	 **2ad**	 **4ai**	68
2	**1b**	 **2ae**	 **4aj**	67
3	**1b**	 **2af**	 **4ak**	82[c]
4	**1b**	 **2ag**	 **4al**	85[c]
5	**1c**	 **2ah**	 **4am**	90[d]

[a] The reactions were performed using *N*-heterocycle **1** (2.0 equiv), 1.0 equiv of the alkyne **2**, and 2.5 equiv of KOH in 1.5 mL of DMSO at 120 °C for 24 h unless otherwise noted. [b] Total yield of two isomers. [c] CuI (5 mol %) and ligand/$BtCH_2OH$ (10 mol %) were added. [d] Time = 1 h.

E-isomer **3ba** as a major product (entry 19). No addition product was obtained at 30 °C and was found to be initiated at 80 °C (entries 20 and 21). The reaction of **1a** with **3ba** at 120 °C afforded the hydraminated product **4ba** in 90% yield within 30 min (entry 22). We have noticed that an increase in reaction time leads to the conversion of the *Z*-isomer to an *E*-isomer (entry 23). In terminal alkynes, use of a catalytic amount of KOH (20 mol %) also afforded **4ba** in good yield (entry 24) in contrast to internal alkynes.

Under optimized conditions (Table 1, entries 5 and 22), the scope and limitations of this process were examined next with various substituted *N*-heterocycles **1a**−**1g** and alkynes **2aa**−**ac**.

Heterocyclic amines with an electron-donating group such as 3-methyl indole (**1b**) and 5-methoxy indole (**1c**) afforded the addition products with *Z*-stereoselectivity (X-ray and NOESY, Figure 1) in good yield in comparison to **1a** (Table 2, entries 1−6). 5-Bromoindole (**1d**) afforded the hydroaminated product **4ag** in 68% yield (entry 7). Pyrrole (**1e**) being more nucleophilic afforded the hydroaminated product **4ah** in lesser reaction time in 75% yield (entry 8). No reaction was observed with electron-deficient *N*-heterocycles such as imidazole **1f** and **1g** with alkyne **2aa** (entries 9 and 10). The addition of *N*-heterocycles **1a**−**1c** and **1e** onto terminal alkynes **2ba**−**2be** provided the corresponding *Z*-products **4ba**−**4bh** in good to excellent yields (Table 3, entries 1−8). It is interesting to note that electron-deficient heterocycle **1f** and **1g** reacted well with terminal alkynes **2bf** and **2ba** and afforded the hydroaminated products **4bi** and **4bj** in 86 and 89% yields respectively (entries 9 and 10). No reaction was observed with 1-hexyne (**2bf**) (entry 11). Table 4 summarizes the scope of the addition of *N*-heterocycles **1b**−**1c** and **1e** on unsymmetrical alkynes **2ad**−**2ah**. The electronic bias of the groups on both carbons of the triple bond plays an important role in the selective attack of the nucleophile. The major isomer in the mixture of the two possible *Z*-regioisomers was assumed to form by preferential attack on a more electrophilic carbon as per the DFT-B3LYP/6-31+G* calculations using Gausian 03 software[10] (Table 4, entry 1 and 2; Figure 2) and was supported by the formation of indolo-[2,1-*a*] isoquinolines **4ak** and **4al** (entries 3 and 4).[8,11] TMS-substituted alkyne **2ah** afforded the product **4am** in 90% yield with the removal of the TMS group, presumably due to the basic conditions employed (entry 5).



2ad **2ag**

Figure 2. Natural population analysis (B3LYP/6-31+G*).

In summary, an efficient base-mediated regio- and stereoselective hydroamination of alkynes has been developed to synthesize a wide array of (*Z*)-styryl and vinylenamines that are useful in organic synthesis. Stereoselectivity was largely affected by the nature of the base and reaction time. The developed protocol avoids the use of expensive catalysts and ligands. Based upon this stereoselective hydroamination, we should be able to develop new synthetic methods to a variety of fused heterocycles. These studies are currently under investigation and will be reported in due course.

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Supporting Information Available. General experimental procedures and characterization data for all starting materials and products are available free of charge via the Internet at http://pubs.acs.org.

(10) Uchiyama, M.; Ozawa, H.; Takuma, K.; Matsumoto, Y.; Yonehara, M.; Hiroya, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5517. Yoshikawa, T.; Shindo, M. *Org. Lett.* **2009**, *11*, 5378.

(11) Yanagisawa, S.; Ueda, K.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 4673.