

Regioselective Synthesis of 3-Hydroxy-4,5-alkyl-Substituted Pyridines Using 1,3-Enynes as Alkynes Surrogates

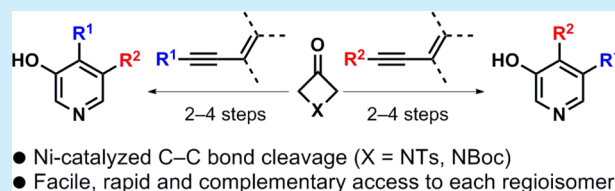
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S Supporting Information

ABSTRACT: The poor regioselectivity of the [4 + 2] cycloaddition of 3-azetidinones with internal alkynes bearing two alkyl substituents via nickel-catalyzed carbon–carbon activation is addressed using 1,3-enynes as substrates. The judicious choice of substitution on the enyne enables complementary access to each regioisomer of 3-hydroxy-4,5-alkyl-substituted pyridines, which are important building blocks in medicinal chemistry endeavors.

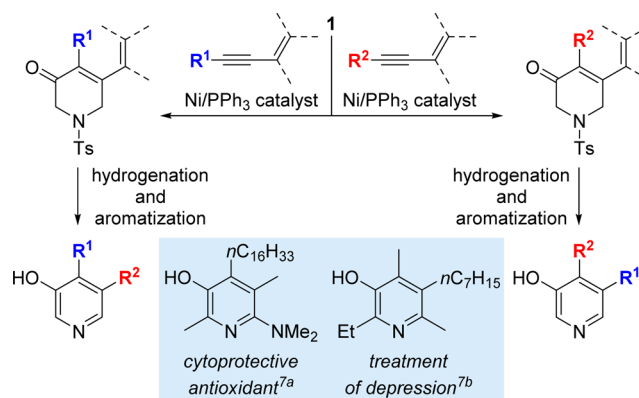


Alkynes are prominent and versatile building blocks for the synthesis of heterocycles by transition-metal-catalyzed cycloadditions.¹ However, poor regioselectivity is often observed in these reactions for internal alkynes bearing two alkyl substituents that are not electronically or sterically strongly biased.² The nickel-catalyzed [4 + 2] cycloaddition of *N*-Ts-3-azetidinone **1** (Ts = *para*-tolylsulfonyl) and alkyne **2** is a typical example illustrating the lack of selectivity when the steric differentiation between the substituents on the alkyne moiety is limited, and an almost equimolar mixture of the regioisomers of dihydropyridinone **3** was thus obtained (Scheme 1).³ Initial attempts to improve the regioselectivity by varying the ligand remained unsuccessful while the conversion to the desired product decreased. Moreover, the regioisomers could not be separated by simple column chromatography.

We therefore decided to explore an alternative strategy consisting of using the inexpensive ligand PPh₃ and 1,3-enynes

as surrogates of alkynes that would otherwise be substituted with two sterically similar alkyl chains R¹ and R² (Scheme 2).

Scheme 2. Strategy for the Regioselective Synthesis of 3-Hydroxy-4,5-bisalkyl Pyridines



Scheme 1. Poor Regioselectivity in the Nickel-Catalyzed [4 + 2] Cycloaddition of *N*-Ts-3-azetidinone and 4-Methyl-pent-2-yne^a

	L	yield (%) ^b	regioisomer ratio ^c
	PPh ₃	97	54:46
	P(cHex) ₃	77	42:58
	PPh ₂ tBu	83	52:48
	PMe ₃ ^d	67	56:44
	IMes ^e	^f	^f

^aThe reactions were carried out with **1** (0.22 mmol) and **2** (0.24 mmol). ^bConversion determined by ¹H NMR. ^cDetermined by ¹H NMR of the crude mixture. ^dUsed as 1 M solution in THF. ^eMade in situ by premixing 1,3-bis(2,4,6-trimethylphenyl)-imidazolium chloride (20 mol %) and *t*BuOK (20 mol %). ^fExtensive decomposition of **1** was observed, and **3** was not formed.

The enhanced regioselectivity of the insertion of 1,3-enynes as compared to internal alkynes bearing two alkyl substituents was previously demonstrated for this reaction albeit with only one example,^{3a,b} but we assumed that this preliminary observation could be generalized to other enynes on the basis of theoretical⁴ and experimental⁵ studies conducted on the related nickel-catalyzed reductive coupling of 1,3-enynes with aldehydes. In a sequence inspired by the work previously reported by Fagnou and co-workers for the synthesis of 2,3-aliphatic-substituted pyrroles and indoles,⁶ we envisioned that the judicious choice of substitution on the 1,3-enyne would enable complementary access to each of the two regioisomers of 3-hydroxy-4,5-alkyl-substituted pyridines, after simple hydrogenation and aroma-

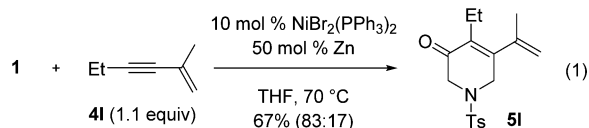
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tization steps (Scheme 2).⁷ Pyridines that have a hydroxyl group in position 3 and two different alkyl groups in positions 4 and 5 are found in compounds that display important biological and pharmaceutical properties and are desirable building blocks in medicinal chemistry endeavors.⁸ The strategy presented herein offers a valuable alternative to previous approaches to this specific pyridine motif⁹ and to metal-catalyzed intermolecular reactions of alkynes that afford other pyridine substitution patterns.¹⁰

As expected, all 1,3-enynes **4a–4h** underwent the nickel-catalyzed [4 + 2] cycloaddition with good regioselectivity (Table 1, entries 1–8), and the major regioisomer of **5** could be isolated easily in most cases, except for **5b**, which explains the moderate yield for this specific example, as opposed to the range of good yields observed for **5a** and **5c–5h** (67–77%). Although the origin of this effect is not known to us, the average yields of duplicate experiments were consistently higher in some cases (entries 1–5) when the loading of PPh₃ was increased from 20 to 30 mol % (see Supporting Information). Moreover, the directing power of the carbon–carbon double bond of the 1,3-enyne motifs was slightly greater for 1,4-disubstituted enynes (entries 2, 4, and 6–8) than for 2,4-disubstituted (entry 3) or trisubstituted enynes (entries 1 and 5). Nevertheless, this directing effect persisted even with two substituents of similar size on the carbon–carbon triple bond. Thus, we observed a 78:22 regioselectivity for 1,3-enynes **4i** and **4j** and the major regioisomer could be isolated in 65% and 64% yield, respectively (Scheme 3). The reaction of a mixture of tri- and tetrasubstituted enynes **4k** led to **5k** in lower yield but with good regioselectivity, an outcome likely influenced by the steric properties of **4k**. The substitution of the alkyl group had a very limited effect on the regioselectivity (Table 1, entries 2, 4, 6, and 8).

The conversion of dihydropyridinones **5a–5h** into pyridines **6a–6h** was effected in two steps by hydrogenation of the carbon–carbon double bond followed by cleavage of the *para*-tolylsulfonyl group and concomitant aromatization using DBU^{9b} (Table 1). Thus, the judicious choice of 1,3-enynes **4a–4h** enabled a rapid three-step access to each of the two regioisomers of 3-hydroxy-4,5-aliphatic-substituted pyridines **6a/6b**, **6c/6d**, **6e/6f**, and **6g/6h**. It was possible to conduct the deprotection/aromatization of compounds **5** prior to hydrogenation, but the resulting pyridines were not suitable substrates for hydrogenation and compounds **6** were thus not obtained.

In addition, we also explored an alternative protocol whereby the active Ni catalyst was generated in situ from air-stable precatalyst NiBr₂(PPh₃)₂ and Zn. Although initial investigations with 1,3-enyne **4l** were promising, the major regioisomer **5l** being isolated in 67% yield (eq 1), yields were in general lower



from enynes **4a–4f** when compared to the method relying on Ni(cod)₂/PPh₃ and the regioselectivity was slightly decreased (Table 2). During the preparation of this manuscript, a report disclosed that the combination of NiBr₂(PPh₃)₂ and Zn in MeCN enabled the [4 + 2] cycloaddition of alkynes and protected azetidin-3-ones.¹¹ However, using this solvent in the case of **4l** led to incomplete conversion and **5l** was isolated in

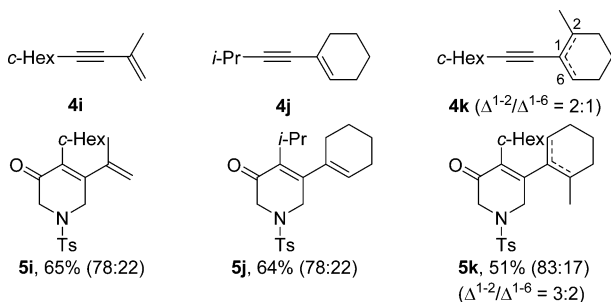
Table 1. Regioselective Synthesis of 3-Hydroxy-4,5-alkyl-Substituted Pyridines Using 1,3-Enynes as Alkynes Surrogates^a

entry	enyne	5, yield ^b	6, yield ^e
1			
2			
3			
4			
5			
6			
7			
8			

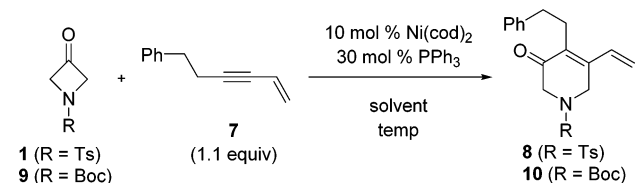
^aAll reactions were carried out with **1** (0.22 mmol), **4** (0.24 mmol), Ni(cod)₂ (0.022 mmol), and PPh₃ (0.044 mmol) except otherwise noted. ^bYield of the isolated major regioisomer only, average of two experiments. ^c30 mol % PPh₃. ^dFrom ¹H NMR of the crude mixture. ^eYield of isolated **6** after two steps. ^fHydrogenation was performed in a flask immersed in a sonication bath for 5 h. ^gHydrogenation for 7.5 h. ^hHydrogenation for 5 h.

14% yield (84:16 regioselectivity). A slightly improved result was obtained by replacing the protective group in **1** with a *tert*-butoxycarbonyl group (27%; 90:10 regioselectivity).

Initially, the cycloaddition of terminal 1,3-enyne **7** with **1** led to a very sluggish reaction and only very low yields of dihydropyridinone **8** (Table 3, entry 1). It was crucial to use commercially available *N*-Boc-3-azetidinone **9** (Boc = *tert*-

Scheme 3. Reactions of Enynes 4i, 4j, and 4k^a^aSame reaction conditions as those listed for Table 1 (entries 1–5).Table 2. Cycloaddition of *N*-Ts-3-Azetidinone with 1,3-Enynes 4a–4f Catalyzed by NiBr₂(PPh₃)₂/Zn^a

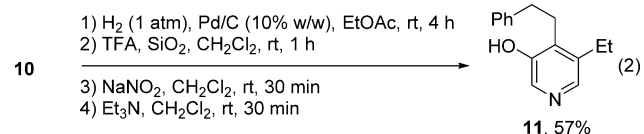
product	yield (%) ^b	ratio of regioisomers ^c
5a	66	85:15
5b	31	91:9
5c	51	85:15
5d	59	91:9
5e	69	87:13
5f	50	91:9

^aReaction conditions are same as those in eq 1. ^bYield of the isolated major regioisomer. ^cFrom ¹H NMR of the crude mixture.Table 3. Nickel-Catalyzed Cycloaddition of 3-Azetidinones with a Terminal 1,3-Enyne^a

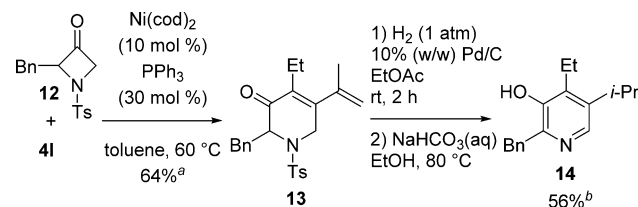
entry	1 or 9	solvent	temp (°C)	t (h)	yield (%) ^b
1	1	toluene	60	144	7
2	9	toluene	60	40	40
3	9	THF	60	40	35
4	9	dioxane	60	16	58 ^c
5	9	dioxane	70	16	41

^aAll reactions were carried out with 1 or 9 (0.22 mmol), 7 (0.24 mmol), Ni(cod)₂ (0.022 mmol), and PPh₃ (0.066 mmol). ^bYield of isolated 8 (entry 1) or 10 (entries 2–5). ^cAverage of two experiments.

butoxycarbonyl) instead of *N*-Ts-3-azetidinone 1 and to use dioxane as solvent (entries 2–4) in order to obtain compound 10 in good yield. Increasing the reaction temperature was not beneficial (entry 5). Importantly, only one regioisomer of 10 was observed. Similarly to 5a–5h, compound 10 could be conveniently converted into 3-hydroxy-pyridine 11 in a few steps (eq 2). A single purification by column chromatography was necessary at the end of this sequence, and compound 11 was isolated in 57% yield.



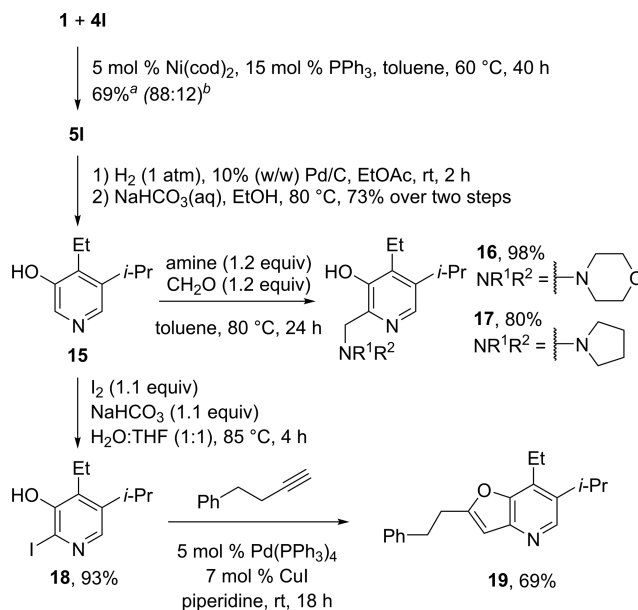
As previously demonstrated by our group and others, α -substituted 3-azetidinones are good substrates for the [4 + 2] Ni-catalyzed cycloadditions with alkynes.³ This remains true for 1,3-enynes, as illustrated with 12 (Scheme 4), which is derived

Scheme 4. Reactions of *N*-Ts-2-benzyl-3-azetidinone 12^aYield of isolated major regioisomer only, average of two experiments.^bYield of isolated product after two steps.

from racemic phenylalanine. The reaction of 4i with 12 was slower than that with nonsubstituted 1, but 13 was easily separated from its regioisomer in 64% yield (91:9 regioselectivity). Then, 13 could be rapidly converted into 14 in good yield after hydrogenation followed by cleavage of the *para*-tolylsulfonyl group and concomitant aromatization using NaHCO₃ in a mixture of ethanol and water as an alternative to DBU.

Although it would in principle be possible to access analogues of 14 from various α -substituted 3-azetidinones, it is more judicious to postpone the functionalization of 3-hydroxy-4,5-alkyl-substituted pyridines at a later stage of the sequence. For example, dihydropyridinone 5l was obtained in good yield after treating a mixture of 1 and 4i with 5 mol % of catalyst and separation of the regioisomers (Scheme 5). Then, hydrogenation and cleavage of the *para*-tolylsulfonyl group with concomitant aromatization gave 15 in 73% over two steps. At this stage, a Mannich reaction with either morpholine or pyrrolidine afforded 2-aminomethylpyridine derivatives 16 and

Scheme 5. Further Functionalization of 3-Hydroxy-4-ethyl-5-isopropylpyridine 15

^aYield of isolated major regioisomer only. ^bRatio of regioisomer in the crude reaction mixture.

17 in excellent yields.¹² Alternatively, **15** could be converted into **18**, which led to furo[*b*]pyridine derivative **19** after a Sonogashira cross-coupling.¹³

In conclusion, we have demonstrated that 1,3-enynes are convenient surrogates of internal alkynes bearing two alkyl substituents in their nickel-catalyzed [4 + 2] cycloaddition with 3-azetidinones. Thus, the judicious choice of 1,3-enyne pairs enables a facile and complementary access to each of the two regioisomers of 3-hydroxy-4,5-alkyl-substituted pyridines, after simple hydrogenation and aromatization steps.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00451.

Detailed experimental procedures and characterization of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) Recent reviews: (a) Varela, J. A.; Saá, C. *Synlett* **2008**, 2008, 2571. (b) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, 16, 11212. (c) Shaaban; Mohamed, R.; El-Sayed, R.; Elwahi, A. H. M. *Tetrahedron* **2011**, 67, 6095. (d) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, 113, 3084. (e) Egi, M.; Akai, S. *Heterocycles* **2015**, 91, 931.
- (2) Selected examples: (a) Chatani, N.; Hanafusa, T. *J. Org. Chem.* **1991**, 56, 2166. (b) Crawley, M. L.; Goljer, I.; Jenkins, D. J.; Mehlmann, J. F.; Nogle, L.; Dooley, R.; Mahaney, P. E. *Org. Lett.* **2006**, 8, 5837. (c) Kajita, Y.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2008**, 130, 17226. (d) Ooguri, A.; Nakai, K.; Kurahashi, T.; Matsubara, S. *J. Am. Chem. Soc.* **2009**, 131, 13194. (e) Miura, T.; Yamauchi, M.; Murakami, M. *Chem. Commun.* **2009**, 40, 1421. (f) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, 132, 18326. (g) Duttwyler, S.; Lu, C.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, 134, 4064. (h) Villuendas, P.; Urriolabeitia, E. P. *J. Org. Chem.* **2013**, 78, 5254. (i) Kurahashi, T.; Matsubara, S. *Acc. Chem. Res.* **2015**, 48, 1703.
- (3) (a) Ho, K. Y. T.; Aissa, C. *Chem. - Eur. J.* **2012**, 18, 3486. (b) Kumar, P.; Louie, J. *Org. Lett.* **2012**, 14, 2026. (c) Ishida, N.; Yuhki, T.; Murakami, M. *Org. Lett.* **2012**, 14, 3898.
- (4) Liu, P.; McCarren, P.; Cheong, P. H.-Y.; Jamison, T. F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, 132, 2050.
- (5) (a) Mahandru, G. M.; Liu, G.; Montgomery, J. *J. Am. Chem. Soc.* **2004**, 126, 3698. (b) Miller, K. M.; Luanphaisarnnont, T.; Molinaro, C.; Jamison, T. F. *J. Am. Chem. Soc.* **2004**, 126, 4130. (c) Miller, K. M.; Jamison, T. F. *Org. Lett.* **2005**, 7, 3077.
- (6) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, 50, 1338.
- (7) For related reactions with 1,3-dienes, see: (a) Thakur, A.; Facer, M. E.; Louie, J. *Angew. Chem., Int. Ed.* **2013**, 52, 12161. (b) Juliá-Hernández, F.; Ziadi, A.; Nishimura, A.; Martin, R. *Angew. Chem., Int. Ed.* **2015**, 54, 9537.

- (8) (a) Alam, M. P.; Khodour, O. M.; Arce, P. M.; Chen, Y.; Roy, B.; Johnson, W. G.; Dey, S.; Hecht, S. M. *Bioorg. Med. Chem.* **2014**, 22, 4935. (b) Pomytkin, I. A. WO 2014012593A1. (c) Kim, D.-G.; Kang, Y.; Lee, H.; Lee, E. K.; Nam, T.-g.; Kim, J.-A.; Jeong, B.-S. *Eur. J. Med. Chem.* **2014**, 78, 126. (d) Hoyt, S. B.; Park, M. K.; London, C.; Xiong, Y.; Bennett, D. J.; Cai, J.; Ratcliffe, P.; Cooke, A.; Carswell, E.; MacLean, J.; Saxena, R.; Kulkarni, B. A.; Gupta, A. WO 2012012478A1.
- (9) (a) Allevi, P.; Longo, A.; Anastasia, M. *Chem. Commun.* **1999**, 559. (b) Donohoe, T. J.; Fishlock, L. P.; Basutto, J. A.; Bower, J. F.; Procopiou, P. A.; Thompson, A. L. *Chem. Commun.* **2009**, 3008. (c) Yoshida, K.; Kawagoe, F.; Hayashi, K.; Horiuchi, S.; Imamoto, T.; Yanagisawa, A. *Org. Lett.* **2009**, 11, 515. (d) Liu, H.; Wang, L.; Tong, X. *Chem. Commun.* **2011**, 47, 12206. (e) Sabot, C.; Oueis, E.; Brune, X.; Renard, P.-Y. *Chem. Commun.* **2012**, 48, 768. (f) Jouanno, L.-A.; Tognetti, V.; Joubert, L.; Sabot, C.; Renard, P.-Y. *Org. Lett.* **2013**, 15, 2530. (g) Lei, C.-H.; Wang, D.-X.; Zhao, L.; Zhu, J.; Wang, M.-X. *J. Am. Chem. Soc.* **2013**, 135, 4708.
- (10) Selected examples: (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, 63, 5306. (b) Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, 2, 3131. (c) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, 66, 8042. (d) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.-J.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, 67, 4414. (e) Varela, J. A.; Castedo, L.; Saá, C. *J. Org. Chem.* **2003**, 68, 8595. (f) Senaiar, R. S.; Young, D. D.; Deiters, A. D. *Chem. Commun.* **2006**, 1313. (g) Tanaka, K.; Suzuki, N.; Nishida, G. *Eur. J. Org. Chem.* **2006**, 2006, 3917. (h) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2008**, 10, 325. (i) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, 130, 3645. (j) Komine, Y.; Tanaka, K. *Org. Lett.* **2010**, 12, 1312. (k) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, 47, 11846. (l) Zhao, M.-N.; Ren, Z.-H.; Wang, Y.-Y.; Guan, Z.-H. *Chem. Commun.* **2012**, 48, 8105. (m) Kim, D.-S.; Park, J.-W.; Jun, C.-H. *Chem. Commun.* **2012**, 48, 11334. (n) Sim, Y.-K.; Lee, H.; Park, J.-W.; Kim, D.-S.; Jun, C.-H. *Chem. Commun.* **2012**, 48, 11787. (o) Martin, R. M.; Bergman, R. G.; Ellman, J. A. *J. Org. Chem.* **2012**, 77, 2501. (p) Yamamoto, S.-i.; Okamoto, K.; Murakoso, M.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2012**, 14, 3182. (q) Satoh, Y.; Obora, Y. *J. Org. Chem.* **2013**, 78, 7771. (r) Lee, H.; Sim, Y.-K.; Park, J.-W.; Jun, C.-H. *Chem. - Eur. J.* **2014**, 20, 323. (s) Wu, J.; Xu, W.; Yu, Z.-X.; Wang, J. *J. Am. Chem. Soc.* **2015**, 137, 9489. (t) Zhong, Y.; Spahn, N. A.; Stolley, R. M.; Nguyen, M. H.; Louie, J. *Synlett* **2015**, 26, 307.
- (11) Thakur, A.; Evangelista, J. L.; Kumar, P.; Louie, J. *J. Org. Chem.* **2015**, 80, 9951.
- (12) Chi, K.-W.; Ahn, Y. S.; Shim, K. T.; Park, T. J.; Ahn, J. S. *Bull. Korean Chem. Soc.* **1999**, 20, 973.
- (13) Yamaguchi, M.; Katsumata, H.; Manabe, K. *J. Org. Chem.* **2013**, 78, 9270.