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Catalytic Carbon Insertion into the β-Vinyl C−H Bond of Cyclic Enones with Alkyl Diazoacetates

Sung Il Lee,[†,‡] Byung Chul Kang,[†] Geum-Sook Hwang,[*,‡] and Do Hyun Ryu[*,†]

Department of Chemistry, Sungkyunkwan University, Suwon, 440-746, Korea, and Korea Basic Science Institute, Seoul, 136-713, Korea

dhryu@skku.edu; gshwang@kbsi.re.kr

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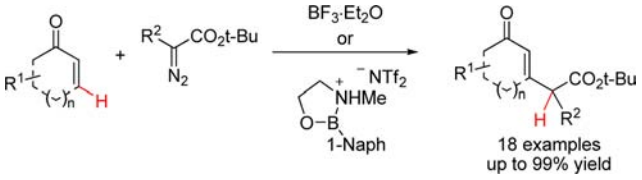
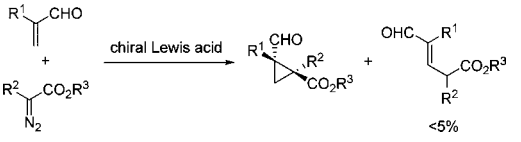
ABSTRACT



The first example of the boron Lewis acid catalyzed C_{sp2}−H functionalization of cyclic enones was achieved using diazoacetates. The insertion of the carbon atom of diazoacetates utilizes BF_3•Et_2O or a newly designed oxazaborolidinium ion as a catalyst to afford β-functionalized cyclic enones from simple cyclic enones in a single step and high yields. The reaction mechanism was investigated with deuterium labeled 2-cyclohexen-1-one.

The selective functionalization of the C−H bond is one of the most progressive and challenging topics in current organic chemistry.[1] An intermolecular C−H functionalization method offers a more ideal strategy for the formation of complex molecules. Recently, our group reported an oxazaborolidinium ion catalyzed asymmetric cyclopropanation of substituted acrolein with diazoacetate.[2] During the course of our study, a trace amount of C−H inserted acrolein was isolated (Scheme 1). The Noels[3] and Maruoka[4] groups have reported similar C−H inserted methacrolein side products in cyclization reactions. We were interested in the potential of this reaction and investigated suitable reaction conditions for selective C−H functionalization.

Scheme 1. Oxazaborolidinium Ion Catalyzed Cyclopropanation and the C−H Functionalization Reaction



β-Substituted enones are versatile intermediates in the synthesis of biologically active molecules and pharmaceuticals. Reported methods to prepare β-substituted enones are illustrated in Scheme 2. One method is initiated by Michael addition and α-selenylation of an enone.

[†] Sungkyunkwan University.
[‡] Korea Basic Science Institute.

(1) For examples of C−H functionalization reactions, see the following. Formyl C_{sp2}−H: (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364. (b) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258. (c) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202. (d) Li, W.; Wang, J.; Hu, X.; Shen, K.; Wang, W.; Chu, Y.; Lin, L.; Liu, X.; Feng, X. *J. Am. Chem. Soc.* **2010**, *132*, 8532. (e) Gao, L.; Kang, B. C.; Hwang, G.-S.; Ryu, D. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 8322. Allylic C_{sp3}−H: (f) Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2070. (g) Bykowski, D.; Wu, K.-H.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 16038. (h) Ventura, D. L.; Li, Z.; Coleman, M. G.; Davies, H. M. L. *Tetrahedron* **2009**, *65*, 3052. (i) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (j) Wang, J.; Boyarskikh, V.; Rainier, J. D. *Org. Lett.* **2011**, *13*, 700. (k) Wang, J.-C.; Xu, Z.-J.; Guo, Z.; Deng, Q.-H.; Zhou, C.-Y.; Wan, X.-L.; Che, C.-M. *Chem. Commun.* **2012**, *48*, 4299. Aromatic C_{sp2}−H: (l) Haldar, P.; Kar, G. K.; Ray, J. K. *Tetrahedron Lett.* **2003**, *44*, 7433. (m) Rodriguez-Cárdenas, E.; Sabala, R.; Romero-Ortega, M.; Ortiz, A.; Olivo, H. F. *Org. Lett.* **2012**, *14*, 238. (n) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (o) Ye, T.; McKervey, A. *Chem. Rev.* **1994**, *94*, 1091. C_{sp3}−H: (p) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422. (q) Slattery, C. N.; Ford, A.; Maguire, A. R. *Tetrahedron* **2010**, *66*, 6681. (r) Doyle, M. P.; Ratnikov, M.; Liu, Y. *Org. Biomol. Chem.* **2011**, *9*, 4007.

(2) Gao, L.; Hwang, G.-S.; Ryu, D. H. *J. Am. Chem. Soc.* **2011**, *133*, 20708.

(3) (a) Noels, A. F.; Braham, J. N.; Hubert, A. J.; Teyssié, P. *J. Org. Chem.* **1977**, *42*, 1527. (b) Noels, A. F.; Braham, J. N.; Hubert, A. J.; Teyssié, P. *Tetrahedron* **1978**, *34*, 3495.

(4) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2006**, *128*, 2174.

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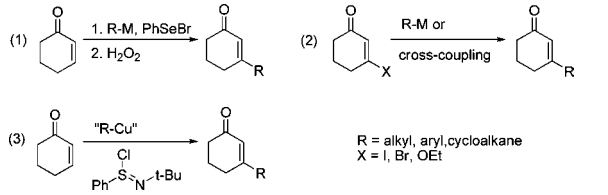
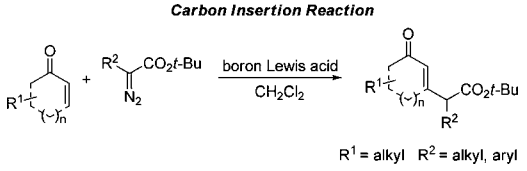
Subsequent oxidation of selenium and pyrolytic *syn* elimination afforded the desired β-substituted enone (eq 1).[5] Other methods for the preparation of β-functionalized enones involve β-halo or alkoxy substituted enones (eq 2).[6] Recently, a novel one-pot sequential preparative method was independently developed by Matsuo[7] and Kerr[8] et al. (eq 3).

Scheme 2. Reported Methods for β-Substituted Cyclohexenone



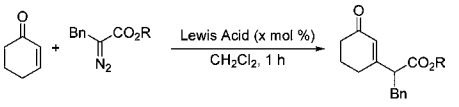
Scheme 3. Boron Lewis Acid Catalyzed Carbon Insertion Reaction of Cyclic Enones



We were inspired by a selective insertion of the carbon atom of diazoacetates into the β-vinyl C−H bond to afford a β-substituted enone in a single step from a nonfunctionalized, commercially available enone. In this report, we describe the boron Lewis acid catalyzed C_{sp2}−H functionalization of cyclic enones using diazoacetates.[9] We also document our mechanistic findings with kinetic isotope effect data from β-deuterated 2-cyclohexen-1-one (Scheme 3).

Investigation of the C−H functionalization was initiated with the screening of suitable enone structures. Interestingly, cyclic α,β-unsaturated ketones predominantly afforded the desired product, whereas acyclic enones did not yield the insertion product.[10] Our next exploration was carried out with *tert*-butyl benzyldiazoacetate and 2-cyclohexen-1-one in the presence of various Lewis acids. The central challenge was to identify a catalytic system that would avoid decomposition of the diazoacetate. Brønsted acids (Table 1, entry 1) and metal Lewis acids such as $TiCl_4$, $Sc(OTf)_3$, and $SnCl_4$ (Table 1, entries 2−4) did not act as catalysts and rapidly decomposed the diazoacetate. Only $BF_3{\bullet}Et_2O$ exhibited catalytic activity toward C−H insertion (Table 1, entry 5). When the reaction was carried out at 0 °C in dichloromethane, 20 mol % of $BF_3{\bullet}Et_2O$ afforded the desired insertion product in 37% yield. To improve the yield, 2-cyclohexen-1-one was used as the limiting reactant. The reaction was successfully performed with 2 equiv of diazoacetate to furnish the β-substituted cyclohexenone in 85% yield (Table 1, entry 6).

Table 1. Lewis Acid Catalyzed Carbon Insertion Reactions with 2-Cyclohexen-1-one and Alkyl Benzyldiazoacetate



1 2 3a

entry	R	Lewis acid	x	temp (°C)	yield(%)[a]
1[b]	*t*-Bu	TfOH	20	0	10
2[b]	*t*-Bu	$TiCl_4$	20	0	10
3[b]	*t*-Bu	$Sc(OTf)_3$	20	0	20
4[b]	*t*-Bu	$SnCl_4$	20	0	20
5[b]	*t*-Bu	$BF_3{\bullet}Et_2O$	20	0	37
6[c]	*t*-Bu	$BF_3{\bullet}Et_2O$	20	0	85
7[c]	*t*-Bu	$BF_3{\bullet}Et_2O$	20	−20	52
8[c]	Me	$BF_3{\bullet}Et_2O$	20	0	50
9[c]	Bn	$BF_3{\bullet}Et_2O$	20	0	52
10[c]	*t*-Bu	$BF_3{\bullet}Et_2O$	10	0	88

[a] Isolated yield. [b] The reaction was performed using 1.2 equiv of 2-cyclohexen-1-one and 1.0 equiv of *tert*-butyl benzyldiazoester. [c] The reaction was performed using 1.0 equiv of 2-cyclohexen-1-one and 2.0 equiv of alkyl benzyldiazoester.

At −20 °C, the reaction stopped before reaching completion (Table 1, entry 7). The ethyl or benzyl ester substituted diazoester did not completely generate the insertion product (Table 1, entries 8 and 9). Fortunately, use of 10 mol % of the catalyst successfully catalyzed the reaction and furnished the C−H inserted cyclohexenone in 88% yield (Table 1, entry 10).

After optimization of the C−H functionalization reaction, the scope of this methodology was investigated with various diazoacetates and cyclic enones (Scheme 4, Method A). For benzyl or allyl substituted diazoacetates, six- and five-membered cyclic enones provided the insertion products in high yield (Scheme 4, **3a**−**3c**, **3l**, **3m**). For *tert*-butyl ethyldiazoacetate, the yield decreased to 71% under the optimized reaction conditions. Fortunately, the reaction carried out at −20 °C furnished the corresponding β-substituted, cyclic enone in excellent yield regardless of ring size (Scheme 4, **3d**, **3n**). Methyl and isopropyl

(5) (a) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434. (b) Liotta, D.; Saidane, M.; Barnum, C.; Zima, G. *Tetrahedron* **1985**, *41*, 4881. (c) Kim, J. H.; Lim, H. J.; Cheon, S. H. *Tetrahedron* **2003**, *59*, 7501. (d) Takemoto, T.; Fukaya, C.; Yokoyama, K. *Tetrahedron Lett.* **1989**, *30*, 723.

(6) (a) Lee, K.; Kim, H.; Mo, J.; Lee, P. H. *Chem.—Asian J.* **2011**, *6*, 2147. (b) d'Augustin, M.; Palais, L.; Alexakis, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1376. (c) Hénon, H.; Mauduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122. (d) Shintani, R.; Takeda, M.; Nishimura, T.; Hayashi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 3969.

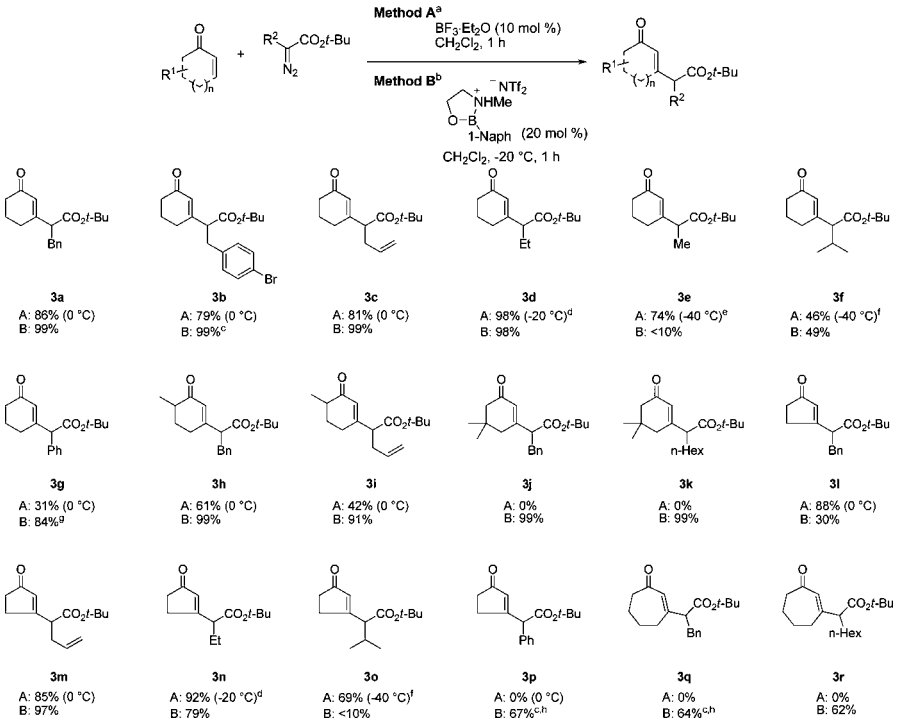
(7) Matsuo, J.; Aizawa, Y. *Chem. Commun.* **2005**, 2399.

(8) Kerr, W. J.; Pearson, C. M.; Thurston, G. J. *Org. Biomol. Chem.* **2006**, *4*, 47.

(9) For selected examples of Lewis acid catalyzed functionalization of ketones with diazoacetates, see: (a) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 6614. (b) Li, W.; Liu, X.; Hao, X.; Hu, X.; Chu, Y.; Cao, W.; Qin, S.; Hu, C.; Lin, L.; Feng, X. *J. Am. Chem. Soc.* **2011**, *133*, 15268. (c) Li, W.; Liu, X.; Hao, X.; Cai, Y.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2012**, *51*, 8644.

(10) Acyclic enone produced 2-pyrazoline as a major product. See: Novikov, R. A.; Platonov, D. N.; Dokichev, V. A.; Tomilov, Y. V.; Nefedov, O. M. *Russ. Chem. Bull., Int. Ed.* **2010**, *59*, 985.

Scheme 4. Scope of the C−H Functionalization (all yields refer to pure isolated product)

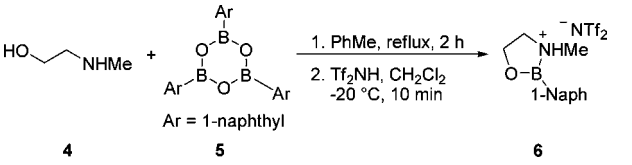


[a] The reaction was performed using 1.0 equiv of cyclic enone and 2.0 equiv of *tert*-butyl diazoester. [b] The reaction was performed using 1.0 equiv of cyclic enone and 1.2 equiv of *tert*-butyl diazoester. [c] Reaction time is 5 h. [d] Reaction time is 3 h. [e] 50 mol % BF_3•Et_2O used. [f] 100 mol % BF_3•Et_2O used. [g] Reaction time is 16 h. [h] 50 mol % of oxazaborolidinium catalyst used.

substituted diazoacetates required a high catalyst loading and gave the insertion product in moderate yield (Scheme 4, **3e** and **3f**, **3o**, respectively). We suspect that the high steric congestion of isopropyldiazoacetate reduces its reactivity with the cyclic enone.

To further evaluate the broad feasibility of the C−H functionalization reaction, we focused on developing a more suitable boron Lewis acid catalyst. The oxazaborolidinium ion is a powerful Lewis acid that catalyzes a wide range of organic reactions.[11] We anticipated that the bulkiness of the oxazaborolidinium ion would inhibit the reactivity of boron toward the diazoester and selectively activate the cyclic enone. We designed the novel and easily accessible achiral oxazaborolidinium ion catalyst **6**. Commercially available 2-(methylamino)ethanol (**4**) and 1-naphthylboroxine (**5**) were selected for the oxazaborolidine as a precursor of **6**. Oxazaborolidinium ion catalyst **6** was prepared by activation of the precursor with triflic imide (Scheme 5). The C−H functionalization reaction with *tert*-butyl benzyldiazoacetate and 2-cyclohexen-1-one in the presence of 20 mol % of catalyst **6** furnished **3a** in quantitative yield without decomposition of the diazoester (Scheme 4, method B).

Scheme 5. Preparation of Oxazaborolidinium Ion



4 **5** **6**

In most of the six-membered cyclic enone cases, oxazaborolidinium ion **6** afforded improved yields of C−H insertion products compared to BF_3•Et_2O and showed a wide substrate scope (Scheme 4, **3a**−**3d**, **3f**−**3k**).[12] The insertion reaction with 6-methyl-2-cyclohexen-1-one was carried out with both catalysts. While BF_3•Et_2O afforded **3h** and **3i** in moderate yields, the same reaction with catalyst **6** furnished the corresponding C−H inserted product in excellent yield.[13] Oxazaborolidinium ion **6** effectively catalyzed the reaction with 5-disubstituted cyclohexenones to quantitatively produce the β-functionalized enone (Scheme 4, **3j**, **3k**). For five-membered cyclic enones, BF_3•Et_2O was a more suitable catalyst than oxazaborolidinium ion **6** (Scheme 4, **3l**−**3o**). In contrast, the BF_3•Et_2O catalyzed insertion reaction with 2-cyclohepten-1-one was

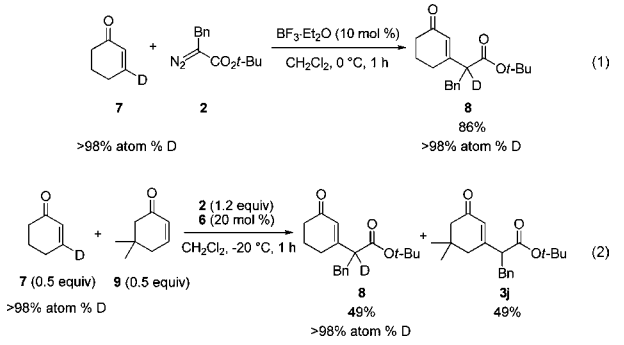
(11) (a) Senapati, B. K.; Hwang, G.-S.; Lee, S.; Ryu, D. H. *Angew. Chem., Int. Ed.* **2009**, *48*, 4398. (b) Gao, L.; Hwang, G.-S.; Lee, M. Y.; Ryu, D. H. *Chem. Commun.* **2009**, 5460. (c) Senapati, B. K.; Gao, L.; Lee, S. I.; Hwang, G.-S.; Ryu, D. H. *Org. Lett.* **2010**, *12*, 5088. (d) Corey, E. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2100. (e) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 5384.

(12) Methyl *tert*-butyldiazoacetate was rapidly decomposed in the presence of oxazaborolidinium catalyst **6**.

(13) A mixture of diastereomers (~1:2) was formed.

unfruitful (Scheme 4, **3q**, **3r**; Method A), with decomposition of the diazoester occurring faster than formation of the product. On the other hand, catalyst **6** was compatible with the diazoester under −20 °C and afforded the cycloheptenone C−H insertion product in moderate yield (Scheme 4, **3q**, **3r**).[14]

Scheme 6. Evidence for Intramolecular C−H Migration Pathway

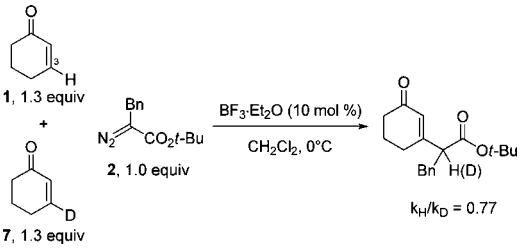


Our attention next turned to elucidating the mechanism of this novel transformation. On treatment of *tert*-butyl benzyldiazoacetate with 3-deuterio-2-cyclohexen-1-one (**7**) under the optimized conditions, the insertion reaction proceeded to give the corresponding deuterated product **8** (Scheme 6, eq 1). The NMR spectrum revealed >98% deuterium incorporated at the α-position of the *tert*-butyl ester. In addition, a double-labeling competitive experiment proved that the insertion reaction proceeded in an intramolecular hydride transfer manner (Scheme 6, eq 2).

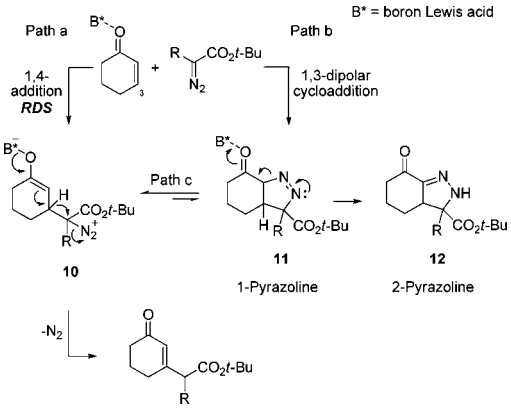
For further mechanistic insight, a kinetic isotope effect (KIE) experiment was conducted with a mixture of deuterated and nondeuterated cyclohexenone, and the k_H/k_D was found to be 0.77 (Scheme 7). These experiments suggest that the insertion is under the influence of an inverse secondary kinetic isotope effect (inverse SKIE).[15]

On the basis of the above observations, a mechanistic proposal is presented in Scheme 8. There are two plausible pathways for C−H functionalization: one path consists of a 1,4-addition and subsequent β-hydride migration process (path a),[16] and the second possible pathway involves initial formation of a 1-pyrazoline (**11**) by 1,3-dipolar cycloaddition and subsequent C−N cleavage to provide the same intermediate **10** (path b→c).[17] According to the KIE experiment, a hybridization change of the 3-C from sp^2 to sp^3 by 1,4-addition is the rate-determining step. Interestingly, 1-pyrazoline **11** resulting from 1,3-dipolar cycloaddition was observed when R is ethyl (path b), and a slow transformation of the 1-pyrazoline to the insertion

Scheme 7. Kinetic Isotope Effect Experiment



Scheme 8. Proposed Mechanism for the C−H Functionalization Reaction



product could be monitored by TLC (path c). Since the 1-pyrazoline rapidly tautomerizes under protic conditions, 2-pyrazoline **12** could be isolated after quenching with water.

In conclusion, we have developed a boron Lewis acid catalyzed C_{sp2}−H functionalization reaction of cyclic enones using diazoacetates. The insertion of the carbon atom of diazoacetates utilizes BF_3•Et_2O or a newly designed oxazaborolidinium ion as a catalyst to afford β-functionalized cyclic enones from simple cyclic enones in a single step and high yields. We believe that the resulting β-functionalized enones could be highly valuable for the synthesis of useful complex molecules. Further extension of this research to the catalytic asymmetric version of this reaction is now in progress.

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Supporting Information Available. Experimental details and chracterization data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(14) The yields based on recovered starting material for **3g**, **3l**, **3n**, and **3p**−**3r** are 99% (Method B).

(15) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*; University Science: 2005; pp 428−430.

(16) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

(17) Hashimoto, T.; Naganawa, Y.; Kano, T.; Maruoka, K. *Chem. Commun.* **2007**, 5143; see Supporting Information.