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Iodine-Catalyzed Direct Olefination of 2-Oxindoles and Alkenes via Cross-Dehydrogenative Coupling (CDC) in Air

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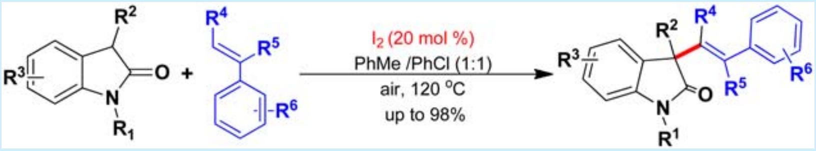
Ⓢ *Supporting Information*



ABSTRACT: A direct intermolecular olefination of sp^3 C−H bond between 2-oxindoles and simple alkenes via a Cross-Dehydrogenative Coupling (CDC) strategy has been developed. In the absence of additional base, moderate to excellent yields have been obtained by using a catalytic amount of iodine with atmospheric oxygen as the reoxidant. Based on the observation of a radical capture experiment, the transformation is proposed to proceed via a radical process.

Selective construction of C−C bonds through a cross-dehydrogenative coupling (CDC) reaction of two C−H bonds has become an important field in organic synthesis.[1] Among them, direct CDC reactions of the sp^3 C−H bond[2] including the olefination reaction has attracted considerable attention. As a highly effective and atom-economic approach to forming sp^2−sp^3 C−C bonds, various direct olefination strategies of sp^3 C−H bonds such as the sp^3 C−H bonds adjacent to the heteroatom[3] and alkane sp^3 C−H bonds[4] have been developed. In 2006, Li and co-workers reported the CDC reaction of tetrahydroisoquinolines with electron-deficient alkenes via iminium ion intermediates.[3a] In 2014, the direct olefination of simple ethers and olefins through a radical process was reported by Lei and co-workers.[3b] For alkane substrates, the olefination methods of the sp^3 C−H bond in the CDC strategy through metal insertion or a radical process were respectively disclosed by Sanford,[4a] Yu,[4b] and Wei.[4c] Despite these promising results, the direct olefination of other types of sp^3 C−H bonds has been less investigated.

In recent years, functionalization of α-sp^3 C−H bonds of the carbonyl group has attracted widespread attention. The α-olefination of carbonyl compounds with vinyl bromides or vinyl triflates could be achieved under Pd- or Ni-catalysis.[5] Meanwhile, the α-aromatization of sp^3 C−H bonds of the carbonyl group via a CDC reaction has made great progress. Baran and co-workers accomplished the total syntheses of various indole alkaloids by an intermolecular CDC of an α-sp^3 C−H bond of the carbonyl group with indoles.[6] Recently, Kündig and Taylor's groups independently explored the synthesis of oxindole derivatives via an intramolecular CDC reaction under Cu (II)-promoted processes.[7] It is noteworthy that although the α-aromatization of carbonyl compounds has been well developed,[6−8] the direct α-olefinatioin of carbonyl compounds through a CDC strategy is limited.[9]

Herein, we would like to report an I_2-catalyzed olefination of 3-substituted-2-oxindoles with simple alkenes in an air atmosphere to give 3-aryl- and 3-alkyl-3-alkenyl-2-oxindoles in moderate to excellent yields. The coupling products could be further converted into fused- and spiro-cyclic compounds bearing an indole moiety.

Transition-metal catalysts were selected for CDC reactions in priority.[10] At first, the reaction of 3-phenyl-2-oxindole **1a** with styrene **2a** in the presence of metal-catalyst $Cu(OAc)_2$ was carried out. Unfortunately, the product was a complicated mixture including a polymer of styrene while no coupling product was detected. Among the transition-metal-free catalysts,[11] iodine is a good candidate for corresponding coupling reactions. It not only is an inexpensive, nontoxic, and environmentally benign reagent but also is able to undergo the electron transfer process in an oxidative process similar to the transition-metal catalyst.[12] So the reaction of **1a** with **2a** was mediated by iodine (1.2 equiv) with additional base ^{t}BuONa (1.0 equiv) in a nitrogen atmosphere. The coupling product (*E*)-3-phenyl-3-styryl-2-oxindole **3aa** was obtained in 84% yield (Table 1, entry 1). The exclusive (*E*)-stereoselectivity of the reaction was observed (see Supporting Information). The equivalent iodine and additional base were essential to the coupling reaction in a N_2 atmosphere (entries 2 and 3). To our delight, if the reaction was performed in an air atmosphere, only a catalytic amount (20 mol %) of iodine was needed without the use of any additional base, affording the coupling product **3aa** in 68% yield (entry 5). The solvent had a strong influence on the yield of the coupling product. When the mixed solvent (PhMe/PhCl = 1:1) was used and the reaction

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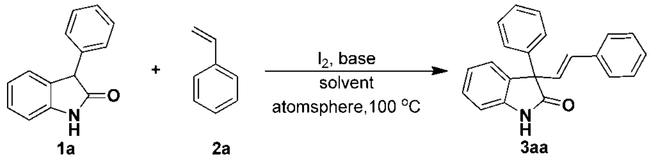
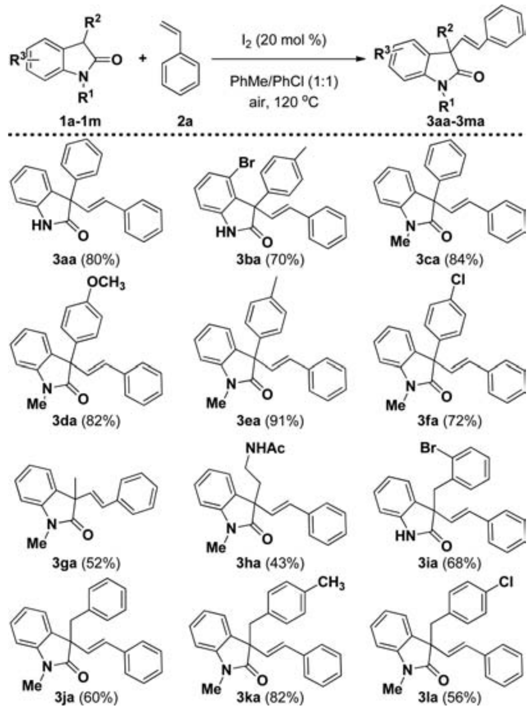
Table 1. Optimization of the Reaction Conditions[a]



entry	base	iodine (mol %)	atmosphere	solvent	temp (°C)	time (h)	yield of **3aa** (%)[b]
1	NaO^{t}Bu (1.0)	120	N_2	PhMe	100	12	84
2	–	120	N_2	PhMe	100	15	21
3	NaO^{t}Bu (1.0)	0	N_2	PhMe	100	12	NR[c]
4	–	10	air	PhMe	100	24	30
5	–	20	air	PhMe	100	24	68
6	–	25	air	PhMe	100	24	58
7	–	30	air	PhMe	100	24	52
8	–	20	air	PhCl	120	12	71
9	–	20	air	PhMe/PhCl (1:1)	120	12	80
10	–	25	air	PhMe/PhCl (1:1)	120	12	83
11	–	30	air	PhMe/PhCl (1:1)	120	12	81
12	–	20	O_2	PhMe/PhCl (1:1)	120	12	42
13	–	20	N_2	PhMe/PhCl (1:1)	120	12	trace

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (1 mmol), solvent (2 mL). [b] Isolated yields. [c] NR = no reaction.

Scheme 1. Scope of 3-Substituted-2-oxindoles[a,b]



[a] Reaction conditions: **1a**–**1m** (0.1 mmol), **2a** (1.0 mmol), and I_2 (0.02 mmol) in 2 mL of PhMe/PhCl (1:1) at 120 °C. [b] Isolated yield.

temperature was changed to 120 °C, the yield of **3aa** increased from 68% to 80–83% (entry 5 vs entries 9–11). To our surprise, the reaction of **1a** with **2a** performed under an oxygen atmosphere gave a lower yield than that under an air atmosphere (entry 12 vs 5). Moreover, under a nitrogen atmosphere, the catalytic amount of iodine was demonstrated to be ineffective for the coupling reaction (entry 13).

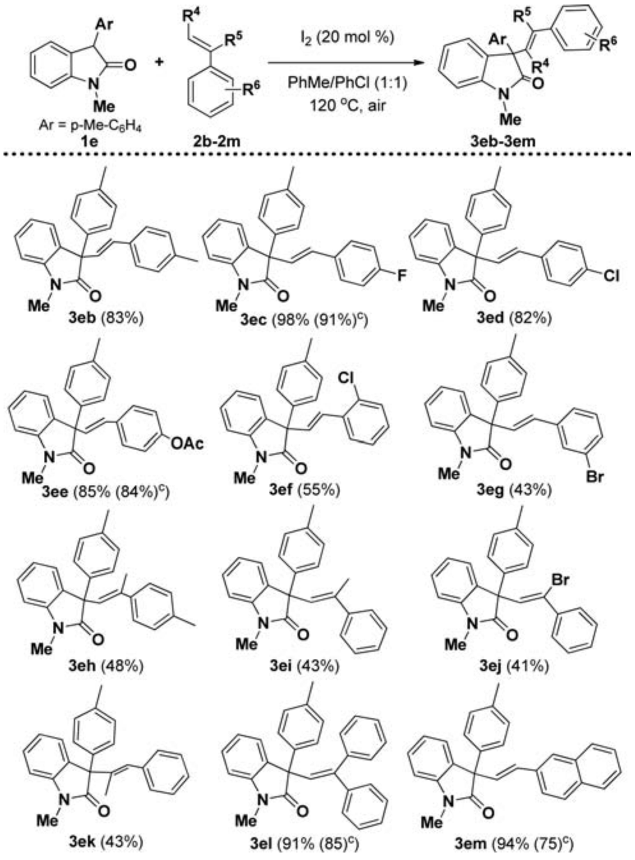
Under the optimized reaction conditions, the approach of iodine-catalyzed olefination was applied to the reactions of various 3-substituted-2-oxindoles with **2a** (Scheme 1). Both N-protected and N-unprotected (R^1 = CH_3 and H)-2-oxindoles were tolerant of the iodine-catalyzed CDC reaction. When the group on N was changed from H to methyl, the yield of the coupling product slightly increased (**3aa** vs **3ca**). The substituents on the C3 position (R^2 = aryl and alkyl) of 2-oxindoles were applicable, but with some influences on the yields of coupling products. 3-Aryl-2-oxindoles provided better yields of the coupling products than 3-benzyl-2-oxindoles (**3aa**–**3fa** vs **3ia**–**3la**).When an electron-withdrawing group was located on the *para*-position of the phenyl group, the yields decreased obviously (**3ca** vs **3fa**). The electron-donating groups on the *para*-positon of the benzyl group could remarkably improve the yields (**3ja** vs **3ka**). Furthermore, when R^2 was an aliphatic group, a moderate yield was obtained (**3ga**–**3ha**).

The scope of alkenes, which reacted with 1-methyl-3-(*p*-tolyl)-2-oxindole **1e**, was also explored (Scheme 2). All the *para*-substituted styrenes provided high to excellent yields (**3ea**–**3ee**). However, when a halogen atom was on the *ortho*- or *meta*-position of the styrene moiety the yield decreased remarkably (**3ef**–**3eg**). For the styrene derivatives with two substituents on the double bond, the iodine-catalyzed CDC reaction afforded the products (**3eh**–**3ek**) in low yields (41–48%), except the product **3el** from 1,1-diphenyl-ethylene. An excellent yield of the product **3em** (94%) was obtained by using 2-vinylnaphthalene as a reaction partner. With methyl acrylate as the substrate, no desired product was obtained.

To evaluate the practicality of this CDC reaction, a gram-scale reaction of **1e** and **2a** was carried out. As shown in Scheme 3, product **3ea** was obtained in 86% yield under a 20 mol % catalyst loading.

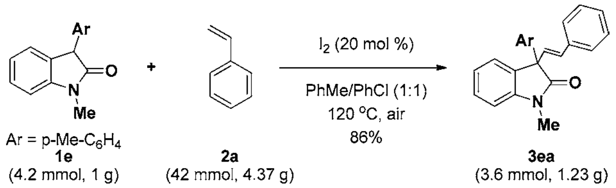
The olefination products of 2-oxindoles could be further converted to the indole alkloids bearing a fused cyclic amine and spiro-cyclic 2-oxindoles. Starting from **3ha**, pyrroloindoline[13] **4** was obtained in 70% overall yield (dr = 7.7:1) through tandem reduction–cyclization in a one-pot process [Scheme 4, eq 1]. Besides, an intramolecular Heck-type reaction of **3ia** catalyzed by $Pd(OAc)_2/PPh_3$ could effectively afford the spirooxindole derivatives[14] **5** in 72% yield [Scheme 4, eq 2].

Scheme 2. Scope of alkenes[a,b]

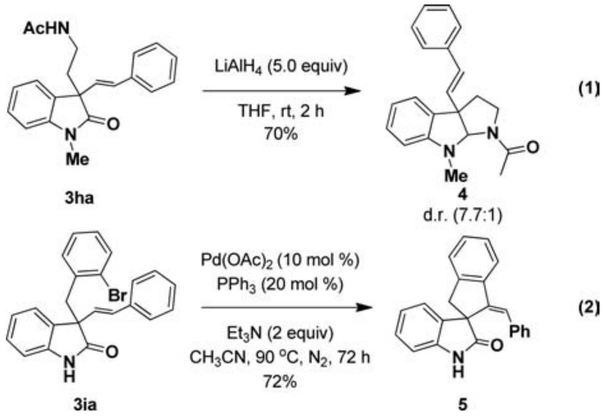


[a]Reaction conditions: **1e** (0.1 mmol), **2b–2m** (1.0 mmol), and I_2 (0.02 mmol) in PhMe/PhCl (1:1) 2 mL at 120 °C. [b]Isolated yield. [c]Isolated yield when 0.5 mmol of alkenes were used.

Scheme 3. Gram-Scale Reaction of 1e with 2a

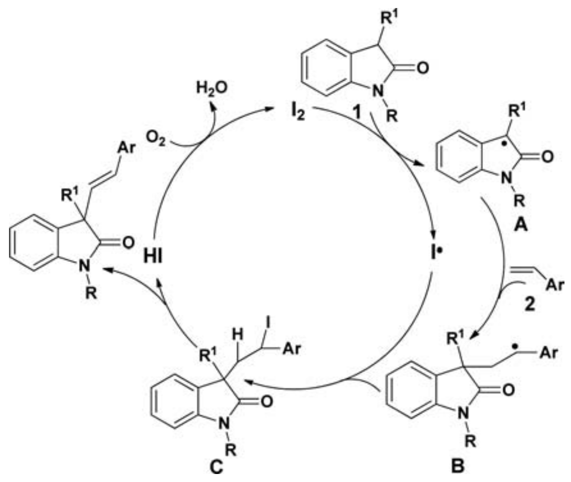


Scheme 4. Subsequent Conversation of the Coupling Products



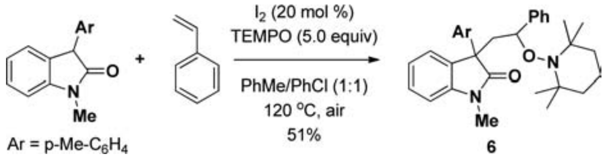
Although the exact reaction mechanism is unclear, one possibility involving a radical pathway has been proposed (Scheme 5). The reaction started with the generation of 2-oxindole radical intermediate **A** through the oxidization of 3-substituted-2-oxindole by iodine. Then, **A** was immediately trapped by styrene **2**,[15] forming a benzyl radical intermediate **B**. which was quenched by an iodine radical to produce intermediate **C**. The formation of radical **B** and an iodine-trapped reaction were superior to other competitive reactions such as homopolymerization of styrene and homodimerization of intermediate **B**. Subsequently, intermediate **C** underwent elimination of hydrogen iodide to give the desired coupling product. Meanwhile, the generated HI was oxidized by oxygen[12d] to produce iodine, and thus the catalytic cycle was completed.

Scheme 5. Proposed Mechanism



Under the iodine-catalysis conditions, the addition of TEMPO (radical scavenger) afforded the capture product **6** in 51% isolated yield (Scheme 6) with a trace of coupling product **3aa**. The TEMPO-trapped reaction strongly supported the formation of the intermediates **B**, in which the radical located at the α-position of ethylbenzene.

Scheme 6. TEMPO Capture Reaction



In conclusion, an iodine-catalyzed olefination of 3-substituted-2-oxindoles with simple alkenes in an air atmosphere through a CDC process has been developed to afford 3-alkenyl-2-oxindoles in moderate to excellent yields. In the course of the iodine-catalyzed olefination reaction, the formation of radical intermediate **B** was confirmed by structural analysis of the TEMPO-trapped product. This synthetic method has a broad substrate scope with high atom economy. The coupling products have great potential to be converted to versatile indole alkaloids bearing fused- and spiro-cyclic moieties.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01662.

Experimental procedures, characterization data, and ^{1}H NMR and ^{13}C NMR spectra for new products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Girard, S. A.; Knauber, T.; Li, C. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74. (b) Guo, X. X.; Gu, D. W.; Wu, Z. X.; Zhang, W. B. *Chem. Rev.* **2015**, *115*, 1622. (c) Shi, W.; Liu, C.; Lei, A. W. *Chem. Soc. Rev.* **2011**, *40*, 2761. (d) Li, B.; Dixneuf, P. H. *Chem. Soc. Rev.* **2013**, *42*, 5744.

(2) For selected examples, see: (a) Zhang, Y. H.; Feng, J. Q.; Li, C. J. *J. Am. Chem. Soc.* **2008**, *130*, 2900. (b) Mo, H. J.; Bao, W. L. *Adv. Synth. Catal.* **2009**, *351*, 2845. (c) Li, Z. P.; Li, C. J. *J. Am. Chem. Soc.* **2005**, *127*, 6968. (d) Li, Y. Z.; Li, B. J.; Lu, X. Y.; Lin, S.; Shi, Z. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3817. (e) Deng, G. J.; Zhao, L.; Li, C. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 6278.

(3) (a) Li, Z. P.; Bohle, D. S.; Li, C. J. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *103*, 8928. (b) Liu, D.; Liu, C.; Li, H.; Lei, A. W. *Chem. Commun.* **2014**, *50*, 3623. (c) Zhang, G.; Ma, Y. X.; Wang, S. L.; Zhang, Y. H.; Wang, R. *J. Am. Chem. Soc.* **2012**, *134*, 12334.

(4) (a) Stowers, K. J.; Fortner, K. C.; Sanford, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 6541. (b) Wasa, M.; Engle, K. M.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 3680. (c) Zhu, Y. F.; Wei, Y. Y. *Chem. Sci.* **2014**, *5*, 2379.

(5) (a) Huang, J.; Bunel, E.; Faul, M. M. *Org. Lett.* **2007**, *9*, 4343. (b) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900. (c) Grigalunas, M.; Ankner, T.; Norrby, P. O.; Wiest, O.; Helquist, P. *J. Am. Chem. Soc.* **2015**, *137*, 7019. (d) Liu, C.; Tang, S.; Liu, D.; Yuan, J. W.; Zheng, L. W.; Meng, L. K.; Lei, A. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 3638. (e) Liu, X. L.; Ma, X. N.; Huang, Y. Z.; Gu, Z. H. *Org. Lett.* **2013**, *15*, 4814. (f) Ankner, T.; Cosner, C. C.; Helquist, P. *Chem. - Eur. J.* **2013**, *19*, 1858.

(6) (a) Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450. (b) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (c) Richter, J. M.; Ishihara, Y.; Masuda, T.; Whitefield, B. W.; Llamas, T.; Pohjakallio, A.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 17938.

(7) (a) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. (b) Jia, Y. X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636.

(8) For selected examples, see: (a) Klein, E. M. N.; Perry, A.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2010**, *12*, 3446. (b) Drouhin, P.; Hurst, T. E.; Whitwood, A. C.; Taylor, R. J. K. *Org. Lett.* **2014**, *16*, 4900. (c) Bhunia, S.; Ghosh, S.; Dey, D.; Bisai, A. *Org. Lett.* **2013**, *15*, 2426. (d) Ghosh, S.; De, S.; Kakde, B. N.; Bhunia, S.; Adhikary, A.; Bisai, A. *Org. Lett.* **2012**, *14*, 5864. (e) Yu, Z.; Ma, L.; Yu, W. *Synlett* **2010**, *2010*, 2607. (f) More, N. Y.; Jeganmohan, M. *Chem. - Eur. J.* **2015**, *21*, 1337. (g) Nicolaou, K. C.; Reingruber, R.; Sarlah, D.; Bräse, S. *J. Am. Chem. Soc.* **2009**, *131*, 2086. (h) Conrad, J. C.; Kong, J.; Laforteza, B. N.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 11640.

(9) (a) Rao, A. V. R.; Rao, B. V.; Reddy, D. R.; Singh, A. K. *J. Chem. Soc., Chem. Commun.* **1989**, 400. (b) Blizzard, T. A.; Mosley, R. T.; Birzin, E. T.; Chan, W.; Hammond, M. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1317. (c) Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2004**, 660.

(10) For reviews, see: (a) Zhang, C.; Tang, C. H.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (b) Xie, J.; Pan, C. D.; Abdukader, A.; Zhu, C. J. *Chem. Soc. Rev.* **2014**, *43*, 5245. (c) Shi, Z.; Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3381. (d) Li, C. J. *Acc. Chem. Res.* **2009**, *42*, 335.

(11) Sun, C. L.; Shi, Z. J. *Chem. Rev.* **2014**, *114*, 9219.

(12) (a) Tang, S.; Wu, Y.; Liao, W. Q.; Bai, R. P.; Liu, C.; Lei, A. W. *Chem. Commun.* **2014**, *50*, 4496. (b) Kuepper, F. C.; Feiters, M. C.; Olofsson, B.; Kaiho, T.; Yanagida, S.; Zimmermann, M. B.; Carpenter, L. J.; Luther, G. W., III; Lu, Z. L.; Jonsson, M.; Kloo, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 11598. (c) Hao, W. J.; Wang, S. Y.; Ji, S. J. *ACS Catal.* **2013**, *3*, 2501. (d) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, K. R. *Org. Lett.* **2013**, *15*, 1092.

(13) (a) Xie, Y.; Jiang, P.; Ge, X.; Wang, H.; Shao, B.; Xie, Q.; Qiu, Z.; Chen, H. *J. Pharm. Biomed. Anal.* **2014**, *96*, 156. (b) Liu, J.; Ng, T.; Rui, Z.; Ad, O.; Zhang, W. *Angew. Chem., Int. Ed.* **2014**, *53*, 136.

(14) Fensome, A.; Adams, W. R.; Adams, A. L.; Berrodin, T. J.; Cohen, J.; Huselton, C.; Illenberger, A.; Kern, J. C.; Hudak, V. A.; Marella, M. A.; Melenski, E. G.; McComas, C. C.; Mugford, C. A.; Slayden, O. D.; Yudt, M.; Zhang, Z.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E. *J. Med. Chem.* **2008**, *51*, 1861.

(15) If there is no addition of styrene, the dimer of radical A is produced; see: Ghosh, S.; Chaudhuri, S.; Bisai, A. *Org. Lett.* **2015**, *17*, 1373.