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Efficient Construction of Fused Indolines with a 2-Quaternary Center via an Intramolecular Heck Reaction with a Low Catalyst Loading

Lei Zhao, Ziyuan Li, Lin Chang, Jinyi Xu, Hequan Yao,* and Xiaoming Wu*

State Key Laboratory of Natural Medicines and Department of Medicinal Chemistry, China Pharmaceutical University, Nanjing 210009, P. R. China

hyao@cpu.edu.cn (H.Y.); xmwu@cpu.edu.cn (X.W.)

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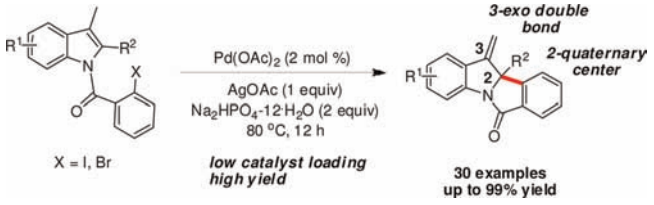
ABSTRACT



An efficient construction of fused indolines with a 2-quaternary center through a palladium-catalyzed intramolecular Heck reaction of *N*-(2(2-halobenzoxyl)-2,3-disubstituted indoles is disclosed. This protocol provided a straightforward access to diverse fused indolines with good functional group tolerance.

In the past few years, intramolecular direct arylation of heteroaromatic compounds to synthesize fused heteroaromatic products, such as fused indoles, via a radical pathway (Scheme 1a),[1] transition-metal-catalyzed single C−H bond activation (Scheme 1a),[2,3] or double C−H bond activation (Scheme 1b)[4] has become a popular method for building carbon−carbon (C−C) bonds of complex molecular skeletons. Although palladium-catalyzed intramolecular arylation at the C2 position of the C2-unsubstituted heteroaromatic substrates has been extensively explored, no example using C2-substituted heteroaromatic compounds as the substrate to build C−C bonds at the C2 position has been reported so far.

In 2006, Knochel and co-workers[5] reported a novel approach for the preparation of various condensed pyrroles from 2,5-dimethylpyrroles; however, this approach underwent a chemoselective palladium-catalyzed intramolecular arylation of the methyl group at the C2 position of the pyrrole ring. Very recently, Rawal et al.[6] developed a palladium-catalyzed benzylation of 2,3-disubstituted indoles to furnish C−C bonds at the C3 position for synthesizing a diverse range of 3-benzylindolenines.[7,8] Although both methods used C2-substituted heteroaromatic compounds as substrates, neither of them generated a C−C bond at the C2 position. In this letter, we wish to report a

(1) For radical pathway, see: (a) Antonio, Y.; De La Cruz, E. M.; Galeazzi, E.; Guzman, A.; Bray, B. L.; Greenhouse, R.; Kurz, L. J.; Lustig, D. A.; Maddox, M. L.; Muchowski, J. M. *Can. J. Chem.* **1994**, *72*, 15. (b) Caddick, S.; Aboutayab, K.; Jenkins, K.; West, R. I. *J. Chem. Soc., Perkin Trans. 1* **1996**, *7*, 675. (c) Kraus, G. A.; Kima, H. *Synth. Commun.* **1993**, *23*, 55.

(2) For excellent reviews, see: (a) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20. (b) Alberico, D.; Scott, N. E.; Lauten, M. *Chem. Rev.* **2007**, *107*, 174. (c) Bellina, F.; Cauteruccio, S.; Rossi, R. *Curr. Org. Chem.* **2008**, *12*, 774. (d) Li, B.-J.; Yang, S. D.; Shi, Z. -J. *Synlett* **2008**, 949. (e) Serigin, I. V.; Gervogyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173.

(3) For selected examples through single C−H bond activation, see: (a) Campeau, L.-C.; Parisien, M.; Jean, A.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 581. (b) Laha, J. K.; Cunny, G. D. *J. Org. Chem.* **2011**, *76*, 8477.

(4) (a) Dwight, T. A.; Rue, N. R.; Charyk, D.; Josselyn, R.; DeBoef, B. *Org. Lett.* **2007**, *9*, 3137. (b) Pintori, D. G.; Greaney, M. F. *J. Am. Chem. Soc.* **2010**, *133*, 1209.

(5) (a) Ren, H.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 3462. (b) Ren, H.; Li, Z.; Knochel, P. *Chem.—Asian J.* **2007**, *2*, 416.

(6) Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2011**, *134*, 111.

(7) For selected examples of Pd-catalyzed allylation reactions of 3-unsubstituted indoles, see: (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, *6*, 3199. (b) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (c) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424.

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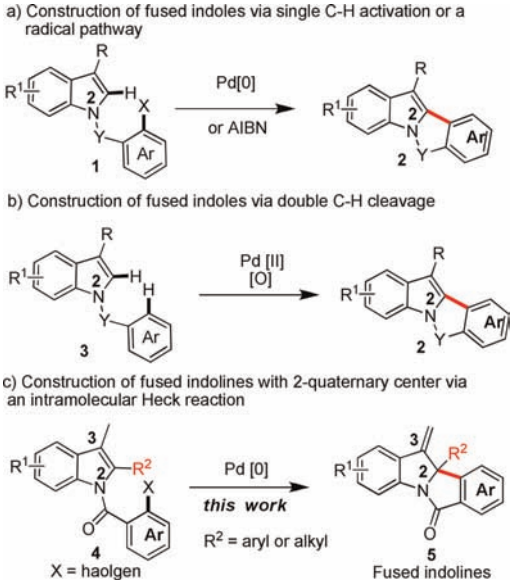
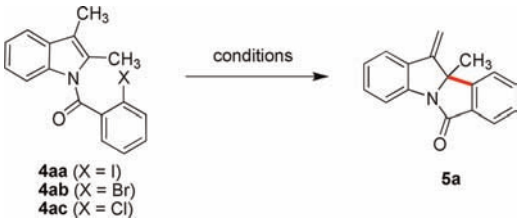
C2-arylation of 2,3-disubstituted indoles through an intramolecular Heck type reaction,[9] leading to the formation of fused indolines with a 2-quarternary center (Scheme 1c), which are similar to the structural skeleton[10] of bioactive natural products, such as Isatisine A and (−)-Isatisine A.[11]

Scheme 1. Construction of Fused Indoles or Indolines



We began our investigation by using *N*-(2-iodobenzoxyl)-2,3-dimethylindole **4aa**[12] as a model substrate. When **4aa** was treated with 10 mol % of $Pd(OAc)_2$, 20 mol % of PPh_3, and 2 equiv of Cs_2CO_3 in DMF at 120 °C for 12 h, we were delighted to find that the corresponding product **5a** was afforded in about 20% yield (Table 1, entry 1). The relative configuration of **5a** was determined by an X-ray structural analysis, showing that the C−C bond at the C2 postion and the 3-*exo* double bond were formed (Figure 1).[13]

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	additive (equiv)	base	temp (°C)	yield (%)[b]
1	$Pd(OAc)_2$ (10)	PPh_3 (0.2)	Cs_2CO_3	120	20
2	$Pd(OAc)_2$ (10)	none	Cs_2CO_3	120	7
3	$Pd(OAc)_2$ (10)	AgOAc (1)	Cs_2CO_3	120	45
4	$Pd(OAc)_2$ (10)	Ag_2O (1)	Cs_2CO_3	120	12
5	$Pd(OAc)_2$ (10)	Ag_2CO_3 (1)	Cs_2CO_3	120	32
6	$Pd(OAc)_2$ (10)	AgOAc (1)	KOAc	120	52
7	$Pd(OAc)_2$ (10)	AgOAc (1)	K_2CO_3	120	42
8	$Pd(OAc)_2$ (10)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	120	99
9	$PdCl_2$ (10)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	120	76
10	$Pd(MeCN)_2Cl_2$ (10)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	120	90
11	$Pd(OAc)_2$ (10)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	100	99
12	$Pd(OAc)_2$ (10)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	80	99
13	$Pd(OAc)_2$ (10)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	60	90[c]
14	$Pd(OAc)_2$ (2)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	80	99 (99[d])
15	$Pd(OAc)_2$ (1)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	80	87[c]
16	none	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	120	0[c]
17[e]	$Pd(OAc)_2$ (2)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	80	80[d]
18[f]	$Pd(OAc)_2$ (10)	AgOAc (1)	$Na_2HPO_4 \cdot 12H_2O$	120	trace

[a] Reaction conditions: **4aa** (0.5 mmol), Pd catalyst, additive, and base (1 mmol) in DMF (2.0 mL) for 12 h. [b] ^1H NMR yield using dibromomethane as an internal standard. [c] 24 h. [d] Isolated yield. [e] **4ab** was used as a substrate. [f] **4ac** was used as a substrate.

Very interestingly, the reaction could take place even without a phosphine ligand (entry 2). Encouraged by these results, a variety of additives, catalysts, and reaction temperatures were then evaluated to optimize the reaction conditions as shown in Table 1. First, we found that the addition of silver salt, such as Ag_2CO_3, Ag_2O, and AgOAc (entries 3−5), could enhance the yield of **5a**.[14] Next screening of bases revealed that the yield of **5a** was increased to

(8) For reactions of 3-substituted indoles, see: (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (b) Kagawa, N.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2008**, *10*, 2381. (c) Repka, L. M.; Ni, J.; Reisman, S. E. *J. Am. Chem. Soc.* **2010**, *132*, 14418. (d) Kieffer, M. E.; Repka, L. M.; Reisman, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 5131.

(9) (a) Heck, R. F.; Nolley, J. P., Jr. *J. Org. Chem.* **1972**, *37*, 2320. (b) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 581. For recent reviews on the Heck reaction, see: (d) Coeffard, V.; Guiry, P. J. *Curr. Org. Chem.* **2010**, *14*, 212. (e) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170. (f) Oestreich, M. *The Mizoroki−Heck Reaction*; Wiley: Chichester, U.K., 2009.

(10) For constructing similar indole skeletons by intramolecular carbopalladation of allenes followed by nucleophilic substitution, see: Hiroi, K.; Hiratsuka, Y.; Watanabe, K.; Abe, I.; Kato, F.; Hiroi, M. *Synlett* **2001**, 263.

(11) For the isolation of isatisines, see: (a) Liu, J. F.; Jiang, Z. Y.; Wang, R. R.; Zheng, Y. T.; Chen, J. J.; Zhang, X. M.; Ma, Y. B. *Org. Lett.* **2007**, *9*, 4127. For the recent total synthesis of isatisines, see: (b) Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1133. (c) Karadeolian, A.; Kerr, M. A. *J. Org. Chem.* **2010**, *75*, 6830. (d) Lee, J.; Panek, J. S. *Org. Lett.* **2011**, *13*, 502. (e) Zhang, X.; Mu, T.; Zhan, F. X.; Ma, L. J.; Liang, G. X. *Angew. Chem., Int. Ed.* **2011**, *50*, 6164. (f) Wu, W.; Xiao, M.; Wang, J.; Li, Y.; Xie, Z. *Org. Lett.* **2012**, *14*, 1642.

(12) See the Supporting Information for the preparation of the substrates.

(13) The crystallographic data for **5a** have been deposited at the Cambridge Crystallographic Data Centre with deposition No. CCDC 861219.

(14) Silver salts were proved to enhance the cross-coupling efficiency; see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Masui, K.; Ikegami, H.; Mori, A. *J. Am. Chem. Soc.* **2004**, *126*, 5074. (c) Xu, D.; Lu, C.; Chen, W. *Tetrahedron* **2012**, *68*, 1466.

99% when $Na_2HPO_4 \cdot 12H_2O$ was employed (entries 6–8). Further trials using other palladium catalysts such as $PdCl_2$ and $Pd(MeCN)_2Cl_2$ led to no improvement in the reaction performance (entries 9, 10). A survey of reaction temperature showed that this reaction proceeded efficiently at 100 and 80 °C, while a longer reaction time was needed at 60 °C (entries 11–13). Gratifyingly, this reaction was also quite effective with a low catalyst loading (entries 14, 15). A control experiment confirmed that a palladium catalyst was necessary to promote this reaction (entry16). This reaction using *N*-(2-bromobenzoxyl)-2,3-dimethylindole **4ab** as a substrate also proceeded smoothly to give **5a** in good yield, while it failed for *N*-(2-chlorobenzoxyl)-2,3-dimethylindole **4ac** (entries 17, 18).

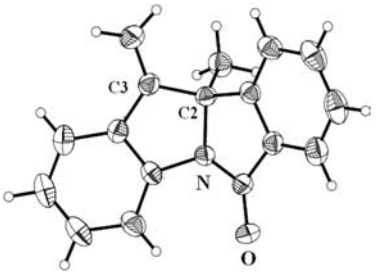
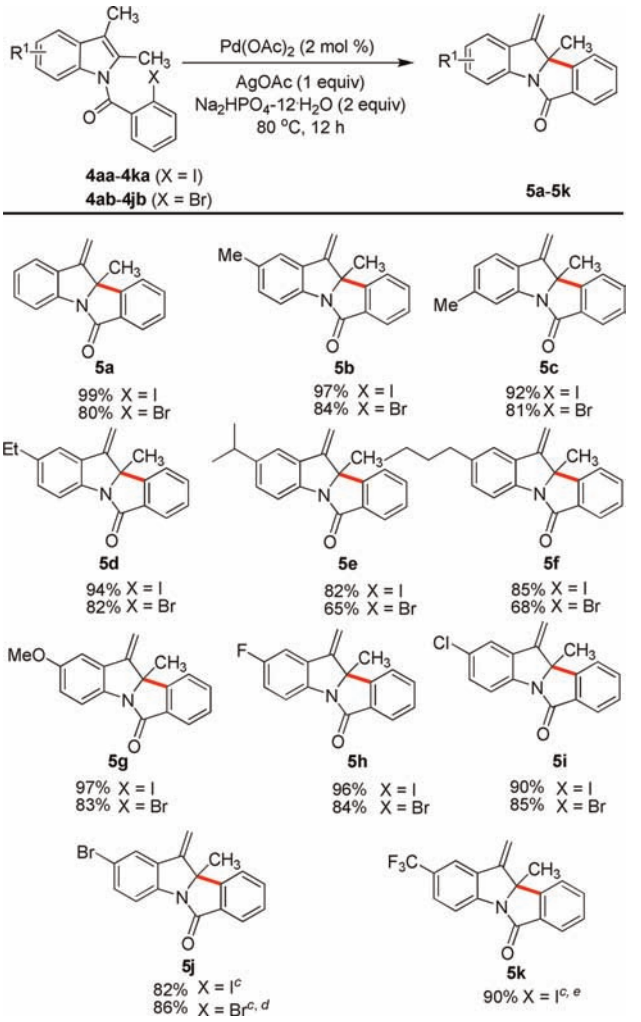


Figure 1. X-ray crystal structure of fused indoline **5a**.

With the optimized conditions established, we then investigated the substrate scope and generality of this method. We first examined the substituent effect on the benzene ring in the indole part of *N*-(2-iodobenzoxyl)-2,3-dimethylindoles. As shown in Scheme 2, a variety of functional groups, such as hydrogen, electron-donating and -withdrawing groups, and halogen were compatible with this intramolecular cross-coupling reaction. The substrates (**4aa**–**5ga**) bearing hydrogen or electron-donating groups such as methyl, ethyl, *i*-propyl, *n*-butyl, or methoxyl could afford the desired products in excellent yields. In addition, the halogen substituted substrates (**4ha**–**5ja**) could also be converted into the desired products in satisfactory yields. It is noteworthy that the chloro and bromo substituted substrates could survive under the optimized conditions. The reaction on the substrate with an electron-withdrawing subsituent, such as CF_3 (**4ka**) on the benzene ring, proceeded smoothly to provide the coupling product in 90% yield, although an increased catalyst loading was needed. Furthermore, the intramolecular cross-couping reactions on *N*-(2-bromobenzoxyl)-2,3-dimethylindoles (**4ab**–**4jb**) were also very effective to afford the desired products in excellent yields.

Next, we investigated the substituent effect at the 2- or 3-position of indole as illustrated in Scheme 3. We were pleased to find that all substrates in Scheme 3 could undergo the cross-coupling reaction under the optimized conditions, resulting in the corresponding products in moderate to excellent yields (**6a**–**7i**). Although steric hindrance at the C2 position of the 2-alkyl substituted indoles **6a** and **6b**

Scheme 2. Substrate Scope[a,b]



[a] Reaction conditions: **4** (0.5 mmol), $Pd(OAc)_2$ (2 mol %), AgOAc (0.5 mmol), and $Na_2HPO_4 \cdot 12H_2O$ (1 mmol) in DMF (2.0 mL) at 80 °C for 12 h. [b] Isolated yield. [c] 120 °C. [d] $Pd(OAc)_2$ (10 mol %) was used. [e] $Pd(OAc)_2$ (5 mol %) was used.

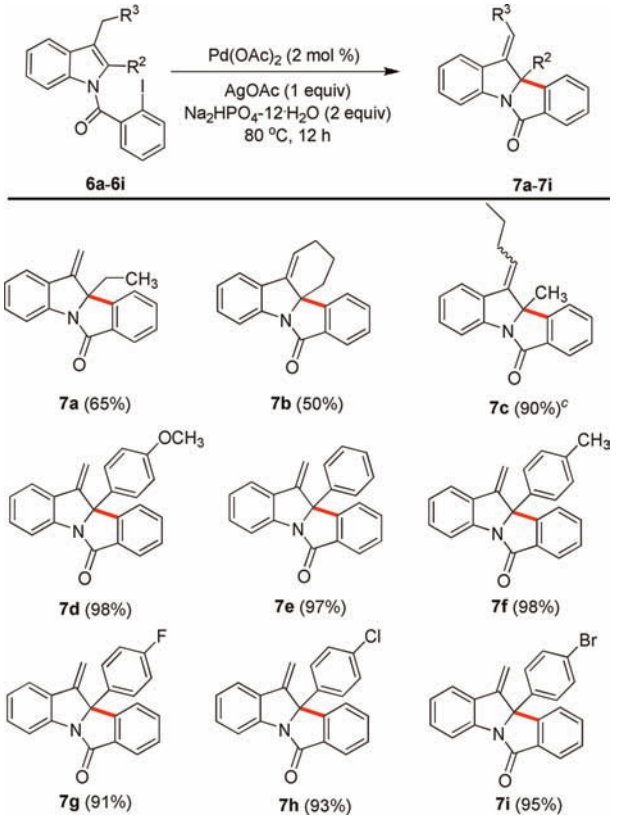
resulted in lower yields of the correspoding products (**7a**, **7b**), steric hindrance at the C3 position exhibited little influence on the reaction yield (**7c**). It should be noted that all 2-phenyl substrates reacted very smoothly to furnish the desired fused indolines (**7d**–**7i**) in excellent yields, despite different types of substituents being introduced on this phenyl ring.

According to the fact that the combination of $Pd(OAc)_2$ and the phosphine ligand worked well for this palladium-catalyzed intramolecular cross-coupling reaction, we proposed that our protocol might be initiated by Pd(0) species as outlined in Scheme 4.[14c,16] First, oxidative addition of

(15) See the Supporting Information.

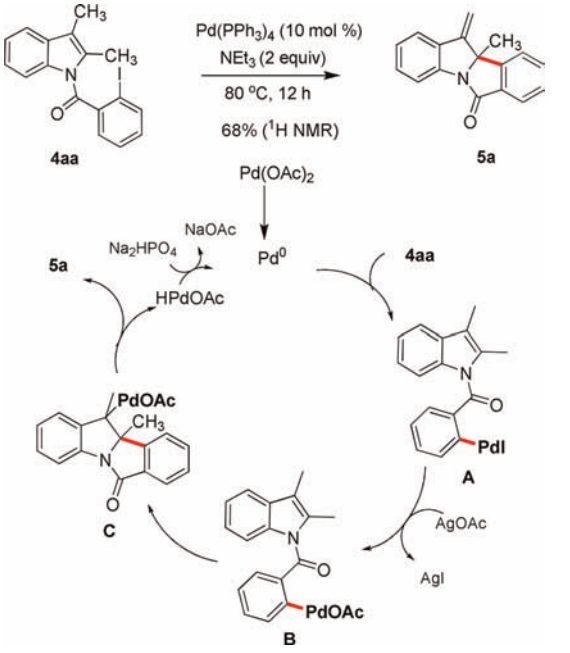
(16) For selected review, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. For selected examples, see: (b) Magill, A. M.; McGuinness, D. S.; Cacell, K, J; Britovsek, G. J. P; Gibson, V. C.; White, A. J. P.; William, D. J.; White, A. H.; Skelton, B. W. *J. Organomet. Chem.* **2001**, *617–618*, 546. (c) Liu, H.; Chen, C.; Wang, L.; Tong, X. *Org. Lett.* **2011**, *13*, 5072.

Scheme 3. Substrate Scope[a,b]



[a] Reaction conditions: **6** (0.5 mmol), $Pd(OAc)_2$ (2 mol %), AgOAc (0.5 mmol) and $Na_2HPO_4 \cdot 12H_2O$ (1 mmol) in DMF (2.0 mL) at 80 °C for 12 h. [b] Isolated yield. [c] Inseperable mixture, E/Z = 10:1 (determined by ^1H NMR and NOE).[15]

Scheme 4. Plausible Mechanism



the Pd(0) species to substrate **4aa** forms Pd(II) intermediate **A** (Ar−PdI), followed by a silver-mediated anion exchange to generate Pd(II) intermediate **B** (Ar-PdOAc). Next, intramolecular coordination of the olefin of the indole part to the palladium center and transmetallation provide intermediate **C**. Finally, **C** undergoes a reductive elimination to afford the desired product **5a** and HPdOAc, which is neutralized with base to give Pd(0) to complete the catalytic cycle.

In conclusion, we have demonstrated a highly efficient approach to construct fused indolines with a newly formed C2-quaternary center and 3-*exo* double bond via an intramolecular Heck reaction with a low catalyst loading. This transformation is effective for 2,3-disubstituted indoles with good functional group tolerance. We anticipate that this methodology would find many applications in the synthesis of complex natural products. Research on the detailed reaction mechanism, extension to other heteroaromatic substrates, and enantioselective synthesis of this protocol are currently underway in our laboratory.

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Supporting Information Available. Experimental procedures and characterization of all title compounds (**5a**−**5k**, **7a**−**7i**). This material is available free of charge via Internet at http://pubs.acs.org.

The authors declare no competing financial interest.