Synthesis of Spiroindanyl-2-oxindoles via PPA-mediated Intramolecular Friedel–Crafts Reaction

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Spirooxindoles are found in numerous biologically interesting synthetic and natural substances.[1] As a result, various synthetic methods of spirooxindoles have been developed.[1,2] Recently, many spirooxindoles bearing indane or indene moieties have been reported.[3,4] As shown in Scheme 1, spiroindanyl-2-oxindole **3a** has been synthesized by Pd or Cu-catalyzed intramolecular coupling of acetanilide derivatives,[3a–c] trifluoroacetic acid-promoted double intramolecular arylation of α-ketoanilides,[3d] Pd-catalyzed domino carbopalladation/C–C bond forming process of *N*-arylacrylamides,[3e,f] and other methods.[3g–l]

Recently, we reported the synthesis of spirooxindoles[5a] and 3-aryl-2-oxindoles[2d,5b] from isatin-derived propargylic alcohol **1a**. As a continuous study, we reasoned out that catalytic hydrogenation of the triple bond of **1a** would provide 3-phenylethyl-2-oxindole **2a**, which could be converted to spiroindanyl-2-oxindole **3a** by intramolecular Friedel–Crafts (IMFC) reaction,[6–8] as shown in Scheme 1. Zhu and co-workers reported the synthesis of **3a** by applying the above-mentioned trifluoroacetic acid-promoted double intramolecular arylation of α-ketoanilides; however, the yield was low (34%).[3d] The intermediate in their synthesis of **3a** was reported as 3-phenylethyl-2-oxindole **2a**. In these respects, we decided to examine the synthesis of **3a** by the IMFC reaction of readily available **2a**.

The required starting material **2a** was prepared from **1a** in high yield (98%) under H_2 balloon atmosphere in EtOAc in the presence of Pd/C (10%, *w*/*w*), according to the reported method.[9] In order to find an optimum condition, we examined the reaction of **2a** in the presence of various acid catalysts, as shown in Table 1. The reaction of **2a** in the presence of CF_3COOH (entry 1)[3d] gave **3a** in low yield (37%). The reaction in the presence of CF_3SO_3H (entry 2) in 1,2-dichloroethane (DCE) afforded **3a** in a slightly improved yield (43%). The use of H_2SO_4 (entry 3) was not effective. When we used polyphosphoric acid (PPA) as a reaction medium, the yield of **3a** increased to 47% (entry 4).[8] The best yield of **3a** (68%) was obtained when we use PPA (500%, *w*/*w*) in refluxing DCE (entry 5).[10] It is interesting to note that the reaction was completely ineffective in CH_3CN (entry 6) and less effective in benzene (entry 7). The use of $Bi(OTf)_3$ (entry 8) or $Yb(OTf)_3$ (entry 9) was inefficient. The use of montmorillonite K-10 (entry 10) was less effective.

Encouraged by the successful results, various spirooxindoles **3b–3l** were synthesized from 3-arylethyl-2-oxindoles **2b–2l** under the optimized condition (entry 5 in Table 1), and the results are summarized in Table 2. The reactions of 5-methyl-, 5-chloro-, 6-chloro-, and 5,7-dimethylisatin derivatives **2b–2e** provided the corresponding spirooxindoles **3b–3e** in good yields (73–90%). Similarly, the reactions of **2f–2i** bearing 4-methylphenyl group (Ar = 4-MeC_6H_4) afforded **3f–3i** in good yields (75–91%). The reactions of 3-methoxyphenyl derivatives **2j** and **2k** (Ar = 3-$MeOC_6H_4$) provided **3j** (71%) and **3k** (62%) in moderate yields.[11] *N*-Unsubstituted spirooxindole **3l** could also be synthesized in moderate yield (63%) by using the NH derivative **2l**. It is interesting to note that the reactions of 5-chloroisatin derivatives **2c**, **2g**, and **2k** required a slightly longer reaction time (2 h).

As shown in Scheme 2, spirooxindole **3a** could also be synthesized by IMFC reaction of the chloride derivative **4**, which was prepared readily by treatment of **2a** with $SOCl_2$,[12] under the influence of PPA in high yield (84%). However, a longer reaction time (15 h) was required for the completion.

As a next experiment, the thionation of **3a** with Lawesson's reagent (LR) was examined, as shown in Scheme 3.[2a,b] The reaction of **3a** and LR (2.5 equiv.) in refluxing toluene afforded spirothiooxindole **5a** in high yield (96%) in short time (1 h). Similarly, **5c** was obtained in high yield (95%). We also examined the synthesis of spiroindenyl-2-oxindole **6a** from **3a**, as also shown in Scheme 3.[4] The dehydrogenation of **3a** was carried out in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 4.0 equiv.)[13] in 1,2-dichlorobenzene (ODCB) for 2 h, albeit in low yield (34%).[14] Similarly, compound **6c** was obtained in a similar yield (35%).

In summary, various spiroindanyl-2-oxindoles have been synthesized via PPA-mediated intramolecular Friedel–Crafts reaction of 3-arylethyl-2-oxindoles. 3-Arylethyl-2-oxindoles were prepared by catalytic hydrogenation of the propargylic alcohols derived from *N*-methylisatins.

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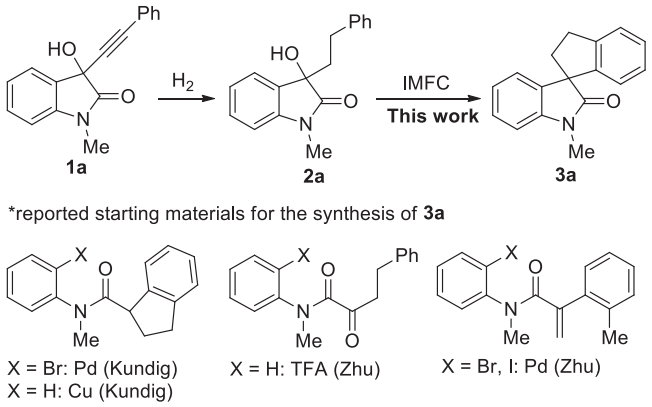


Scheme 1. Synthetic rationale of spiroindanyl-2-oxindole.

Experimental

Typical procedure for the synthesis of 3a. To a stirred solution of **2a** (134 mg, 0.5 mmol) in DCE (2.0 mL) was added PPA (670 mg, 500%, *w*/*w*), and the reaction mixture was heated to reflux for 1 h. After the usual aqueous extractive workup and column chromatographic purification process (*n*-hexane/CH_2Cl_2/Et_2O, 10:5:2), compound **3a** was isolated as a pale yellow solid, 85 mg (68%).[3a–d] Other compounds were synthesized similarly, and the selected spectroscopic data of **3b**, **3e**, **3l**, and **5a** are as follows.

Compound **3b**[3d]: 73%; yellow oil; IR (film) 1705, 1497, 1346 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.31 (s, 3H), 2.38–2.48 (m, 1H), 2.67–2.76 (m, 1H), 3.20–3.30 (m, 1H), 3.28 (s, 3H), 3.42–3.52 (m, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 6.90 (s, 1H), 7.08–7.15 (m, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 26.5, 31.8, 37.9, 60.3, 107.7, 123.4, 124.2, 125.0, 126.9, 127.9, 128.4, 132.4, 134.7, 141.2, 144.3, 145.0, 179.6; ESIMS *m*/*z* 264 $[M + H]^+$. Anal. calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.94; H, 6.75; N, 5.28.

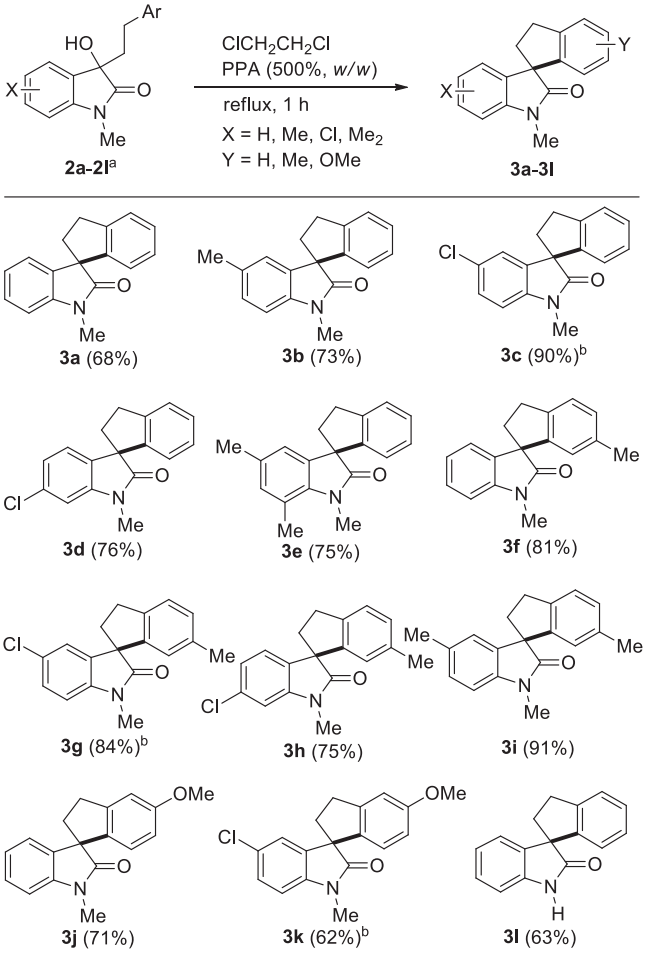
Compound **3e**: 75%; yellow solid, mp 102–104°C; IR (KBr) 1703, 1375, 1341 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.23 (s, 3H), 2.32–2.42 (m, 1H), 2.61 (s, 3H), 2.63–2.72 (m, 1H), 3.16–3.26 (m, 1H), 3.37–3.49 (m, 1H), 3.53 (s, 3H), 6.70 (d, *J* = 7.5 Hz, 1H), 6.70 (s, 1H), 6.84 (s, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 18.9, 20.8, 29.7, 31.8, 38.4, 59.8, 119.2, 122.1, 123.4, 124.9, 126.8, 127.8, 132.26, 132.27, 135.5, 138.8, 144.6,

Table 1. Optimization of reaction conditions for the synthesis of **3a**.

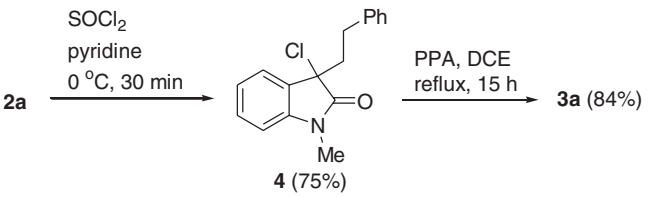
Entry	Conditions[a]	**3a** (%)[b]
1	CF_3COOH, reflux, 2 h	37
2	$ClCH_2CH_2Cl$, CF_3SO_3H (10 equiv.), 0°C, 1 h	43
3	$ClCH_2CH_2Cl$, H_2SO_4 (10 equiv.), rt, 1 h	<5
4	PPA, 80°C, 2 h	47
5	$ClCH_2CH_2Cl$, PPA (500%, *w*/*w*), reflux, 1 h	68
6	CH_3CN, PPA (500%, *w*/*w*), reflux, 1 h	0
7	Benzene, PPA (500%, *w*/*w*), reflux, 1 h	44
8	$ClCH_2CH_2Cl$, Bi(OTf)$_3$ (10 mol%), reflux, 2 h	0
9	CH_3NO_2, Yb(OTf)$_3$ (10 mol%), 80°C, 2 h	0
10	Toluene, K-10 (500%, *w*/*w*), reflux, 3 h	14

[a] **2a** (0.5 mmol).
[b] Isolated yield.

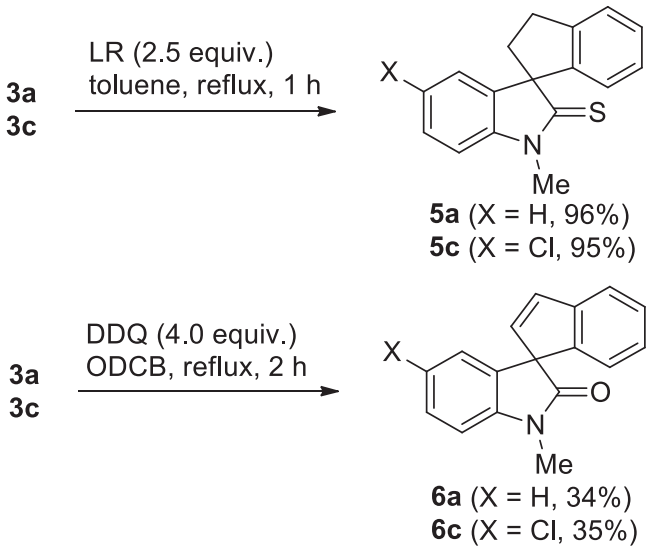
Table 2. Synthesis of spiroindanyl-2-oxindole.



[a] Substrate (0.5 mmol): **2a**: X = H, Ar = Ph; **2b**: X = 5-Me, Ar = Ph; **2c**: X = 5-Cl, Ar = Ph; **2d**: X = 6-Cl, Ar = Ph; **2e**: X = 5,7-Me_2, Ar = Ph; **2f**: X = H, Ar = 4-MeC_6H_4; **2g**: X = 5-Cl, Ar = 4-MeC_6H_4; **2h**: X = 6-Cl, Ar = 4-MeC_6H_4; **2i**: X = 5-Me, Ar = 4-MeC_6H_4; **2j**: X = H, Ar = 3-$MeOC_6H_4$; **2k**: X = 5-Cl, Ar = 3-$MeOC_6H_4$; **2l**: NH derivative of **2a**.
[b] Reaction time was 2 h.



Scheme 2. Synthesis of **4** and its IMFC reaction.



Scheme 3. Synthesis of **5** and **6**.

145.0, 180.3; ESIMS *m/z* 278 $[M + H]^+$. Anal. calcd for $C_{19}H_{19}NO$: C, 83.28; H, 6.90; N, 5.05. Found: C, 83.19; H, 7.01; N, 4.84.

Compound **3l**: 63%; yellow solid, mp 204–206°C; IR (KBr) 3211, 1702, 1618, 1470 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.40–2.50 (m, 1H), 2.70–2.79 (m, 1H), 3.18–3.28 (m, 1H), 3.40–3.50 (m, 1H), 6.76 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 7.01–7.04 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.19–7.28 (m, 2H), 7.38 (d, *J* = 7.5 Hz, 1H), 8.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.7, 37.9, 60.6, 109.6, 122.9, 123.4, 123.8, 125.0, 127.0, 128.0, 128.1, 135.2, 140.5, 143.9, 145.0, 181.7; ESIMS *m/z* 236 $[M + H]^+$. Anal. calcd for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.40; H, 5.77; N, 5.89.

Compound **5a**: 96%; white solid, mp 102–104°C; IR (KBr) 1610, 1463, 1428, 1361, 1309 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.42–2.52 (m, 1H), 2.77–2.87 (m, 1H), 3.23–3.32 (m, 1H), 3.51–3.61 (m, 1H), 3.71 (s, 3H), 6.55 (d, *J* = 7.7 Hz, 1H), 7.03–7.15 (m, 4H), 7.23 (td, *J* = 7.5, 1.1 Hz, 1H), 7.31–7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 31.6, 31.8, 41.7, 71.0, 109.3, 123.5, 123.6, 124.5, 124.9, 127.0, 127.9, 128.1, 139.6, 144.2, 144.6, 146.3, 210.0; ESIMS *m/z* 266 $[M + H]^+$. Anal. calcd for $C_{17}H_{15}NS$: C, 76.94; H, 5.70; N, 5.28. Found: C, 77.07; H, 5.90; N, 5.03.

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Supporting Information. Additional supporting information including experimental procedure and spectroscopic data is available in the online version of this article.

References

1. For reviews on spirooxindoles, see: (a) B. Yu, D.-Q. Yu, H.-M. Liu, *Eur. J. Med. Chem.* **2015**, *97*, 673; (b) M. M. M. Santos, *Tetrahedron* **2014**, *70*, 9735; (c) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas III. , *ACS Catal.* **2014**, *4*, 743; (d) L. Hong, R. Wang, *Adv. Synth. Catal.* **2013**, *355*, 1023; (e) G. S. Singh, Z. Y. Desta, *Chem. Rev.* **2012**, *112*, 6104; (f) N. R. Ball-Jones, J. J. Badillo, A. K. Franz, *Org. Biomol. Chem.* **2012**, *10*, 5165; (g) B. M. Trost, M. K. Brennan, *Synthesis* **2009**, 3003; (h) C. Marti, E. M. Carreira, *Eur. J. Org. Chem.* **2003**, 2209; (i) R. Moradi, G. M. Ziarani, N. Lashgari, *Arkivoc* **2017**, *i*, 148.
2. For our recent synthesis of spirooxindoles, see: (a) K. H. Kim, H. R. Moon, J. Lee, J. Kim, J. N. Kim, *Adv. Synth. Catal.* **2015**, *357*, 1532; (b) K. H. Kim, H. R. Moon, J. Lee, J. N. Kim, *Adv. Synth. Catal.* **2015**, *357*, 701; (c) J. W. Lim, H. R. Moon, S. Y. Kim, J. N. Kim, *Tetrahedron Lett.* **2016**, *57*, 133; (d) H. J. Roh, J. W. Lim, J. Y. Ryu, J. Lee, J. N. Kim, *Tetrahedron Lett.* **2016**, *57*, 4280; (e) S. Y. Kim, H. J. Roh, D. Y. Seo, J. Y. Ryu, J. Lee, J. N. Kim, *Tetrahedron Lett.* **2017**, *58*, 914.
3. For spirooxindoles bearing indane moiety, see: (a) Y.-X. Jia, E. P. Kundig, *Angew. Chem. Int. Ed.* **2009**, *48*, 1636; (b) Y.-X. Jia, D. Katayev, G. Bernardinelli, T. M. Seidel, E. P. Kundig, *Chem. Eur. J.* **2010**, *16*, 6300; (c) D. Katayev, Y.-X. Jia, A. K. Sharma, D. Banerjee, C. Besnard, R. B. Sunoj, E. P. Kundig, *Chem. Eur. J.* **2013**, *19*, 11916; (d) I. Gorokhovik, L. Neuville, J. Zhu, *Org. Lett.* **2011**, *13*, 5536; (e) T. Piou, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2012**, *51*, 11561; (f) T. Piou, A. Bunescu, Q. Wang, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12385; (g) M. Perez-Gomez, S. Hernandez-Ponte, D. Bautista, J.-A. Garcia-Lopez, *Chem. Commun.* **2017**, *53*, 2842; (h) J.-N. Desrosiers, L. Hie, S. Biswas, O. V. Zatolochnaya, S. Rodriguez, H. Lee, N. Grinberg, N. Haddad, N. K. Yee, N. K. Garg, C. H. Senanayake, *Angew. Chem. Int. Ed.* **2016**, *55*, 11921; (i) Z. Yu, H. Qiu, L. Liu, J. Zhang, *Chem. Commun.* **2016**, *52*, 2257; (j) M. Gasonoo, D. A. Klumpp, *Tetrahedron Lett.* **2015**, *56*, 4737; (k) S. Chowdhury, M. Chafeev, S. Liu, J. Sun, V. Raina, R. Chui, W. Young, R. Kwan, J. Fu, J. A. Cadieux, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3676; (l) G. N. Walker, D. Alkalay, R. T. Smith, *J. Org. Chem.* **1965**, *30*, 2973.
4. For spirooxindoles-bearing indene moiety, see: (a) D. Basavaiah, K. R. Reddy, *Org. Lett.* **2007**, *9*, 57; (b) H.-Y. Huang, L. Cheng, J.-J. Liu, D. Wang, L. Liu, C.-J. Li, *J. Org. Chem.* **2017**, *82*, 2656; (c) T. Saito, Y. Sonoki, T. Otani, N. Kutsumura, *Org. Biomol. Chem.* **2014**, *12*, 8398.
5. For our recent synthetic applications of isatin-derived propargylic alcohols, see: (a)H. J. Roh, S. Y. Kim, B. K. Min, J. N. Kim, *Tetrahedron Lett.* **2017**, *58*, 21; (b) H. J. Roh, D. Y. Seo, J. Y. Ryu, J. Lee, J. N. Kim, *Bull. Korean Chem. Soc.* **2017**, *38*, 582.
6. For our selected papers on IMFC reaction, see: (a) J. Yu, S. Lee, H. R. Moon, J. N. Kim, *Bull. Korean Chem. Soc.* **2015**, *36*, 1990; (b) B. R. Park, S. H. Kim, Y. M. Kim, J. N. Kim, *Tetrahedron Lett.* **2011**, *52*, 1700; (c) K. H. Kim, H. S. Lee, J. N. Kim, *Tetrahedron Lett.* **2009**, *50*, 1249; (d) S. Gowrisankar, K. Y. Lee, C. G. Lee, J. N. Kim, *Tetrahedron Lett.* **2004**, *45*, 6141.

7. For synthesis of spirooxindoles by Friedel-Crafts approach, see: (a) N. Kumarswamyreddy, V. Kesavan, *Eur. J. Org. Chem.* **2016**, 5301; (b) M. Luo, R. Yuan, X. Liu, L. Yu, W. Wei, *Chem. Eur. J.* **2016**, *22*, 9797; (c) X. Zhao, X. Liu, Q. Xiong, H. Mei, B. Ma, L. Lin, X. Feng, *Chem. Commun.* **2015**, *51*, 16076; (d) S. Muthusamy, M. Prakash, C. Ramakrishnan, M. M. Gromiha, V. Kesavan, *ChemCatChem* **2016**, *8*, 1708.
8. For PPA-catalyzed IMFC reaction, see: (a) H. R. Moon, S. Y. Kim, J. W. Lim, J. N. Kim, *Bull. Korean Chem. Soc.* **2015**, *36*, 2773; (b) H. R. Moon, J. Yu, K. H. Kim, J. N. Kim, *Bull. Korean Chem. Soc.* **2015**, *36*, 1189; (c) K. H. Kim, S. H. Kim, K. Y. Lee, J. N. Kim, *Bull. Korean Chem. Soc.* **2011**, *32*, 1387; (d) W. Gao, X. Xing, Y. Li, S. Lan, *Tetrahedron* **2014**, *70*, 2180; (e) W. Gao, G. Lin, Y. Li, X. Tao, R. Liu, L. Sun, *Beil. J. Org. Chem.* **2012**, *8*, 1849.
9. N. Xu, D.-W. Gu, J. Zi, X.-Y. Wu, X.-X. Guo, *Org. Lett.* **2016**, *18*, 2439.
10. In the reaction, an acid-catalyzed dehydration reaction occurred to some extent and *N*-methyl-3-phenylethylidene-2-oxindole was isolated in low yield (5%). The amount of PPA was not critical in the reaction. Actually, the yield of **3a** was similar (64–68%) with variable amounts of PPA (50–1000%, *w*/*w*) in refluxing DCE; however, a longer reaction time (3 h) was required when we use small amount of PPA (50%, *w*/*w*).
11. Based on the ^{1}H NMR spectra of **3j** and **3k**, a small amount (ca. 5%) of the corresponding regioisomer was contaminated.
12. For chlorination of similar compounds with thionyl chloride, see: (a) S. Ma, X. Han, S. Krishnan, S. C. Virgil, B. M. Stoltz, *Angew. Chem. Int. Ed.* **2009**, *48*, 8037; (b) P. Magnus, R. Turnbull, *Org. Lett.* **2006**, *8*, 3497.
13. For dehydrogenation of similar compounds with DDQ, see: (a) T. Thiemann, M. Watanabe, S. Mataka, *New J. Chem.* **2001**, *25*, 1104; (b) Y.-S. Chung, H. Kruk, O. M. Barizo, M. Katz, E. Lee-Ruff, *J. Org. Chem.* **1987**, *52*, 1284.
14. The dehydrogenation was slow below 170°C. In addition, compound **6a** was somewhat unstable under the condition, and it was decomposed slowly into intractable polar compounds. The synthesis of **6a** by Pd/C-catalyzed dehydrogenation was ineffective even at high temperature (diphenyl ether, reflux).

