An Expedient Synthesis of Pyrrolo[3,2,1-*ij*]quinoline-1,2-diones via Intramolecular Friedel–Crafts Cyclization Protocol

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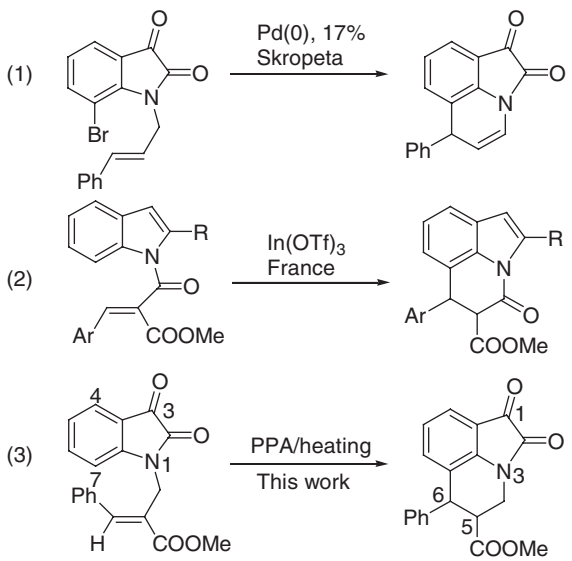
The pyrrolo[3,2,1-*ij*]quinolines and their reduced or oxidized derivatives have received much attention due to their diverse biological functions including analgesic, anti-inflammatory, anti-epileptic, and anticancer activities.[1–3] In spite of the broad applicability and rising interest from synthetic chemists, the reported methods for the preparation of pyrrolo[3,2,1-*ij*] quinolines are rather scarce.[1–3] Recently, Skropeta and co-workers reported the synthesis of pyrrolo[3,2,1-*ij*]quinoline-1,2-diones via a palladium-catalyzed C_7-*N* annulation of 7-bromo-*N*-substituted isatins (Scheme 1, Eq. 1).[2a] However, the yields were very low (8–39%). France *et al*. reported the synthesis of pyrrolo[3,2,1-*ij*]quinolin-4-ones via an $In(OTf)_3$-mediated intramolecular Friedel–Crafts (IMFC) approach (Scheme 1, Eq. 2).[2b]

During our recent interest in IMFC reactions[4] and the chemical transformations of isatin derivatives,[5] we reasoned out that pyrrolo[3,2,1-*ij*]quinoline-1,2-diones could be prepared via an IMFC approach as shown in Scheme 1 (Eq. (3)). We expected that the IMFC reaction would proceed under suitable reaction condition although the benzene ring of isatin moiety is deactivated because of the presence of an electron-withdrawing carbonyl group. To the best of our knowledge, there is no report on inter- and intramolecular Friedel–Crafts alkylation of isatins.

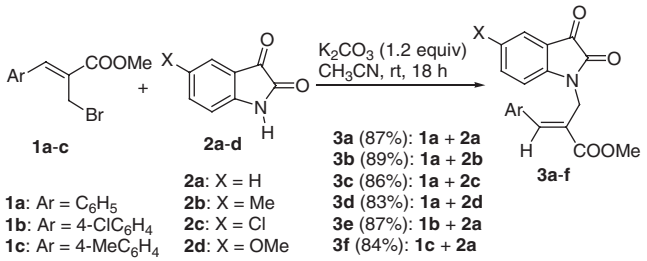


Scheme 1. Synthesis of pyrrolo[3,2,1-*ij*]quinoline.

The starting materials **3a–f** were prepared from Morita–Baylis–Hillman (MBH) bromides **1** and isatins **2** in the presence of K_2CO_3 in CH_3CN at room temperature, as shown in Scheme 2.[6,7] The yields of **3a–f** were good (83–89%).

Initially, we examined the IMFC reaction of **3a** in polyphosphoric acid (PPA)[8] at 90 °C. To our delight, pyrrolo[3,2,1-*ij*] quinoline-1,2-dione **4a** was obtained in good yield (68%) along with Friedel–Crafts acylation product **5a** in low yield (15%). Compound **4a** was formed diastereoselectively, and the relative stereochemistry between the substituents at 5- and 6-positions would be a trans relationship, as France and co-workers reported in a similar IMFC reaction.[2b] On exposure of **4a** to PPA for a long time, a slow decomposition to intractable polar compounds was observed. The decomposition was accelerated at elevated temperature (120 °C) in PPA presumably by the cleavage of the amide bond of the isatin moiety. The 6,5,6-tricyclic ring system of **4a** was somewhat strained,[2a,c] thus an amide bond cleavage of the isatin moiety could proceed under the acidic conditions.[9] The reaction of **3a** in the presence of H_2SO_4 (5.0 equiv) in 1,2-dichloroethane (reflux, 2 h) was ineffective. The formation of **4a** was observed on TLC; however, both **3a** and **4a** were decomposed rapidly to intractable polar compounds. The use of CH_3SO_3H and $AlCl_3$ were also ineffective.

Thus, the IMFC reactions of **3b–f** were carried out in PPA (90 °C), and the results are summarized in Table 1. The reactions of **3b** (entry 2), **3e** (entry 5), and **3f** (entry 6) showed



Scheme 2. Preparation of starting materials.

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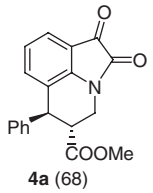
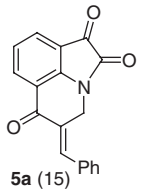
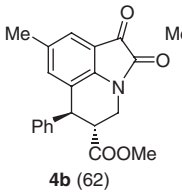
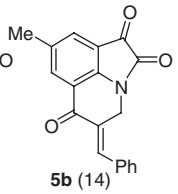
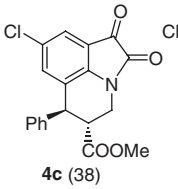
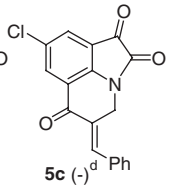
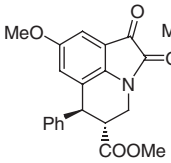
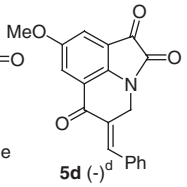
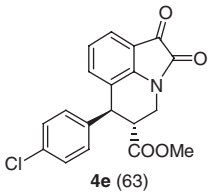
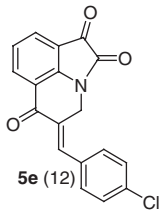
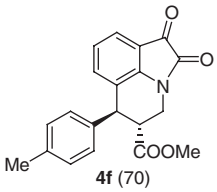
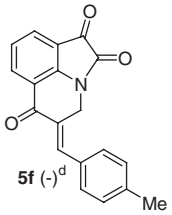
Table 1. Synthesis of pyrrolo[3,2,1-*ij*]quinolines **4a-4f**.[a]

Entry	Substrate	Time (h)	Products (%)
1	**3a**	4	 **4a** (68)  **5a** (15)
2	**3b**	4	 **4b** (62)  **5b** (14)
3[b]	**3c**	9	 **4c** (38)  **5c** (-)[d]
4[c]	**3d**	2	 **4d** (42)  **5d** (-)[d]
5	**3e**	4	 **4e** (63)  **5e** (12)
6	**3f**	4	 **4f** (70)  **5f** (-)[d]

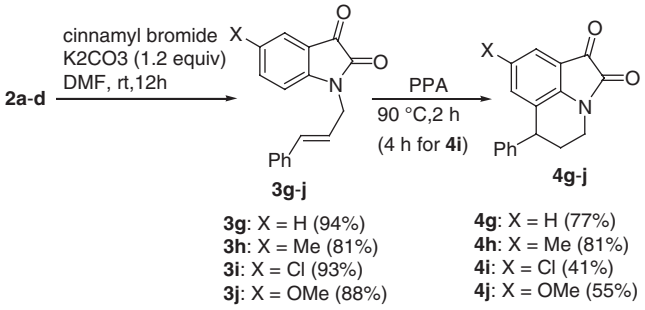
[a] Substrate **3** (0.5 mmol) was used in PPA (1.0 g) at 90 °C for given time.
[b] Compound **3c** (9%) was recovered.
[c] Compound **3d** (12%) was recovered.
[d]Compounds **5c**, **5d** and **5f** were not isolated in appreciable amounts.

similar reactivity as that of **3a**, and the corresponding products **4b**, **4e**, and **4f** were obtained in good yields (62–70%). However, the reaction of 5-chloroisatin derivative **3c** (entry 3) showed somewhat sluggish reactivity, and **4c** was obtained in low yield (38%) for 9 h. When we increased the reaction time, the yield of **4c** decreased because of decomposition to polar side products. The situation was similar for 5-methoxyisatin derivative **3d** (entry 4), and compound **4d** was obtained in low yield (42%). The Friedel–Crafts acylation products **5b** (entry 2) and **5e** (entry 5) were isolated in low yields; however, **5c**, **5d**, and **5f** could not be isolated in appreciable amount.

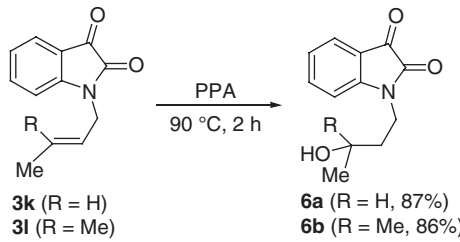
As a next entry, we prepared **3g–j** by the alkylation of isatins **2a–d** with cinnamyl bromide, as shown in Scheme 3. The reactions of **3g–j** under the standard condition (PPA, 90 °C) afforded **4g–j** in good to moderate yields (41–81%). As we observed for the synthesis of **4c** and **4d** (entries 3 and 4 in Table 1), the yields of **4i** and **4j** were relatively low compared to the other products **4g** and **4h**.

In contrast to *N*-cinnamyl derivatives **3g–j**, unfortunately, the reactions of *N*-(but-2-enyl)isatin (**3k**) and *N*-(3-methylbut-2-enyl)isatin (**3l**) failed to afford the corresponding IMFC reaction products, as shown in Scheme 4. Under the typical reaction condition, hydration products **6a** and **6b** were formed in good yields (87 and 86%, respectively). The reactions of **3k** and **3l** in PPA at elevated temperature (120 °C, 4 h) showed complete decomposition to intractable polar compounds.

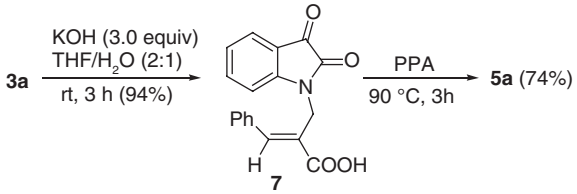
5-Benzylidenepyrrolo[3,2,1-*ij*]quinoline-1,2,6-trione derivative **5a** could be synthesized as a major product by using the carboxylic acid derivative of **3a**, as shown in Scheme 5. Base hydrolysis of **3a** afforded **7** in good yield (94%), and



Scheme 3. Synthesis of pyrrolo[3,2,1-*ij*]quinolines **4g-j**.



Scheme 4. Trials of IMFC reaction of **3k** and **3l**.



Scheme 5. Selective synthesis of **5a**.

the IMFC reaction of **7** gave **5a** as the sole product (74%). The corresponding Friedel–Crafts alkylation product was not formed in the reaction, and the result showed that Friedel–Crafts acylation is more effective than the alkylation with the carboxylic acid derivative **7**.

In summary, the first successful IMFC cyclization of *N*-cinnamylisatin derivatives in PPA provided pyrrolo[3,2,1-*ij*] quinoline-1,2-diones in good to moderate yields. The electron-deficient benzene ring of isatin could be used effectively in the IMFC reaction in PPA, although some restrictions are still present.

Experimental

The starting materials **3a–l** were prepared according to the reported method,[5a,5b,7] and the spectroscopic data of the unknown compounds are reported in Supporting Information.

Typical Procedure for the Synthesis of 4a and 5a. A mixture of **3a** (161 mg, 0.5 mmol) and PPA (1.0 g) was heated to 90 °C for 4 h. After the usual aqueous extractive work-up and column chromatographic purification process (hexanes/CH_2Cl_2/Et_2O, 10:10:1), compounds **4a** (110 mg, 68%) and **5a** (22 mg, 15%) were isolated as orange solids. Other compounds were synthesized similarly, and the selected spectroscopic data of **4a–d**, **4g**, **5a**, and **5b** are as follows:

Compound 4a: 68%; orange solid, m.p. 186–188 °C; IR (KBr) 1740, 1626, 1603, 1474 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.14 (ddd, J = 7.2, 6.6 and 4.2 Hz, 1H), 3.61 (s, 3H), 3.89 (dd, J = 13.2 and 4.2 Hz, 1H), 4.03 (dd, J = 13.2 and 7.2 Hz, 1H), 4.52 (d, J = 6.6 Hz, 1H), 7.02 (t, J = 7.2 Hz, 1H), 7.12–7.16 (m, 3H), 7.31 (t, J = 7.2 Hz, 1H), 7.34–7.39 (m, 2H), 7.48 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 38.05, 43.19, 44.99, 52.51, 115.60, 122.43, 123.80, 123.93, 127.78, 128.45, 129.02, 137.80, 140.07, 146.58, 156.69, 171.42, 183.18; ESIMS *m/z* 322 [M^++H]. Anal. Calcd. for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.91; H, 4.93; N, 4.18.

Compound 4b: 62%; orange solid, m.p. 182–184 °C; IR (KBr) 1740, 1624, 1489, 1349 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H), 3.10 (ddd, J = 6.6, 6.3 and 4.2 Hz, 1H), 3.60 (s, 3H), 3.80 (dd, J = 13.5 and 4.2 Hz, 1H), 4.04 (dd, J = 13.5 and 6.6 Hz, 1H), 4.49 (d, J = 6.3 Hz, 1H), 6.96 (s, 1H), 7.09–7.16 (m, 2H), 7.26–7.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.94, 37.78, 43.01, 45.16, 52.51, 115.63, 122.01, 124.36, 127.72, 128.43, 129.00, 133.74, 138.15, 140.33, 144.47, 156.79, 171.50, 183.44; ESIMS *m/z* 336 [M^+ + H]. Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.81; H, 5.30; N, 4.11.

Compound 4c: 38%; orange solid, m.p. 214–216 °C; IR (KBr) 1744, 1621, 1602, 1476 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.15 (ddd, J = 6.9, 6.6 and 4.2 Hz, 1H), 3.64 (s, 3H), 3.86 (dd, J = 13.5 and 4.2 Hz, 1H), 4.07 (dd, J = 13.5 and 6.9 Hz, 1H), 4.52 (d, J = 6.6 Hz, 1H), 7.10–7.17 (m, 3H), 7.31–7.44 (m, 3H), 7.47 (d, J = 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.94, 42.97, 44.79, 52.65, 116.36, 123.92, 124.11, 128.07, 128.35, 129.21, 129.72, 137.07, 139.44, 144.97, 156.13, 171.14, 182.07; ESIMS *m/z* 356 [M^+ + H], 358 [M^++H + 2].

Compound 4d: 42%; red solid, m.p. 166–168 °C; IR (KBr) 1739, 1630, 1616, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.12 (ddd, J = 6.9, 6.6 and 4.2 Hz, 1H), 3.60 (s, 3H), 3.71 (s, 3H), 3.83 (dd, J = 13.2 and 4.2 Hz, 1H), 4.01 (dd, J = 13.2 and 6.9 Hz, 1H), 4.48 (d, J = 6.6 Hz, 1H), 6.71 (d, J = 2.4 Hz, 1H), 7.02 (d, J = 2.4 Hz, 1H), 7.10–7.16 (m, 2H), 7.26–7.39 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.91, 43.16, 45.25, 52.52, 55.92, 108.39, 115.89, 123.63, 124.20, 127.81, 128.44, 129.03, 139.96, 140.72, 156.66, 156.77, 171.42, 183.44; ESIMS *m/z* 352 [M^++H].

Compound 4g: 77%; orange solid, m.p. 137–139 °C; IR (KBr) 1737, 1601, 1473, 1353 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.09–2.24 (m, 1H), 2.26–2.39 (m, 1H), 3.68–3.86 (m, 2H), 4.14 (dd, J = 7.5 and 4.5 Hz, 1H), 6.97 (t, J = 7.5 Hz, 1H), 7.08–7.18 (m, 3H), 7.26–7.41 (m, 3H), 7.44 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 29.27, 36.72, 40.60, 115.75, 123.40, 123.55, 124.48, 127.33, 128.20, 128.92, 137.55, 141.92, 147.56, 156.85, 183.87; ESIMS *m/z* 264 [M^+ + H]. Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.51; H, 5.13; N, 5.19.

Compound 5a: 74%; orange solid, m.p. 198–200 °C; IR (KBr) 1744, 1663, 1619, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 5.13 (d, J = 2.4 Hz, 2H), 7.24 (dd, J = 8.4 and 7.2 Hz, 1H), 7.42 (d, J = 7.2 Hz, 2H), 7.46–7.53 (m, 3H), 7.78 (dd, J = 7.2 and 1.2 Hz, 1H), 8.00 (t, J = 2.4 Hz, 1H), 8.17 (dd, J = 8.4 and 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 41.91, 116.39, 117.31, 124.07, 126.03, 129.02, 130.27, 130.52, 130.75, 133.75, 135.35, 140.77, 152.02, 156.82, 179.99, 181.16; ESIMS *m/z* 290 [M^+ + H]. Anal. Calcd. for $C_{18}H_{11}NO_3$: C, 74.73; H, 3.83; N, 4.84. Found: C, 74.95; H, 4.01; N, 4.81.

Compound 5b: 14%; orange solid, m.p. 196–198 °C; IR (KBr) 1737, 1672, 1623, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H), 5.09 (d, J = 2.7 Hz, 2H), 7.37–7.53 (m, 5H), 7.58 (s, 1H), 7.94 (s, 1H), 7.97 (t, J = 2.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.92, 41.88, 116.48, 117.07, 126.32, 128.99, 130.20, 130.50, 131.54, 133.81, 134.26, 135.03, 140.53, 150.09, 156.91, 180.10, 181.39; ESIMS *m/z* 304 [M^++H].

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Supporting Information. Additional supporting information is available in the online version of this article.

References

1. For the synthesis and biological activity of pyrrolo[3,2,1-*ij*]quinolines and related compounds, see:(a) M. Layek, M. A. Reddy, A. V. D. Rao, M. Alvala, M. K. Arunasree, A. Islam,

K. Mukkanti, J. Iqbal, M. Pal, *Org. Biomol. Chem.* **2011**, *9*, 1004; (b) L. L. R. Rix, B. M. Kuenzi, Y. Luo, E. Remily-Wood, F. Kinose, G. Wright, J. Li, J. M. Koomen, E. B. Haura, H. R. Lawrence, U. Rix, *ACS Chem. Biol.* **2014**, *9*, 353; (c) H. S. Kim, M. G. Banwell, A. C. Willis, *J. Org. Chem.* **2013**, *78*, 5103; (d) D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M. J. Peck, D. Jasserand, *J. Med. Chem.* **1995**, *38*, 669; (e) M. Isaac, A. Slassi, A. O'Brien, L. Edwards, N. MacLean, D. Bueschkens, D. K. H. Lee, K. McCallum, I. D. Lannoy, L. Demchyshyn, R. Kamboj, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 919; (f) R. L. Dorow, P. M. Herrinton, R. A. Hohler, M. T. Maloney, M. A. Mauragis, W. E. McGhee, J. A. Moeslein, J. W. Strohbach, M. F. Veley, *Org. Process Res. Dev.* **2006**, *10*, 493; (g) R. S. Al-awar, J. E. Ray, K. A. Hecker, J. Huang, P. P. Waid, C. Shih, H. B. Brooks, C. D. Spencer, S. A. Watkins, B. R. Patel, N. B. Stamm, C. A. Ogg, R. M. Schultz, E. L. Considine, M. M. Faul, K. A. Sullivan, S. P. Kolis, J. L. Grutsch, S. Joseph, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3217.

2. For the synthetic approaches of pyrrolo[3,2,1-*ij*]quinolines, see: (a) L. Matesic, J. M. Locke, K. L. Vine, M. Ranson, J. B. Bremner, D. Skropeta, *Tetrahedron* **2012**, *68*, 6810; and further references cited therein; (b) D. V. Patil, M. A. Cavitt, P. Grzybowski, S. France, *Chem. Commun.* **2012**, *48*, 10337; (c) D. S. Black, P. A. Keller, N. Kumar, *Tetrahedron* **1992**, *48*, 7601; (d) D. S. Black, N. Kumar, P. S. R. Mitchell, *J. Org. Chem.* **2002**, *67*, 2464; (e) X.-F. Yang, X.-H. Hu, T.-P. Loh, *Org. Lett.* **2015**, *17*, 1481.
3. For the construction of pyrrolo[3,2,1-*ij*]quinoline-1,2-diones by using oxalyl chloride (Stolle isatin synthesis), ethyl glyoxalate, or carbon monoxide, see:(a) M. Shamsi, M. M. Baradarani, A. Afghan, J. A. Joule, *ARKIVOC* **2011**, *ix*, 252; (b) S. M. Medvedeva, M. Y. Krysin, F. I. Zubkov, E. V. Nikitina, K. S. Shikhaliev, *Chem. Heterocycl. Compd.* **2014**, *50*, 1280; (c) W. Li, Z. Duan, X. Zhang, H. Zhang, M. Wang, R. Jiang, H. Zeng, C. Liu, A. Lei, *Angew. Chem. Int. Ed.* **2015**, *54*, 1893; (d) T. Liu, H. Yang, Y. Jiang, H. Fu, *Adv. Synth. Catal.* **2013**, *355*, 1169.
4. For our recent reports on IMFC reactions, see:(a) H. R. Moon, J. Yu, K. H. Kim, J. N. Kim, *Bull. Korean Chem. Soc.* **2015**, *36*, 1189; (b) K. H. Kim, H. S. Lee, J. N. Kim, *Tetrahedron Lett.* **2009**, *50*, 1249; (c) B. R. Park, S. H. Kim, Y. M. Kim, J. N. Kim, *Tetrahedron Lett.* **2011**, *52*, 1700; (d) S. Gowrisankar, K. Y. Lee, C. G. Lee, J. N. Kim, *Tetrahedron Lett.* **2004**, *45*, 6141.
5. For our recent chemical transformations of isatin derivatives including palladium-catalyzed C_7-*N* annulations, see: (a) H. S. Lee, K. H. Kim, Y. M. Kim, J. N. Kim, *Bull. Korean Chem. Soc.* **2010**, *31*, 1761; (b) H. S. Lee, S. H. Kim, S. Gowrisankar, J. N. Kim, *Tetrahedron* **2008**, *64*, 7183; (c) S. C. Kim, K. Y. Lee, S. Gowrisankar, J. N. Kim, *Bull. Korean Chem. Soc.* **2006**, *27*, 1133; (d) S. C. Kim, S. Gowrisankar, J. N. Kim, *Tetrahedron Lett.* **2006**, *47*, 3463.
6. For the general review on Morita-Baylis-Hillman reaction, see: (a) D. Basavaiah, A. J. Rao, T. Satyanarayana, *Chem. Rev.* **2003**, *103*, 811; (b) D. Basavaiah, B. S. Reddy, S. S. Badsara, *Chem. Rev.* **2010**, *110*, 5447; (c) V. Singh, S. Batra, *Tetrahedron* **2008**, *64*, 4511; (d) V. Declerck, J. Martinez, F. Lamaty, *Chem. Rev.* **2009**, *109*, 1; (e) E. Ciganek, In *Organic Reactions*, Vol. *51*, L. A. Paquette Ed., John Wiley & Sons, New York, **1997**, p. 201; (f) J. N. Kim, K. Y. Lee, *Curr. Org. Chem.* **2002**, *6*, 627; (g) K. Y. Lee, S. Gowrisankar, J. N. Kim, *Bull. Korean Chem. Soc.* **2005**, *26*, 1481; (h) S. Gowrisankar, H. S. Lee, S. H. Kim, K. Y. Lee, J. N. Kim, *Tetrahedron* **2009**, *65*, 8769; (i) M. Shi, F.-J. Wang, M.-X. Zhao, Y. Wei, *The Chemistry of the Morita-Baylis-Hillman Reaction*, RSC Publishing, Cambridge, UK, **2011**.
7. (a) H. S. Lee, K. H. Kim, S. H. Kim, J. N. Kim, *Adv. Synth. Catal.* **2012**, *354*, 2419; (b) S. B. Kumar, M. Ravinder, G. Kishore, V. J. Rao, P. Yogeeswari, D. Sriram, *Med. Chem. Res.* **2014**, *23*, 1934.
8. For our recent contributions on Friedel-Crafts reactions in PPA, see:(a) C. G. Lee, K. Y. Lee, S. Gowrisankar, J. N. Kim, *Tetrahedron Lett.* **2004**, *45*, 7409; (b) C. G. Lee, K. Y. Lee, S. Lee, J. N. Kim, *Tetrahedron* **2005**, *61*, 1493; (c) K. H. Kim, S. H. Kim, K. Y. Lee, J. N. Kim, *Bull. Korean Chem. Soc.* **2011**, *32*, 1387; (d) S. C. Kim, S. Gowrisankar, J. N. Kim, *Bull. Korean Chem. Soc.* **2005**, *26*, 1001.
9. For ring-opening of isatin derivatives, see:(a) T. Le, W. C. Cheah, K. Wood, D. S. Black, M. D. Willcox, N. Kumar, *Tetrahedron Lett.* **2011**, *52*, 3645; (b) H. Li, B. Cheng, N. Boonnak, A. Padwa, *Tetrahedron* **2011**, *67*, 9829; (c) Y. Zhang, L. Wang, Y. Zhu, J.-H. Xu, *Eur. J. Org. Chem.* **2004**, 527; (d) Y. M. Chung, J. M. Kim, J. N. Kim, *Bull. Korean Chem. Soc.* **2003**, *24*, 141; (e) Y. M. Chung, J. H. Gong, J. N. Kim, *Bull. Korean Chem. Soc.* **2002**, *23*, 1363.

