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Synthesis of fully-substituted alkenylimidazoles from *N*-(cyanoalkyl)amides via the In-mediated allylation of nitrile and dehydrative cyclization cascade

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ABSTRACT

The reaction of allylindium reagents and *N*-(cyanoalkyl)amides afforded fully-substituted 4-alkenylimidazoles in moderate yields via the In-mediated Barbier-type allylation of nitrile and the following dehydrative cyclization cascade.

Imidazole derivatives are important constituents in many biologically active substances and provide a scaffold for designing drugs, and many functional organic materials.[1] Numerous synthetic methodologies of imidazoles are available; however, they suffer from many drawbacks such as harsh reaction conditions and multistep synthesis.[2,3] Especially the synthesis of imidazoles having a *C*-alkenyl moiety required an indirect method; a sequential regio-controlled halogenation of imidazole, metallation, and the following introduction of alkenyl moiety.[3] The *C*-alkenylimidazoles can be used for the synthesis of cyclic compounds via the ring-closing metathesis (RCM) reaction or via the Pd-catalyzed cyclization.[4] Thus, an efficient synthesis of *C*-alkenylimidazoles in a direct way is highly required.

Allylindium reagents have been used extensively for the introduction of an allyl group in a Barbier-type manner to various electrophiles.[5–7] Although many reactive electrophiles such as aldehydes and imines have been used in the indium-mediated allylations,[5] the reaction of less reactive nitrile has not been reported much except in the first successful results of Yamamoto and Fujiwara,[6] and in our recent papers.[7]

Recently, we reported a series of indium-mediated Barbier-type allylations of nitrile groups in γ-cyanoesters,[7a] γ-ketonitriles,[7b] δ-ketonitriles,[7c] *ortho*-cyanobenzoates,[7d] and *N*-(*ortho*-cyanoaryl)amides.[7e] From the recent studies, we found that the intrinsic reactivity of a nitrile group toward allylindium reagents is sufficient to form the corresponding imine or enamine intermediates, and the intermediates can form various cyclic compounds when the molecule has a suitable electrophilic quencher such as an ester[7a,d] or a sterically hindered ketone group.[7b,c] Very recently, we reported an efficient synthesis of quinazoline derivatives via the In-mediated Barbier-type allylation and dehydrative cyclization protocol from *N*-(*ortho*-cyanoaryl)amides.[7e] The results stated that an amide group could be used as an electrophilic quencher effectively for the imine intermediate.

Thus we strongly believed that a *C*-allylimidazole scaffold could be constructed from *N*-(cyanoalkyl)amide derivatives **1**, as shown in Scheme 1. The starting materials **1** were prepared by benzoylation of the corresponding α-aminonitriles, which were prepared from mandelonitrile and amine.[8] Some of the α-aminonitriles were prepared by addition of KCN to imines, generated in situ from the corresponding aldehyde and amine in the presence of $NaHSO_3$.[9]

As shown in Table 1, the reaction of **1a** produced an allyl imidazole **2a** and a propenyl derivative **3a** in variable yields depending on the reaction conditions. The highest yield of imidazoles (79%, **2a** + **3a**) was obtained when the reaction was run with allyl bromide (3.0 equiv) and indium (1.5 equiv) in refluxing THF for 40 min (entry 2, condition B). In the reaction, 4-allylimidazole **2a** was isolated in 62% along with a 1-propenyl derivative **3a** in small amounts (17%).[10] The yield and the ratio of **2a**/**3a** seemed to be dependent on many parameters including solvent, temperature, reaction time, and the amounts of allylindium reagents (see also Table 2). The reaction in DMF at a higher temperature (entry 4) or the reaction for a long time (entry 5) reduced the yields of products.

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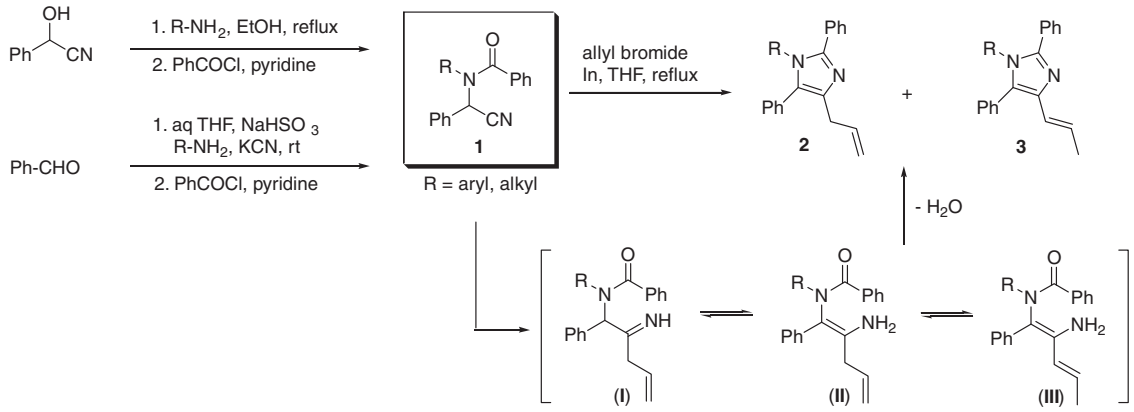
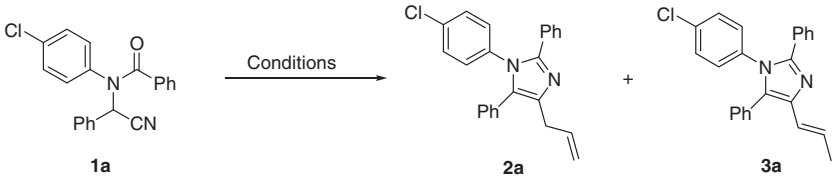


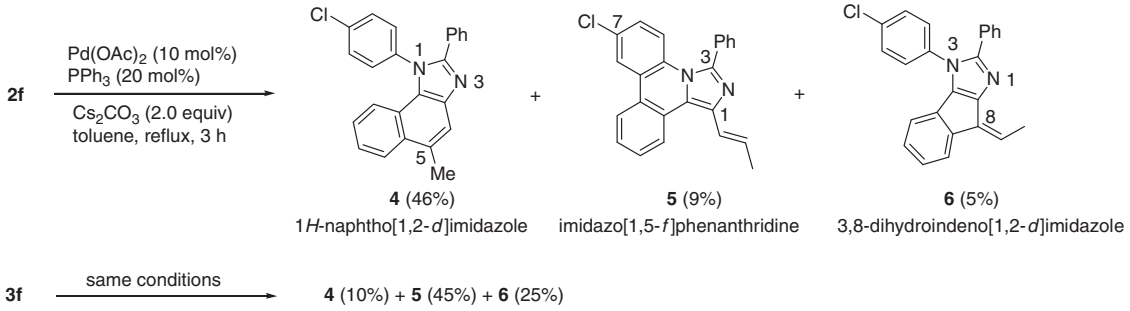
Scheme 1.

Table 1
Optimization of reaction conditions



Entry	Conditions[a]	Yield (**2a**:**3a**)[b]
1	Allyl bromide (2.0 equiv), In (1.0 equiv), THF, reflux, 60 min (condition A)	51:25
2	Allyl bromide (3.0 equiv), In (1.5 equiv), THF, reflux, 40 min (condition B)	62:17
3	Allyl bromide (4.0 equiv), In (2.0 equiv), THF, reflux, 60 min (condition C)	59:5
4[c]	Allyl bromide (4.0 equiv), In (2.0 equiv), 120–130 °C, 60 min	42:4
5	Allyl bromide (3.0 equiv), In (1.5 equiv), THF, reflux, 300 min	35:14

[a] Reactions were carried out under N_2 atmosphere for the given time.
[b] Isolated yield.
[c] The reaction in DMF at 60–70 °C showed sluggish reactivity.

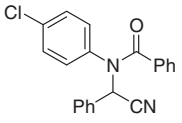
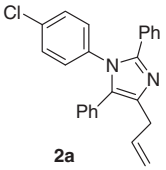
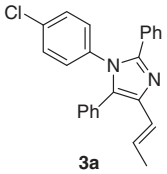
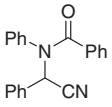
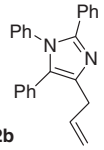
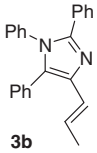
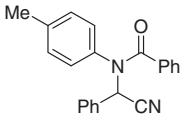
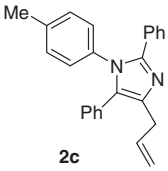
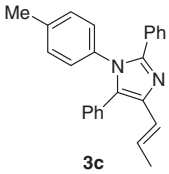
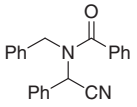
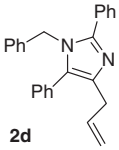
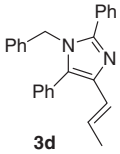
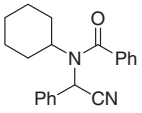
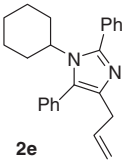
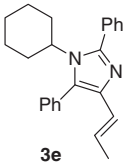
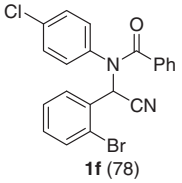
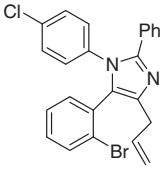
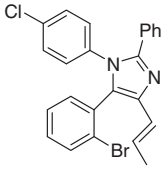
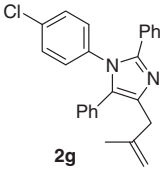
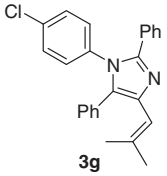


Scheme 2.

The reaction mechanism could be suggested as an indium-mediated Barbier-type allylation of nitrile to form imine or enamine intermediates (**I**)–(**III**) and the following dehydrative cyclization, as shown in Scheme 1. Attempted isomerization of **2a** into **3a** failed under basic (DBU, CH_3CN, reflux)[7e] and acidic conditions (*p*-TsOH, toluene, reflux). In addition, exposure of **2a** under the influence of allylindium reagents (allyl bromide, In, THF, reflux) did not produce **3a** at all. The results stated that the isomerization of allyl to 1-propenyl group might occur prior to the formation of the imidazole ring. Thus we proposed the mechanism involving an isomerization of (**I**) to the enamine intermediates (**II**) and (**III**) prior to the dehydrative cyclization step, tentatively.

Encouraged by the results we prepared various *N*-benzoyl α-aminonitriles **1b**–**f**,[8,9] and examined the reactions with allylindium (or methallylindium) reagents, and the results are summarized in Table 2. The reactions of **1b**–**f** (entries 2–6) and allylindium reagents showed similar results to that of **1a**. The reactions under condition B showed higher combined yields (**2** + **3**) than under the other conditions in most entries. Starting materials remained in some entries under condition A (entries 2 and 4). Methallyl bro-

Table 2
Synthesis of alkenylimidazole derivatives

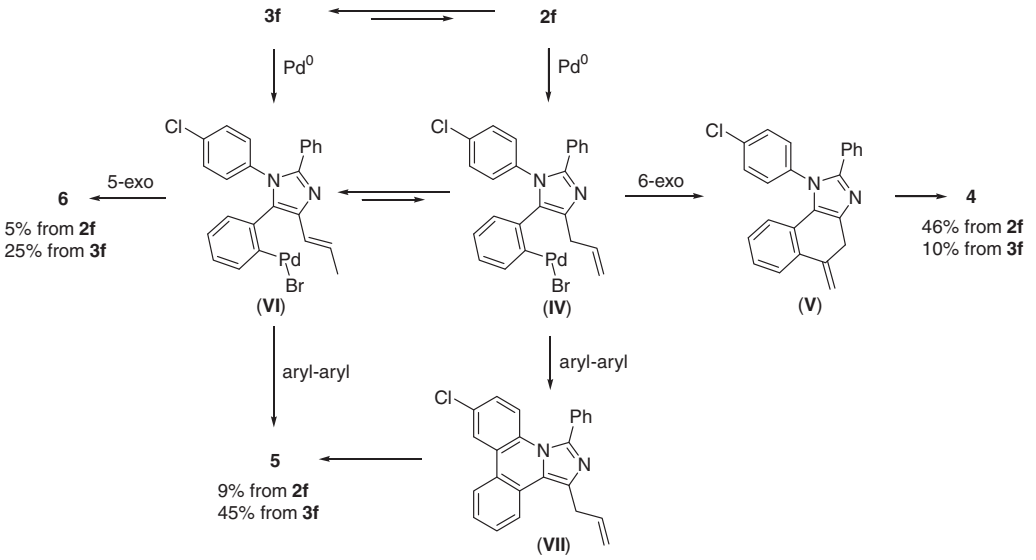
Entry	Substrate (%)[a]	Products (**2** + **3**)		Conditions: yield (%)
1	 **1a** (88)	 **2a**	 **3a**	A: **2a** (51), **3a** (25) B: **2a** (62), **3a** (17) C: **2a** (59), **3a** (5)
2	 **1b** (87)	 **2b**	 **3b**	A: **2b** (35), **3b** (25), **1b** (15) B: **2b** (40), **3b** (23) C: **2b** (39), **3b** (8)
3	 **1c** (85)	 **2c**	 **3c**	B: **2c** (30), **3c** (25) C: **2c** (21), **3c** (13)
4	 **1d** (89)	 **2d**	 **3d**	A: **2d** (37), **3d** (26), **1d** (20) B: **2d** (36), **3d** (30) C: **2d** (37), **3d** (13)
5	 **1e** (51)	 **2e**	 **3e**	B: **2e** (40), **3e** (21)
6	 **1f** (78)	 **2f**	 **3f**	B: **2f** (41), **3f** (27)
7[b]	**1a**	 **2g**	 **3g**	B: **2g** (50), **3g** (–) C: **2g** (54), **3g** (–)

[a] Starting materials were prepared as reported,[8,9] and the yield refer to benzoylation of the corresponding α-aminonitriles.
[b] Methallyl bromide was used.

mide could be used in the same manner to form 2-isobutenylimidazole **2g**; however, the corresponding 1-isobutenyl derivative **3g** was not formed (entry 7), but the reason is not clear at this stage.

In order to show the synthetic applicability of the synthesized *C*-alkenylimidazoles we carried out the Pd-catalyzed cyclizations of compounds **2f** and **3f**, as shown in Scheme 2. The Pd-catalyzed cyclization of **2f** produced three compounds **4**–**6**.[10,11] The formation of 1*H*-naphtho[1,2-*d*]imidazole **4** (46%) could be explained via the sequential 6-*exo*-*trig* carbopalladation of the arylpalladium intermediate (**IV**), β-H elimination to form (**V**), and double bond isomerization,[12,13] as shown in Scheme 3. Imidazo[1,5-*f*]phenanthridine derivative **5** (9%) must be formed via the aryl–aryl coupling of (**IV**) to form (**VII**) and isomerization of allyl to 1-propenyl group.[12] A trace amount of indeno[1,2-*d*]imidazole derivative **6** (5%) was also formed most likely via the initial isomerization of allyl to 1-propenyl and the following 5-*exo*-*trig* cyclization of (**VI**).

It is interesting to note that the same compounds **4**–**6** were formed in the reaction of 1-propenyl derivative **3f**, albeit in a different products' ratio. The plausible mechanism for the formation of **4**–**6** from **3f** is also summarized in Scheme 3. The compound **5** was formed as a major product (45%) via an aryl–aryl coupling of (**VI**), and **6** was formed (25%) via the 5-*exo*-*trig* carbopalladation of (**VI**). The formation of **4** (10%) could be the result of 6-*endo*-*trig* cyclization of (**VI**) or 6-*exo*-*trig* cyclization of (**IV**). All of the above double bond isomerization processes might be catalyzed by HPdBr formed in the reaction progress. Such an isomerization catalyzed by hydrido palladium bromide (HPdBr) species has been known in many examples.[12]



Scheme 3.

In summary, a facile synthesis of fully-substituted *C*-alkenylimidazoles has been disclosed starting from *N*-(cyanoalkyl)amides in moderate yields via the In-mediated Barbier-type allylation of nitrile and the following dehydrative cyclization cascade.

Acknowledgments

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10. *Typical procedure for the synthesis of* **2a** *and* **3a***:* A stirred mixture of **1a** (173 mg, 0.5 mmol), allyl bromide (182 mg, 1.5 mmol), and indium (86 mg, 0.75 mmol) in THF (1.0 mL) was heated to reflux for 40 min. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 10:1:1), we obtained compound **2a** (115 mg, 62%) and **3a** (32 mg, 17%) as a white solid. Other compounds were synthesized similarly, and the selected spectroscopic data of **2a**, **3a**, **2d**, **3d**, **2f**, **3f**, and **2g** are as follows.
Compound **2a***:* 62%; white solid, mp 168–170 °C; IR (KBr) 1600, 1493, 1466, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.43 (dt, J = 6.3 and 1.5 Hz, 2H), 5.05–5.17 (m, 2H), 6.07–6.20 (m, 1H), 6.90–6.95 (m, 2H), 7.03–7.09 (m, 2H), 7.18–7.29 (m, 8H), 7.30–7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.15, 115.44, 127.54, 128.10, 128.13, 128.20, 128.93, 129.29, 129.33, 129.68, 130.23, 130.34, 130.67, 133.80, 135.87, 136.92, 138.06, 146.41; ESIMS m/z 371 (M^++H), 373 (M^++H+2). Anal. Calcd for $C_{24}H_{19}ClN_2$: C, 77.72; H, 5.16; N, 7.55. Found: C, 77.96; H, 5.25; N, 7.39.
Compound **3a***:* 17%; white solid, mp 149–151 °C; IR (KBr) 1593, 1493, 1445 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.86 (dd, J = 6.6 and 1.5 Hz, 3H), 6.33 (dd, J = 15.6 and 1.5 Hz, 1H), 6.61–6.72 (m, 1H), 6.90–6.96 (m, 2H), 7.07–7.10 (m, 2H), 7.20–7.30 (m, 8H), 7.35–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.42, 121.46, 126.10, 127.68, 128.18, 128.25, 128.43, 129.07, 129.36 (2C), 129.44, 130.30, 130.55, 133.93, 135.68, 137.62, 147.17 (one carbon is overlapped); ESIMS 371 (M^++H), 373 (M^++H+2). Anal. Calcd for $C_{24}H_{19}ClN_2$: C, 77.72; H, 5.16; N, 7.55. Found: C, 77.85; H, 5.32; N, 7.51.
Compound **2d***:* 36%; pale yellow oil; IR (film) 1670, 1496, 1452, 1400 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.36 (dt, J = 6.3 and 1.5 Hz, 2H), 4.95–5.11 (m, 2H), 5.13 (s, 2H), 6.00–6.13 (m, 1H), 6.72–6.75 (m, 2H), 7.11–7.24 (m, 5H), 7.26–7.40 (m, 6H), 7.54–7.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.02, 48.36, 115.06, 125.88, 127.17, 127.97, 128.30, 128.37, 128.44, 128.58, 128.90, 130.18,

130.31, 130.40, 130.93, 137.06, 137.63, 137.67, 147.74; ESIMS *m*/*z* 351 (M^++H). Anal. Calcd for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.56; H, 6.57; N, 7.72.

Compound **3d***:* 30%; pale yellow oil; IR (film) 1603, 1496, 1488, 1451 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.81 (dd, *J* = 6.6 and 1.5 Hz, 3H), 5.11 (s, 2H), 6.23 (dd, *J* = 15.6 and 1.5 Hz, 1H), 6.52–6.64 (m, 1H), 6.71–6.75 (m, 2H), 7.12–7.17 (m, 4H), 7.19–7.25 (m, 2H), 7.30–7.42 (m, 5H), 7.53–7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.33, 48.32, 121.73, 124.98, 126.00, 127.27, 128.10, 128.46, 128.48 (2C), 128.83, 129.07, 129.96, 130.17, 130.57, 130.97, 137.44, 137.51, 148.61; ESIMS *m*/*z* 351 (M^++H). Anal. Calcd for $C_{25}H_{22}N_2$: C, 85.68; H, 6.33; N, 7.99. Found: C, 85.86; H, 6.16; N, 7.87.

Compound **2f***:* 41%; white solid, mp 121–122 °C; IR (KBr) 1605, 1494, 1467 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.22–3.40 (m, 2H), 4.95–5.08 (m, 2H), 5.95–6.08 (m, 1H), 6.96–7.00 (m, 2H), 7.14–7.27 (m, 8H), 7.36–7.40 (m, 2H), 7.53–7.56 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 32.41, 115.57, 126.57, 127.03, 128.15, 128.28, 128.75, 129.04, 129.12, 129.82, 130.20, 130.35, 131.30, 132.64, 133.72, 133.86, 135.74, 135.99, 138.61, 146.43; ESIMS *m*/*z* 449 (M^++H), 451 (M^++H+2), 453 (M^++H+4). Anal. Calcd for $C_{24}H_{18}BrClN_2$: C, 64.09; H, 4.03; N, 6.23. Found: C, 64.24; H, 4.11; N, 6.17.

Compound **3f***:* 27%; white solid, mp 79–80 °C; IR (KBr) 1597, 1493, 1446 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.82 (dd, *J* = 6.6 and 1.5 Hz, 3H), 6.06 (dd, *J* = 15.6 and 1.5 Hz, 1H), 6.48–6.60 (m, 1H), 6.94–6.99 (m, 2H), 7.14–7.32 (m, 8H), 7.35–7.43 (m, 2H), 7.55–7.59 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.41, 121.44, 125.91, 126.46, 127.15, 128.19, 128.46, 128.85, 129.02, 129.13, 129.26, 130.13, 130.40, 131.05, 132.80, 133.71, 133.90, 135.51, 138.15, 147.06; ESIMS *m*/*z* 449 (M^++H), 451 (M^++H+2), 453 (M^++H+4). Anal. Calcd for $C_{24}H_{18}BrClN_2$: C, 64.09; H, 4.03; N, 6.23. Found: C, 64.37; H, 4.14; N, 6.07.

Compound **2g***:* 50%; white solid, mp 162–163 °C; IR (KBr) 1600, 1493, 1443 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.81 (s, 3H), 3.35 (s, 2H), 4.75 (s, 1H), 4.84 (s, 1H), 6.92–6.96 (m, 2H), 7.05–7.08 (m, 2H), 7.19–7.25 (m, 8H), 7.32–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.87, 35.80, 111.42, 127.50, 128.06, 128.10, 128.14, 128.94, 129.28, 129.36, 129.81, 130.13, 130.39, 131.27, 133.77, 135.96, 137.83, 144.59, 146.30; ESIMS *m*/*z* 385 (M^++H), 387 (M^++H+2). Anal. Calcd for $C_{25}H_{21}ClN_2$: C, 78.01; H, 5.50; N, 7.28. Found: C, 78.33; H, 5.71; N, 7.23.

Typical procedure for the Pd-catalyzed reaction of **2f***:* A stirred mixture of **2f** (180 mg, 0.4 mmol), $Pd(OAc)_2$ (9 mg, 10 mol %), PPh_3 (21 mg, 20 mol %), Cs_2CO_3 (260 mg, 0.8 mmol) in toluene (1.5 mL) was heated to reflux for 3 h. After the usual aqueous workup and column chromatographic purification process (hexanes/CH_2Cl_2/EtOAc, 20:2:1), we obtained compound **4** (68 mg, 46%), **5** (13 mg, 9%), and **6** (7 mg, 5%) as pale yellow solids. The reaction of **3f** was carried out similarly, and the spectroscopic data of **4**–**6** are as follows.

Compound **4***:* 46%; pale yellow solid, mp 197–198 °C; IR (KBr) 1541, 1508, 1276 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.79 (s, 3H), 7.22–7.35 (m, 5H), 7.36–7.57 (m, 7H), 7.82 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.30, 120.09, 120.36, 122.12, 124.20, 125.40, 125.69, 128.27, 129.04, 129.30, 129.36, 130.13, 130.33 (2C), 130.38, 130.87, 135.58, 137.40, 140.13, 151.31; ESIMS *m*/*z* 369 (M^++H), 371 (M^++H+2). Anal. Calcd for $C_{24}H_{17}ClN_2$: C, 78.15; H, 4.65; N, 7.59. Found: C, 78.41; H, 4.77; N, 7.48.

Compound **5***:* 9%; pale yellow solid, mp 208–210 °C; IR (KBr) 1541, 1458, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03 (dd, *J* = 6.6 and 1.5 Hz, 3H), 6.73–6.84 (m, 1H), 7.00 (dd, *J* = 15.6 and 1.5 Hz, 1H), 7.07 (dd, *J* = 9.0 and 2.4 Hz, 1H), 7.30 (d, *J* = 9.0 Hz, 1H), 7.42–7.65 (m, 7H), 8.12–8.15 (m, 1H), 8.17 (d, *J* = 2.4 Hz, 1H), 8.23 (dd, *J* = 8.1 and 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 18.82, 119.89, 122.76, 122.84, 122.95, 123.79, 124.11, 125.36, 125.59, 126.58, 126.69, 127.59, 129.07, 129.25, 129.36, 129.55, 129.70, 130.75, 130.90, 133.32, 134.39, 143.24; ESIMS *m*/*z* 369 (M^++H), 371 (M^++H+2). Anal. Calcd for $C_{24}H_{17}ClN_2$: C, 78.15; H, 4.65; N, 7.59. Found: C, 78.21; H, 4.90; N, 7.38.

Compound **6***:* 5%; pale yellow solid, mp 198–199 °C; IR (KBr) 1541, 1508, 1398, 1274 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.58 (d, *J* = 7.2 Hz, 3H), 6.68 (q, *J* = 7.2 Hz, 1H), 6.78–6.81 (m, 1H), 7.05–7.15 (m, 2H), 7.24–7.36 (m, 5H), 7.41–7.48 (m, 4H), 7.59–7.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 16.05, 116.30, 120.46, 124.85, 126.79, 128.02, 128.35, 128.47, 128.71, 129.10, 129.21, 129.90, 130.31, 134.51, 136.25, 138.99, 140.31, 145.77, 150.52 (one carbon is overlapped); ESIMS *m*/*z* 369 (M^++H), 371 (M^++H+2). Anal. Calcd for $C_{24}H_{17}ClN_2$: C, 78.15; H, 4.65; N, 7.59. Found: C, 78.36; H, 4.89; N, 7.52.

11. For the synthesis and biological activities of similar compounds, see: (a) Toja, E.; Di Francesco, G.; Barone, D.; Baldoli, E.; Corsico, N.; Tarzia, G. *Eur. J. Med. Chem.* **1987**, *22*, 221–228; (b) Michael, F. U.S. 4548943, 1985; *Chem. Abstr.* **1986**, *104*, 75034
12. For the examples on double bond isomerization during the Pd-catalyzed cyclizations caused by HPdX species, see: (a) Huang, Q.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 7342–7349; (b) Larock, R. C.; Takagi, K.; Burkhart, J. P.; Hershberger, S. S. *Tetrahedron* **1986**, *42*, 3759–3762; (c) Yip, K.-T.; Zhu, N.-Y.; Yang, D. *Org. Lett.* **2009**, *11*, 1911–1914; (d) Nasveschuk, C. G.; Frein, J. D.; Jui, N. T.; Rovis, T. *Org. Lett.* **2007**, *9*, 5099–5102; (e) Soderberg, B. C. G.; Hubbard, J. W.; Rector, S. R.; O'Neil, S. N. *Tetrahedron* **2005**, *61*, 3637–3649; (f) Soderberg, B. C. G.; Rector, S. R.; O'Neil, S. N. *Tetrahedron Lett.* **1999**, *40*, 3657–3660; (g) Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894–3900.
13. Trials for the separation of the *exo*-methylene intermediate (**V**) in the reaction mixture failed. In order to reduce the HPdBr-catalyzed isomerization process,[12] we carried out the reaction of **2f** in the presence of an organic base (Et_3N, toluene, reflux, 24 h). However, we failed again to obtain (**V**) in an appreciable amount. The reaction was somewhat slow, and compounds **4** (25%), **5** (6%), and **6** (24%) were isolated.