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Pd-mediated synthesis of 2-arylquinolines and tetrahydropyridines from modified Baylis–Hillman adducts

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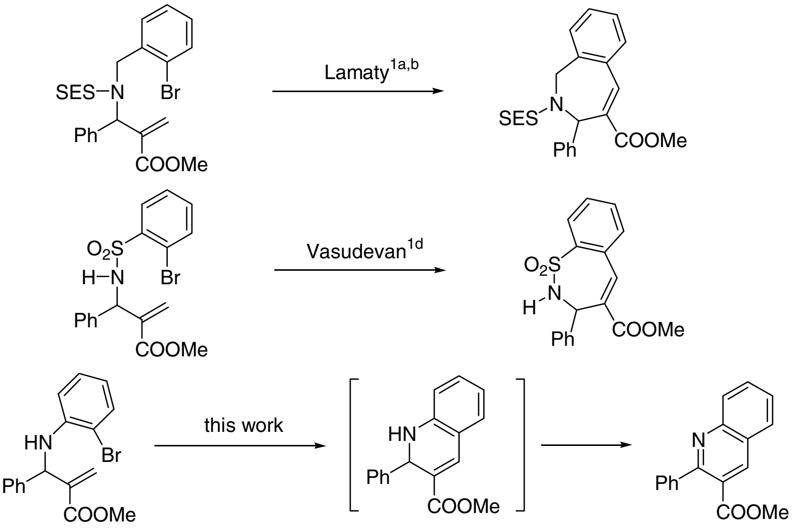
Abstract

We synthesized 2-arylquinolines and tetrahydropyridines via palladium-mediated Heck type reactions starting from the Baylis–Hillman adducts. 2-Arylquinolines were prepared via the Heck type cyclization followed by concomitant aerobic oxidation.

Keywords: 2-Arylquinolines; Tetrahydropyridines; Baylis–Hillman adducts; Palladium

Although palladium-mediated cyclizations have been investigated extensively using various substrates, examples on the synthesis of heterocyclic compounds starting from Baylis–Hillman adducts were somewhat limited.[1] Trost and co-workers used Pd-mediated synthesis of dihydrobenzofuran from Baylis–Hillman adducts.[1e,f] Very recently Lamaty and co-workers reported the synthesis of nitrogen-containing seven-membered ring compounds and oxygen-containing five-membered ring compounds (Scheme 1).[1a–c] In addition, Vasudevan and co-workers reported the



Scheme 1.

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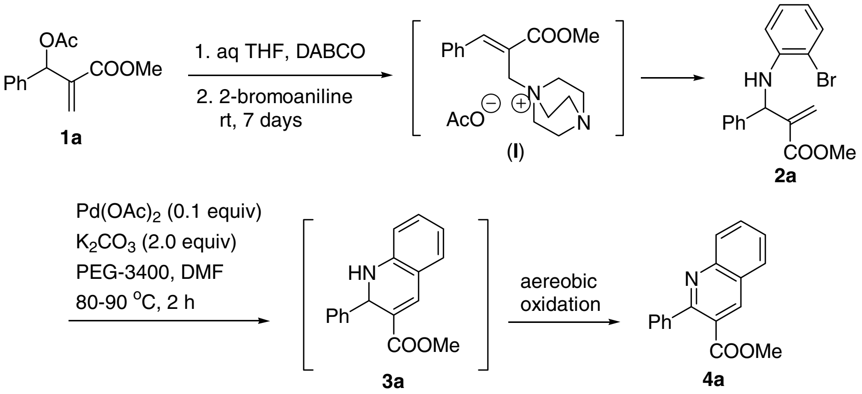
synthesis of seven-membered cyclic compounds containing sulfonamide linkage (Scheme 1).[1d]

However, Heck type cyclizations using Baylis–Hillman adducts as starting materials for the synthesis of quinolines has not been reported to the best of our knowledge (Scheme 1).[1–3] Syntheses of suitably substituted quinolines have received much attention due to their biological activity and the usefulness of them in organic synthesis for further transformations.[2–4] In these contexts, we decided to examine the feasibility for the synthesis of quinolines starting from Baylis–Hillman adducts. Scheme 1 showed our synthetic rationale, which involved Pd-mediated Heck reaction (6-*endo*) and concomitant aerobic oxidation.[5]

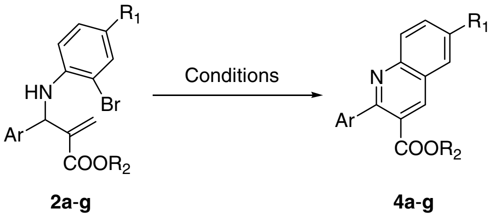
Thus we synthesized starting material **2a** from Baylis–Hillman acetate **1a** and 2-bromoaniline by using the well-known DABCO salt concept (sequential S_N2'–S_N2' displacement reaction as in Scheme 2) in the Baylis–Hillman chemistry.[2c,d,h] However, the introduction of 2-bromoaniline at the secondary position required very long reaction time (7–14 days at room temperature).[2c,d] When we elevated the reaction temperature the reaction showed the formation of many side products to make the separation of desired product tedious and make the yield eventually low. Actually the best yield of compound **2a** (56%) was obtained at room temperature after 7 days. With this compound **2a** in our hand, we examined a few reaction conditions and we found that the conditions of Lamaty ($Pd(OAc)_2/K_2CO_3$/PEG-3400/DMF/80–90 °C)[1a–c] showed the best results.[6] We obtained desired 2-phenylquinoline-3-carboxylic acid derivative **4a** directly in moderate yield (58%),[4d–f,7] presumably via the Pd-mediated aerobic oxidation[5] of the intermediate dihydroquinoline **3a** (Scheme 2). Encouraged by the results, we prepared **2b**–**g** (40–71%) from the reactions between the corresponding Baylis–Hillman acetates and 2-bromoanilines. After that, we examined the generality of the novel one-pot reaction of sequential Heck type cyclization and the following aerobic oxidation. The results are summarized in Table 1. Desired quinolines **4b**–**g** were obtained in 53–69% yields in short time in a one-pot reaction.



Scheme 2.

Table 1

Pd-mediated cyclizations of modified Baylis–Hillman adducts

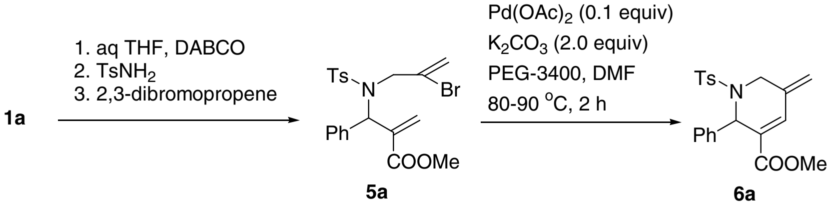


a: Ar = Ph, R_1 = H, R_2 = Me
b: Ar = Ph, R_1 = H, R_2 = Et
c: Ar = 4-ClC_6H_4-, R_1 = H, R_2 = Me
d: Ar = 2-naphthyl, R_1 = H, R_2 = Me
e: Ar = Ph, R_1 = Me, R_2 = Me
f: Ar = 3-MeC_6H_4-, R_1 = Me, R_2 = Me
g: Ar = 4-PhC_6H_4-, R_1 = Me, R_2 = Me

Entry	Substrate[a] (%)	Conditions[b]	Product (%)
1	**2a** (56)	80–90 °C, 2 h	**4a** (58)
2	**2b** (71)	80–90 °C, 1.5 h	**4b** (66)
3	**2c** (68)	80–90 °C, 1.5 h	**4c** (69)
4	**2d** (59)	90–100 °C, 1.5 h	**4d** (53)
5	**2e** (40)	80–90 °C, 1 h	**4e** (60)
6	**2f** (43)	80–90 °C, 1 h	**4f** (64)
7	**2g** (61)	90–100 °C, 2 h	**4g** (63)

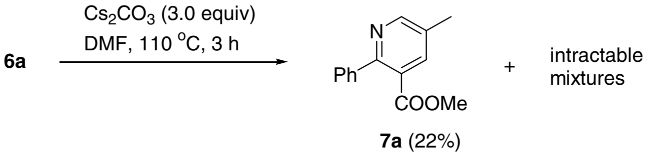
[a] Conditions: (i) Baylis–Hillman acetates **1** (1.0 equiv), aq THF, DABCO (1.1 equiv), rt, 15 min; (ii) 2-bromoanilines (1.0 equiv), rt, 7–14 days (7 days for **2a**–**c** and 14 days **2d**–**g**).

[b] Conditions: substrate (1.0 equiv), $Pd(OAc)_2$ (0.1 equiv), K_2CO_3 (2.0 equiv), PEG-3400, DMF.



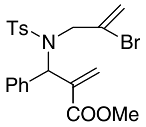
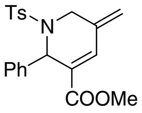
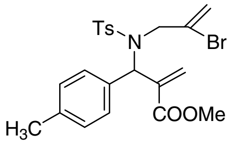
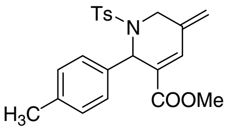
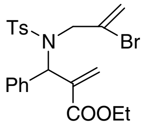
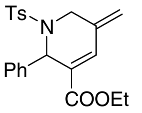
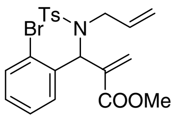
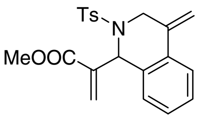
Scheme 3.

As a next step, to synthesize 2,3,5-trisubstituted pyridine derivative such as **7a** (vide infra) by using the same protocol of quinolines (Scheme 2 and Table 1), we tried the synthesis of 2-bromoprophenylamine (–NHCH=C(Br)CH_3 or –$NHCH_2C(Br)=CH_2$) moiety-substituted Baylis–Hillman adducts at the secondary position. However, the synthesis was very difficult, thus we changed our strategy as shown in Scheme 3 involving the use of *N*-tosyl analog **5a** as the starting material instead of N–H analog. We imagined that elimination of *p*-toluenesulfinic acid and concomitant double bond isomerization process after the Heck cyclization of **5a** could provide desired 2,3,5-trisubstituted pyridine **7a** (Scheme 4, vide infra). Thus we prepared starting materials **5a**–**d** as in Scheme 3 and Table 2 by following the process: (i) introduction of tosylamide via the DABCO salt of the corresponding Baylis–Hillman acetates,[2c,d,h] (ii) alkylation with 2,3-dibromopropene (for **5a**–**c**) or with allyl bromide (for **5d**). Heck type cyclization of **5a** produced *exo*-methylene tetrahydropyridine **6a** in moderate yield (62%) under the conditions of $Pd(OAc)_2/K_2CO_3$/PEG-3400/DMF/80–90 °C (entry 1 in Table 2). However, it was very difficult to convert **6a** into the corresponding 2,3,5-trisubstituted pyridine **7a**. We obtained only low yield (22%) of **7a** under the influence of 3.0 equiv of Cs_2CO_3 in DMF at elevated temperature (Scheme 4). We synthesized **6b**–**d** under similar conditions in view of the importance of tetrahydropyridines[8] and the synthetic applicability of these *exo*-methylene tetrahydropyridines.[8] The yield of compound **6d** was relatively low (34%) under the same conditions, however, the yield was improved slightly (up to 46%) by using the conditions of Vasudevan ($Pd(OAc)_2$/P(*o*-Tol)$_3$/Et_3N/100–110 °C, entry 4).[1d] The whole results are summarized in Table 2 and further synthetic applications of these compounds are currently underway.



Scheme 4.

Table 2
Pd-mediated cyclizations of modified Baylis–Hillman adducts

Entry	Substrate[a] (%)		Conditions	Product (%)	
1		**5a** (92)	$Pd(OAc)_2$ (0.1 equiv) K_2CO_3 (2.0 equiv) PEG-3400, DMF 80–90 °C, 2 h		**6a** (62)
2		**5b** (84)	$Pd(OAc)_2$ (0.1 equiv) K_2CO_3 (2.0 equiv) PEG-3400, DMF 90–100 °C, 2.5 h		**6b** (60)
3		**5c** (88)	$Pd(OAc)_2$ (0.1 equiv) K_2CO_3 (2.0 equiv) PEG-3400, DMF 90–100 °C, 2 h		**6c** (58)
4		**5d** (97)	$Pd(OAc)_2$ (0.2 equiv) P(*o*-Tol)$_3$ (2.0 equiv) Et_3N (solvent) 100–110 °C, 4 h		**6d** (46)[b]

[a] Conditions: (i) *N*-tosyl *aza*-Baylis–Hillman adducts (1.0 equiv),[2h] 2,3-dibromopropene (for **5a**–**c**, 1.2 equiv)/allyl bromide (for **5d**, 1.2 equiv), K_2CO_3 (1.2 equiv), DMF, rt, 6 h, and the yields refer to the last alkylation step.

[b] Compound **6d** was obtained in 34% yield under the conditions: $Pd(OAc)_2$ (0.1 equiv), K_2CO_3 (2.0 equiv), PEG-3400, DMF, 110–120 °C, 4 h.

In summary, we prepared some 2-arylquinoline derivatives via the palladium-mediated sequential cyclization and concomitant aerobic oxidation process in a one-pot reaction from modified Baylis–Hillman adducts. In addition, we prepared some *exo*-methylene tetrahydropyridine derivatives.

References and notes

1. For the Pd-mediated synthesis of hetero- and carbocyclic compounds from modified Baylis–Hillman adducts, see: (a) Ribiere, P.; Declerck, V.; Nedellec, Y.; Yadav-Bhatnagar, N.; Martinez, J.; Lamaty, F. *Tetrahedron* **2006**, *62*, 10456–10466; (b) Declerck, V.; Ribiere, P.; Nedellec, Y.; Allouchi, H.; Martinez, J.; Lamaty, F. *Eur. J. Org. Chem.* **2007**, 201–208; (c) Szlosek-Pinaud, M.; Diaz, P.; Martinez, J.; Lamaty, F. *Tetrahedron* **2007**, *63*, 3340–3349; (d) Vasudevan, A.; Tseng, P.-S.; Djuric, S. W. *Tetrahedron Lett.* **2006**, *47*, 8591–8593; (e) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *125*, 13155–13164; (f) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616–11617; (g) Park, J. B.; Ko, S. H.; Hong, W. P.; Lee, K.-J. *Bull. Korean Chem. Soc.* **2004**, *25*, 927–930.
2. For the synthesis of quinolines, pyridines, and related compounds from Baylis–Hillman adducts in our group, see: (a) Park, D. Y.; Lee, M. J.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 8799–8803; (b) Lee, M. J.; Kim, S. C.; Kim, J. N. *Bull. Korean Chem. Soc.* **2006**, *27*, 439–442; (c) Lee, C. G.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron* **2005**, *61*, 1493–1499; (d) Kim, S. C.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1001–1004; (e) Lee, C. G.; Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 7409–7413; (f) Lee, K. Y.; Kim, J. M.; Kim, J. N. *Tetrahedron* **2003**, *59*, 385–390; (g) Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341–8344; (h) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737–3740; (i) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343–345.
3. For the synthesis of quinolines and related compounds from Baylis–Hillman adducts by other groups, see: (a) Pathak, R.; Madapa, S.; Batra, S. *Tetrahedron* **2007**, *63*, 451–460; (b) Madapa, S.; Singh, V.; Batra, S. *Tetrahedron* **2006**, *62*, 8740–8747; (c) Narender, P.; Srinivas, U.; Ravinder, M.; Ananda Rao, B.; Ramesh, C.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Jayathirtha Rao, V. *Bioorg. Med. Chem.* **2006**, *14*, 4600–4609; (d) Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron Lett.* **2006**, *47*, 73–77; (e) Basavaiah, D.; Reddy, R. M.; Kumaragurubaran, N.; Sharada, D. S. *Tetrahedron* **2002**, *58*, 3693–3697; (f) O'Dell, D. K.; Nicholas, K. M. *J. Org. Chem.* **2003**, *68*, 6427–6430; (g) O'Dell, D. K.; Nicholas, K. M. *Tetrahedron* **2003**, *59*, 747–754; (h) Familoni, O. B.; Klaas, P. J.; Lobb, K. A.; Pakade, V. E.; Kaye, P. T. *Org. Biomol. Chem.* **2006**, *4*, 3960–3965; (i) Familoni, O. B.; Kaye, P. T.; Klaas, P. J. *Chem. Commun.* **1998**, 2563–2564; (j) Yi, H.-W.; Park, H. W.; Song, Y. S.; Lee, K.-J. *Synthesis* **2006**, 1953–1960; (k) Hong, W. P.; Lee, K. J. *Synthesis* **2006**, 963–968.
4. For the synthesis of authentic samples of synthesized quinolines and pyridines, see: (a) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709–2710; (b) Rosa, A. M.; Lobo, A. M.; Branco, P. S.; Prabhakar, S.; Pereira, A. M. D. L. *Tetrahedron* **1997**, *53*, 269–284; (c) Shao, H. W.; Cai, J. C. *Chinese Chem. Lett.* **1997**, *8*, 493–496; (d) Leleu, S.; Papamicael, C.; Marsais, F.; Dupas, G.; Levacher, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3919–3928; (e) Penhoat, M.; Levacher, V.; Dupas, G. *J. Org. Chem.* **2003**, *68*, 9517–9520; (f) Kanomata, N.; Nakata, T. *Heterocycles* **1998**, *48*, 2551–2558.
5. For the palladium-catalyzed aerobic oxidation of amines, see: (a) Wang, J.-R.; Fu, Y.; Zhang, B.-B.; Cui, X.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2006**, *47*, 8293–8297; (b) Wang, J.-R.; Yang, C.-T.; Liu, L.; Guo, Q.-X. *Tetrahedron Lett.* **2007**, *48*, 5449–5453.
6. We examined a few conditions involving the variation of base (K_2CO_3, Cs_2CO_3, Et_3N) and solvent (CH_3CN, DMF).
7. *Typical procedure for the synthesis of* **2a** *and* **4a**: To a stirred solution of the Baylis–Hillman acetate (**1a**, 234 mg, 1.0 mmol) in aqueous THF (5 mL, 1:1) was added DABCO (123 mg, 1.1 mmol) at room temperature. After 15 min, 2-bromoaniline (172 mg, 1.0 mmol) was added to the reaction mixture and stirred at room temperature for 7 days. After the usual aqueous workup and column chromatographic purification process (hexanes/ether, 95:5) we obtained **2a** (194 mg, 56%) as colorless oil. A stirred mixture of **2a** (173 mg, 0.5 mmol), palladium acetate (11 mg, 0.05 mmol, 10 mol %), K_2CO_3 (138 mg, 1.0 mmol) in PEG-3400 (160 mg)/DMF (2 mL) was heated to 80–90 °C for 2 h under N_2. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 9:1) we obtained **4a** (77 mg, 58%) as colorless oil. Other compounds were synthesized analogously and some selected spectroscopic data of compounds **2a**, **4a**, **4e**, **5a**, **6a**, and **6d** are as follows: Compound **2a**: colorless oil; 56%; IR (film) 3410, 1720, 1593, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.72 (s, 3H), 4.85 (br s, 1H), 5.50 (s, 1H), 5.89 (s, 1H), 6.39 (s, 1H), 6.52–6.61 (m, 2H), 7.09–7.15 (m, 1H), 7.29–7.44 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.02, 58.60, 109.95, 112.52, 118.40, 126.26, 127.43, 127.94, 128.38, 128.85, 132.37, 139.90, 139.97, 143.44, 166.51; ESIMS m/z 346 (M^++1).
   Compound **4a**: colorless oil; 58%; IR (film) 2924, 1730, 1487, 1269, 1232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.74 (s, 3H), 7.42–7.51 (m, 3H), 7.58–7.66 (m, 3H), 7.79–7.85 (m, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 8.20 (d, $J = 8.4$ Hz, 1H), 8.66 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 52.41, 125.06, 125.80, 127.27, 128.21 (2C), 128.55, 128.66, 129.57, 131.62, 139.20, 140.55, 148.45, 158.03, 168.37; ESIMS m/z 264 (M^++1). Anal. Calcd for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.41; H, 5.12; N, 5.24.
   Compound **4e**: colorless oil; 60%; IR (film) 2949, 1728, 1437, 1269 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.56 (s, 3H), 3.73 (s, 3H), 7.42–7.50 (m, 3H), 7.61–7.65 (m, 4H), 8.07 (d, $J = 8.4$ Hz, 1H), 8.55 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.57, 52.33, 124.95, 125.81, 126.91, 128.15, 128.49, 128.50, 129.18, 133.95, 137.28, 138.47, 140.64, 147.06, 157.11, 168.50; ESIMS m/z 278 (M^++1). Anal. Calcd for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 78.04; H, 5.42; N, 4.97.
   Compound **5a**: sticky oil; 92%; IR (KBr) 2952, 1724, 1630, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.41 (s, 3H), 3.62 (s, 3H), 4.08 (d, $J = 17.7$ Hz, 1H), 4.21 (d, $J = 17.7$ Hz, 1H), 5.29–5.31 (m, 1H), 5.50–5.52 (m, 1H), 5.59 (d, $J = 1.5$ Hz, 1H), 6.22 (s, 1H), 6.39 (d, $J = 1.2$ Hz, 1H), 7.06–7.09 (m, 2H), 7.20–7.23 (m, 5H), 7.62 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.52, 52.08, 53.43, 62.12, 118.79, 127.60, 127.93, 128.01, 128.52, 128.56, 128.68, 129.41, 136.46, 137.25, 138.65, 143.54, 166.19; ESIMS m/z 464 (M^++1).
   Compound **6a**: colorless oil; 62%; IR (film) 2925, 1726, 1342, 1163 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 3.67 (s, 3H), 3.62–3.68 (m, 1H), 4.37 (d, $J = 16.8$ Hz, 1H), 5.19 (s, 1H), 5.24 (s, 1H), 6.00 (s, 1H), 7.06 (s, 1H), 7.16 (d, $J = 8.4$ Hz, 2H), 7.27–7.33 (m, 5H), 7.61 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.51, 43.10, 52.11, 55.36, 120.27, 127.46, 128.15, 128.16, 128.53 (2C), 129.26, 135.70, 136.55, 137.37, 137.42, 143.44, 165.43; ESIMS m/z 384 (M^++1). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.57; H, 5.76; N, 3.39.
   Compound **6d**: colorless oil; 46%; IR (film) 2924, 1724, 1599, 1439 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H), 3.83 (s, 3H), 4.12 (d, $J = 17.1$ Hz, 1H), 4.42 (d, $J = 17.1$ Hz, 1H), 4.94 (s, 1H), 5.08 (s, 1H), 5.42 (s, 1H), 6.13 (s, 1H), 6.33 (s, 1H), 6.94 (d, $J = 8.4$ Hz, 2H), 6.95–7.00 (m, 1H), 7.05–7.18 (m, 2H), 7.30–7.34 (m, 1H), 7.45 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.33, 45.34, 52.26, 57.07, 109.44, 123.59, 127.46, 127.69, 127.77, 128.13, 128.73, 129.71, 131.45, 132.00, 135.20, 136.13, 140.50, 142.90, 166.22; ESIMS m/z 384 (M^++1). Anal. Calcd for $C_{21}H_{21}NO_4S$: C, 65.78; H, 5.52; N, 3.65. Found: C, 65.63; H, 5.85; N, 3.49.
8. For the palladium-mediated synthesis of tetrahydropyridines and tetrahydroquinolines and their synthetic applications, see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Masciocchi, N.; Sottocornola, S. *Org. Lett.* **2006**, *8*, 4521–4524; (b) Soderberg, B. C. G.; Hubbard, J. W.; Rector, S. R.; O'Neil, S. N. *Tetrahedron* **2005**, *61*, 3637–3649; (c) Grigg, R.; Kordes, M. *Eur. J. Org. Chem.* **2001**, 707–712; (d) Gai, X.; Grigg, R.; Koppen, I.; Marchbank, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, *44*, 7445–7448; (e) Grigg, R.; Sridharan, V.; Thayaparan, A. *Tetrahedron Lett.* **2003**, *44*, 9017–9019; (f) Oh, C. H.; Park, S. J. *Tetrahedron Lett.* **2003**, *44*, 3785–3787.