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Controlled and Efficient Synthesis of Quinoline Derivatives from Morita–Baylis–Hillman Adducts by Palladium-Catalyzed Heck Reaction and Cyclization

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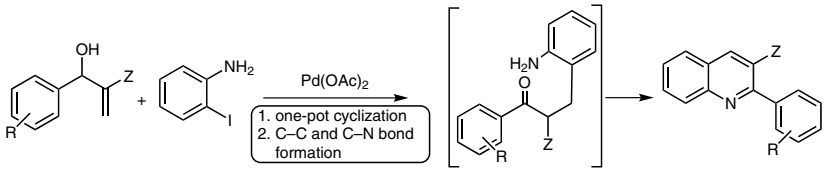

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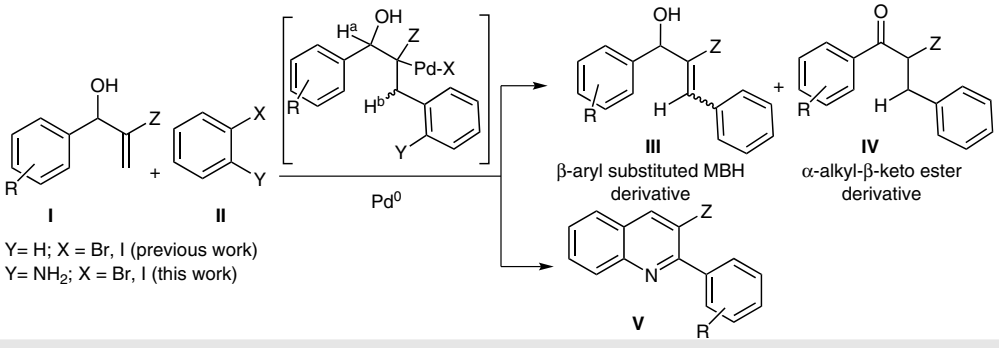
Abstract An efficient synthesis of 2,3-disubstituted quinoline derivatives from easily accessible (het)aryl-substituted Morita–Baylis–Hillman (MBH) adducts was achieved by an approach involving a palladium-catalyzed Heck reaction and cyclization. This strategy converts the MBH adducts into α-benzyl β-keto ester derivatives that can cyclize into the corresponding quinolines in good yields.

Key words quinolines, cyclizations, catalysis, palladium, Heck reactions, tandem reactions

Quinolines are an important class of compounds, owing to their significant applications in areas of materials and pharmaceutical chemistry.[1] In particular, disubstituted quinoline derivatives have shown a broad spectrum of biological activities, such as antimalarial, antidiabetic, antiinflammatory, antiasthmatic, and antihypertensive activities and tyrosine kinase inhibiting properties.[2] Consequently, numerous approaches to the synthesis of these compounds have been developed.[3]

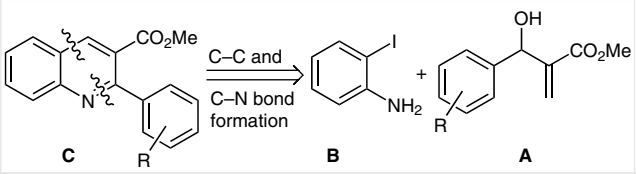
Larock developed a palladium-catalyzed synthesis of quinoline derivatives from allyl alcohols through α-benzyl β-keto ester intermediates.[4] Recently, a number of stepwise syntheses of quinoline derivatives have been reported that use allyl alcohols and enones as starting materials.[5] As an extension of our interest in novel synthetic applications of Morita–Baylis–Hillman (MBH) adducts, we proposed their use in a one-pot synthesis of quinolines. However, the palladium-catalyzed Heck reaction of MBH adducts **I** with halobenzenes **II** (X = Br, I; Y = H) has been shown to give mixtures of α-benzyl β-keto esters **IV** and β-aryl-substituted derivatives **III** (Scheme 1).[6] The slight difference in acidity between adjacent protons H^a and H^b of the organopalladium complex causes the Heck reaction of MBH adduct to be very sluggish during the β-hydride elimination step.[7] To avoid this limitation, Gowrisankar and co-workers reported a stepwise strategy for the synthesis of quinoline derivatives from MBH adducts, but the procedure required prolonged reaction times (seven days).[8] Furthermore, no one-pot difunctionalization of the MBH adduct of benzaldehyde has yet been achieved.[5d,9] We surmised that the formation of the β-aryl-substituted derivative might be suppressed if



Scheme 1

the α-benzyl β-keto ester derivative were to be continuously converted into quinolines **V** during the reaction. Here, we describe an efficient one-pot synthesis of (het)aryl quinoline derivatives from isolable intermediates from MBH adducts by a palladium-catalyzed Heck reaction and cyclization.

Our retrosynthetic analysis (Scheme 2) suggested that quinoline derivatives **C** might be synthesized from the MBH adducts **A** and 2-iodoaniline (**B**) by a palladium-catalyzed Heck reaction and cyclization strategy.



Scheme 2 Retrosynthetic analysis

In a preliminary study, a mixture of MBH adduct **1a**, 2-iodoaniline (**2a**; 2.1 equiv.), $Pd(OAc)_2$ (10 mol%), $NaHCO_3$ (2.5 equiv), and tetrabutylammonium bromide (2.1 equiv) in refluxing tetrahydrofuran was stirred for 12 hours to give a mixture of dihydroquinoline **3a** and quinoline **4a** in 35% yield after column chromatography (Scheme 3).

In the ^1H NMR spectrum of dihydroquinoline **3a**, the characteristic methylene and N–H protons appeared as a singlet and a broad singlet at δ = 3.91 and 5.77 ppm, respectively.

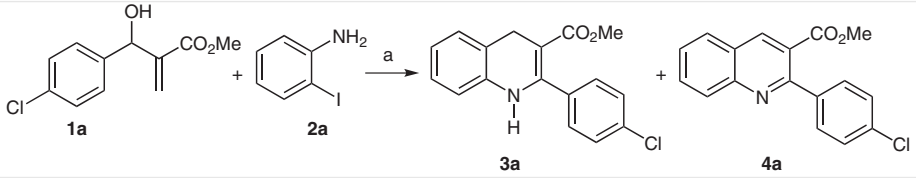
To establish a suitable solvent system for the reaction of with **1a** and **2a**, we screened a number of solvents such as acetonitrile, tetrahydrofuran, and *N*,*N*-dimethylformamide (Table 1, entries 1–3). Of these, acetonitrile (entry 3) showed promise for the tandem cyclization. A slight improvement in yield was achieved when the MBH adduct was added to the reaction mixture after a 15 minute delay (entry 4). In screening various bases,[6a] we observed that potassium bases resulted in decomposition of the starting material (entries 5 and 6). When pyridine was used, the product was obtained in moderate yield (entry 7). The best result, however, was obtained when the reaction was carried out with 0.6 equivalents of 1,4-diazabicyclo[2.2.2]octane (DABCO), which gave an 84% yield (entry 9). The use of excess base or catalyst led to a reduction in the yield or decomposition of the starting material (entries 8 and 10). Although 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated aromatization of heterocyclic compounds is well established,[10] attempts to perform a DBU-mediated one-pot tandem cyclization and aromatization resulted in decomposition of the starting material (entry 11).[10c] Other additives such as 4-(*N*,*N*-dimethylamino)pyridine, triphenylphosphine, quinuclidine, or diisopropylamine either gave low yields or recovery of the starting materials (entries 12–16).

Table 1 Optimization of the Palladium-Mediated Tandem Cyclization[a]

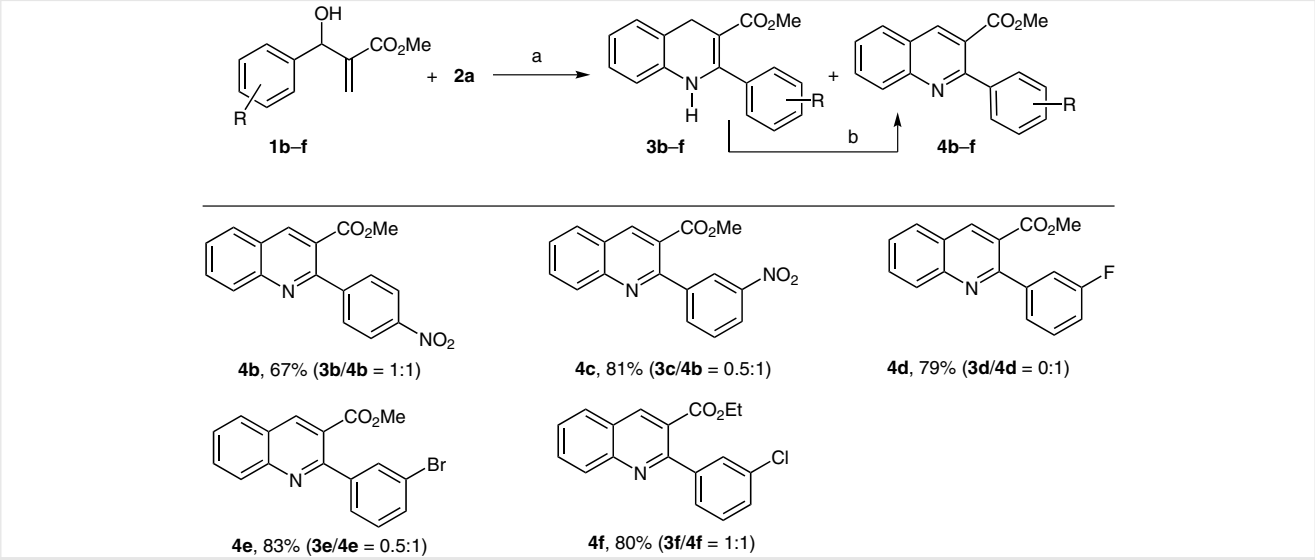
Entry	Solvent	Base	Product ratio **3a**/**4b**	Yield (%) of **3a** + **4b**
1	THF	$NaHCO_3$	0.5:1	35
2	MeCN	$NaHCO_3$	0.5:1	46
3	DMF	$NaHCO_3$	0.5:1	32
4	MeCN[b]	$NaHCO_3$	0.5:1	51
5	MeCN	K_2CO_3	–	decomposed
6	MeCN	$KHCO_3$	–	decomposed
7	MeCN	pyridine	0.4:1	54
8	MeCN	DABCO	1:1	62
9	MeCN	**DABCO**[c]	**1:1**	**84**
10	MeCN	DABCO[c]	1:1	43[d]
11	MeCN	DBU[c]	–	decomposed
12	MeCN	Et_3N	1:1	45[e]
13	MeCN	DMAP	–	no reaction
14	MeCN	Ph_3P	–	traces
15	MeCN	quinuclidine	1:1	23[e]
16	MeCN	$(i\text{-}Pr)_2NH$	1:1	48[e]

[a] Reaction conditions: **1a** (100 mg, 0.442 mmol), $Pd(OAc)_2$ (10 mol%), **2a** (2.1 equiv), solvent (2 mL), base (1.0 equiv), reflux, 12 h.
[b] **1a** added after a delay of 15 min.
[c] 0.6 equiv.
[d] $Pd(OAc)_2$ (30 mol%).
[e] Some starting material was present even after 24 h.

Next, we examined the substrate scope for a broad range of MBH adducts of various aryl and hetaryl aldehydes under the optimized reaction conditions.[11] All the substrates gave the desired products in moderate to good yields (48–82%); the results are summarized in Scheme 4 and Scheme 5.



Scheme 3 Synthesis of quinolines from the MBH adduct of benzaldehyde. *Reaction conditions*: (a) $Pd(OAc)_2$ (10 mol%), TBAB (2.1 equiv), $NaHCO_3$ (2.5 equiv), THF, reflux, 12 h.

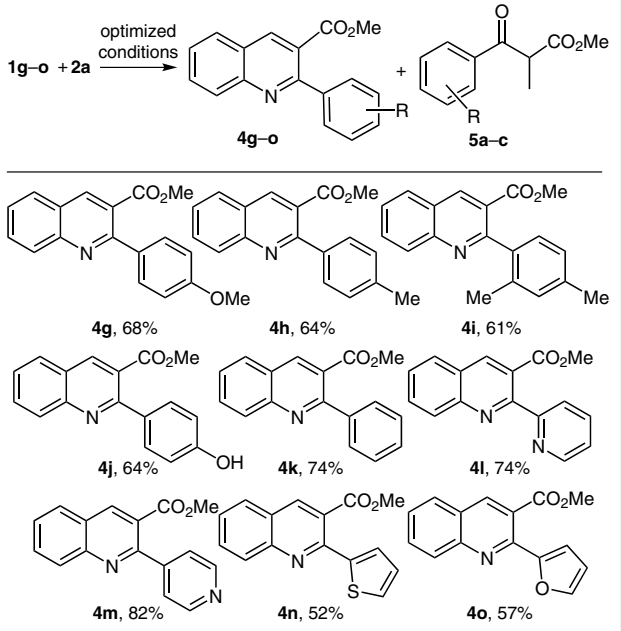


Scheme 4 Synthesis of quinoline derivatives via tandem cyclization. *Reaction conditions*: (a) **1** (100 mg), $Pd(OAc)_2$ (10 mol%), **2a** (2.1 equiv), MeCN (2 mL), DABCO (1.0 equiv), reflux. (b) DBU (1.5 equiv), MeCN, 24 h. Product ratios were determined by ^1H NMR analysis of the crude samples. Reported yields are isolated yields after column chromatography based on the MBH adducts **1**.

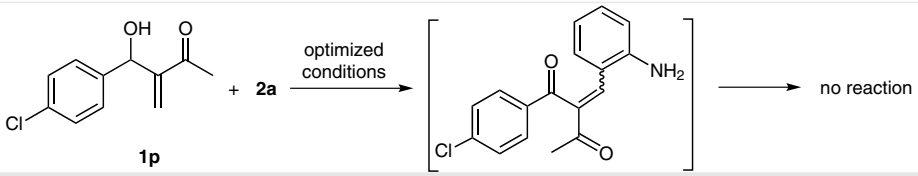
An obvious trend was observed in that MBH adducts containing electron-withdrawing substituents gave better yields of mixtures of products **3** and **4** than did MBH adducts containing electron-donating substituents (Schemes 4 and 5).

The crude product mixtures were filtered through a pad of Celite and, where necessary, subjected to one-pot DBU-mediated aromatization to convert the 1,4-dihydroquinolines **3** into quinolines **4**. The 3-nitro MBH adduct **1c** proved to be a better substrate than the 4-nitro MBH adduct **1b**. The 4-fluoro MBH adduct **1d** gave quinoline **4d** in 79% yield, whereas the 4-bromo MBH adduct **1e** gave a good yield of a mixture of compounds **3e** + **4e**, and 4-chloro MBH adduct ethyl ester **1f** gave a good yield of **3f** + **4f**; these mixtures were subjected to subsequent aromatization to give the appropriate quinolines **4**.

The Heck reaction and cyclization of MBH adducts **1** containing electron-donating substituents with 2-iodoaniline gave the desired products **4g**–**i**, along with the corresponding α-methyl β-keto ester derivatives **5a**–**c** as byproducts in 8–12% yield in short reaction times (3–5 h). The formation of **5** is implies that a palladium species generated by β-hydride elimination might undergo coupling with the MBH adduct **1** (see Supporting Information).[12] The unprotected 4-hydroxylated MBH adduct and the benzaldehyde MBH adduct gave the desired compounds **4j** and **4k**, respectively, in moderate to good yields. Interestingly, the 2- and 4-pyridine-substituted MBH adducts gave the corresponding quinoline derivatives **4l** and **4m** in good yields (74 and 82%, respectively). Furthermore, the less-stable hetaryl MBH adducts gave the corresponding hetaryl-substituted quinoline derivatives **4n** and **4o** in moderate yields. However, the corresponding pyrrole-substituted MBH adduct and 2-iodoaniline did not give the desired product under the optimized reaction conditions.



Scheme 5 Synthesis of quinoline derivatives via tandem cyclization. *Reaction conditions*: (a) **1** (100 mg), $Pd(OAc)_2$ (10 mol%), **2a** (2.1 equiv), MeCN (2 mL), DABCO (1.0 equiv), reflux. (b) DBU (1.5 equiv), MeCN, 24 h. Product ratios were determined by ^1H NMR analysis of the crude samples. Reported yields are isolated yields after column chromatography based on the MBH adducts **1**.



Scheme 6 Competitive tandem cyclization of MBH adduct **1p**

When MBH adduct **1p** was subjected to tandem cyclization under the optimized conditions, the substrate did not undergo a Heck reaction (Scheme 6).[13]

The palladium-catalyzed Heck reaction and cyclization described here can be rationalized by invoking a mechanism proposed in an earlier report.[7]

In conclusion, we have demonstrated an efficient one-pot synthesis of 2,3-disubstituted quinoline derivatives from readily available multifunctionalized MBH adducts of (het)aryl aldehydes. The isolable α-benzyl β-keto ester derivatives can be converted into the corresponding quinoline derivatives under the optimized conditions.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379938.

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(11) **1,4-Dihydroquinolines 3 and Quinolines 4; General Procedure**

A mixture of 2-iodoaniline (**2a**; 2.1 equiv), Pd $(OAc)_2$ (10 mol%), DABCO (0.6 equiv), and TBAB (2.1 equiv.) in MeCN (2 mL) was refluxed under argon. After 15 min, the MBH adduct **1** (100 mg) was added. When the reaction was complete (TLC), the mixture was allowed to cool to r.t. and filtered through a Celite pad. The resulting mixture of compounds **3** and **4** was subjected to aromatization with DBU and purified by column chromatography (silica gel) to give the quinoline **4**.

Methyl 2-(4-Chlorophenyl)-1,4-dihydroquinoline-3-carboxylate (3a) + Methyl 2-(4-Chlorophenyl)quinoline-3-carboxylate

Yellow oil; yield: 110 mg (84%); IR (CH_2Cl_2): 3389, 3096, 1728, 1622, 1593, 1485, 1366, 755cm^{-1}; ^{1}H NMR (500.1 MHz, $CDCl_3$): δ = 3.50 (s, 3 H), 3.78 (s, 3 H), 3.91 (s, 2 H), 5.77 (br s, 1 H), 6.57 (m, 1 H), 6.94 (m, 1 H), 6.96 (m, 2 H), 7.08 (m, 2 H), 7.38 (m, 2 H), 7.45 (m, 2 H), 7.58 (m, 2 H), 7.62 (t, *J* = 7.0 Hz, 1 H), 7.83 (m,

1 H), 7.92 (d, *J* = 8 Hz, 1 H), 8.16 (d, *J* = 8.5 Hz, 1 H), 8.65 (s, 1 H); ^{13}C NMR (125.7 MHz, CDCl): δ = 27.94, 50.87, 52.53, 95.58, 114.31, 121.38, 123.34, 124.61, 125.88, 127.08, 127.52, 128.30 (2 C), 128.43 (2 C), 128.59 (2 C), 129.09 (2 C), 129.31 (2 C), 129.53 (2 C), 130.01, 131.88, 134.81, 134.90, 136.62, 139.04, 139.58, 148.45, 156.89, 167.57, 168.00; FAB: *m/z* [M + 1]$^+$ calcd for $C_{17}H_{12}ClNO_2$: 297.06; found: 298.31: *m/z* [M + 1]$^+$ calcd for $C_{17}H_{14}ClNO_2$: 299.07; found: 300.28.

Methyl 2-Pyridin-2-ylquinoline-3-carboxylate (4l)

Pale-yellow solid; yield: 101 mg (74%); mp 109–110 °C; IR (KBr): 2932, 1718, 1625, 1598, 1488 cm^{-1}; ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 3.93 (s, 3 H), 6.49 (m, 1 H), 6.77 (m, 1 H), 7.14 (t, *J* = 8.0 Hz, 1 H), 7.23 (t, *J* = 7.5 Hz, 1 H), 7.50 (m, 1 H), 7.83 (m, 2 H), 8.13 (m, 1 H), 8.47 (s, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.46, 120.09, 122.19, 122.45, 122.90, 124.52, 125.97, 126.99, 127.47, 127.84, 128.67, 130.31, 130.77, 135.61, 144.18, 166.47; FAB: *m/z* [M$^+$] calcd for $C_{16}H_{12}N_2O_2$: 264.09; found: 264.45.

Methyl 2-(2-Thienyl)quinoline-3-carboxylate (4n)

Pale-yellow oil; yield: 71 mg (52%); IR (KBr): 2932, 1722, 1624, 1585, 1492 cm^{-1}.

^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 3.92 (s, 3 H), 7.12 (m, 1 H), 7.26 (s, 1 H), 7.40 (m, 1 H), 7.48 (d, *J* = 8.5 Hz, 1 H), 7.57 (d, *J* = 7.5 Hz, 1 H), 7.78 (m, 1 H), 8.12 (m, 1 H), 8.45 (s, 1 H); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 52.08, 99.39, 99.89, 107.19, 110.43, 115.44, 116.74, 118.95, 126.88, 128.08, 139.39, 142.39, 147.42, 154.11, 166.48; FAB: *m/z* [M$^+$] calcd for $C_{15}H_{11}NO_2S$: 269.05; found: 269.37.

(12) Usually, short-lived **H–Pd–I** species undergo immediate reductive elimination with a base, but MBH adducts with electron-donating substituents can undergo coupling with **H–Pd–I**, presumably under the influence of the +I effect of the electron-donating group.

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