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An Improved Larock Synthesis of Quinolines via a Heck Reaction of 2-Bromoanilines and Allylic Alcohols

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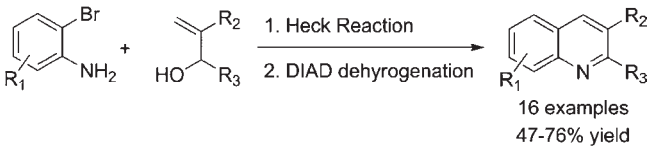
ABSTRACT



A modified Larock method has been developed for the one-pot synthesis of substituted quinolines via a Heck reaction of 2-bromoanilines and allylic alcohols followed by dehydrogenation with diisopropyl azodicarboxylate (DIAD).

Substituted quinoline cores are important biologically active motifs, and are found in both natural products[1] and active pharmaceutical ingredients (APIs) including Cethromycin (antibacterial),[2] Pitavastatin (statin),[3] Montelukast (asthma and allergy),[4] and many antimalarial drugs.[5] Given their potent bioactivity, a number of strategies to assemble the quinoline structure have been reported.[6−11] While many of these techniques have seen frequent use, their substrate scope is often limited due to the requirement of harsh reaction conditions and/or a lack of regioselectivity for *meta*-substituted anilines. Some established methods also require synthetically complex substrates, which are several steps from commercially available materials.

In 1991 Larock demonstrated a relatively mild and regioselective procedure to synthesize substituted quinolines from the Heck reaction of 2-iodoaniline with four different allylic alcohols.[12] This transformation proceeds first via a Heck reaction/isomerization sequence to give a β-aryl ketone,[13−15] which further proceeds through an intramolecular condensation to form the 3,4-dihydroquinoline (Figure 1a). Under the reaction conditions the dihydroquinoline subsequently undergoes a palladium-catalyzed dehydrogenation reaction to provide the desired quinoline product. Unfortunately, disproportionation of the dihydroquinoline to the tetrahydroquinoline was also observed during the reaction unless toxic hexamethylphosphoramide (HMPA) was used as the solvent (Figure 1b). We felt that the utility of this transformation could be greatly improved if more widely available 2-bromoanilines could be employed as substrates and a more efficient dehydrogenation of the 3,4-dihydroquinoline could be established. Herein, we report an improved Larock

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(1) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187.
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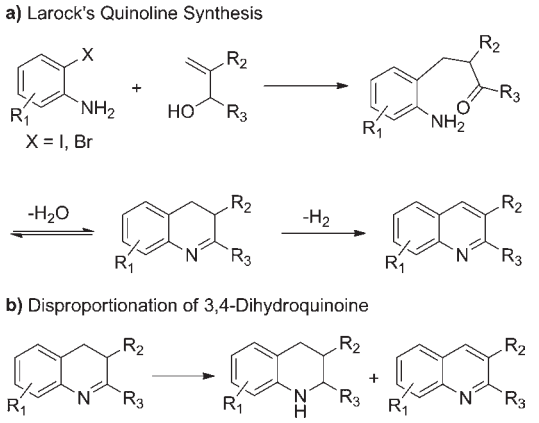

Figure 1. Larock's synthesis of quinoline from 2-haloanilines and allylic alcohols (a) and the observed disproportionation of the 3,4-dihydroquinoline intermediate (b).

synthesis of substituted quinolines based on a Heck reaction of readily available 2-bromoanilines and allylic alcohols, followed by a notably efficient dehydrogenation with diisopropyl azodicarboxylate (DIAD).

The initial conditions examined for the Heck reaction of 2-bromoaniline and 3-buten-2-ol were based on a procedure earlier developed for use in a microreactor.[16] At 90 °C, the reaction proceeded to full conversion in under an hour. However, both 2-methylquinoline and 2-methyl-1,2,3,4-tetrahydroquinoline were isolated from the reaction mixture, suggesting that disproportionation of 2-methyl-3,4-dihydroquinoline was occurring under the reaction conditions.

To address this problem, several strategies for the dehydrogenation of the dihydroquinoline intermediate were investigated. Treatment with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) gave an intractable paste, and while the use of palladium on carbon with a sacrificial alkene did provide the desired quinoline product, it was accompanied by significant amounts of decomposition. It was hypothesized that an effective alternative for the desired dehydrogenation might include an imine surrogate. However, since imines are prone to hydrolysis, more stable azo compounds were examined instead. Gratifyingly, it was found that performing the reaction with 3 equiv of azobenzene increased the yield of the desired quinoline product from 50% to 75% (Table 1, entries 1–4). Unfortunately, some tetrahydroquinoline formation was still observed, and the large excess of azobenzene complicated purification of the product.

As an alternative azo compound, diisopropyl azodicarboxylate (DIAD) was next considered, since similar compounds have been reported to be effective for the dehydrogenation of tertiary amines[17] and thus might allow

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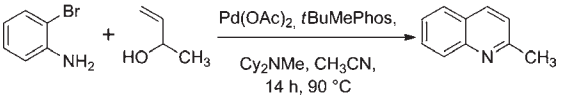
(17) Xu, X.; Li, X.; Ma, L.; Ye, N.; Weng, B. *J. Am. Chem. Soc.* **2008**, *130*, 14048–14049.

Table 1. Screening of Azo Compounds for Dehydrogenation

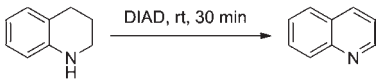


entry	azo additive	equiv	yield[a]
1	none	0	50%
2	azobenzene	1.2	65%
3	azobenzene	2.0	71%
4	azobenzene	3.0	75%
5[b]	DIAD	1.0	79%
6[b]	DIAD	2.0	77%

[a] GC yield. [b] The Heck reaction was allowed to proceed for 1 h. Then DIAD was added and allowed to react for 1 h at 90 °C. Note: *t*BuMePhos is 2-di-*tert*-butylphosphino-2′-methylbiphenyl.

both the dihydroquinoline and the tetrahydroquinoline byproduct to be converted to the desired quinoline. Indeed, an investigation into the dehydrogenation of 1,2,3,4-tetrahydroquinoline showed that the use of DIAD resulted in complete conversion to the desired quinoline product in less than 30 min at room temperature (Table 2). We hypothesize that this dehydrogenation occurs through the generation of a dihydroquinoline intermediate, which was observed by gas chromatography. While the amine base required for the Heck reaction impeded dehydrogenation of tetrahydroquinoline, we found that at 90 °C the

Table 2. Dehydrogenation of Tetrahydroquinoline with DIAD



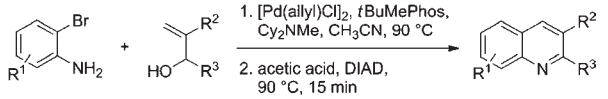
entry	solvent	additive	equiv	yield[a]
1	dioxane	none	2.4	85%
2	dioxane	none	1.2	34%
3	acetonitrile	none	2.4	82%
4	acetonitrile	Cy_2NMe	2.4	27%
5[b]	acetonitrile	$[Cy_2MeNH]Br$	2.4	89%

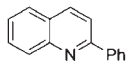
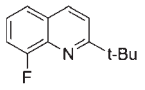
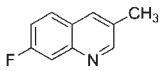
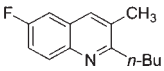
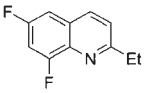
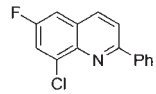
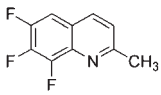
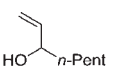
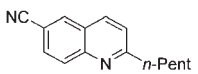
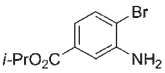
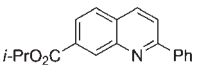
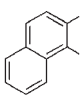
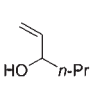
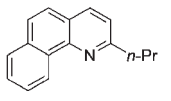
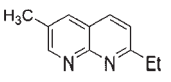
[a] GC yield. [b] Run at 90 °C to keep $[Cy_2MeNH]Br$ in solution.

protonated ammonium bromide salt present at the end of the Heck reaction had no analogous negative effect (Table 2, entries 4–5). Finally, to confirm the activity of DIAD in a one-pot procedure, it was added after the Heck reaction of 2-bromoaniline and 3-buten-2-ol and found to give the desired 2-methylquinoline (Table 1, entries 5–6).

With a viable two-step, one-pot procedure realized, we next sought to optimize the transformation. For the Heck reaction, an allylpalladium(II) chloride dimer was discovered to provide a more active catalyst in combination with the biaryl phosphine ligand relative to palladium(II) acetate. Additionally, the efficiency of the dehydrogenation was further improved (~5%) by adding acetic acid (0.5 equiv) prior to DIAD addition to

Table 3. Quinoline Synthesis with Various Substrates[a]



entry	ArBr	allylic alcohol	product	yield[b] (reaction time)
1[c]				71% (30 min)
2				58% (1 h)
3				51% (3.5 h)
4[d]				61% (19 h)
5				75% (15 min)
6[c]				56% (1 h)
7				75% (15 min)
8				68% (2 h)
9[c,e]				67% (2 h)
10[d,e]				63% (1 h)
11[d]				51% (1.5 h)

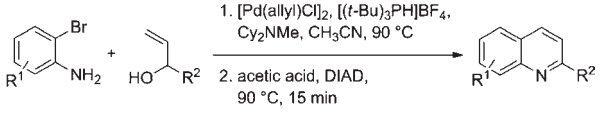
[a] Reaction conditions: ArBr (1.5 mmol), allylic alcohol (1.8 mmol), Cy_2NMe (1.8 mmol), Pd (1 mol %), and ligand (3 mol %). [b] Isolated yields (average of 2 runs). [c] Allylic alcohol (1.5 mmol). [d] Pd (2 mol %) and ligand (6 mol %). [e] Dioxane used as a cosolvent.

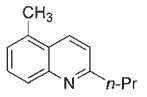
ensure complete formation of the ammonium salt. To prevent solidification of the reaction mixture due to precipitation of the ammonium salt, the acetic acid and DIAD were added and allowed to react at an elevated temperature (90 °C). It is important to note that DIAD should be added slowly on larger scales due to an observed exotherm.

To demonstrate the generality of the transformation, the optimized conditions were applied to a variety of 2-bromoanilines and allylic alcohols (Table 3). In general, 2- and 3-substituted quinolines could be obtained in reasonable yields. Unfortunately, attempts to synthesize 4-substituted quinoline products were hampered by a lack of regioselectivity during palladium insertion into the internal alkene of the allylic alcohol. For most substrates, a small excess of the allylic alcohol was used (1.2 equiv), with the exception of α-vinylbenzyl alcohol. When greater than 1.0 equiv of α-vinylbenzyl alcohol was used the product yield was decreased and side products were observed (Table 3, entries 1, 6, 9). Notably, the method proved to be mild enough to tolerate esters and nitriles, which can be degraded under harsher reaction conditions (Table 3, entries 8–9).

Unfortunately, incomplete conversion of the aryl bromide was generally observed for substrates requiring reaction times in excess of 6 h. This cessation of reactivity is likely due to decomposition of the allylic alcohol via isomerization to the corresponding ketone. By simply increasing the palladium loading to 2 mol %, full conversion of the starting materials could be achieved for most of these difficult substrates (Table 3, entries 4, 10–11). However, this strategy was unsuccessful when a substituent was

Table 4. Quinoline Synthesis with More Difficult Substrates[a]



entry	ArBr	allylic alcohol	product	yield[b] (reaction time)
1				69% (30 min)
2[c]				47% (30 min)
3[c]				76% (1 h)
4				63% 30 min
5[c]				46% (1 h)

[a] Reaction conditions: ArBr (1.5 mmol), allylic alcohol (1.8 mmol), Cy_2NMe (1.8 mmol), Pd (1 mol %), and ligand (1 mol %). [b] Isolated yields (average of 2 runs). [c] Pd (2 mol %) and ligand (2 mol %).

located *ortho* to the bromide, which precludes the synthesis of 5-substitued quinolines using this protocol.

To address this limitation a number of alternative phosphine ligands were examined, and it was found that using tri-*tert*-butylphosphine in the ligand to palladium ratio reported by Fu provided a significantly more active catalyst for the synthesis of 5-substituted quinolines (Table 4, entries 1−3).[18,19] Modest increases in yield were also observed when this protocol was applied to other challenging substrates, including 3-bromo-4,5-diaminobenzotrifluoride and methyl 2-hydroxy-3-butenoate (Table 4, entries 4, 5). However, the use of tri-*tert*-butylphosphine with the substrates reported in Table 1 did not significantly influence product yields.

Of particular note is the utility of our method for the preparation of fluorinated quinolines from commercially available fluorinated 2-bromoanilines, since fluorinated compounds constitute a significant number of APIs.[20−22] The position of the fluorine groups on the quinoline ring is known to strongly influence its mutogenicity and rate of *in vivo* degradation.[23−28] We have demonstrated that all four 2-bromofluoroaniline regioisomers are suitable substrates for this procedure, allowing the synthesis of 5-, 6-, 7-, or 8-substituted fluoroquinolines. Facile access to these structures is desirable in a medicinal chemistry setting to perform SAR studies.[21,29−31]

In summary, we have developed a mild method for the synthesis of substituted quinolines via a two-step, one-pot palladium-catalyzed Heck reaction followed by a DIAD-mediated dehydrogenation using readily available 2-bromoanilines and allylic alcohols as substrates.

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Supporting Information Available. Procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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