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Diversely Substituted Quinolines via Rhodium-Catalyzed Alkyne Hydroacylation

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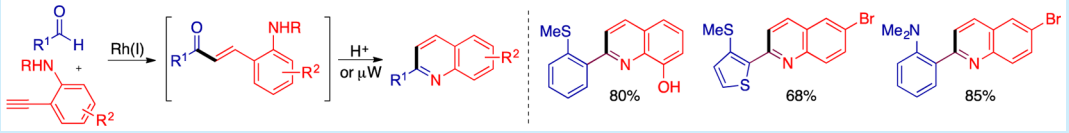
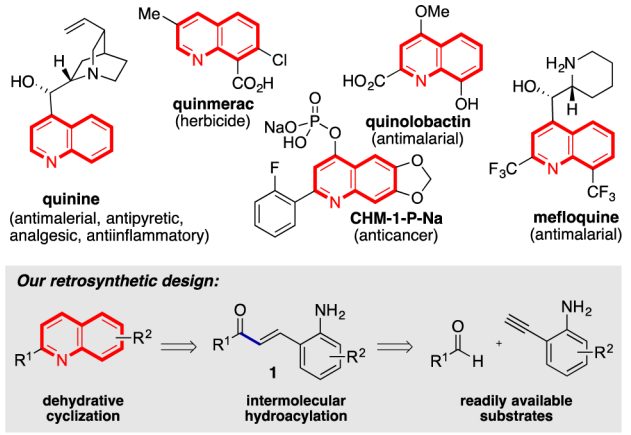
Supporting Information



ABSTRACT: The Rh-catalyzed hydroacylative union of aldehydes and *o*-alkynyl anilines leads to 2-aminophenyl enones, and onward to substituted quinolines. The mild reaction conditions employed in this chemistry result in a process that displays broad functional group tolerance, allowing the preparation of diversely substituted quinolines in high yields. Extension to the use of *o*-alkynyl nitro arenes as substrates leads to 2-nitrochalcones, from which both quinolines and quinoline *N*-oxides can be accessed.

Heterocyclic scaffolds are ubiquitous in pharmaceutical, agrochemical, and many other fine-chemical applications.[1] In particular, quinolines represent privileged structures for a wide range of functions, including anticancer, herbicidal, and antimalarial agents,[2] with quinine being used as a multipurpose treatment since the 17th century (Scheme 1).[3]

Scheme 1. Quinoline Ring System in Pharmaceutical and Agrochemical Compounds, and Our Proposed Retrosynthetic Route



As such, their synthesis has been of great interest to the synthetic and medicinal chemistry community, and while many methods have been developed for the synthesis of the quinoline ring system, classical syntheses typically involve harsh reaction conditions, poor functional group tolerance, and difficulty in controlling regioselectivity.[4] The de novo synthesis of high value quinoline rings from simple, readily accessible starting materials is an area that has received much attention in recent years.[5] There are a number of transition metal-catalyzed processes to achieve this transformation,[6] although many are limited to simple substituents and specific substitution patterns.

Rhodium-catalyzed hydroacylation reactions, formally the atom economic addition of the acyl and hydrogen moieties of an aldehyde across alkenes or alkynes,[7] deliver substituted carbonyl-containing products and as such have great potential as key transformations for heterocycle synthesis. For metal-catalyzed reactions, deleterious reductive−decarbonylation pathways can often limit the efficiency of hydroacylation transformations;[8] however, by employing chelating aldehydes as substrates these pathways can be suppressed and efficient catalysis achieved.[9,10] The low catalyst loadings and mild reaction conditions associated with these transformations often translate into excellent functional group tolerance.

Our laboratory has previously demonstrated the application of intermolecular alkyne hydroacylation to the synthesis of highly substituted furans,[11] while the Dong group has applied alkene hydroacylation to the synthesis of benzofurans.[12] Furthermore, both our laboratory[13] and the Stanley group[14] have described intramolecular conjugate addition procedures to generate dihydroquinolones and chromanones, respectively, using alkyne hydroacylation as the key C−C bond forming transformation. By targeting an intermediate (**1**) on the classical Friedländer synthesis (Scheme 1),[4a,b] we proposed that we could access functionalized quinolines from the union of simple aldehydes (**2**) and 2-alkynyl anilines (**3**). Such a route would not suffer from issues of regioselectivity and should reflect the diversity of groups tolerated in hydroacylation reactions.

For our initial investigation, we selected the coupling of *o*-SMe-benzaldehyde (**2a**) and *o*-ethynyl aniline. However, it was soon apparent that using an alkyne component with a free

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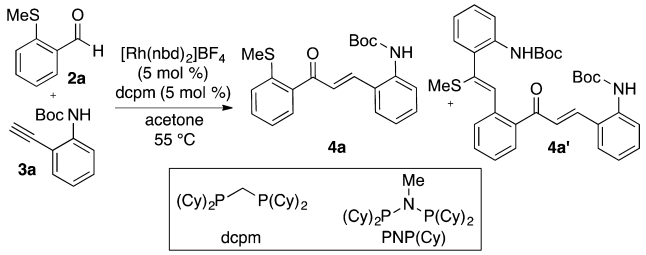
NH_2-group was problematic due to competing imine formation, and thus we moved to the *N*-Boc variant (**3a**). We were pleased to find that the coupling of aldehyde **2a** and alkyne **3a** could be achieved using 5 mol % of a Rh(I)-catalyst incorporating the small-bite-angle phosphine dcpm.[15a] Unfortunately, in addition to the desired product (**4a**), a side product originating from hydroacylation followed by alkyne carbothiolation (**4a′**)[16] was also isolated (Table 1, entry 1). Shortening the reaction time

Table 1. Optimization of the Coupling of Aldehyde 2a and Alkyne 3a[a]



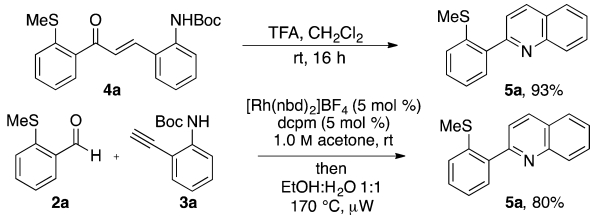
entry	2a:3a	concn (M)	time (h)	ligand	yield (%)	4a:4a′
1	1:1.5	0.5	16	dcpm	85	2:1
2	1:1.5	0.5	3	dcpm	81	4:1
3	1.2:1	0.5	3	dcpm	83	20:1
4[b]	1.2:1	1.0	3	dcpm	96	>20:1
5	1:1.5	1.0	3	PNP(Cy)	90	>20:1

[a]Isolated yields product ratios determined by ^{1}H NMR spectroscopy. [b]Reaction performed at rt.

reduced the extent of this side reaction, although significant carbothiolation was still observed (entry 2). Using alkyne **3a** as the limiting reagent resulted in carbothiolation formation being largely attenuated (entry 3). Gratifyingly, reducing the reaction temperature to ambient fully suppressed carbothiolation, and by using high reaction concentrations the product was isolated in a 96% yield (entry 4). Alternative conditions that could tolerate an excess of alkyne were also developed, utilizing the ligand PNP(Cy),[15b] although for operational simplicity it was preferable to continue to use commercially available dcpm.

Exposure of the isolated enone **4a** to standard TFA/CH_2Cl_2 Boc-deprotection conditions resulted in a deprotection−cyclization cascade, and quinoline **5a** was isolated in an excellent 93% yield (Scheme 2). Unfortunately, any attempt to

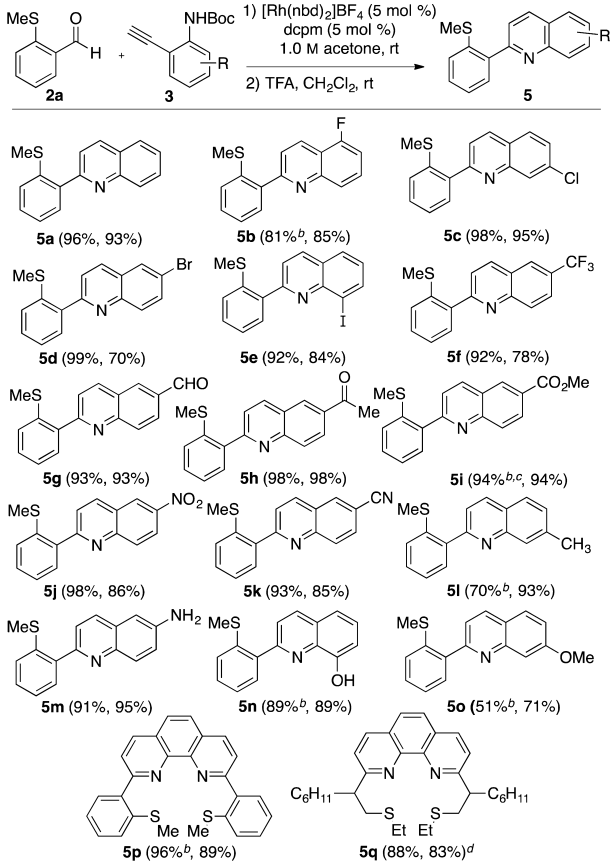
Scheme 2. Deprotection and Cyclizations of Hydroacylation Adduct 4a



combine this acidic deprotection−cyclization sequence with the initial hydroacylation reaction in a one-pot process resulted in a complex mixture of products and only a moderate yield of the quinoline. However, by combining the hydroacylation step with a microwave promoted thermal deprotection−cyclization, quinoline **5a** was obtained in 80% yield (Scheme 2).

Using the high yielding two-step procedure the scope of the alkyne component was explored (Scheme 3). Incorporation of

Scheme 3. Substrate Scope of the Alkyne Component[a]



[a]Reaction conditions: (1) **2a** (0.24 mmol), alkyne (0.2 mmol), $[Rh(nbd)_2]BF_4$ (5 mol %), dcpm (5 mol %), acetone (0.1 mL), rt; (2) TFA (24 equiv), CH_2Cl_2 (0.04 M), rt, 16 h. [b]Reaction at 55 °C. [c]DCE as solvent. [d]dr = 1:1 measured by NMR spectroscopy.

various halides at each individual position around the benzene ring was possible (**5b**−**5e**). In general, electron-withdrawing substituents led to fast, efficient reactions, with such examples as CF_3 (**5f**), various carbonyl groups (**5g**−**5i**), NO_2 (**5j**), and CN (**5k**), all proving to be excellent reaction partners.

The formation of quinolines featuring aldehyde (**5g**) and methyl ketone (**5h**) groups is noteworthy, as they would both be poorly tolerated in many classical syntheses, especially the Friedländer route. More electron-rich quinolines were also prepared, with Me (**5l**), NH_2 (**5m**), and OH (**5n**) substituted products obtained in excellent yields. The only example attempted which showed poor reactivity was the OMe substituted alkyne (**5o**), although moderate yields were still achievable. Finally, by employing dialkynes as the reaction partner it was possible to access a new class of tetradentate phenanthrolines (**5p** and **5q**). All of the hydroacylation reactions described above were performed using 5 mol % of catalyst. However, when conducting a larger scale reaction (1.0 g of alkyne **3a**) just 2 mol % of the catalyst was sufficient to achieve an 84% yield (1.43 g) of enone **4a**.

The aldehyde scope was similarly broad, with electron-rich (Scheme 4, **5r**) and electron-poor (**5s**) aromatic aldehydes equally reactive, as was a thiophene-derived example (**5t**). Employing alkyl aldehydes demonstrates the advantage of a

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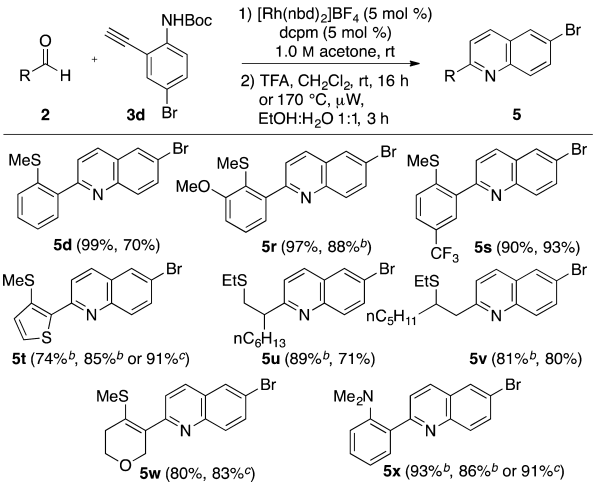
Scheme 4. Substrate Scope of the Aldehyde Component[a]

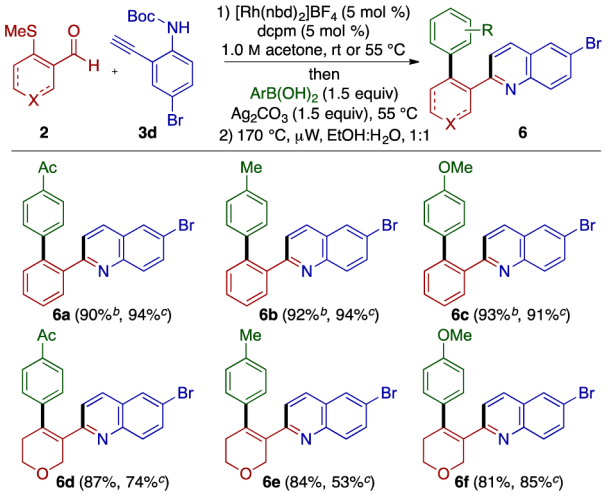


[a]Reaction conditions: (1) **2** (0.24 mmol), **3d** (0.2 mmol), [Rh(nbd)$_2$]BF$_4$ (5 mol %), dcpm (5 mol %), acetone (0.1 mL), rt; (2) TFA (24 equiv), CH_2Cl_2 (0.04 M), rt, 16 h. [b]Reaction at 55 °C. [c]EtOH (1.5 mL), H_2O (1.5 mL), 170 °C, μW, 3 h.

hydroacylation approach to quinolines, as a traditional route to these types of products would likely encounter regioselectivity issues; in the present case, both α-(**5u**) and β-(**5v**) substituted alkyl aldehydes reacted well. The use of alkenyl aldehyde (**5w**) and an amino-directed substrate (**5x**) was also possible.

All of the examples shown in Schemes 3 and 4 employ chelating aldehydes. Although a variety of coordinating groups and substitution patterns can be employed, access to tether-free products would greatly expand the utility of our approach. To achieve this we were able to combine Rh-catalyzed hydroacylation with a second Rh-catalyzed process, namely a Suzuki-type reaction combining aryl sulfides with boronic acids.[17] In the present study (Scheme 5), this was shown to be successful

Scheme 5. Quinoline Formation Using Cascade Hydroacylation/C−S Suzuki-Type Coupling[a]

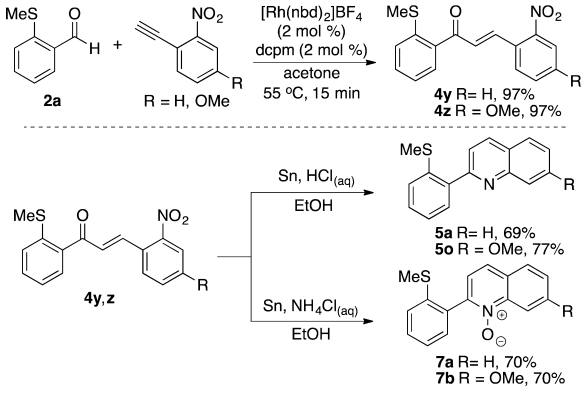


[a]Reaction conditions: (1) **2** (0.24 mmol), **3d** (0.20 mmol), [Rh(nbd)$_2$]BF$_4$ (5 mol %), dcpm (5 mol %), acetone (0.1 mL), then ArB(OH)$_2$ (0.3 mmol), Ag_2CO_3 (0.3 mmol), DCE (0.5 mL); (2) EtOH (1.5 mL), H_2O (1.5 mL), 170 °C, μW, 3 h. [b]Reaction at 55 °C. [c]Reaction at rt.

for both aryl and alkenyl sulfides, employing a range of boronic acids, using only 5 mol % of Rh-catalyst to promote both transformations. Cyclizations provided the sulfur-free quinolines in good yields.

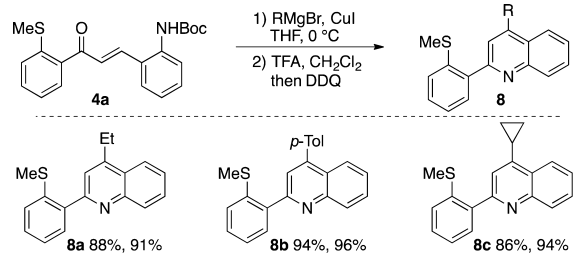
The alkyne scope presented in Scheme 3 shows the broad trend that aryl alkynes bearing electron-withdrawing groups were faster-reacting, higher-yielding substrates than those substituted with electron-donating groups. The methoxy-substituted example (**5o**), in particular, resulted in a low yielding hydroacylation. To address this issue we were attracted to the use of *o*-alkynyl nitro arenes as substrates. The resultant nitro-substituted chalcones are known precursors to quinolines as well as quinoline *N*-oxides.[18] Pleasingly, both the parent arene and an OMe-variant underwent coupling with aldehyde **2a** in 15 min using only 2 mol % catalyst (Scheme 6). Literature conditions then allowed access to both the quinolines (**5a,o**) and quinoline *N*-oxides (**7a,b**) in good yields.

Scheme 6. Quinoline Approach via 2-Nitrochalcones



The 1,4-addition of cuprates into the intermediate enones proved successful as a means to introduce further functionality onto the quinoline core (Scheme 7). Simple alkyl (**8a**) and aryl

Scheme 7. Further Substitution via Intermediate Functionalization



(**8b**) substituents required only catalytic copper, whereas the less reactive cyclopropyl required a preformed cuprate (**8c**). A deprotection−cyclization step, followed by in situ dehydrogenation with DDQ, afforded the 2,4-disubstituted quinolines in excellent yields.

In conclusion, we have developed an efficient and regioselective quinoline synthesis based on the combination of aldehydes and either *o*-alkynyl anilines or *o*-alkynyl nitro arenes, utilizing a commercially available Rh-precatalyst and ligand. The reactions proceed under mild conditions and display excellent functional group tolerance. We were also able to show that by using a tandem hydroacylation/C−S

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functionalization process, the three-component assembly of quinolines could be achieved.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00390.

Experimental procedures and full characterization for all compounds
(PDF)

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Notes

The authors declare no competing financial interest.

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