Synthesis of 1,2-Dihydroquinolines via Hydrazine-Catalysed Ring-Closing Carbonyl-Olefin Metathesis

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Abstract: The synthesis of 1,2-dihydroquinolines by the hydrazine-catalysed ring-closing carbonyl-olefin metathesis (RCCOM) of N-prenylated 2-aminobenzaldehydes is reported. Substrates with a variety of substitution patterns are shown, and the compatibility of these conditions with a range of additives is demonstrated. With an acid-labile protecting group on the nitrogen atom, in situ deprotection and autoxidation furnishes quinolines. In comparison to related oxygen-containing substrates, the cycloaddition step of the catalytic cycle is shown to be slower, but the cycloreversion is found to be more facile.

Quinolines and their partially saturated derivatives are heterocyclic ring systems that commonly occur in molecules with a broad-spectrum of biological activities (Figure 1A).[1] As such, the development of novel synthetic strategies to construct these motifs has remained a perennial interest for synthetic chemists.[2] Traditional methods, including several named reactions (e.g. Skraup,[3] Friedländer,[4] Combes[5]) have long proven valuable for the construction of quinoline structures, although they often necessitate conditions (e.g. strong acid) that are incompatible with many complex molecules. In more recent times, a number of transition metal-catalysed reactions have been reported that enable the construction of quinolino-moieties under mild and selective conditions.[6] Nevertheless, one of the goals of organic synthetic chemistry is to invent technologies that enable the creation of a given molecular target from an ever-growing set of precursor substrates, thereby expanding the flexibility of the chemist to devise optimal synthetic campaigns. In this regard, a missing capability in the quinoline synthesis repertoire is the ability to convert readily available *N*-allyl 2-aminobenzaldehydes **4** (anthranilaldehydes[7]) to 1,2-dihydroquinolines **5** via ring-closing carbonyl-olefin metathesis (RCCOM) (Figure 1B). Here, we show that this goal can be achieved with high efficiency via hydrazine catalysis.

Despite a long history of stoichiometric variants, carbonyl-olefin metathesis (COM) reactions have only recently succumbed to catalysis.[8,9] Our group's contribution to this area has been through the introduction of a hydrazine-catalysed strategy that involved [3+2] cycloadditions and cycloreversions.[10] Recently, we reported that this strategy enabled the synthesis of 2*H*-chromenes via RCCOM of *O*-allyl salicylaldehyde derivatives.[10c] Given the obvious analogies between those substrates and the corresponding nitrogen analogues, we expected that similar success might be found here as well (Figure 1B). On the other hand, given the greater donating power of the nitrogen atom, it was not clear to what degree the rate of the cycloaddition step might be inhibited, or the intermediate cycloadduct **7** shunted down a different mechanistic pathway by premature rupture of the benzylic C-N bond. Despite these concerns, we have found that the RCCOM reaction operates efficiently and with even greater facility than the oxygen congener.

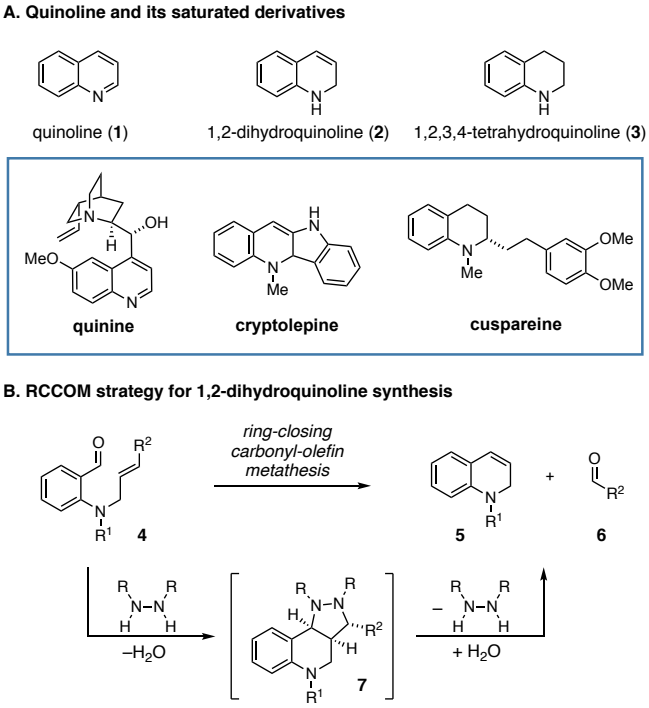

Figure 1. (A) Quinoline, its saturated derivatives 1,2-dihydroquinoline and 1,2,3,4-tetrahydroquinoline, and some natural products containing these ring systems. (B) Hydrazine-catalysed RCCOM strategy to form 1,2-dihydroquinolines.

To determine if it would be possible to achieve such a transformation, we followed our previous strategy[10c] by conducting the cycloaddition and cycloreversion steps independently to determine their efficiency (Scheme 1). Thus, aldehyde **8** was treated with a stoichiometric quantity of hydrazine **9** as the bis-trifluoracetate (TFA) salt in isopropanol at 80 °C. Although the rate for this reaction was slower than the corresponding ether **12** (see Figure 2A), the cycloadduct **10** was isolated in 75% yield. The structure of **10** was confirmed by single-crystal X-ray analysis.[11] Next, we found that cycloreversion of **10** to furnish dihydroquinoline **11** occurred efficiently in 93% yield by heating at 140 °C for 10 min (Scheme 1). In this case, the rate of cycloreversion was significantly faster than with the corresponding ether **13** (Figure 2B). Clearly, the greater donating power of the nitrogen atom retards the rate of bond formation in

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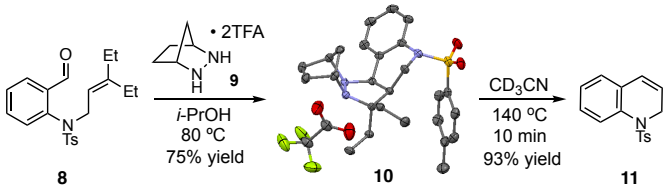
the cycloaddition but assists bond breaking in the cycloreversion. The success of the two reactions shown in Scheme 1 gave us optimism that catalysis might be an effective strategy for this transformation.



Scheme 1. Investigation of RCCOM to form dihydroquinoline **11** by stepwise cycloaddition and cycloreversion reactions.

In our previous work for the RCCOM of *O*-allylsalicylaldehydes, we had found that the use of a 3,3-diethylallyl or similar group was necessary to achieve reasonable reaction rate and to discourage deallylation side reactions. In the current case, given the facility and efficiency of the cycloreversion step, we speculated that simpler allyl groups might suffice. We thus conducted a brief study of the impact of varying this structural component under unoptimized catalytic conditions (Table 1). As seen previously, neither an allyl (**15a**, entry 1) nor a cinnamyl group (**15b**, entry 2) were effective participants for this reaction, but sterically demanding groups such as adamantylidene (**15c**, entry 3) and diethylidene (**15d**, entry 4) provided excellent yields of adduct **11**. In contrast to our previous study, however, an *N*-prenyl group led to a reasonable yield of the RCCOM product (**15e**, entry 5). Although less efficient than the diethylallyl group, prenyl bromide, from which substrate **15e** is derived, is an inexpensive, commercially available building block. We thus selected this group for further optimization (Table 2).

Solvent was found to be an important parameter for this transformation. When methanol (entry 2) was used as solvent instead of acetonitrile (entry 1), nearly full conversion but no increase in yield was observed. Analysis of the crude reaction mixture revealed that dimethyl acetal formation had consumed significant amounts of the starting material. Changing the alcohol solvent to ethanol (entry 3), which we reasoned would have a slower rate of acetalization, improved the yield to 80%. On the other hand, 10% of the diethyl acetal derivative was still observed in the reaction. Switching to isopropanol proved to be most effective (entry 4), leading to essentially full conversion and an 86% yield as determined by ^{1}H NMR (82% isolated yield). We found that good conversion and yield could also be obtained at a reaction temperature of 120 °C (entry 5), although the conversion and yield were somewhat diminished for the same 12 h time frame. Importantly, no reaction occurred when 20% of TFA was used as the catalyst (entry 6), demonstrating the crucial role of the hydrazine catalyst **9**. Other *N*-protecting groups like benzoyl (Bz) and *t*-butyloxycarbonyl (Boc) were also tested, and product yields of 72% and 64% were obtained (entries 7 and 8). On the other hand, an *N*-methyl substrate was fully decomposed under the reaction conditions and delivered no product (entry 9).

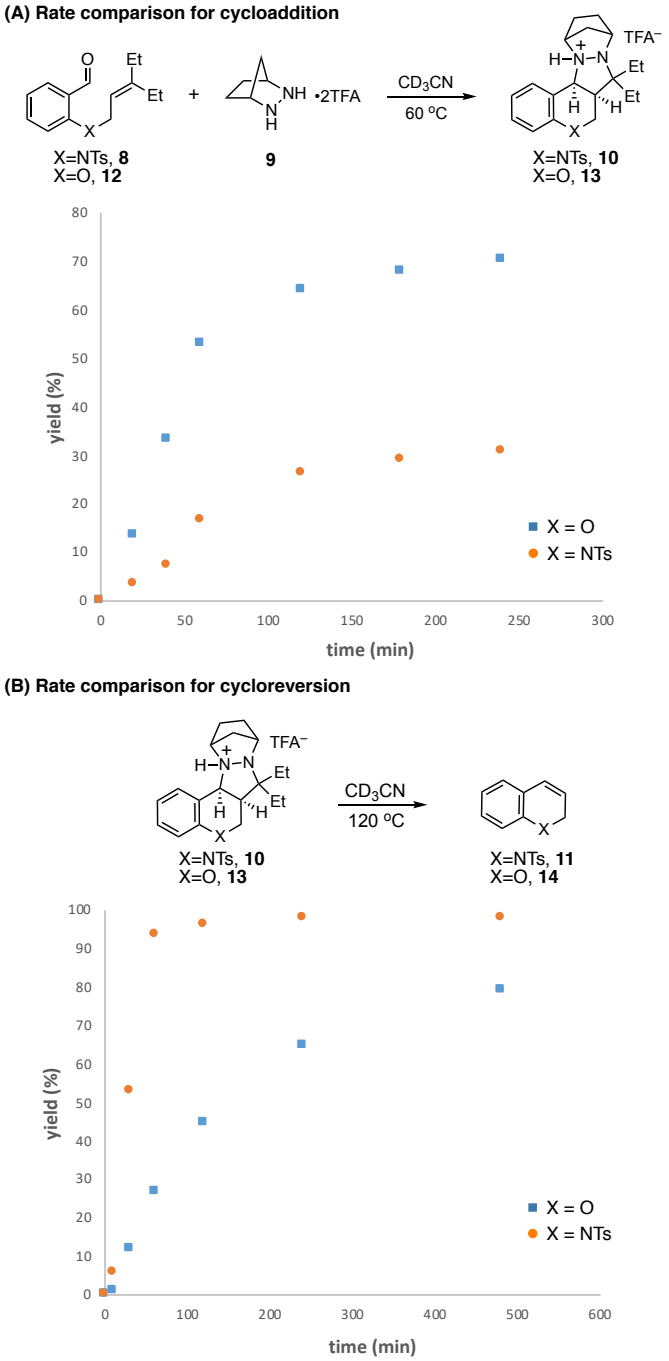
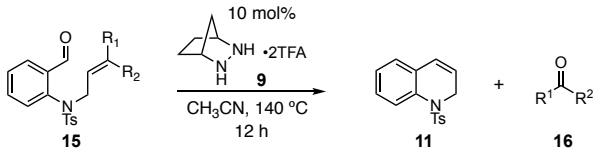


Figure 2 Comparision of conversion rates of O (blue dots) and NTs (orange dots) derivatives for (A) cycloaddition and (B) cycloreversion. Studies performed at lower temperatures (i.e. 60 and 120 °C) than the optimal conditions to aide comparison.

Table 1 Evaluation of the effect of alkene substituents.

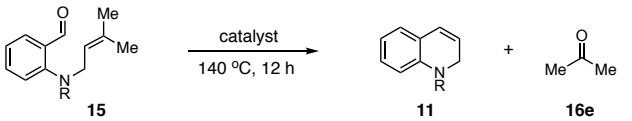


15 **11** **16**

entry	substrate		**15** consumption (%)	**11** yield (%)[a]
1		**15a**	13	0
2		**15b**	11	0
3		**15c**	91	78
4		**15d**	89	73
5		**15e**	71	47

[a] Conversions and yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard.

Table 2 Optimization of reaction conditions.



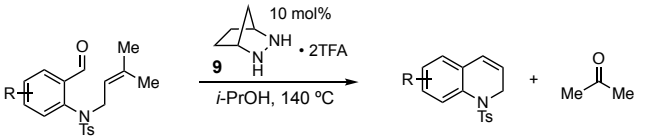
15 **11** **16e**

entry	R	catalyst (mol%)	solvent	conv. (%)	**11** yield (%)[a]
1	Ts	**9**	CH_3CN	71	47
2	Ts	**9**	MeOH	96	49
3	Ts	**9**	EtOH	97	80
4	Ts	**9**	*i*-PrOH	97	86 (82)[b]
5[c]	Ts	**9**	*i*-PrOH	88	75
6	Ts	TFA[d]	*i*-PrOH	15	0
7	Bz	**9**	*i*-PrOH	98	72[b]
8	Boc	**9**	*i*-PrOH	97	64[b,e]
9	Me	**9**	*i*-PrOH	100	0

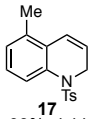
[a] Conversions and yields were determined by ^{1}H NMR using CH_2Br_2 as an internal standard. [b] Isolated yield. [c] At 120 °C. [d] 20% of TFA. [e] 15% of quinoline was observed.

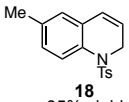
The optimized reaction conditions proved to be efficient for accessing a range of 1,2-dihydroquinolines (Table 3). In addition to **11** (entry 1), we explored the impact of methyl substitution around the ring structure. In terms of the aryl ring, 5-, 6-, and 7-methyl substituted products **17**-**19** were formed in high yield (entries 2-4). In contrast, substitution at the 8-position led to a very poor yield of **20** (entry 5), likely due to severe steric conflict between the methyl substituent and the tosyl group during the cycloaddition. On the hand, methyl substitution on the 2- and 3-positions was well-tolerated (entries 6 and 7), furnishing adducts **21** and **22** in 75% and 71% yields respectively. Halogen substitution in various positions was also feasible (entries 8-11), including for the production of the 7-fluoro adduct **26** (entry 11). Electron-donating methoxy (entry 12) and trifluoromethoxy (entry 13) products **27** and **28** were generated in high yield, while an electron-withdrawing trifluoromethyl-bearing product **29** was also accessible (entry 14). Lastly, the tricyclic adduct **30** was furnished in high yield from a naphthalene substrate (entry 15).

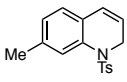
Table 3 Substrate scope studies for hydrazine **9**-catalyzed RCCOM of 1,2-dihydroquinolines.

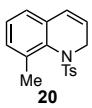


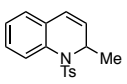
(1) 
11
82% yield

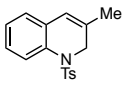
(2) 
17
93% yield

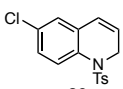
(3) 
18
85% yield

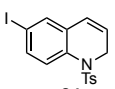
(4) 
19
85% yield

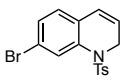
(5) 
20
17% yield

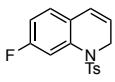
(6) 
21
75% yield

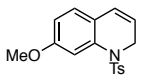
(7)[a] 
22
71% yield

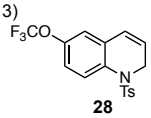
(8) 
23
81% yield

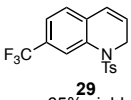
(9) 
24
85% yield

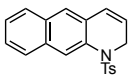
(10) 
25
80% yield

(11) 
26
82% yield

(12) 
27
88% yield

(13) 
28
80% yield

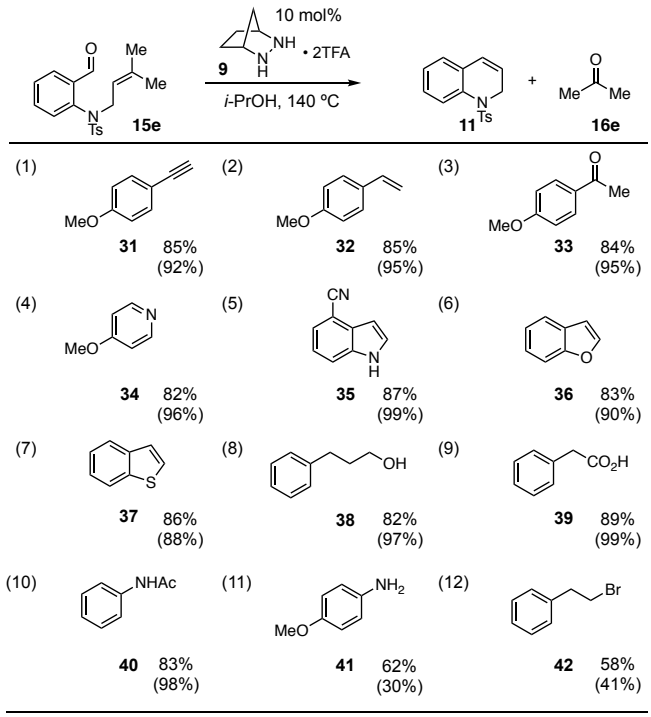
(14) 
29
65% yield

(15) 
30
88% yield

[a] Diethylidene compound was used instead of prenylated moiety.

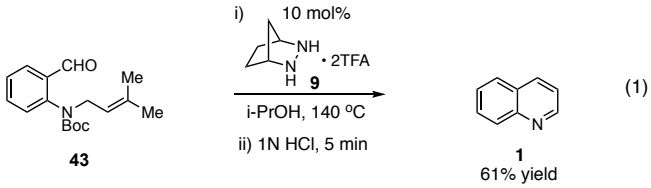
As we showed in our previous work, the conditions for this chemistry are compatible with a broad range of functionality. To demonstrate this fact, we conducted a functional group tolerance screen by adding various compounds to the standard reaction (Table 4).[12] We found that additives like electron-rich terminal alkyne (**31**), alkene (**32**), ketone (**33**), pyridine (**34**), indole (**35**), benzofuran (**36**), benzothiophene (**37**), alkyl alcohol (**38**), alkyl carboxylic acid (**39**) and amide (**40**) all had no adverse effect on the yield of the reaction (entries 1-10), and the additives were largely recovered intact. Additives that did diminish the yield included an aniline (**41**) and an alkyl halide (**42**), presumably due to competitive reaction with either the aldehyde or the catalyst.

Table 4 Additive effect on the hydrazine-catalysed RCCOM to form **11**.[a,b]



[a] Yields of product **11** were determined with ^{1}H NMR. [b] Values in parentheses are recovery yields of the additives determined by ^{1}H NMR.

As mentioned above, the reaction of an *N*-Boc protected substrate led to a 64% yield of 1,2-dihydroquinoline **11** (see Table 2, entry 8); however, we observed the formation of 15% of quinoline **1** as well. Recognizing the importance of the quinoline motif, we developed a procedure to increase the yield of this product (eq 1). Thus, following the RCCOM reaction of **43** under standard conditions, treatment of the reaction mixture with a 1 M solution of HCl for 5 min led to removal of the Boc group and autoxidation to furnish quinoline (**1**) in 61% isolated yield.



To further illustrate some of the synthetic possibilities of this RCCOM reaction, we conducted the transformations shown in Figure 3. First, we found that reaction of 2-fluorobenzaldehyde (**44**) with *N*-tosyl prenylamine (**45**) under classic S_NAr conditions,[13] followed by **9**-catalysed RCCOM led to the formation of adduct **11** in 59% yield over two steps. Second, we found that RCCOM of substrate **46** under standard conditions followed by solvent exchange to CH_2Cl_2 and subjection to Lewis acid-mediated cycloaddition with quinone **47** according to the literature procedure[14] furnished the azapterocarpan analogue **48**[15] in 52% yield over the two telescoped steps.

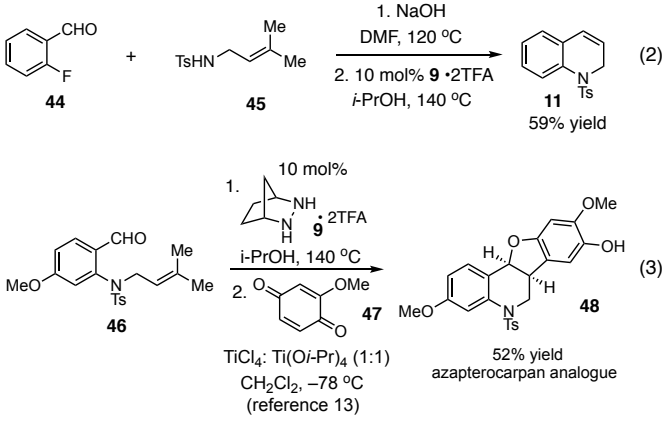


Figure 3. (A) S_NAr and hydrazine-catalysed RCCOM. (B) Telescoped RCCOM / cycloaddition for the synthesis of azapterocarpan analogue **48**.

In conclusion, we have developed a novel approach to the synthesis of dihydroquinolines via hydrazine-catalysed ring-closing carbonyl-olefin metathesis of *N*-prenyl-2-aminobenzaldehydes. In comparison to the analogous ether substrates, the anilides underwent the rate-determining cycloreversion at a more facile rate, which enabled the use of commercially available prenyl bromide as the ultimate alkene source. The simple conditions of alcohol solvent and heat along with the mild nature of the buffered hydrazine catalyst render a wide variety of functionality compatible with this chemistry. This work thus offers a new tool for the construction of a privileged heterocyclic motif and expands the scope of catalytic carbonyl-olefin metathesis chemistry.

Acknowledgements

Financial support for this work was provided by the National Institutes of Health (R35GM127135).

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