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**COMMUNICATION**

# Intermolecular radical addition to *N*-acylhydrazones as a stereocontrol strategy for alkaloid synthesis: formal synthesis of quinine†‡

**Gregory K. Friestad,* An Ji, Chandra Sekhar Korapala§ and Jun Qin¶**

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**Stereocontrolled Mn-mediated radical addition of alkyl iodides to chiral *N*-acylhydrazones enables strategic C–C bond disconnection of chiral amines. This strategy was examined in the context of a total synthesis of quinine, generating new findings of functional group compatibility leading to a revised strategy. Completion of a formal synthesis of quinine is presented, validating the application of Mn-mediated radical addition as a useful new C–C bond construction method for alkaloid synthesis. The Mn-mediated addition generates the chiral amine substructure of quinine with complete stereocontrol. Subsequent elaboration includes two successive ring closures to forge the azabicyclo[2.2.2]octane ring system of quincorine, linked to quinine through two known reactions.**

The long-established antimalarial properties of quinine (Fig. 1) fueled great interest in its synthesis since the very early days of natural product chemistry, endowing quinine with special historical importance in the field.[1,2] Successful syntheses are highlighted by the Woodward–Doering formal synthesis of quinine in 1944,[3] practical approaches to quinine and quinidine (Fig. 1) by Uskokovic, Taylor, and Gates in the 1970s,[4] and the first asymmetric total synthesis of quinine as reported by Stork in 2001.[5] More recently, syntheses by Jacobsen,[6] Kobayashi,[7] Williams (7-hydroxyquinine),[8] Krische,[9] and Aggarwal[10] have highlighted a variety of strategies for construction of the azabicyclo[2.2.2]octane ring system of quinine.

Quinine attracted our interest in the course of a program to develop new C–C bond construction approaches to chiral amines.[11] While numerous indirect methods involving C–N bond construction are available, an attractive alternative is a C–C bond construction *via* addition to the C═N bond of carbonyl imino derivatives (Fig. 2a).[12] We introduced novel chiral *N*-acylhydrazones **A**[13] (Fig. 2b) and their use in a variety of addition reactions under mild conditions,[14,15] including additions of carbon-centered radicals.[16] In general, intermolecular radical additions to imino compounds are attractive complements to polar addition reactions for reasons of functional group compatibility. Despite seminal work by Naito[17] and Bertrand[18] and others[19] to develop such reactions, their strategic use for stereocontrol in total synthesis of multifunctional natural product targets is rare;[20] such applications have been slow to emerge because methods exhibiting versatility with respect to both radical and acceptor are limited. On the other hand, the emergence of Mn-mediated intermolecular radical additions has significantly expanded the scope, enabling effective use of primary iodides and precursors bearing electrophilic functionality in either of the coupling components.[21] Still, the intermolecular radical addition to imino compounds has yet to be validated as a stereocontrol strategy en route to a complex synthetic target. As an alkaloid of some complexity and synthetic challenge, quinine presented a worthy adversary against which to test the limits of this reaction in a multifunctional molecular setting in natural product synthesis.[22]

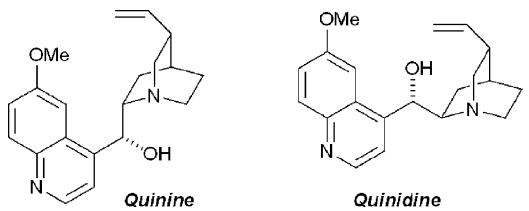


**Fig. 1** Structures of quinine, quinidine, and quinotoxine.

Our initial approach to quinine focused upon strategic application of Mn-mediated hybrid radical–ionic annulation, a type of radical–polar crossover reaction[23] which we have reported as an entry to piperidine and pyrrolidine synthesis.[21a,21b,21e] This would entail intermolecular Mn-mediated radical addition (with stereocontrol as indicated in Fig. 2c) using multifunctional iodide **B** as the radical precursor for addition to hydrazone **1** (Scheme 1), bearing the 6-methoxyquinoline group characteristic of quinine. The piperidine annulation would then be completed *via* $S_N2$-type cyclization employing a suitable leaving group X. The alkene would serve as a handle for a late-stage oxidative cleavage to unveil a two-carbon bridge needed for construction of the quinuclidine ring system.

*Department of Chemistry, University of Iowa, Iowa City, Iowa, 52242. E-mail: gregory-friestad@uiowa.edu*

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§ Current Address: Syngene International, Bangalore, India

¶ Current Address: Merck-Kenilworth, Kenilworth, NJ, USA

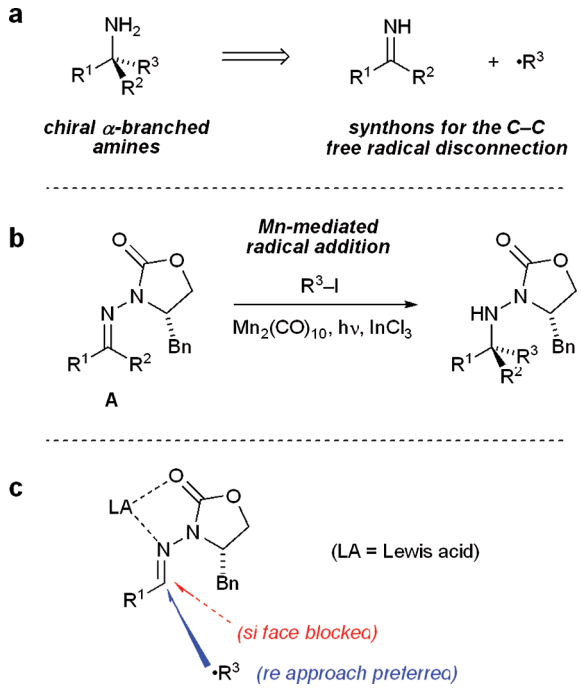
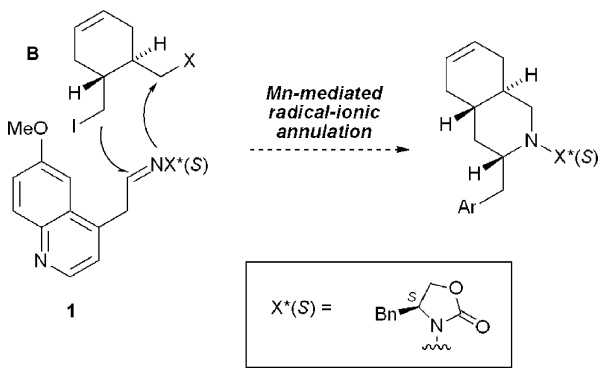
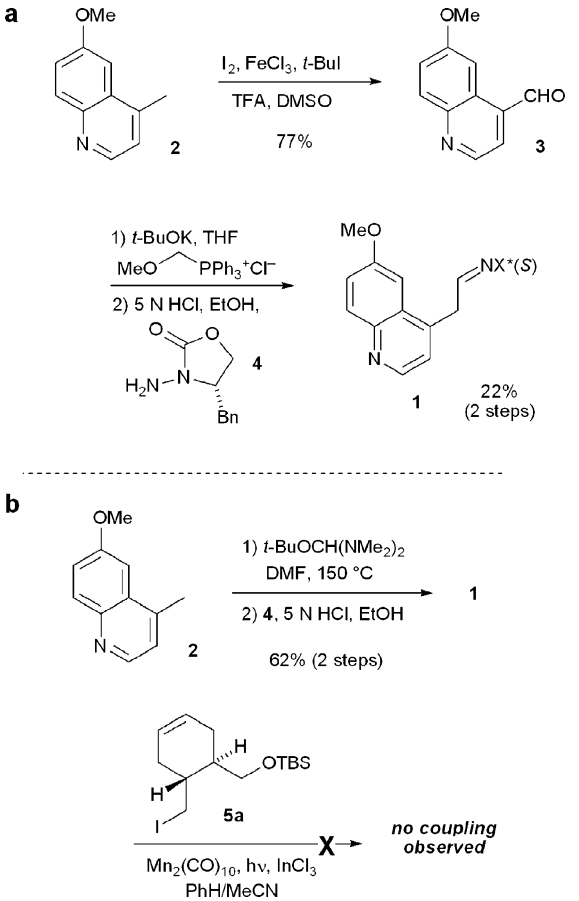



**Fig. 2** Asymmetric radical addition in chiral amine synthesis. (a) Strategic C–C bond disconnection. (b) The Mn-mediated radical addition to chiral *N*-acyl hydrazones. (c) Stereocontrol model for radical addition to chiral *N*-acyl hydrazones.




**Scheme 1**

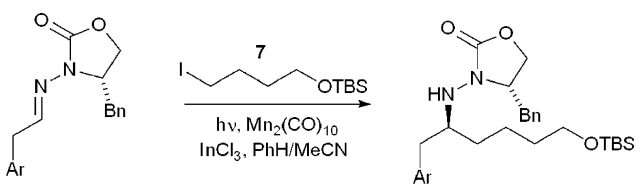
Testing this approach required the *N*-acylhydrazone of homoquininaldehyde, prepared *via* homologation of quininaldehyde (**3**), which in turn was available from 6-methoxy-4-methylquinoline (**2**).[24] Oxidation of **2** according to Minisci *et al.*[25] afforded **3** in 77% yield (Scheme 2a). Wittig reaction with (methoxymethyl)triphenylphosphorane and condensation with *N*-aminooxazolidinone **4** delivered hydrazone **1** in low yield (22%, 2 steps). A more efficient route to **1** (Scheme 2b) was achieved *via* sequential condensations of 6-methoxy-4-methylquinoline with Bredereck's reagent[26] and *N*-aminooxazolidinone **4**, furnishing hydrazone **1** in 62% yield for two steps. Its proposed coupling partner, radical precursor **5a**, was prepared as previously described.[22] The stage was set to attempt the key Mn-mediated coupling. A mixture of hydrazone **1**, iodide **5a**, and $Mn_2(CO)_{10}$ was subjected




**Scheme 2**

to photolysis (Rayonet, 300 nm) in the presence of $InCl_3$, but to our dismay no coupling product was observed.

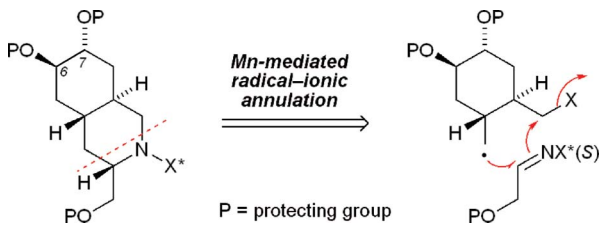
The anomalous failure of the Mn-mediated coupling of **1** and **5a** led us to consider which structural features of the chiral *N*-acyl hydrazone partner might be interfering with the reaction. Mn-mediated radical additions of iodides containing the silyl ether moiety had previously been successful in various contexts,[21b–e] so we turned our attention to the functionalized aryl unit. Its compatibility was addressed by a series of control experiments with hydrazones **6a–6c** and iodide **7** (Scheme 3).[27] Successful Mn-mediated radical addition was observed with hydrazones **6a** and **6b**, leading to the expected products **8a** and **8b** in moderate yield (*ca.* 40%). However, hydrazone **6c**, now containing the pyridyl unit, failed to undergo the Mn-mediated




**Scheme 3**

coupling reaction at all, consistent with the observations on hydrazone **1**. This indicated that the heteroaromatic nitrogen of the quinoline substructure interfered with the Mn-mediated coupling reaction.

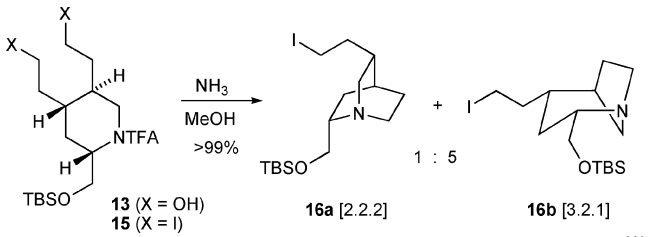
The findings above, taken together with a separate series of experiments demonstrating the detrimental effect of the alkene functionality on yield,[22] led to a revision of the strategy which entailed two main changes (Scheme 4). First, the 6-methoxyquinoline would need to be introduced during a later stage in the synthesis, perhaps using an organometallic reagent prepared from 4-bromo-6-methoxyquinoline,[28] Second, the original late-stage C6–C7 bond cleavage tactic (*e.g.*, alkene ozonolysis) was changed to oxidative cleavage of a vicinal diol, which would require oxidation of the C6–C7 alkene prior to the radical addition.




**Scheme 4**

Synthesis according to this revised plan required diastereoselective preparation of iodide **5b** (Scheme 5), accomplished in seven steps from enantiopure diester **9**. As previously reported, the key Mn-mediated coupling of **5b** and **10** was achieved in 93% yield using only a slight excess of the iodide radical precursor.[22] This prior result was a very attractive way to access adduct **11**, but its synthetic utility remained to be realized.

To convincingly demonstrate the utility of the foregoing Mn-mediated coupling, conversion of adduct **11** to quinine (or a known precursor to quinine) would be required. First, the radical–ionic annulation was completed in a stepwise fashion. The $S_N2$-type cyclization of a tosylate derived from **11** proceeded to a piperidine structure analogous to **12**,[22] but that material could not be advanced due to difficulties in N–N bond cleavage. After some experimentation, it was found that cleavage of the N–N bond prior to piperidine ring construction led to an efficient overall process (Scheme 5). Successive treatment of **11** with *n*-BuLi, TFAA, and $SmI_2$ cleaved the N–N bond; Mitsunobu conditions then completed the annulation sequence in an efficient manner, albeit stepwise, furnishing piperidine **12** on 1.1 mmol scale. Next, in preparation to forge the bicyclic quinuclidine ring system characteristic of the cinchona alkaloids, hydrogenative debenzylation of **12** (Scheme 5) afforded the corresponding vicinal diol; exposure to sodium periodate and hydride reduction furnished diol **13** in excellent yield.

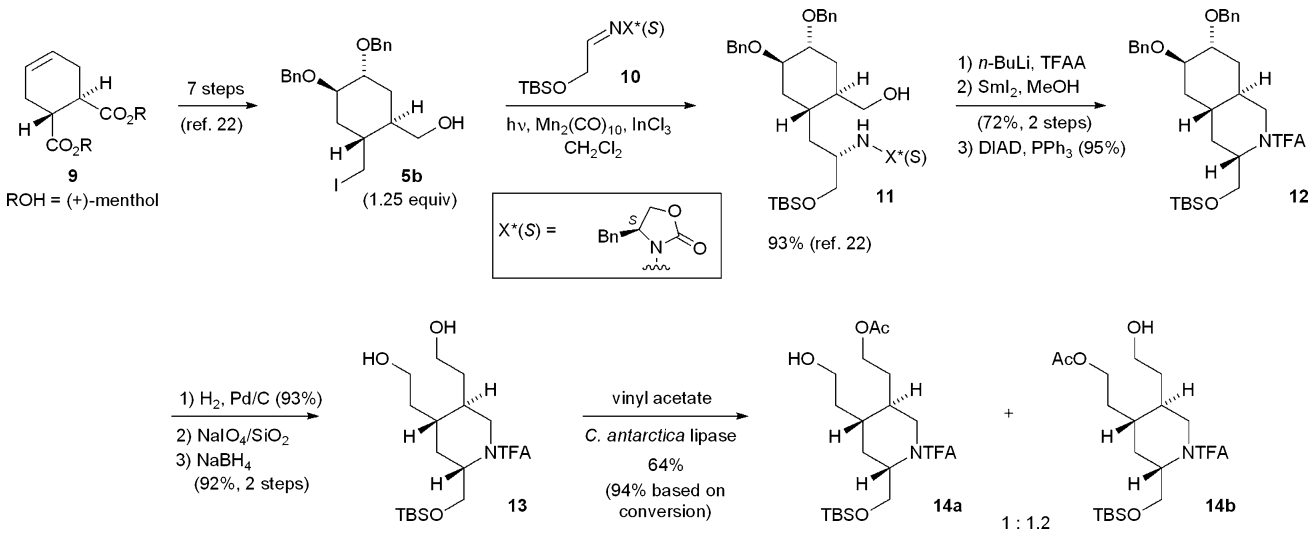



(1)

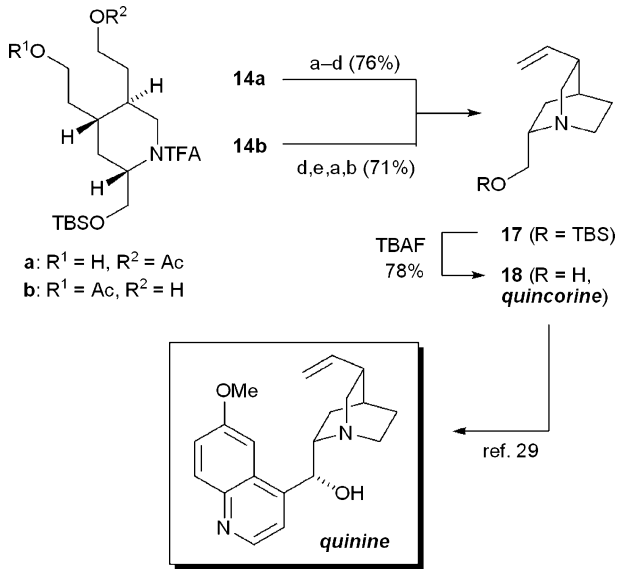
To access the azabicyclic quinuclidine ring system, a group selective cyclization of **13**, possessing two nearly equivalent hydroxyethyl substituents, was attempted. The diiodide **15** was procured from diol **13** by a standard method ($PPh_3/I_2$), but when cyclization was attempted in methanolic ammonia, the result was a mixture of bicyclic tertiary amines **16** (eqn (1)) favoring an undesired [3.2.1] bicyclic structure **16b**.

Prior differentiation of the two hydroxyethyl groups would be needed as a consequence of the undesirable selectivity in cyclization of the diiodide. To this end, when diol **13** was exposed to vinyl acetate in the presence of *Candida antarctica* lipase (Scheme 5), a 64% yield of a mixture of regioisomeric monoacetates **14a** and **14b** was obtained in a 1 : 1.2 ratio, along with 32% of starting material (94% yield based on conversion).

A regio-convergent approach was then adopted as a practical way to make use of both monoacetates **14a** and **14b**; these were both processed with the same set of standard transformations (Scheme 6), converting both to the same bicyclic quinuclidine




**Scheme 5**




**Scheme 6** Conditions: a) $I_2$, $PPh_3$, imidazole; b) $NH_3$, MeOH; c) $Ba(OH)_2$; d) $NO_2C_6H_4SeCN$, then $H_2O_2$ (for **14a**) or MCPBA (for **14b**); e) NaOMe, MeOH.

product **17**. For **14a**, the sequence entailed conversion of the free hydroxyl group to the corresponding iodide, cyclization in methanolic ammonia, acetate saponification, and selenoxide elimination to generate the vinyl group, producing **17** in 76% overall yield. For **14b**, essentially the same tactics were applied in a different order to furnish **17** in 71% yield. Finally, after desilylation (TBAF), the material obtained from both sequences was found to match an authentic sample of quincorine (**18**). Two known transformations[29] complete the synthetic pathway from **18** to quinine, and this route therefore constitutes a formal synthesis.

In conclusion, a Mn-mediated radical–ionic annulation strategy was validated as a synthetic route to quinine. Structural features which interfere with the Mn-mediated radical addition were uncovered *via* a series of control experiments, which guided revision of the synthetic strategy. After completing the radical–ionic annulation in a stepwise fashion, a problematic group-selectivity issue was surmounted by a regio-convergent process for assembling the quinuclidine ring system, completing a formal synthesis of quinine. This synthesis of quinine offers the first demonstration of the utility of intermolecular radical addition to imino compounds as a stereocontrol strategy in synthesis of complex multifunctional targets.

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