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Quinine Synthesis Studies: A Radical–Ionic Annulation via Mn-Mediated Addition to Chiral *N*-Acylhydrazones

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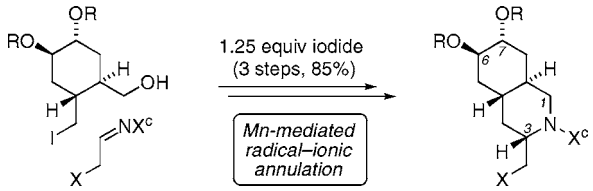
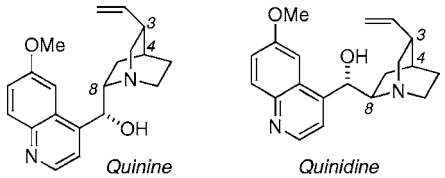
ABSTRACT



A radical–ionic annulation approach to functionalized perhydroisoquinolines involving Mn-mediated coupling of alkyl iodides and chiral *N*-acylhydrazones was achieved using only 1.25 equiv of the alkyl iodide. Application of this reaction to alkene-containing substrates en route to quinine offered modest yields, decreasing on scaleup. Control experiments revealed that the alkene interfered with the coupling reaction. A revised approach involving prior oxidation of the alkene offered 93% yield in the Mn-mediated coupling, with the adduct obtained as a single diastereomer.

The long-established antimalarial properties of quinine have fueled great interest in synthetic efforts toward quinine since the very early days of natural product synthesis.[1] A surge of media attention accompanied Woodward's formal synthesis of quinine in 1944,[2] but even with practical developments led by Uskokovic, Taylor, and Gates in the 1970s[3] for access to quinine and quinidine, there was still no total synthesis with complete configurational control until 2001. Quinine finally succumbed to the first asymmetric total synthesis as reported by Stork in 2001,[4] and syntheses by Jacobsen[5] and Kobayashi[6] appeared in 2004.

Quinine attracted our interest in the course of our program to develop new C−C bond construction approaches to chiral



amines.[7] Toward this end, we have introduced an efficient and highly stereoselective free-radical coupling of alkyl iodides and chiral *N*-acylhydrazones.[8,9] In general, radical additions to imino compounds are attractive complements to polar methods for reasons of functional group compat-

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(1) Kaufman, T. S.; Rúveda, E. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 854−885.

(2) Woodward, R. B.; Doering, W. E. *J. Am. Chem. Soc.* **1945**, *67*, 860−874.

(3) (a) Uskokovic, M.; Gutzwiller, J.; Henderson, T. *J. Am. Chem. Soc.* **1970**, *92*, 203−204. Gutzwiller, J.; Uskokovic, M. *J. Am. Chem. Soc.* **1970**, *92*, 204−205. (b) Gates, M.; Sugavanam, B.; Schreiber, W. L. *J. Am. Chem. Soc.* **1970**, *92*, 205−207. (c) Taylor, E. C.; Martin, S. F. *J. Am. Chem. Soc.* **1974**, *96*, 8095−8102.

(4) Stork, G.; Niu, D.; Fujimoto, A.; Koft, E. R.; Balkovec, J. M.; Tata, J. R.; Dake, G. R. *J. Am. Chem. Soc.* **2001**, *123*, 3239−3242.

(5) Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 706−707.

(6) Igarashi, J.; Katsukawa, M.; Wang, Y.-G.; Acharya, H. P.; Kobayashi, Y. *Tetrahedron Lett.* **2004**, *45*, 3783−3786.

(7) Review: Friestad, G. K. *Eur. J. Org. Chem.* **2005**, 3157−3172.

(8) (a) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2000**, *122*, 8329−8330. (b) Shen, Y.; Friestad, G. K. *J. Org. Chem.* **2002**, *67*, 6236−6239. (c) Friestad, G. K.; Draghici, C.; Soukri, M.; Qin, J. *J. Org. Chem.* **2005**, *70*, 6330−6338.

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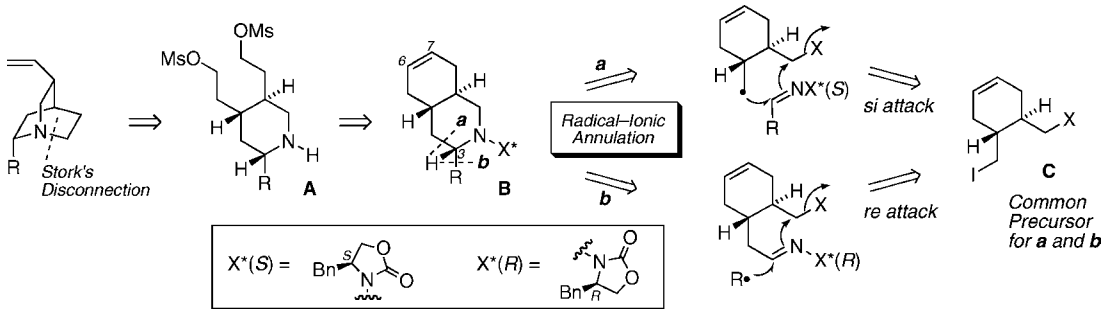
Scheme 1



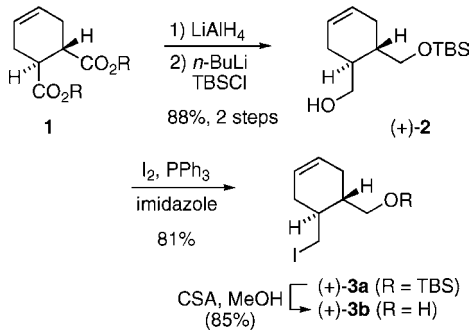
ibility, but applications to total synthesis have lagged because methods exhibiting versatility with respect to both radical and acceptor are limited.[10] The emergence of Mn-mediated photolytic initiation of these intermolecular radical additions has addressed this problem to some extent, enabling application to precursors bearing electrophilic functionality in either of the coupling components.[11] Quinine presented an ideal challenge to the applicability of these Mn-mediated coupling reactions to synthetic problems in a multifunctional molecular setting.

Our approach to quinine focuses on strategic application of our Mn-mediated hybrid radical−ionic annulation, a radical−polar crossover reaction,[12] which had previously been described for preparation of simple pyrrolidines and piperidines.[11a,b] Employing Stork's disconnection of the azabicyclo[2.2.2]octane ring system suggested a 2,4,5-trisubstituted piperidine precursor **A**, which in turn would derive from oxidative cleavage of the C6−C7 bond of an isoquinoline such as **B** (Scheme 1). We envisaged an efficient access to the isoquinoline ring system through Mn-mediated radical addition to construct either of the two C−C bonds at the C3 stereogenic carbon (disconnections ***a*** and ***b***). The stereoselective radical addition would be followed by closed-shell nucleophilic displacement of a leaving group X by the imino nitrogen to complete the piperidine heterocycle.

Some important aspects of this strategy warrant specific mention. First, the Mn-mediated coupling enables interchange of the iodide and hydrazone functionality, such that either component could serve as radical precursor or acceptor. Thus, the choice of path ***a*** or ***b*** is flexible, to be defined at the benchtop according to optimal yields or selectivities. Second, the strategy reveals a common precursor **C**, for which C_2 symmetry could be exploited in an efficient access to both sets of coupling components. Finally, if the chiral auxiliary X* is the dominant control element (as was expected from all available precedents), then the enantiomeric iodide (e.g., *ent*-C) could generate the C8−C3/4 stereochemical relationship of quinidine.

Testing these hypotheses began with preparation of an iodide encompassing the structural features of **C**. For this purpose, the C_2-symmetric diester **1** (ROH = (−)-menthol) was acquired using the known enantioselective Diels−Alder reaction of dimenthyl fumarate[13] (Scheme 2). Reductive removal of the (−)-menthol and monosilylation of the

Scheme 2[a]



[a] ROH = (−)-menthol; the antipodes employed (+)-menthol.

(9) For other applications of chiral *N*-acylhydrazones, see the following. (a) Allylsilane additions: Friestad, G. K.; Ding, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 4491−4493. Friestad, G. K.; Korapala, C. S.; Ding, H. *J. Org. Chem.* **2006**, *71*, 281−289. (b) Radical additions: Fernández, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461−2464. (c) Allylindium additions: Cook, G. R.; Maity, B. C.; Kargbo, R. *Org. Lett.* **2004**, *6*, 1749−1752. (d) Mannich-type reactions: Jacobsen, M. F.; Ionita, L.; Skrydstrup, T. *J. Org. Chem.* **2004**, *69*, 4792−4796. (e) Strecker reactions: Ding, H.; Friestad, G. K. *Heterocycles* **2006**, *70*, 185−199. (f) Hydride additions: Qin, J.; Friestad, G. K. *Tetrahedron* **2003**, *59*, 6393−6402.

(10) Reviews: (a) Friestad, G. K. *Tetrahedron* **2001**, *57*, 5461−5496. (b) Bertrand, M.; Feray, L.; Gastaldi, S. *C. R. Acad. Sci. Paris, Chim.* **2002**, *5*, 623−638. (c) Miyabe, H.; Ueda, M.; Naito, T. *Synlett* **2004**, 1140−1157. For selected recent developments in intermolecular radical addition to C=N bonds, see: (d) Yamada, K.; Yamamoto, Y.; Maekawa, M.; Akindele, T.; Umeki, H.; Tomioka, K. *Org. Lett.* **2006**, *8*, 87−89. (e) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190−6193. (f) McNabb, S. B.; Ueda, M.; Naito, T. *Org. Lett.* **2004**, *6*, 1911−1914. (g) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. *J. Org. Chem.* **2005**, *70*, 3324−3327. (h) Clerici, A.; Cannella, R.; Pastori, N.; Panzeri, W.; Porta, O. *Tetrahedron* **2006**, *62*, 5986−5994. (i) Risberg, E.; Fischer, A.; Somfai, P. *Tetrahedron* **2005**, *61*, 8443−8450. (j) Fernández, M.; Alonso, R. *Org. Lett.* **2003**, *5*, 2461−2464.

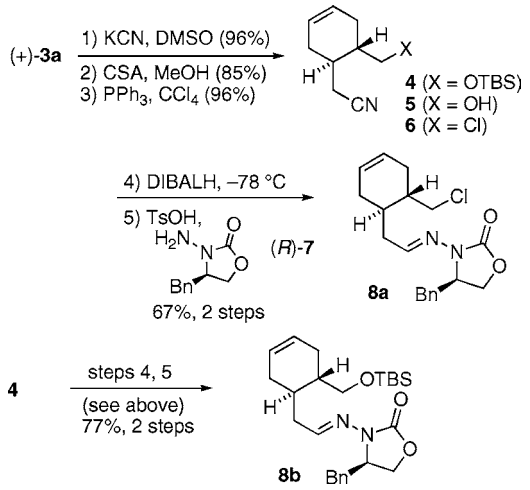
(11) (a) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922−9923. (b) Friestad, G. K.; Qin, J.; Suh, Y.; Marié, J.-C. *J. Org. Chem.* **2006**, *71*, 7016−7027. (c) Friestad, G. K.; Deveau, A. M.; Marié, J.-C. *Org. Lett.* **2004**, *6*, 3249−3252.

(12) (a) Review: Murphy, J. A. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol 1, pp 298−316. For leading references, see: (b) Callaghan, O.; Lampard, C.; Kennedy, A. R.; Murphy, J. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 995−1001. (c) Jahn, U.; Muller, M.; Aussieker, S. *J. Am. Chem. Soc.* **2000**, *122*, 5212−5213. (d) Rivkin, A.; Nagashima, T.; Curran, D. P. *Org. Lett.* **2003**, *5*, 419−422. (e) Denes, F.; Chemla, F.; Normant, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 4043−4046. (f) Tojino, M.; Uenoyama, Y.; Fukuyama, T.; Ryu, I. *Chem. Commun.* **2004**, 2482−2483. (g) Bazin, S.; Feray, L.; Vanthuyne, N.; Bertrand, M. P. *Tetrahedron* **2005**, *61*, 4261−4274. (h) Ueda, M.; Miyabe, H.; Sugino, H.; Miyata, O.; Naito, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6190−6193.

resulting C_2-symmetric diol furnished desymmetrized (+)-**2**, which was readily converted to the corresponding iodide (+)-**3a**. The silyl ether was cleaved by acidic methanolysis to afford the corresponding alcohol (+)-**3b**. Both enantiomers of **1**−**3** were prepared in similar fashion.

Iodide **3a** was prepared as a radical precursor; to test the alternative C−C bond construction (path ***b*** of Scheme 1) it was also necessary to interchange the functionality from iodide to the homologous *N*-acylhydrazone. This was readily accomplished via a simple five-step sequence (Scheme 3).

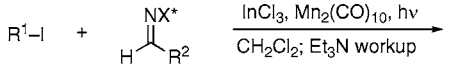
Scheme 3



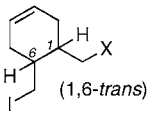
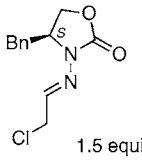
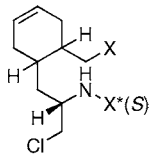
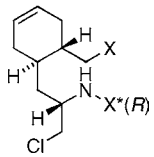
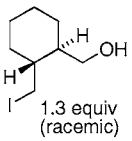
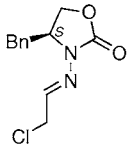
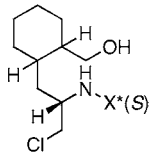
Cyanide homologation and conversion of OTBS to Cl was followed by partial reduction of the nitrile to the corresponding aldehyde and condensation with *N*-aminooxazolidinone (*R*)-**7**. This furnished radical acceptor **8a** in an overall 56% yield. The related acceptor **8b** was prepared in three steps from **3a** with an overall yield of 74%. Benzoate and acetate analogues were synthesized from **3a** by a related dithiane-based homologation route.[14]

With a set of radical precursors **3a**,**b** and acceptors **8a**−**d** at hand, screening their Mn-mediated addition reactions with hydrazone **9**[11a] and chloroiodomethane, respectively, was examined (Table 1). In the presence of $InCl_3$ (employed as a chelating Lewis acid[11b]), the desired adducts were obtained, generally as single diastereomers.[15] Unfortunately, the yields in these couplings never exceeded ca. 50% (entries 1−6), and a slight scaleup decreased the yield from 49% to 31% (entries 3 and 7). Even more troubling was the poor mass balance; in contrast to our prior experience with these Mn-mediated coupling reactions, no starting material was recoverable from lower yielding runs. Moreover, no tractable side products were found, which obscured any obvious corrections to the conditions.

Table 1. Mn-Mediated Addition Studies[a]



X* = 4-benzyl-2-oxazolidinone, (*R*) or (*S*)

entry	iodide	hydrazone	product
	 (1,6-*trans*) 1 equiv	 1.5 equiv	
1	(–)-**3a** (X = OTBS)	**9**	**10**, 26%[b]
2	(+)-**3b** (X = OH)	**9**	**11**, 30%
	 10 equiv		
3		**8a** (X = Cl)	**12a,** 49%
4		**8b** (X = OTBS)	**12b**, --[c]
5		**8c** (X = OBz)	**12c**, 36%
6		**8d** (X = OAc)	**12d**, 33%
7		**8a** (X = Cl)[d]	**12a**, 31%
	 1.3 equiv (racemic)		
8	(±)-**3c**	**9**	**13**, 67%[e]

[a] Conditions: $InCl_3$ (2.2 equiv) and hydrazone (ca. 0.2 mmol) in CH_2Cl_2 (0.02 M), 40 min at rt, then R−I and $Mn_2(CO)_{10}$ (1.2 equiv), irradiation (300 nm, Rayonet) for 10−20 h; Et_3N (5 equiv) then silica gel flash chromatography. [b] Solvent = 10:1 PhH/MeCN, DBU in place of Et_3N.[c] Ca. 25% yield, but inseparable impurities prevented characterization of **12b**. [d] 0.65 mmol scale. [e] dr 1:1 (both trans).

The question remained of whether the remote alkene functionality of **3a**,**b** could interfere in some unanticipated manner.[16] This was easily tested by experiment. Thus, a saturated analogue (±)-**3** was prepared and subjected to the coupling. The racemic diacid (±)-*trans*-cyclohexane-1,2-dicarboxylic acid was transformed to saturated iodide (±)-**3c** via a sequence analogous to Scheme 2. Now absent the alkene functionality, the radical addition of (±)-**3c** to **9** was significantly improved, furnishing 67% yield of **13** without any optimization (Table 1, entry 8).[17] This control experiment confirmed that the alkene interfered with the Mn-mediated coupling.[18]

With this clear guidance for improving the key C−C bond construction, the original C6−C7 bond cleavage (e.g., by alkene ozonolysis) was revised to a plan entailing oxidation of the C6−C7 alkene to a diol prior to the radical addition,

(13) Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 4507−4710.

(14) See the Supporting Information.

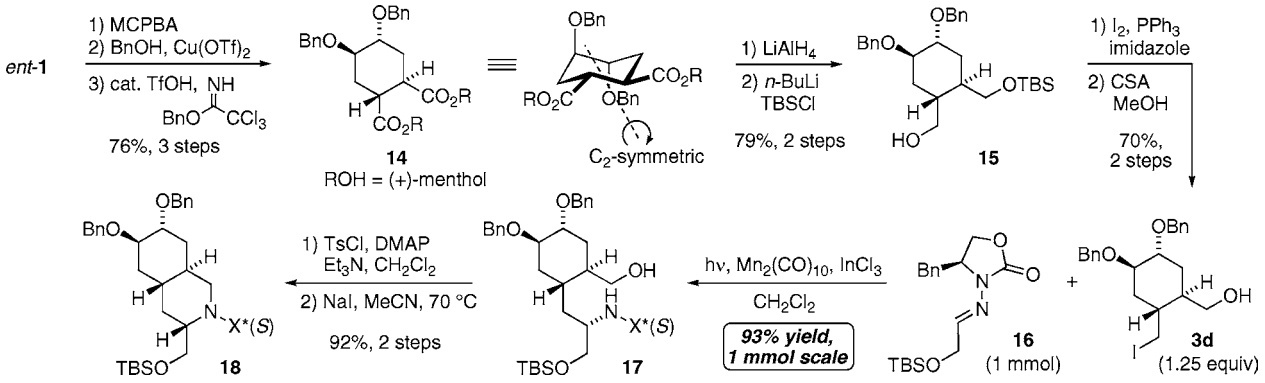
(15) (a) In Table 1, only entry 1 showed evidence of a minor diastereomer (dr 94:6 by ^{1}H NMR); others were obtained with dr >95:5. (b) Configurations of **10**, **11**, **12a**−**d**, and **13** were assigned on the basis of precedent (refs 7−9 and 11), supported by NOE analysis of **18**.

(16) Cyclization of radicals derived from **3a**,**b** onto the alkene functionality may be proposed, but significant ring strain would be expected in the relevant bicyclic 4-*exo* or 5-*endo* transition states.

(17) The addition of racemic (±)-**3c** (1.3 equiv) to **9** afforded only two of the four possible diastereomeric adducts.

(18) At this time, there is insufficient evidence to draw conclusions regarding potential mechanisms of interference by alkene functionality.

Scheme 4



with periodate cleavage to take place at a later stage. In the revised plan (Scheme 4), diastereoselective preparation of a C_2-symmetric *trans*-diol preserved the simplifying desymmetrization aspect of the strategy. The enantiopure diester *ent*-**1** was treated with m-CPBA, and the resulting epoxide was subjected to acidic alcoholysis with benzyl alcohol. Acid-catalyzed protection of the remaining free hydroxyl with benzyl trichloroacetimidate furnished bis-benzyl ether **14**. Reduction to the C_2-symmetric diol, monosilylation to **15**, and conversion to iodide **3d** followed the previously established sequence.

In the key Mn-mediated coupling of **3d** and **16**,[19] we were pleased to find quite remarkable yields. In most intermolecular radical additions to imino compounds, large excesses (10−20 equiv or more) of radical precursors are required. Clearly this would be a prohibitive stoichiometric requirement for an iodide such as **3d**, prepared through several synthetic steps. To our great delight, the Mn-mediated coupling of **3d** with only 1.25 equiv of **16** proceeded in 93% yield in 1 mmol scale, giving **17** as a single diastereomer.[20] Efficient addition of the multifunctional alkyl group of **3d** to an imino compound by other existing methods is improbable.[21]

Completion of the hybrid radical−ionic annulation would ideally occur in situ during the Mn-mediated coupling, but this goal has not yet been achieved. However, a stepwise radical−ionic annulation process proved efficient; successive treatment with TsCl and NaI provided decahydroisoquinoline **18** in a quite satisfactory overall yield (85% for three steps).[22] Further studies to elaborate the azabicyclic ring system of quinine are in progress.

In conclusion, a challenging Mn-mediated coupling of a multifunctional alkyl iodide and a chiral *N*-acylhydrazone was addressed by prior oxidation of a remote alkene functionality, affording efficient access to a functionalized perhydroisoquinoline. Notably, the optimized conditions required only 1.25 equiv of alkyl iodide, a finding which should enable broader applications of this Mn-mediated coupling process in complex target synthesis.

Acknowledgment. We thank the NIH (R01-GM67187) for generous support of this work and Dr. M. Soukri for preparation of **1**.

Supporting Information Available: Preparative details and characterization data for **2**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Hydrazone **16** was prepared by condensation of glycolaldehyde dimer with (S)-**7**, followed by *O*-silylation.

(20) The indicated configuration of **17** was established by NOE analysis of **18** and was in accord with all prior examples of Mn-mediated addition to chiral *N*-acylhydrazones (refs 7−9 and 11).

(21) (a) For a review of asymmetric addition to C=N bonds, see: Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541−2569. (b) For example, diorganozinc additions are powerful methods for alkyl addition to imino compounds, yet still require 2−6 molar equiv of the diorganozinc reagent (i.e., 4−12 equiv of the organic fragment).

(22) Related ring closures affording decahydroisoquinolines are uncommon. Chatterjee, A.; Sahu, A.; Saha, M.; Benerji, J. *Indian J. Chem. Sect. B* **1997**, *36*, 121−122. Lohse, C.; Detterbeck, R.; Acklin, P.; Borschberg, H.-J. *Helv. Chim. Acta* **2002**, *85*, 945−962. Hattori, K.; Grossman, R. B. *J. Org. Chem.* **2003**, *68*, 1409−1417.