

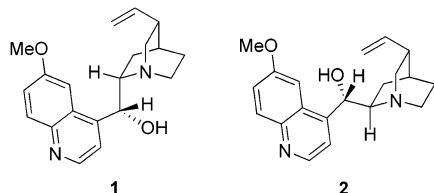
## Catalytic Asymmetric Total Syntheses of Quinine and Quinidine

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Cinchona alkaloids constitute an extraordinarily versatile class of natural products, serving both as medicinally important compounds<sup>1</sup> and as privileged catalysts and ligands for asymmetric catalysis.<sup>2</sup> Quinine (**1**), in particular, has also played a historic role in organic chemistry as a target for structural determination and total synthesis,<sup>1a</sup> although it was only recently that its first stereoselective total synthesis was achieved by Stork et al.<sup>3</sup> Progress made in synthetic methodology over the past several years makes it possible to address targets such as the cinchona alkaloids through relatively simple strategies by means of highly efficient catalytic reactions. This is illustrated herein, with the first catalytic, enantioselective syntheses of quinine and quinidine (**2**).



Our strategy relied on creation of the quinuclidine core through a N1–C8 bond disconnection analogous to that applied in the Uskokovic quinine synthesis.<sup>4</sup> However, in contrast to previous approaches, we envisioned a stereospecific construction of the bicyclic framework, introducing the relative and absolute stereochemistry at the C8 and C9 positions by means of catalyst-controlled stereoselective oxidation. Olefin **3** could be accessed by a convergent, catalytic cross coupling between a methoxyquinoline derivative **4** and vinyl metal species **5**. Access to enantioenriched **5** was addressed using the recently developed (salen)Al-catalyzed conjugate addition of methyl cyanoacetate<sup>5</sup> to provide **6**, with conversion to the core structure of **5** through hydrogenative lactamization. The  $\alpha,\beta$ -unsaturated imide (**9**) required for the key conjugate addition was prepared with high trans selectivity by olefination of aldehyde **8**<sup>6</sup> with known phosphonate imide **7**<sup>7</sup> (Scheme 1). Conjugate addition of methyl cyanoacetate in the presence of (salen)Al complex (*S,S*)-**11** proceeded cleanly to provide **10** in 92% ee. Adduct **10** was then subjected to hydrogenation with Raney nickel to afford lactam **12** as a 1.7:1 trans/cis mixture of diastereomers. After extensive screening, it was found that deprotonation with LDA followed by reprotonation with 5% H<sub>2</sub>O/THF at –78 °C led to selective formation of the desired diastereomer in 3:1 cis/trans ratio. The mixture was then subjected to reduction with LAH, and the resulting piperidine was protected to afford a readily separable mixture of CBz derivatives. Installation of the vinyl group was effected via alcohol oxidation<sup>8</sup> and Wittig olefination. A 3.3% NOE between H3 and H4 in **13** confirmed the required cis stereochemistry. Removal of the TBS protecting group followed by oxidation<sup>8</sup> provided the C8 aldehyde, which was alkylated under modified Takai conditions with Cl<sub>2</sub>CHB(pinacolate) (**15**)<sup>9</sup> to provide the (*E*)-vinyl pinacolatoboronic ester **14** directly in a >20:1 *E/Z* ratio.

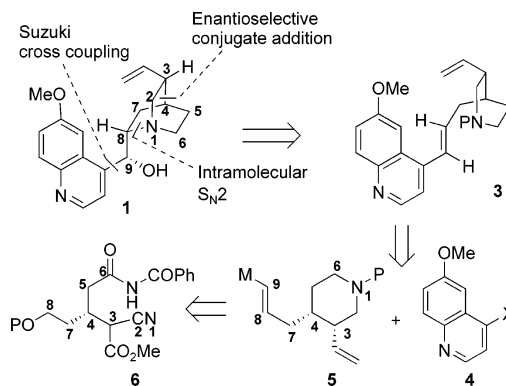
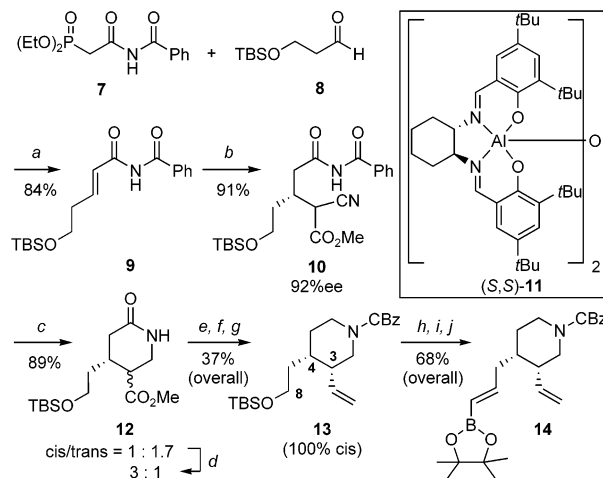


Figure 1. Retrosynthetic analysis.

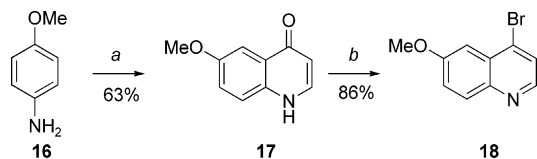
### Scheme 1<sup>a</sup>



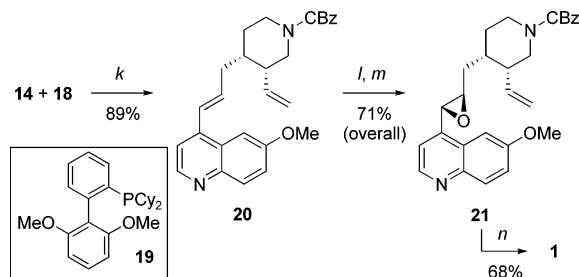
<sup>a</sup> Conditions: (a) *n*-BuLi, THF, –78 °C to 0 °C, >50:1 *E/Z*; (b) methyl cyanoacetate, (*S,S*)-**11** (5 mol %), *t*-BuOH, C<sub>6</sub>H<sub>12</sub>, rt; (c) Raney Ni, H<sub>2</sub>, toluene/MeOH (3:1), 650 psi, 80 °C, 12 h, 89%; (d) i. LDA, THF, –78 °C; ii. H<sub>2</sub>O/THF (5%), –78 °C; (e) i. LAH, THF; ii. CBZ<sub>2</sub>O, TEA, CH<sub>2</sub>Cl<sub>2</sub>, 51%, separation of diastereomers by flash chromatography; (f) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>; (g) methyltriphenylphosphonium bromide, KO<sup>t</sup>Bu, THF, 0 °C, 73% (two steps); (h) TBAF, THF; (i) TPAP, NMO, CH<sub>2</sub>Cl<sub>2</sub>, 86% (two steps); (j) Cl<sub>2</sub>CHB(pinacolate) (**15**), CrCl<sub>2</sub>, LiI, THF, >20:1 *E/Z*, 79%.

The simple structure of **4** belies the dearth of straightforward methods for preparation of this type of substituted quinoline derivative. We were therefore gratified to discover a particularly efficient route involving treatment of *p*-anisidine **16** with ethyl propiolate to afford known quinolinone **17**,<sup>10</sup> followed by microwave-assisted bromination to **18** (Scheme 2).

Efforts to effect cross coupling of boronate ester **14** with bromoquinoline **18** under standard Suzuki conditions proved unsuccessful.<sup>11</sup> However, the protocol employing Pd(OAc)<sub>2</sub>/**19** developed recently by Buchwald<sup>12</sup> afforded excellent results. Full conversion was achieved at room temperature with 2.5 mol % catalyst loading, and trans olefin **20** was thereby prepared selectively

Scheme 2<sup>a</sup>

<sup>a</sup> Conditions: (a) i. ethyl propiolate, MeOH, rt, 12 h; ii. Dowtherm A, 250 °C, 30 min; (b) Ph<sub>3</sub>PBr<sub>2</sub>, CH<sub>3</sub>CN, microwave, 170 °C, 15 min.

Scheme 3<sup>a</sup>

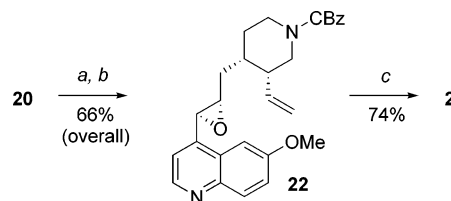
<sup>a</sup> Conditions: (k) Pd(OAc)<sub>2</sub>, **19** (2.5 mol %), K<sub>3</sub>PO<sub>4</sub>·H<sub>2</sub>O, THF, 16 h, rt, >20:1 E/Z, 89%; (l) ADmix-β, CH<sub>3</sub>SO<sub>2</sub>NH<sub>2</sub>, *t*BuOH, H<sub>2</sub>O, 0 °C, >96:4 dr, 88%; (m) i. trimethylorthoacetate, PPTS (cat), CH<sub>2</sub>Cl<sub>2</sub>; ii. acetyl bromide, CH<sub>2</sub>Cl<sub>2</sub>; iii. K<sub>2</sub>CO<sub>3</sub>, MeOH, 81%; (n) Et<sub>2</sub>AlCl, thioanisole, 0 °C to rt, then microwave, 200 °C, 20 min, 68%.

in 89% yield. Attempts to access **21** directly via established asymmetric catalytic epoxidation methods<sup>13</sup> led to unsatisfactory results in model systems. In contrast, application of the Sharpless dihydroxylation proved highly successful. Dihydroxylation of **20** with dihydroquinidine-based ADmix-β<sup>14</sup> provided the (*R,R*) diol in >96:4 dr, and afforded only trace amounts of the tetraol and terminal vinyl dihydroxylation products. Sequential treatment of the diol with trimethylorthoacetate, acetyl bromide, and K<sub>2</sub>CO<sub>3</sub> in one pot<sup>15</sup> provided epoxide **21** in 81% yield (Scheme 3).

Removal of the benzyl carbamate was accomplished with Et<sub>2</sub>-AlCl/thioanisole.<sup>16</sup> Other deprotection strategies either led to no reaction or resulted in decomposition to complex mixtures. The long reaction times generally required to effect cyclization to the quinuclidine core<sup>4,17</sup> proved unnecessary as a result of a second implementation of microwave technology; irradiation at 200 °C in CH<sub>3</sub>CN for only 20 min provided a 68% isolated yield of synthetic quinine.

Quinidine, a natural product that serves as a pseudo-enantiomeric ligand and catalyst relative to quinine, is in fact epimeric to quinine at C8 and C9. Trans epoxide **22** (diastereomeric to **21**) was accessed with high selectivity using dihydroquinidine-based ADmix-α. Deprotection and thermal cyclization afforded quinidine (Scheme 4). Both synthetic products were found to match the spectroscopic and physical properties of authentic samples (HRMS, <sup>1</sup>H NMR, <sup>13</sup>C NMR).<sup>5,18</sup>

Asymmetric catalyst-based syntheses open the possibility of accessing diastereomeric products by a common route by simply varying the stereochemistry of the catalysts,<sup>19</sup> as is illustrated compellingly in these enantioselective syntheses of quinine and quinidine. The fact that classical and challenging synthetic targets such as the cinchona alkaloids can be accessed efficiently (16 steps in the longest linear sequence, with overall yields of ca. 5%) stands as testament to the ever-growing scope and utility of modern asymmetric catalysis.

Scheme 4<sup>a</sup>

<sup>a</sup> Conditions: (a) ADmix-α, CH<sub>3</sub>SO<sub>2</sub>NH<sub>2</sub>, *t*BuOH, H<sub>2</sub>O, 0 °C, 86%; (b) i. trimethylorthoacetate, PPTS (cat), CH<sub>2</sub>Cl<sub>2</sub>; ii. acetyl bromide, CH<sub>2</sub>Cl<sub>2</sub>; iii. K<sub>2</sub>CO<sub>3</sub>, MeOH, 77%; (c) i. Et<sub>2</sub>AlCl, thioanisole, 0 °C to rt, then microwave, 200 °C, 20 min, 74%.

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**Supporting Information Available:** Complete experimental procedures and characterization data for products and all isolated intermediates (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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