Heterocycle Synthesis

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# Enantioselective Rhodium-Catalyzed Dearomative Arylation or Alkenylation of Quinolinium Salts

*Yan Wang, Yunlong Liu, Dongdong Zhang, Hao Wei,* Min Shi, and Feijun Wang**

***Abstract:*** *A highly enantioselective rhodium(I)-catalyzed dearomative arylation or alkenylation of easily available N-alkylquinolinium salts is reported, thus providing an effective and practical approach to the synthesis of dihydroquinolines in up to 99 % ee. This reaction tolerates a wide range of functional groups with respect to both the organic boronic acids and the quinoline starting materials. Moreover, the synthetic utility of this protocol is demonstrated in the formal asymmetric synthesis of bioactive tetrahydroquinoline and the total syntheses of (−)-angustureine and (+)-cuspareine.*

**1,2,3,4-T**etrahydroquinolines bearing a substituent group at the C2-position constitute an important class of compounds widely present in naturally occurring and synthetic substances with a broad bioactivity spectrum, and they were recently summarized in a comprehensive review delivered by Menéndez and co-workers.[1] Some selected bioactive and natural tetrahydroquinolines are shown in Figure 1.

Owing to this importance, there is an ongoing interest in the development of convenient and general protocols to construct the chiral 2-substituted tetrahydroquinoline motif.[1,2] However, asymmetric approaches to access such an enantiopure motif remains a challenge to synthetic chemists, despite the fact that asymmetric hydrogenation of expensive or not commercially available 2-substituted quinolines has been achieved in recent years with either chiral Brønsted acids[3] or chiral transition-metal catalysts, such as iridium,[4] ruthenium,[5] and rhodium[6] complexes.

Activation of nitrogen-containing aromatics toward nucleophilic addition by means of N-acylation and N-alkylation represents one of the most important and general strategies to construct new C–C bonds in heterocyclic chemistry.[7] Specifically, asymmetric attack of nucleophiles onto easily available quinolinium salts is very attractive because it offers direct access to functionalized dihydroquinolines which can be easily further converted into tetrahydroquinolines by different transformations (Scheme 1 a). Great

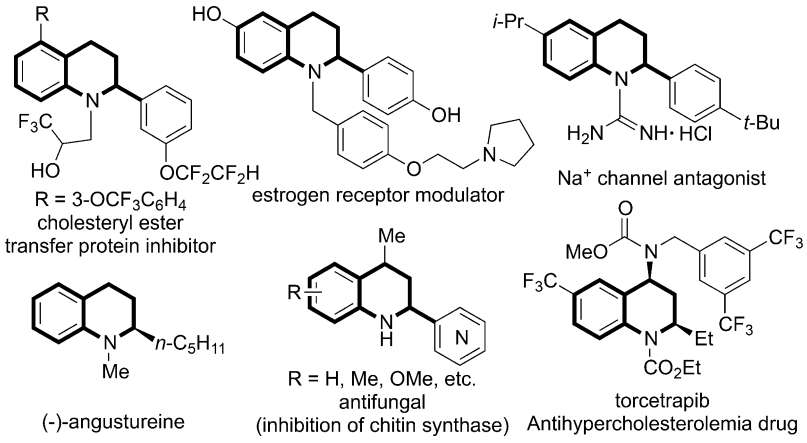


***Figure 1.*** Selected bioactive and natural tetrahydroquinolines.

progress has been achieved in this area because of the seminal contributions from the groups of Shibasaki,[8] Takemoto,[9] Doyle,[10] Schaus,[11] Arndtsen,[12] Alexakis,[13] and Aponick.[14] However, because of the lack of an accessible coordination site in the iminium species, enantioselective transition-metal-catalyzed nucleophilic addition of quinolinium salts are scarce. To date, only enantioselective copper-catalyzed alkynylation[12,14] of quinolinium salts and nickel-catalyzed arylation[10] of quinolinium salts generated in situ from quinoline-derived allylic N,O-acetals have been described. Considering these methods, limited functional groups (aryl and alkynyl) were stereoselectively introduced at the C2-position of quinolines. Inspired by the reported rhodium-catalyzed enantioselective addition of boronic acids, albeit to only activated N-benzylnicotinate salts,[15] we envisioned that the π-electron system of quinoline ring may enhance its coordination capabilities to the rhodium complex, which was employed to achieve the enantioselective addition of boronic acids to quinolinium salts (Scheme 1 b). To address this

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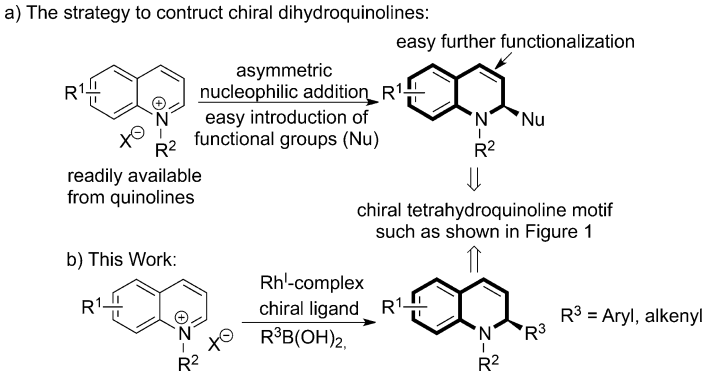
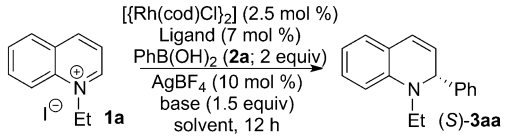


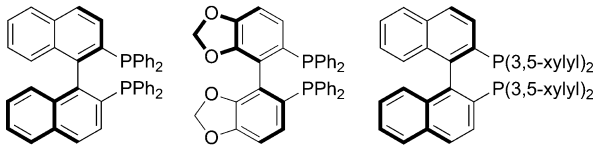

***Scheme 1.*** Enantioselective nucleophilic addition to quinolinium salts.

challenge and in pursuit of asymmetric transformations of organic boronic acids,[16] herein, we report a highly enantioselective rhodium-catalyzed nucleophilic addition of aryl and alkenyl boronic acids to quinolinium salts, and its application in the formal asymmetric synthesis of bioactive tetrahydroquinoline and in the total synthesis of the naturally occurring tetrahydroquinolines.

To initiate the study, *N*-ethyl quinolinium iodide (**1a**) was chosen as a model substrate for the rhodium-catalyzed asymmetric nucleophilic addition[17] (Table 1). In the presence of [{Rh(cod)Cl}$_2$](2.5 mol%), $AgBF_4$ (10 mol%), (*R*)-BINAP (**L1**; 7 mol%), and $Cs_2CO_3$ (1.5 equiv), reaction of **1a** with phenylboronic acid (**2a**) in tetrahydrofuran (THF) at an ambient temperature for 12 hours proceeded smoothly to give the dearomative arylation product (*S*)-**3aa** in 49% yield and 93% *ee* (entry 1). From the screening of added inorganic bases, it was found that $K_3PO_4{\cdot}3H_2O$ delivered the best result in terms of enantioselectivity and yield (entry 3). Organic bases such as $NEt_3$ also gave good *ee* values for **3aa** (entry 5). Subsequent assessment of the solvent revealed that the transformation was very sensitive to the reaction medium. Toluene (entry 6) gave a slightly higher yield of **3aa** with the same *ee* value compared to those obtained in THF. Raising the reaction temperature has a strong effect on the yield of **3aa**, but with almost no effect on the enantioselectivity. Performing the reaction at 45°C afforded **3aa** in 79% yield with 95% *ee* (entry 10). Further exploration of other commercially available bis(phosphine) ligands showed that, compared to the *ee* value of **3aa** using (*R*)-BINAP (**L1**) as the ligand, (*S*)-SegPhos (**L2**) also gave a similar result (entry 12), while (*R*)-3,5-xylyl-BINAP (**L3**) delivered a slightly lower *ee* value (entry 13). Recently, palladium(II)-catalyzed additions of arylboronic acids to imines have been achieved with great progress.[18] Hence, [Pd(PhCN)$_2$Cl$_2$] (5 mol%), $AgBF_4$ (10 mol%), and **L1** (7 mol%) as the chiral catalytic system was also tried in the nucleophilic addition of **1a** to **2a**, but only trace amounts of **3aa** were obtained.

***Table 1:*** Optimization of reaction conditions.[a]




| Entry | Solvent | Base | *T* [°C] | Ligand | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|---|---|
| 1 | THF | $Cs_2CO_3$ | RT | **L1** | 49 | 93 |
| 2 | THF | $K_2CO_3$ | RT | **L1** | 45 | 40 |
| 3 | THF | $K_3PO_4{\cdot}3H_2O$ | RT | **L1** | 54 | 93 |
| 4 | THF | KO*t*Bu | RT | **L1** | 50 | 90 |
| 5 | THF | $NEt_3$ | RT | **L1** | 51 | 86 |
| 6 | toluene | $K_3PO_4{\cdot}3H_2O$ | RT | **L1** | 56 | 93 |
| 7 | EtOH | $K_3PO_4{\cdot}3H_2O$ | RT | **L1** | 44 | 69 |
| 8 | DCM | $K_3PO_4{\cdot}3H_2O$ | RT | **L1** | 47 | 55 |
| 9 | 1,4-dioxane | $K_3PO_4{\cdot}3H_2O$ | RT | **L1** | 54 | 73 |
| 10 | toluene | $K_3PO_4{\cdot}3H_2O$ | 45 | **L1** | 79 | 95 |
| 11 | toluene | $K_3PO_4{\cdot}3H_2O$ | 80 | **L1** | 60 | 94 |
| 12 | toluene | $K_3PO_4{\cdot}3H_2O$ | 45 | **L2** | 78 | −95 |
| 13 | toluene | $K_3PO_4{\cdot}3H_2O$ | 45 | **L3** | 67 | 88 |

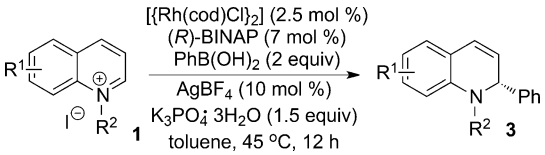
[a] Reaction conditions: **1** (0.1 mmol), [{Rh(cod)Cl}$_2$] (2.5 mol%), ligand (7 mol%), $AgBF_4$ (10 mol%), base (1.5 equiv), solvent (3 mL), 12 h. [b] Yield of isolated product. [c] Determined by chiral-phase HPLC. cod = 1,5-cyclooctadiene, DCM = dichloromethane, THF = tetrahydrofuran.

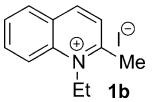
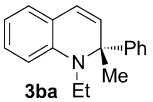
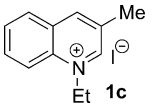
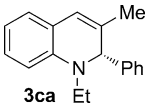
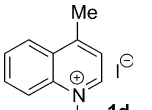
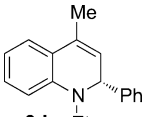
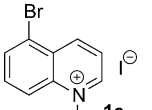
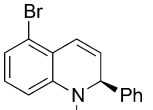
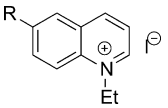
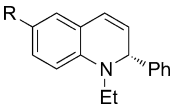
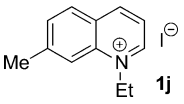
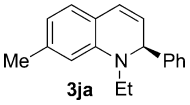
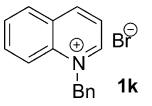
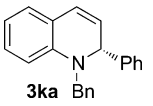
With these optimized reaction conditions in hand, we turned our attention to the investigation of the scope with respect to substituted quinolinium salts from easily available quinolines, and the results are summarized in Table 2. Generally speaking, the quinolinium salts **1**, bearing various substituent groups at different positions of the quinoline ring, performed quite well in the reaction, thus affording the desired products in high enantiomeric excess. It is noteworthy that under the standard reaction conditions, the reaction of the 2-substituted quinolinium salt **1b** with **2a** proceeded smoothly to give the dihydroquinoline **3ba**, having a chiral tetrasubstituted carbon center, in 98% *ee* and 38% yield (entry 1). A methyl group at the 2-, 3-, 4-, 6-, and 7-positions in the quinoline ring had an effect on the *ee* value and yield of corresponding dihydroquinoline for this rhodium(I)-catalyzed nucleophilic addition (entries 1–3, 8 and 9). It seems that a methyl group situated nearer to the reacting carbon center led to the corresponding product in lower yield, probably because of the suppression of nucleophilic addition by steric hindrance. Given the easy deprotection of the N-substituted group, the quinolinium salt **1k**, prepared from the reaction of quinoline and BnBr, was tested in this reaction to afford the desired product **3ka** in 69% yield and 85% *ee*.

Subsequently, various substituted arylboronic acids (**2**) were also tested to demonstrate the generality of the dearomative arylation. The results are summarized in Table 3. Arylboronic acids bearing either an electron-donating or electron-withdrawing group led to the corresponding dihydroquinolines in moderate to good yields and excellent *ee* values. To further explore the scope of organic boronic

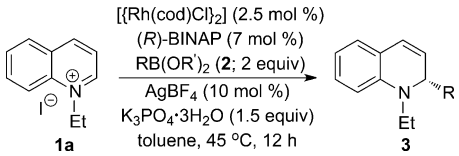
***Table 2:*** Rhodium-catalyzed asymmetric nucleophilic addition of phenylboronic acid **2a** to substituted quinolinium salts **1**.[a]

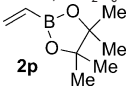



| Entry | Substrate | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 |  **1b** |  **3ba** | 38 | 98(*R*) |
| 2 |  **1c** |  **3ca** | 47 | 94(*R*) |
| 3[d,e] |  **1d** |  **3da** | 55 | 99(*R*) |
| 4[e,f] |  **1e** |  **3ea** | 80 | 92(*S*) |
| |  |  | | |
| 5[d,e] | **1f** (R = Cl) | **3fa** | 60 | 90(*R*) |
| 6[d,e] | **1g** (R = Br) | **3ga** | 53 | 89(*R*) |
| 7[d–f] | **1h** (R = OMe) | **3ha** | 65 | 95(*S*) |
| 8[e] | **1i** (R = Me) | **3ia** | 68 | 95(*R*) |
| 9[f] |  **1j** |  **3ja** | 70 | 90(*S*) |
| 10 |  **1k** |  **3ka** | 69 | 85(*R*) |

[a] Reaction conditions: **1** (0.1 mmol), **2a** (0.2 mmol), $[Rh(cod)Cl]_2$ (2.5 mol%), (*R*)-BINAP (7 mol%), $AgBF_4$ (10 mol%), $K_3PO_4 \cdot 3\,H_2O$ (1.5 equiv), toluene (3 mL), 12 h at 45 °C. [b] Yield of the isolated product. [c] Determined by chiral-phase HPLC analysis, and the absolute configuration was determined by comparison of its optical rotation data with that of its analogues. [d] $[Rh(cod)_2]BF_4$ was used instead of cationic rhodium catalyst generated in situ from $[\{Rh(cod)Cl\}_2]$ and $AgBF_4$. [e] THF as the solvent. [f] (*S*)-SegPhos (**L2**) as the ligand.

***Table 3:*** Rhodium-catalyzed asymmetric nucleophilic addition of an organic boronic acid (**2**) to the quinolinium salt **1a**.[a]



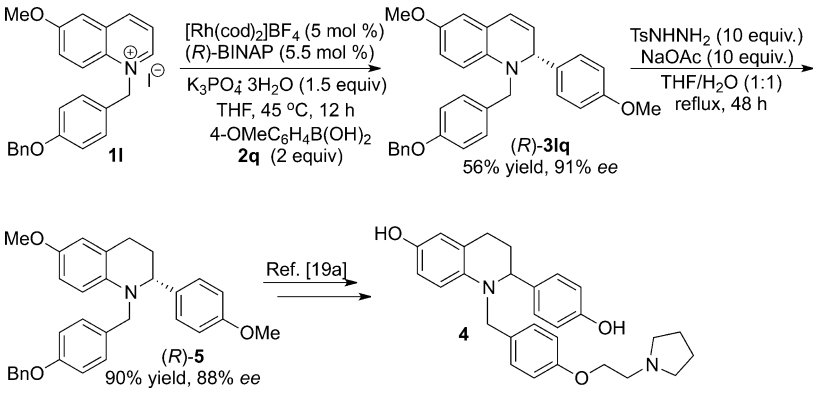

| Entry | **2** | Product | Yield [%][b] | *ee* [%][c] |
|---|---|---|---|---|
| 1 | **2b**: 2-$FC_6H_4B(OH)_2$ | **3ab** | 92 | 98(*R*) |
| 2[d] | **2c**: 2-$OMeC_6H_4B(OH)_2$ | **3ac** | 71 | 90(*S*) |
| 3 | **2d**: 2-$ClC_6H_4B(OH)_2$ | **3ad** | 74 | 91(*R*) |
| 4[d] | **2e**: 2-$OHC_6H_4B(OH)_2$ | **3ae** | 51 | 95(*S*) |
| 5 | **2f**: 3-$OMeC_6H_4B(OH)_2$ | **3af** | 75 | 93(*R*) |
| 6[d] | **2g**: 3-$CH_3C_6H_4B(OH)_2$ | **3ag** | 71 | 94(*S*) |
| 7 | **2h**: 3-$ClC_6H_4B(OH)_2$ | **3ah** | 56 | 95(*R*) |
| 8 | **2i**: 3-$FC_6H_4B(OH)_2$ | **3ai** | 59 | 91(*R*) |
| 9[d] | **2j**: 4-$CH_3C_6H_4B(OH)_2$ | **3aj** | 56 | 94(*S*) |
| 10[e] | **2k**: 4-$CF_3C_6H_4B(OH)_2$ | **3ak** | 46 | 94(*R*) |
| 11[e] | **2l**: 4-$FC_6H_4B(OH)_2$ | **3al** | 55 | 93(*R*) |
| 12[d] | **2m**: 4-$ClC_6H_4B(OH)_2$ | **3am** | 67 | 95(*S*) |
| 13 | **2n**: 3,5-$F_2C_6H_3B(OH)_2$ | **3an** | 71 | 93(*R*) |
| 14 | **2o**: 3,5-$Cl_2C_6H_3B(OH)_2$ | **3ao** | 61 | 96(*R*) |
| 15[d,f] |  **2p** | **3kp** | 50 | 96(*R*) |

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.2 mmol), $[\{Rh(cod)Cl\}_2]$ (2.5 mol%), (*R*)-BINAP (7 mol%), $AgBF_4$ (10 mol%), $K_3PO_4 \cdot 3\,H_2O$ (1.5 equiv), toluene (3 mL), 12 h at 45 °C. [b] Yield of the isolated product. [c] Determined by chiral-phase HPLC analysis, and the absolute configuration was determined by comparison of its optical rotation data with that of its analogues. [d] (*S*)-SegPhos as the ligand. [e] THF as the solvent. [f] Used **1k** instead of **1a**, 5 mol% $[Rh(cod)_2]BF_4$, and $CH_3CN$ as the solvent.

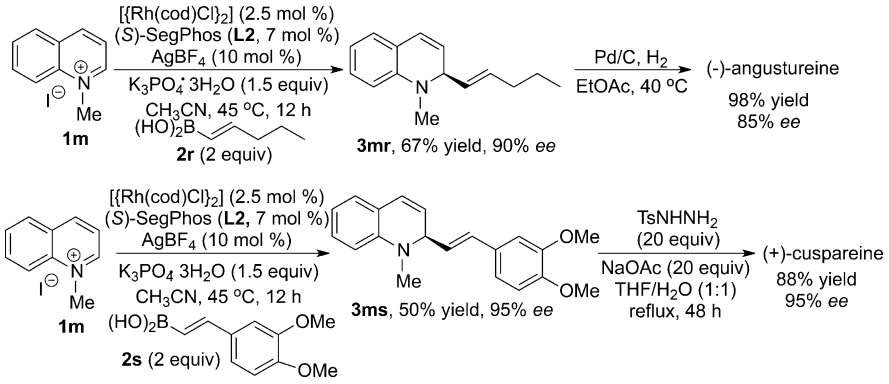
acids, vinylboronic acid pinacolester **2p** was also reacted with **1k**, and the dearomative alkenylation product **3kp** was obtained in 50% yield with 96% *ee* (entry 15). Meanwhile, protodeboronation,[17] a common side reaction in the rhodium-catalyzed transformations of organic boronic acids, was observed in the reaction of **1** with **2**, and may be responsible for the low yields of addition products **3**.

With the well-established rhodium(I)-catalyzed dearomative arylation of N-alkylquinolinium salts in hand, we turned our attention to the formal asymmetric synthesis of the chiral tetrahydroquinoline **4** (Scheme 2), which is a selective estrogen receptor modulator (SERM) and a potent inhibitor of MCF-7 proliferation ($IC_{50}$ 68 nM).[19] In the presence of the $[Rh(cod)_2]BF_4$/(*R*)-BINAP catalytic system, **1l** reacted with **2q** to give the desired dihydroquinoline **3lq** in 56% yield and 91% *ee*. By using tosyl hydrazide as the reduction reagent,[20] hydrogenation of the **3lq** afforded the known tetrahydroquinoline (*R*)-**5** (90% yield, 88% *ee*),[19b] which is a key intermediate in the preparation of bioactive the tetrahydroquinoline **4**.[19a] The absolute configuration of **3lq** was determined based on the absolute configuration of (*R*)-**5**, and the absolute configurations of other dihydroquinolines (**3**) were similarly assigned by analogy to the configuration of (*R*)-**3lq**.

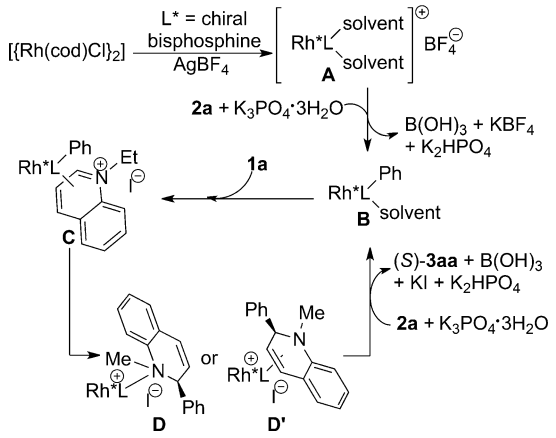
Furthermore, the application of rhodium(I)-catalyzed dearomative alkenylation using alkenylboronic acids as the nucleophilic reagents in the total synthesis of natural alkaloids was also investigated. As shown in Scheme 3, rhodium(I)-catalyzed nucleophilic additions of either the alkenylboronic acid **2r** or **2s** to the quinolinium salt **1m** proceeded smoothly, and, respectively afforded the desired 2-alkenyldihydroquinoline **3mr** or **3ms** in moderate yields with high *ee* values. Further hydrogenation of **3mr** and **3ms** were carried out, thus affording the corresponding natural alkaloids (−)-angustureine[21] and (+)-cuspareine,[22] respectively. It is worth noting that these total synthesis routes only require




***Scheme 2.*** Formal asymmetric synthesis of the bioactive tetrahydroquinoline **4**. Ts = 4-toluenesulfonyl.




***Scheme 3.*** Enantioselective synthesis of natural alkaloids.




***Scheme 4.*** A possible mechanism for the rhodium-catalyzed nucleophilic addition.

three steps from very cheap and readily available quinoline. The absolute configurations of **3mr** and **3ms** were determined by the comparison of optical rotation data of their hydrogenated product with that of natural (−)-angustureine and (+)-cuspareine, respectively.

A catalytic cycle for the reaction of rhodium-catalyzed nucleophilic addition of **2a** to **1a** is illustrated in Scheme 4. With the treatment of $AgBF_4$ and chiral bisphosphine, $[\{Rh(cod)Cl\}_2]$ is converted into a cationic chiral rhodium(I) complex (**A**), which readily undergoes transmetalation with the arylboronic acid **2a** to produce the arylrhodium species **B**,[17,23] $K_2HPO_4$, $KBF_4$, and $B(OH)_3$. The coordination of **1a** to **B** produces the intermediate **C**, followed by an insertion of the iminium species of **1a** into the C–Rh bond of **C** to give either the N-coordinated rhodium species **D** or olefin-coordinated rhodium species **D′**. The transmetalation of either **D** or **D′** with **2a** affords **3aa** and regenerates **B**.

In conclusion, we have developed a highly enantioselective rhodium-catalyzed nucleophilic addition protocol, thus achieving the dearomative arylation and alkenylation of quinolinium salts from easily available quinolines using organic boronic acids as the nucleophiles. The reaction tolerates a wide range of functional groups with respect to both the organic boronic acids and the quinoline starting materials, and represents an attractive and practical approach to the synthesis of the dihydroquinolines with high *ee* values. Moreover, this protocol was successfully applied in the formal asymmetric synthesis of the bioactive tetrahydroquinoline **4** and the total syntheses of (−)-angustureine and (+)-cuspareine, and all are accomplished in only three steps from cheap quinolone starting materials. Currently, efforts are being directed towards expanding the scope of this new asymmetric transformation involving the addition of organic boronic acids to easily available nitrogen heterocycles, having an iminium species, such as functionalized pyridinium and isoquinolinium salts.

## Experimental Section

General procedure for rhodium-catalyzed asymmetric nucleophilic addition: $[\{Rh(cod)Cl\}_2]$ (2.5 mol%, 1.2 mg), (*R*)-BINAP (7 mol%, 4.4 mg), and $AgBF_4$ (10 mol%, 1.9 mg) in toluene (3 mL) were stirred under argon atmosphere at ambient temperature. After 15 minutes, the quinolinium salt **1** (0.1 mmol) and organic boronic acid **2** (0.2 mmol) were added, and the resulting mixture was stirred for an additional 12 hours at 45 °C under an argon atmosphere. The reaction mixture was then concentrated and the residue was purified by column chromatography (silica gel, petroleum ether/AcOEt) to afford the addition product **3**. Optical purity of product **3** was determined by chiral-phase HPLC.

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