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# Catalyst-Controlled Switch in Diastereoselectivities: Enantioselective Construction of Functionalized 3,4-Dihydro-2*H*-thiopyrano[2,3-*b*]quinolines with Three Contiguous Stereocenters

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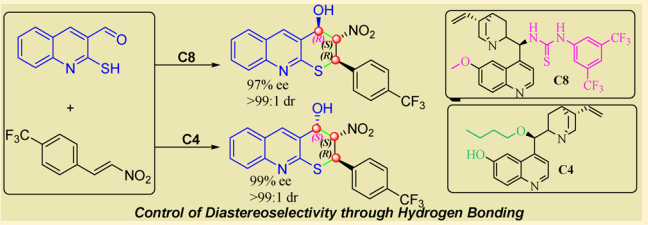
Supporting Information

**ABSTRACT:** A tandem Michael−Henry reaction of 2-mercaptoquinoline-3-carbaldehydes with nitroolefins using hydrogen-bonding-based cooperative organocatalysts for the highly diastereodivergent synthesis of chiral functionalized 3,4-dihydro-2*H*-thiopyrano[2,3-*b*]quinolines with three contiguous tertiary stereocenters has been developed.




Development of novel catalytic asymmetric methods for the construction of structurally and stereochemically diverse compound collections represents a major challenge in synthetic organic and medicinal chemistry. The search for more highly enantio- and diastereoselective reactions which generate complex molecular architectures with multiple stereogenic carbon atoms from simple chemicals in one step continues to be a multifaceted endeavor in both academic and industrial domains. It is well-known that complementary enantioselectivity can be readily obtained by a pair of enantiomeric or pseudoenantiomeric chiral reagents in asymmetric synthesis. However, the number of catalytic asymmetric methods on how to establish complementary diastereoselectivity in these reactions is quite small[1] because the formation of one of these diastereomers is inherently preferred, while the other diastereomer is inherently unpreferred.[2] Efficient direct access to unpreferred diastereomers very often represents an unsolved problem. Recently, a few catalytic asymmetric methods for diastereodivergent access to diastereomers have been developed.[3−5] For example, Zhao et al. reported the tandem asymmetric Michael/Henry reaction of 2-mercaptobenzaldehydes with *β*-nitrostyrenes to generate all-trans 2,3,4-trisubstituted thiochromanes catalyzed by cupreine (Scheme 1, eq 1).[6] Subsequently, Arai developed a new method for the synthesis of a novel stereoisomer of 2,3,4-trisubstituted thiochromanes using an imidazoline−aminophenol−nickel-catalyzed Michael/Henry reaction (Scheme 1, eq 2).[7] However, the development of new and more general catalytic asymmetric methods on how to establish complementary diastereoselectivity still represents a major challenge in asymmetric synthesis.

The importance of quinoline and its annulated derivatives is well recognized by their special place as building blocks in natural products, pharmaceutical agents, materials, and chiral lingand.[8,9] Among the quinoline derivatives, thiopyranoquinolines, which contains both quinoline ring and thiopyran moieties, are heterocyclic ring systems of considerable interest due to several biological and pharmaceutical activities.[10] However, there are few reports on the direct catalytic asymmetric method for the synthesis of optically active thiopyranoquinoline derivatives.[11] Especially, a diastereodivergent domino reaction for the synthesis of optically active thiopyranoquinoline derivatives has yet to be accomplished. To address this important issue, herein we present an efficient diastereodivergent, organocatalytic tandem Michael−Henry process for the preparation of chiral 2*H*-thiopyrano [2,3-*b*]quinolines with three contiguous stereocenters controlled by hydrogen-bonding-based cooperative organocatalysts.

Over the past few years, many efforts have been made on the development of domino reactions through H-bonding activation in our group.[12] Recently, we have demonstrated an unexpected domino reaction to prepare 2-mercaptoquinoline-3-carbaldehyde **1a** from *o*-isothiocyanato-(*E*)-cinnamaldehyde (Scheme 1, eq 3).[13] On the basis of the successful H-bonding activation in our group and the successful results,[6,7] we envisioned that a diastereodivergent, organocatalytic tandem Michael−Henry process would be possible between 2-mercaptoquinoline-3-carbaldehyde **1a** and nitroolefin **2a**, giving a facile protocol to diastereomers of 2*H*-thiopyrano[2,3-*b*]quinolines with three contiguous stereocenters (Scheme 1, eq 3).

The tandem Michael−Henry reaction of 2-mercaptoquinoline-3-carbaldehyde **1a** with nitroolefin **2a** was first investigated to reveal potential effects of the organocatalysts on the diastereomers (Table 1). Quinine and its derivatives

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**Scheme 1. Strategies of Stereochemically Divergent Synthesis**

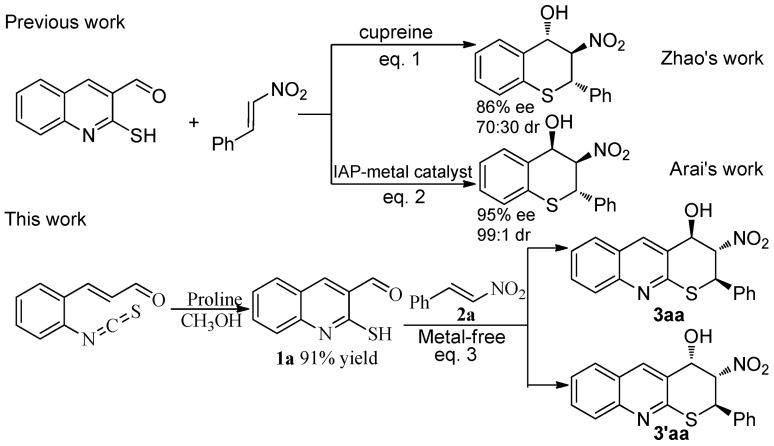
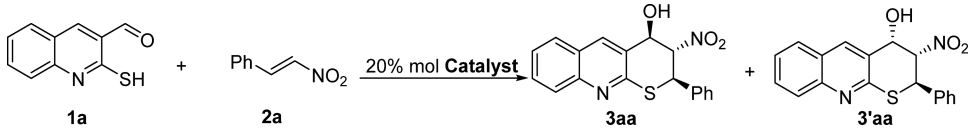



**Table 1. Optimization of Reaction Conditions Using Model Substrates**[a]




| entry | cat. | solvent | $T$ (°C) | yield (%)[b] | ee (%)[c] | 3aa/3′aa[d] |
|---|---|---|---|---|---|---|
| 1 | **C1** | DCM | −10 | 92 | 23/25 | 60:40 |
| 2 | **C2** | DCM | −10 | 87 | 58/58 | 43:57 |
| 3 | **C3** | DCM | −10 | 93 | 71/66 | 30:70 |
| 4 | **C4** | DCM | −10 | 95 | −/83 | 10:90 |
| 5 | **C5** | DCM | −10 | 90 | 76/68 | 30:70 |
| 6 | **C6** | DCM | −10 | 92 | 65/58 | 55:45 |
| 7 | **C7** | DCM | −10 | 93 | 71/− | 88:12 |
| 8 | **C8** | DCM | −10 | 96 | 80/− | 94:6 |
| 9 | **C9** | DCM | −10 | 90 | 73/− | 90:10 |
| 10 | **C4** | THF | −10 | 84 | −/53 | 35:65 |
| 11 | **C4** | toluene | −10 | 89 | −/54 | 18:82 |
| 12 | **C4** | $CHCl_3$ | −10 | 92 | −/63 | 30:70 |
| 13 | **C4** | DCM | −30 | 96 | −/93 | 4:96 |
| 14 | **C8** | DCM | −30 | 96 | 96/− | 98:2 |

[a]All reactions were carried out with **1a** (0.1 mmol) and **2a** (0.20 mmol) in DCM (2.00 mL) with the indicated catalysts for 8 h. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Determined by HPLC analysis.

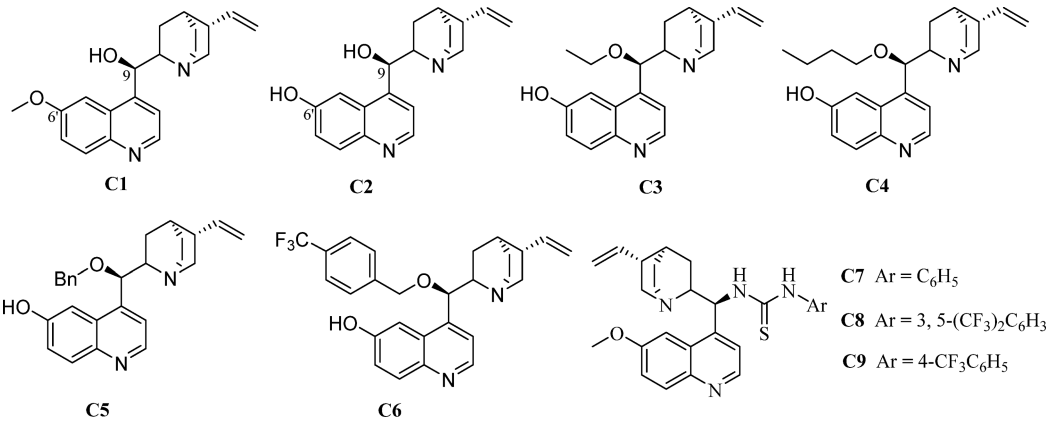



**Figure 1.** Structure of organocatalysts **C1**−**9**.

(**C1**−**9**, Figure 1), which have been identified recently as effective bifunctional catalysts for the enantioselective conjugate addition,[14] were found to effect the tandem Michael−Henry reaction. Initially, natural quinine **C1** was investigated as the organocatalyst and 1,2-*anti* diastereomer **3aa** was obtained as the main product with excellent yield, while both the diastereo- and enantioselectivities were poor (Table1, entry 1). Interestingly, when the tandem Michael−Henry reaction was



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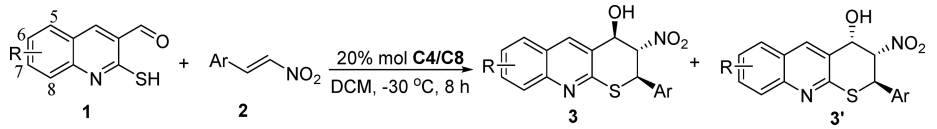
**Table 2. Diastereodivergency for Different Substrates**[a]




| entry | cat. | R | Ar | product | yields (%)[a] | ee (%)[b] | dr[c] |
|---|---|---|---|---|---|---|---|
| 1 | **C8** | H | $C_6H_5$ | **3aa** | 96 | 96 | 98:2 |
| 2 | **C4** | | | **3′aa** | 96 | 93 | 96:4 |
| 3 | **C8** | 6-Br | $C_6H_5$ | **3ba** | 90 | 99 | 97:3 |
| 4 | **C4** | | | **3′ba** | 93 | 99 | >99:1 |
| 5 | **C8** | 6-$CH_3$ | $C_6H_5$ | **3ca** | 97 | 93 | 97:3 |
| 6 | **C4** | | | **3′ca** | 97 | 99 | 91:9 |
| 7 | **C8** | H | *p*-$BrC_6H_4$ | **3ab** | 98 | 94 | >99:1 |
| 8 | **C4** | | | **3′ab** | 95 | 94 | 96:4 |
| 9 | **C8** | H | *p*-$CF_3C_6H_4$ | **3ac** | 97 | 97 | >99:1 |
| 10 | **C4** | | | **3′ac** | 99 | 99 | >99:1 |
| 11 | **C8** | H | *m*-$CH_3OC_6H_4$ | **3ad** | 91 | 98 | >99:1 |
| 12 | **C4** | | | **3′ad** | 91 | 99 | 98:2 |
| 13 | **C8** | H | *p*-$CH_3OC_6H_4$ | **3ae** | 93 | 96 | 98:2 |
| 14 | **C4** | | | **3′ae** | 96 | 98 | 95:5 |

[a]Unless otherwise noted, reactions performed with 0.1 mmol of **1**, 0.2 mmol of **2**, and 20 mol % of **C8** or **C4** in 2 mL of DCM at −30 °C for 8 h. [b]Isolated yield. [c]Determined by HPLC analysis.

catalyzed by quinine derivative **C2** bearing a 6′-hydroxyquinoline ring, in contrast, 1,2-*syn* diastereomer **3′aa** was obtained as the main product (Table1, entry 2). Based on the above results, we think that the hydrogen bond donor of cinchona alkaloid derivatives plays a significant role in establishing complementary diastereoselectivity in this tandem reaction. Further studies showed that the cinchona alkaloids (**C2**−**6**) bearing a 6-hydroxyquinoline ring has a significant impact on both diastereo- and enantioselectivity and 1,2-*syn* diastereomer **3′aa** was obtained as the main product except for **C6** in the tandem reaction. Especially, when the C9 hydroxy function was protected as a *n*-butyl ether, both diastereo- and enantioselectivity were dramatically enhanced. In order to obtain the other diastereomer **3aa**, quinine-derived thioureas **C7**−**9** were screened under the same conditions. Quinine-derived thioureas **C6**−**9** also exhibited high catalytic activity, and the expected diastereomer **3aa** was obtained in a 94:6 diastereomeric ratio (dr) and 80% ee when the tandem reaction was catalyzed by chiral thiourea **C8**. Through careful screening, we eventually found that the sense of diastereoselectivity by **C4** and **C8** were found to be complementary to each other in this reaction. Subsequently, a variety of solvents were further screened; unfortunately inferior results were generally observed. The temperature has a significant effect on the reaction. Lowering the temperature to −30 °C resulted in high diastereo- and enantioselectivity. Under the optimized reaction conditions, 1,2-*anti* diastereomer **3aa** and 1,2-*syn* diastereomer **3′aa** were obtained with high diastereo- and enantioselectivities from **C4** and **C8**, respectively (Table 1, entries 13, 14).

To probe the generality of the diastereodivergency, bifunctional catalysts **C4** and **C8** were applied to various substrate combinations under the optimized conditions (Table 2). As shown in Table 2, the tandem reaction with a variety of nitroolefins **2** and 2-mercaptoquinoline-3-carbaldehydes **1** proceeded smoothly in high diastereoselectivity (91:9 → 99:1), enantioselectivity (93−99% ee), and excellent yield (90−99%), and a switch of the dominant diastereomer was achieved in all investigated examples. It appeared that the electronic nature of substituents on the aryl ring had minimal impact on the tandem reaction, and similar reactivity as well as diastereo- and enantioselectivity to those with model substrate **1a** were observed for 2-mercaptoquinoline-3-carbaldehydes **1** equipped with electron-withdrawing and -donating substituents (Table 2, entries 3 and 4 and 5 and 6, respectively) on aromatic residues R. For example, pure 1,2-syn diastereomer **3′ba** (1,2-syn/1,2-anti >99:1) was obtained in the tandem reaction of an electron-withdrawing substituent on the aryl ring (Ar) of 2-mercaptoquinoline-3- carbaldehyde **1b** in excellent yields with up to 99% enantioselectivity (Table 2, entry 4). Nitroolefins with electron-withdrawing and -donating substituents on the aromatic ring were also well tolerated in the reactions and provided both diastereomers in high enantio- and diastereoselectivities (Table 2, entries 7−14). To determine the absolute configuration of both diastereomers, a single crystal suitable for X-ray crystallographic analysis was successfully obtained from enantiopure **3ae** and **3′ae** (Figure 2). The absolute configurations of other products were assigned by analogy.

The stereochemical outcome in the domino Michael/Henry reaction can be rationalized by the following proposed models. First, the $\alpha$-proton of nitroalkane was deprotonated by the tertiary nitrogen atom of the chiral thiourea **C8**, and then the protonated chiral thiourea acted as a Bronsted acid to activate both donors and acceptors simultaneously and could control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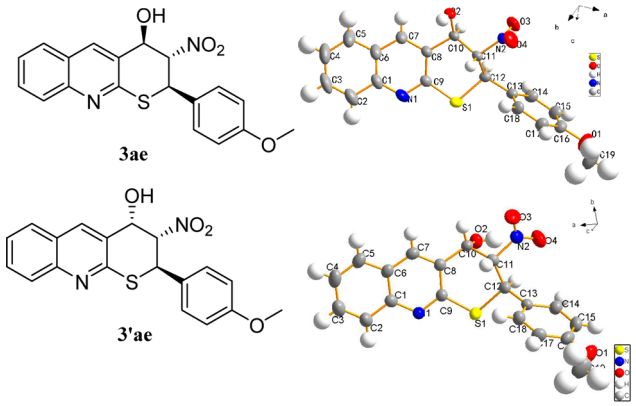



**Figure 2.** Displacement ellipsoids are drawn at the 30% probability level.

the approach of a nitroalkane to aldehyde. As shown in Scheme 2, we speculate that the 2*S*,3*R*,4*R* configuration results from an *si*-face attack (**TS-1**), whereas the 2*R*,3*S*,4*R* stereochemical outcome comes from a preferred reface addition to aldehyde (**TS-2**). This difference is presumably due to the steric hindrance induced by the aromatic ring (e.g., Ph group), which leads to a less hindered *re* face approach. On the other hand, when the domino reaction was catalyzed by **C4**, the carbonyl group was activated by the phenolic OH through hydrogen bonding (**TS-3**). As such, the *syn*-adduct **3′aa** with an internal H-bonding between the OH and $NO_2$ group was formed. Nevertheless, the real domino reaction mechanism still remains to be explored.

In conclusion, we have developed a tandem Michael−Henry reaction of nitroolefins **2** and 2-mercaptoquinoline-3-carbaldehydes **1** to produce the epimeric 2*H*-thiopyrano[2,3-*b*]-quinolines by using quinine derivatives as oganocatalysts. All the reactions proceeded smoothly, and the products bearing 1,2,3-tertiary contiguous stereocenters were obtained in high yields with excellent diastereo- and enantioselectivities. Notably, both bifunctional organocatalysts **C4** and **C8** were derived from the same chiral molecule quinine. And the hydrogen-bonding interaction between **C8** with nitroolefins **2** and 2-mercaptoquinoline-3-carbaldehydes **1**, as well as the hydrogen-bonding interactions between **C4** with **1** and **2**, play a key role in the switch in diastereoselectivity.

## EXPERIMENTAL SECTION

**General Methods.** NMR spectra were recorded with tetramethylsilane as the internal standard. TLC was performed on glass-backed silica plates. Column chromatography was performed using silica gel (150−200 mesh) eluting with ethyl acetate and petroleum ether. $^1$H NMR spectra were recorded at 600 MHz, and $^{13}$C NMR spectra were recorded at 150 MHz. Chemical shifts ($\delta$) are reported in ppm downfield from $CDCl_3$ ($\delta$ = 7.26 ppm) or DMSO ($\delta$ = 2.50 ppm) for $^1$H NMR and relative to the central $CDCl_3$ resonance ($\delta$ = 77.0 ppm) or DMSO resonance ($\delta$ = 39.5 ppm) for $^{13}$C NMR spectroscopy. Coupling constants ($J$) are given in Hz. An ESI-HRMS spectrometer was measured with an ion trap mass spectrometer. Optical rotations were measured at 589 nm at 25 °C in a 1 dm cell, and specific rotations are given in $10^{-1}$ deg cm$^2$ g$^{-1}$. The enantiomeric excess was determined by HPLC analysis using a Chiralpak column (4.6 mm × 250 mm, 5 $\mu$m).

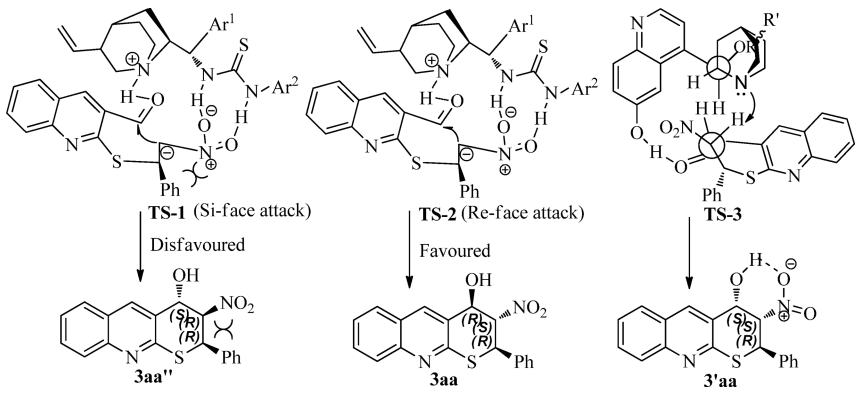
*1. Typical Procedure for the Tandem Michael−Henry Reaction.* A mixture of 2-mercaptoquinoline-3-carbaldehyde **1a** (19.0 mg 0.10 mmol), nitroolefin **2a** (30 mg, 0.20 mmol), and catalyst **C8** (12 mg, 0.02 mmol) was stirred in $CH_2Cl_2$ (2 mL) at −30 °C for 8 h. Afterward, the product was purified directly by flash chromatography on silica gel (20% ethyl acetate/petroleum ether) to give **3aa** as a white solid (33 mg, 96% yield).

*(2R,3S,4R)-3-Nitro-2-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b]-quinolin-4-ol (**3aa**).* The spectra (NMR and ESI-HRMS) are in accordance with the literature.[9] White solid (33 mg, 96% yield), mp 201−203 °C (Lit.[9] 200−202 °C). $^1$H NMR (600 MHz, DMSO) $\delta$ 8.48 (s, 1H), 8.03 (d, $J$ = 8.0 Hz, 1H), 7.86 (d, $J$ = 8.4 Hz, 1H), 7.74 (t, $J$ = 7.3 Hz, 1H), 7.63−7.52 (m, 3H), 7.42 (dt, $J$ = 6.9, 4.7 Hz, 3H), 7.01 (d, $J$ = 8.1 Hz, 1H), 5.69−5.61 (m, 1H), 5.56−5.45 (m, 2H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 156.3, 147.1, 134.8, 131.8, 131.0, 129.7, 129.5, 129.1, 129.5, 129.1 128.7, 127.3, 126.4, 125.8, 91.9, 70.5, 45.7. ESI-HRMS: calcd for $C_{18}H_{14}N_2O_3S$ + H, 339.0803, found 339.0783. $[\alpha]^{25}_D$ +150 ($c$ 0.5, $CHCl_3$), 96% ee, 98:2 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak OD column (15% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 23.7 min, $t_{minor}$ = 15.0 min.

*(2R,3S,4S)-3-Nitro-2-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b]-quinolin-4-ol (**3′aa**).* White solid (32 mg, 96% yield), mp 186−187 °C. $^1$H NMR (600 MHz, DMSO) $\delta$ 8.47 (s, 0.14H), 8.42 (s, 1H), 7.98 (d, $J$ = 8.1 Hz, 1H), 7.85 (d, $J$ = 8.4 Hz, 1H), 7.77−7.73 (m, 1H), 7.65 (d, $J$ = 7.3 Hz, 2H), 7.57−7.54 (m, 1H), 7.42 (t, $J$ = 6.6 Hz, 2H), 7.36 (t, $J$ = 7.4 Hz, 1H), 6.72 (d, $J$ = 5.6 Hz, 1H), 6.15 (dd, $J$ = 11.5, 2.4 Hz, 1H), 5.51−5.47 (m, 2H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 156.7, 147.9, 138.4, 136.9, 131.3, 129.5, 129.4, 129.4, 129.2, 129.09, 129.09, 129.05, 128.7, 127.4, 126.4, 125.8, 87.8, 70.0, 41.3. ESI-HRMS: calcd for $C_{18}H_{14}N_2O_3S$ + H, 339.0803, found 339.0774. $[\alpha]^{25}_D$ +54 ($c$ 0.5, $CHCl_3$), 93% ee, 96:4 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak OD column (15% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 27.7 min, $t_{minor}$ = 21.3 min.

*(2R,3S,4R)-7-Bromo-3-nitro-2-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol (**3ba**).* The spectra (NMR and ESI-

**Scheme 2. Proposed Model for the Modified Quinine-Catalyzed Henry reactions**



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HRMS) are in accordance with the literature.[9] White solid (37 mg, 90% yield), mp 200−202 °C (Lit.[9] 199−201 °C). $^1$H NMR (600 MHz, DMSO) $\delta$ 8.46 (s, 1H), 8.40 (s, 0.18H), 8.34 (d, $J$ = 2.1 Hz, 1H), 7.83 (dd, $J$ = 8.9, 2.1 Hz, 1H), 7.78 (d, $J$ = 8.9 Hz, 1H), 7.56 (d, $J$ = 6.8 Hz, 2H), 7.44−7.39 (m, 3H), 7.07 (d, $J$ = 8.1 Hz, 1H), 5.66 (t, $J$ = 10.7 Hz, 1H), 5.49 (dd, $J$ = 9.6, 4.8 Hz, 2H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 157.2, 145.7, 134.6, 134.0, 133.0, 130.6, 129.8, 129.6, 1296, 129.5, 129.4, 129.1, 129.1 127.2, 119.1, 91.6, 70.4, 45.7. ESI-HRMS: calcd for $C_{18}H_{13}BrN_2O_3S$ + H, 416.9903, found 416.9874. $[\alpha]^{25}_D$ +32 ($c$ 0.5, $CHCl_3$), 99% ee, 97:3 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak AD column (10% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 43.5 min, $t_{minor}$ = 38.8 min.

*(2R,3S,4S)-7-Bromo-3-nitro-2-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3′ba***). White solid (39 mg, 93% yield), mp 157−159 °C. $^1$H NMR (400 MHz, DMSO) $\delta$ 8.47 (s, 0.25H), 8.40 (s, 1H), 8.28 (s, 1H), 7.85 (d, $J$ = 1.5 Hz, 1H), 7.81−7.76 (m, 1H), 7.64 (d, $J$ = 7.2 Hz, 2H), 7.39 (dd, $J$ = 14.8, 7.2 Hz, 3H), 6.80 (s, 1H), 6.15 (d, $J$ = 11.4 Hz, 1H), 5.50 (s, 1H), 5.47 (d, $J$ = 5.2 Hz, 1H). $^{13}$C NMR (101 MHz, DMSO) $\delta$ 157.6, 146.4, 137.4, 136.7, 134.3, 130.5, 130.1, 129.6, 129.4, 129.4, 129.0, 129.0, 127.1, 119.0, 87.6, 69.8, 41.3. ESI-HRMS: calcd for $C_{18}H_{13}BrN_2O_3S$ + H, 416.9909, found 416.9870. ESI-HRMS: calcd for $C_{18}H_{13}BrN_2O_3S$ + H, 416.9903, found 416.9874. $[\alpha]^{25}_D$ +162 ($c$ 0.5, $CHCl_3$), 99% ee, >99:1 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak AD column (10% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 101.7 min, $t_{minor}$ = 36.7 min.

*(2R,3S,4R)-7-Methyl-3-nitro-2-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3ca***). The spectra (NMR and ESI-HRMS) are in accordance with the literature.[9] White solid (34 mg, 97% yield), mp 209−210 °C (Lit.[9] 208−210 °C). $^1$H NMR (600 MHz, DMSO) $\delta$ 8.35 (s, 1H), 7.80−7.70 (m, 2H), 7.56 (dd, $J$ = 11.0, 4.2 Hz, 3H), 7.45−7.35 (m, 3H), 6.99 (d, $J$ = 8.1 Hz, 1H), 5.65−5.56 (m, 1H), 5.46 (dd, $J$ = 9.7, 5.2 Hz, 2H), 2.47 (s, 3H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 155.0, 145.7, 135.9, 134.8, 134.2, 133.1, 131.7, 129.7, 129.5, 129.5, 129.1, 129.1, 127.3, 127.1, 125.8, 92.0, 70.5, 45.6, 21.5. ESI-HRMS: calcd for $C_{19}H_{16}N_2O_3S$ + H, 353.0960, found 353.0933. $[\alpha]^{25}_D$ +300 ($c$ 0.5, $CHCl_3$), 93% ee, 97:3 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 34.5 min, $t_{minor}$ = 26.0 min.

*(2R,3S,4S)-7-Methyl-3-nitro-2-phenyl-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3′ca***). White solid (34 mg, 97% yield), mp 181−182 °C. $^1$H NMR (600 MHz, DMSO) $\delta$ 8.38 (s, 1H), 8.32 (s, 1H), 7.78−7.74 (m, 2H), 7.65 (d, $J$ = 7.4 Hz, 2H), 7.60 (dd, $J$ = 8.7, 1.4 Hz, 1H), 7.42 (t, $J$ = 7.4 Hz, 2H), 7.37 (t, $J$ = 7.3 Hz, 1H), 6.72 (d, $J$ = 5.7 Hz, 1H), 6.15 (dd, $J$ = 11.5, 2.2 Hz, 1H), 5.49 (d, $J$ = 11.4 Hz, 2H), 2.50 (s, 3H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 155.5, 146.5, 137.8, 137.0, 135.8, 133.4, 129.4, 129.4, 129.2, 129.06, 129.06, 129.00, 127.29, 127.26, 125.8, 87.9, 70.0, 41.2, 21.5. ESI-HRMS: calcd for $C_{19}H_{16}N_2O_3S$ + H, 353.0960, found 353.0935. $[\alpha]^{25}_D$ +109 ($c$ 0.5, $CHCl_3$), 99% ee, 91:9 dr. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (10% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 76.0 min, $t_{minor}$ = 28.9 min.

*(2R,3S,4R)-2-(4-Bromophenyl)-3-nitro-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3ab***). The spectra (NMR and ESI-HRMS) are in accordance with the literature.[9] White solid (39 mg, 93% yield), mp 163−165 °C (Lit.[9] 161−163 °C). $^1$H NMR (600 MHz, DMSO) $\delta$ 8.47 (s, 1H), 8.01 (d, $J$ = 8.0 Hz, 1H), 7.84 (d, $J$ = 8.4 Hz, 1H), 7.73 (t, $J$ = 7.5 Hz, 1H), 7.63 (d, $J$ = 8.2 Hz, 2H), 7.59−7.51 (m, 3H), 7.06 (d, $J$ = 7.9 Hz, 1H), 5.67 (t, $J$ = 10.6 Hz, 1H), 5.53 (d, $J$ = 11.1 Hz, 1H), 5.47 (t, $J$ = 8.9 Hz, 1H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 156.0, 147.1, 134.8, 134.3, 132.5, 132.5, 131.8, 131.3, 131.3, 131.0, 128.7, 127.3, 126.5, 125.8, 123.0, 91.6, 70.3, 45.0. ESI-HRMS: calcd for $C_{18}H_{13}BrN_2O_3S$ + H, 416.9903, found 416.9879. $[\alpha]^{25}_D$ +75 ($c$ 0.5, $CHCl_3$), 94% ee, 99:1 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak OD column (15% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 33.9 min, $t_{minor}$ = 23.09 min.

*(2R,3S,4S)-2-(4-Bromophenyl)-3-nitro-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3′ab***). White solid (40 mg, 95% yield), mp 133−135 °C. $^1$H NMR (600 MHz, DMSO) $\delta$ 8.47 (s, 0.2H), 8.43 (s, 1H), 7.98 (d, $J$ = 7.6 Hz, 1H), 7.85 (d, $J$ = 8.4 Hz, 1H), 7.77−7.74 (m, 1H), 7.63 (t, $J$ = 3.6 Hz, 3H), 7.58−7.53 (m, 2H), 6.74 (d, $J$ = 5.5 Hz, 1H), 6.16 (dd, $J$ = 11.4, 2.4 Hz, 1H), 5.51 (d, $J$ = 11.6 Hz, 1H), 5.50−5.48 (m, 1H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 156.4, 147.8, 138.5, 136.5, 132.6, 132.4, 131.4, 131.38, 131.34, 129.1, 128.7, 127.4, 126.5, 125.8, 122.3, 87.6, 69.9, 40.7. ESI-HRMS: calcd for $C_{18}H_{13}BrN_2O_3S$ + H, 416.9903, found 416.9879. $[\alpha]^{25}_D$ +105 ($c$ 0.5, $CHCl_3$), 94% ee, 96:4 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak OD column (15% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 45.5 min, $t_{minor}$ = 38.5 min.

*(2R,3S,4R)-3-Nitro-2-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3ac***). White solid (39 mg, 97% yield), mp 195−197 °C. $^1$H NMR (600 MHz, DMSO) $\delta$ 8.49 (s, 1H), 8.02 (d, $J$ = 8.0 Hz, 1H), 7.85 (dd, $J$ = 8.3, 4.4 Hz, 3H), 7.81 (d, $J$ = 8.4 Hz, 2H), 7.77−7.69 (m, 1H), 7.54 (dd, $J$ = 11.1, 4.0 Hz, 1H), 7.10 (d, $J$ = 7.9 Hz, 1H), 5.75 (dd, $J$ = 12.0, 9.2 Hz, 1H), 5.67 (d, $J$ = 11.1 Hz, 1H), 5.50 (dd, $J$ = 13.2, 4.7 Hz, 1H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 155.8, 147.1, 139.6, 134.9, 131.8, 131.1, 130.2, 130.2 (q, $J_{C-F}$ = 30.8 Hz), 128.7, 127.3, 126.5, 126.5, 126.5 (q, $J_{C-F}$ = 4.1 Hz), 125.9, 125.2, 123.4 (q, $J_{C-F}$ = 269.3 Hz), 91.4, 70.3, 45.1. ESI-HRMS: calcd for $C_{19}H_{13}F_3N_2O_3S$ + H, 407.0677, found 407.0649. $[\alpha]^{25}_D$ −17 ($c$ 0.5, $CHCl_3$), 97% ee, >99:1 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak AD column (15% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 16.1 min, $t_{minor}$ = 14.1 min.

*(2R,3S,4S)-3-Nitro-2-(4-(trifluoromethyl)phenyl)-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3′ac***). White solid (40 mg, 99% yield), mp 122−123 °C. $^1$H NMR (600 MHz, DMSO) $\delta$ 8.49 (s, 0.09H), 8.45 (s, 1H), 7.99 (d, $J$ = 7.6 Hz, 1H), 7.93 (d, $J$ = 8.2 Hz, 2H), 7.86 (d, $J$ = 8.3 Hz, 1H), 7.80 (d, $J$ = 8.2 Hz, 2H), 7.76 (ddd, $J$ = 8.4, 6.9, 1.4 Hz, 1H), 7.58−7.55 (m, 1H), 6.80 (d, $J$ = 5.5 Hz, 1H), 6.27 (dd, $J$ = 11.4, 2.4 Hz, 1H), 5.63 (d, $J$ = 11.4 Hz, 1H), 5.53 (dd, $J$ = 5.4, 2.4 Hz, 1H). $^{13}$C NMR (151 MHz, DMSO) $\delta$ 156.2, 147.8, 141.9, 138.6, 131.4 (q, $J_{C-F}$ = 32.4 Hz), 130.0, 130.0, 129.1, 128.7, 127.4, 126.5, 126.4, 125.8, 125.3 (q, $J_{C-F}$ = 6.5 Hz), 123.5 (q, $J_{C-F}$ = 270.3 Hz), 87.4, 69.9, 40.8. ESI-HRMS: calcd for $C_{19}H_{13}F_3N_2O_3S$ + H, 407.0677, found 407.0646. $[\alpha]^{25}_D$ +76 ($c$ 0.5, $CHCl_3$), 99% ee, >99:1 dr; The enantiomeric ratio was determined by HPLC on Chiralpak AD column (15% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 19.4 min, $t_{minor}$ = 10.7 min.

*(2R,3S,4R)-2-(3-Methoxyphenyl)-3-nitro-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3ad***). White solid (33 mg, 91% yield), mp 199−200 °C. $^1$H NMR (600 MHz, DMSO) $\delta$ 8.47 (s, 1H), 8.00 (d, $J$ = 7.9 Hz, 1H), 7.84 (d, $J$ = 8.3 Hz, 1H), 7.73 (t, $J$ = 7.5 Hz, 1H), 7.54 (t, $J$ = 7.4 Hz, 1H), 7.33 (t, $J$ = 7.8 Hz, 1H), 7.15 (s, 1H), 7.09 (dd, $J$ = 17.7, 7.6 Hz, 2H), 6.96 (d, $J$ = 7.8 Hz, 1H), 5.66 (t, $J$ = 10.6 Hz, 1H), 5.50−5.40 (m, 2H), 3.76 (s, 3H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 160.0, 156.3, 147.1, 136.3, 134.8, 131.9, 131.0, 130.6, 128.7, 127.3, 126.4, 125.8, 121.2, 115.0, 114.8, 91.6, 70.4, 55.7, 45.6. ESI-HRMS: calcd for $C_{19}H_{16}N_2O_4S$ + H, 369.0909, found 369.0917. $[\alpha]^{25}_D$ +89 ($c$ 0.5, $CHCl_3$), 98% ee, >99:1 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak OD column (15% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 27.3 min, $t_{minor}$ = 15.8 min.

*(2R,3S,4S)-2-(3-Methoxyphenyl)-3-nitro-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3′ad***). White solid (34 mg, 91% yield), mp 170−172 °C. $^1$H NMR (600 MHz, DMSO) $\delta$ 8.47 (s, 0.06H), 8.41 (s, 1H), 7.98 (d, $J$ = 7.9 Hz, 1H), 7.85 (d, $J$ = 8.4 Hz, 1H), 7.77−7.72 (m, 1H), 7.55 (t, $J$ = 7.5 Hz, 1H), 7.32 (t, $J$ = 7.9 Hz, 1H), 7.24 (s, 1H), 7.20 (d, $J$ = 7.7 Hz, 1H), 6.93 (dd, $J$ = 8.2, 2.1 Hz, 1H), 6.72 (d, $J$ = 5.5 Hz, 1H), 6.17 (dd, $J$ = 11.4, 2.4 Hz, 1H), 5.48 (dd, $J$ = 7.0, 4.5 Hz, 2H), 3.77 (s, 3H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 160.0, 156.7, 147.9, 138.5, 138.5, 131.3, 130.5, 129.2, 128.7, 127.4, 126.4, 125.8, 121.2, 114.7, 114.4, 87.6, 69.9, 55.6, 41.3. ESI-HRMS: calcd for $C_{19}H_{16}N_2O_4S$ + H, 369.0909, found 369.0895. $[\alpha]^{25}_D$ +75 ($c$ 0.5, $CHCl_3$), 99% ee, 98:2 dr. The enantiomeric ratio was determined by HPLC on Chiralpak OD column (15% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 32.6 min, $t_{minor}$ = 20.1 min.

*(2R,3S,4R)-2-(4-Methoxyphenyl)-3-nitro-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol* (***3ae***). The spectra (NMR and ESI-HRMS) are in accordance with the literature.[9] White solid (34 mg, 93% yield), mp 168−170 °C (Lit.[9] 167−169 °C). $^1$H NMR (600 MHz, DMSO) $\delta$ 8.46 (s, 1H), 8.01 (d, $J$ = 8.1 Hz, 1H), 7.85 (d, $J$ = 8.4



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Hz, 1H), 7.74 (t, $J$ = 7.5 Hz, 1H), 7.60−7.46 (m, 3H), 6.99 (dd, $J$ = 16.8, 8.3 Hz, 3H), 5.59 (t, $J$ = 10.6 Hz, 1H), 5.52−5.41 (m, 2H), 3.78 (s, 3H). $^{13}$C NMR (150 MHz, DMSO) $\delta$ 160.2, 156.4, 147.1, 134.8, 131.8, 131.0, 130.4, 130.4, 128.7, 127.3, 126.4, 126.2, 125.8, 114.9, 114.9, 92.1, 70.5, 55.6, 45.2. ESI-HRMS: calcd for $C_{19}H_{16}N_2O_4S$ + H, 369.0909, found 369.0915. $[\alpha]^{25}_D$ +66 ($c$ 0.5, $CHCl_3$), 89% ee, 94:6 dr. The enantiomeric ratio was determined by HPLC on a Chiralpak AD column (20% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 17.4 min, $t_{minor}$ = 15.3 min.

*Crystal Data for* ***3ae***. $C_{19}H_{16}N_2O_4S$ (368.40), monoclinic, $P2(1)$; $a$ = 11.1928(3) Å, $\alpha$ = 90°; $b$ = 5.26350(10) Å, $\beta$ = 109.1950(10)°; $c$ = 15.5946(4) Å, $\gamma$ = 90°; $U$ = 867.65(4) Å$^3$, $Z$ = 2, $T$ = 296(2) K, absorption coefficient = 0.214 mm$^{-1}$, reflections collected +29 266, unique = 3995 [$R$(int) = 0.0395], refinement by full-matrix least-squares on $F^2$, data/restraints/parameters 3995/1/239, goodness-of-fit on $F^2$ = 0.329, final $R$ indices [$I > 2\sigma(I)$] R1 = 0.0327, wR2 = 0.0861; $R$ indices (all data) R1 = 0.0360, wR2 = 0.0953, largest diff. peak and hole = 0.180 and −0.221e·Å$^{-3}$, respectively.

*(2R,3S,4S)-2-(4-Methoxyphenyl)-3-nitro-3,4-dihydro-2H-thiopyrano[2,3-b]quinolin-4-ol (**3′ae**).* White solid (38 mg, 96% yield), mp 156−158 °C. $^1$H NMR (600 MHz, DMSO) $\delta$ 8.40 (s, 1H), 7.97 (d, $J$ = 7.8 Hz, 1H), 7.85 (d, $J$ = 8.4 Hz, 1H), 7.77−7.72 (m, 1H), 7.58−7.52 (m, 3H), 6.96 (d, $J$ = 8.7 Hz, 2H), 6.69 (d, $J$ = 5.7 Hz, 1H), 6.07 (dd, $J$ = 11.5, 2.4 Hz, 1H), 5.45 (dd, $J$ = 9.5, 6.5 Hz, 2H), 3.76 (s, 3H). $^{13}$C NMR (151 MHz, DMSO) $\delta$ 159.7, 156.9, 147.8, 138.3, 131.3, 130.4, 130.4, 129.2, 128.6, 128.4, 127.4, 126.3, 125.8, 114.7, 114.7, 88.0, 70.0, 55.6, 40.8. ESI-HRMS: calcd for $C_{19}H_{16}N_2O_4S$ + H, 369.0909, found 369.0916. $[\alpha]^{25}_D$ +63 ($c$ 0.5, $CHCl_3$), 98% ee, 98:2 dr. The enantiomeric ratio was determined by HPLC on Chiralpak AD column (20% 2-propanol/hexane, 1 mL/min), $t_{major}$ = 44.7 min, $t_{minor}$ = 13.6 min.

*Crystal Data for* ***3′ae***. $C_{19}H_{16}N_2O_4S$ (368.40), orthorhombic, $P2(1)2(1)2(1)$; $a$ = 10.112(5) Å, $\alpha$ = 90°; $b$ = 10.996(6) Å, $\beta$ = 90°; $c$ = 15.378(8) Å, $\gamma$ = 90°; $U$ = 1709.9(15) Å$^3$, $Z$ = 22, $T$ = 296(2) K, absorption coefficient = 0.217 mm$^{-1}$, reflections collected +12 115, unique = 3944 [R(int) = 0.0722], refinement by full-matrix least-squares on $F^2$, data/restraints/parameters 3944/0/236, goodness-of-fit on $F^2$ = 1.011, final $R$ indices [$I > 2\sigma(I)$] R1 = 0.0561, wR2 = 0.0990; $R$ indices (all data) R1 = 0.1030, wR2 = 0.1175, largest diff. peak and hole = 0.275 and −0.304 e·Å$^{-3}$, respectively.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02688.

$^1$H, $^{13}$C NMR and HPLC spectra for all new compounds (PDF)

X-ray structural data for **3ae** (CIF)

X-ray structural data for **3′ae** (CIF)

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### Notes

The authors declare no competing financial interest.

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