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Enantioselective Michael reaction of nitroalkanes onto nitroalkenes catalyzed by cinchona alkaloid derivatives

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ABSTRACT

An effective asymmetric synthesis of optically active 1,3-dinitro compounds via the direct Michael addition of nitroalkanes onto nitroalkenes has been described. In the presence of readily modified cinchona alkaloid derivatives, nitroethane reacted well with a variety of aromatic and heterocyclic aromatic nitroalkenes to afford products with good diastereoselectivities (dr up to 72/28) and enantioselectivities (ee up to 94%). The catalyst loading can be decreased to 2 mol % without compromising the asymmetric induction or the reaction rate.

1. Introduction

The Michael reaction of stabilized carbanions to α,β-unsaturated systems is one of the most valuable reactions in organic synthesis, which allows the efficient construction of new carbon–carbon bonds. In recent years, catalytic enantioselective Michael reactions have been widely investigated, α,β-unsaturated carbonyl compounds, nitroalkenes, and some activated olefins are usually chosen as Michael acceptors, while nitroalkanes and activated methylene compounds are used as Michael donors.[1–6] However, the direct Michael addition of nitroalkanes onto nitroalkenes is rather rare despite the fact that the 1,3-dinitro compounds are useful synthetic intermediates, which can be readily transformed into a variety of functionalities.[7–10]

In 2006, Du et al. reported the first catalytic enantioselective conjugate addition of nitroalkanes onto nitroolefins using Et_2Zn/$Ti(OiPr)_4$/bis(oxazoline) or bis(thiozoline) as the chiral catalyst.[11] However, this system is not suitable for highly sterically hindered nitroalkanes because of their decreased nucleophilic activities. Feng et al. developed another efficient metal-catalyzed system for this Michael reaction by using a chiral $La(OTf)_3$/*N*,*N*′-dioxide complex.[12] Some groups have focused on this asymmetric reaction and developed a number of efficient organocatalytic systems. Wang et al. were the first to propose an organocatalytic enantioselective Michael reaction using cinchona alkaloid-derived catalyst **Q-1**,[13] albeit 10 mol % catalyst loading and a long reaction time (6 days) were needed to ensure good stereoselectivities. Wulff[14] and Wang[15] have independently developed organocatalytic processes with excellent asymmetric inductions utilizing bifunctional thiourea catalysts. Du et al. reported a chiral squaramide-catalyzed enantioselective Michael reaction of nitroalkanes to nitroalkenes.[16] Toy et al. used amine-thiourea bifunctional polymeric organocatalysts for this reaction.[17] Additionally, Maruoka et al. achieved an efficient conjugate addition of silyl nitronates onto nitroalkenes using a phase-transfer catalyst.[18] Despite these successes, the development of efficient catalytic systems with readily prepared catalysts, low catalyst loading, and mild reaction conditions remains a challenge.

On the other hand, cinchona derivatives have already been used to catalyze a wide range of chemical reactions, often with remarkable stereoselectivity.[19] Although Wang et al. have proved that the presence of two –OH groups (6′-OH, 9-OH) in the cinchona alkaloid **Q-1** is necessary for achieving high enantioselectivity for the conjugate addition reaction of nitroalkanes with nitroolefins,[13] we also noticed that some cinchona derivatives that lacked either a 9-OH or a 6′-OH served as effective catalysts for some structurally related Michael reactions, such as 1,3-dicarbonyl compounds to nitroalkenes.[20–23]

In our previous work, we have already synthesized a series of cinchona alkaloid derived catalysts, and found that **QD-2** without a 9-OH group exhibited good catalytic activity in the asymmetric Mannich-type reactions of isocyanoacetates to imines.[24] Cinchona alkaloids can activate electrophiles in several ways via both covalent and nonvalent interactions. Small modifications on the cinchona scaffold can have a dramatic impact on both the diastereoselectivity and the enantioselectivity. Herein we want to further explore the performance of 9-substituted cinchona alkaloid on the direct Michael reaction of nitroalkanes onto nitroolefins. Selected organocatalysts include those with different sterically hindered protecting groups at the 9-position of the cinchona alkaloids while bearing a hydroxyl group or another hydrogen-bonding donor at the 6′-position (Fig. 1).

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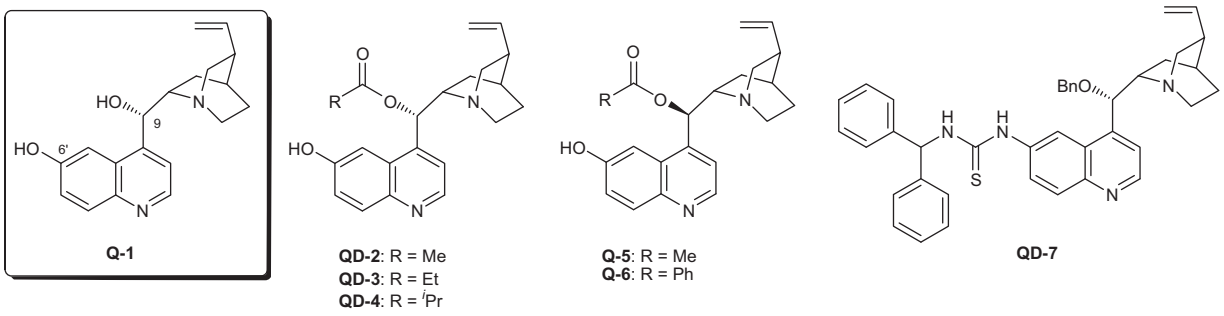


Figure 1. Cinchona alkaloid catalysts used herein.

2. Results and discussion

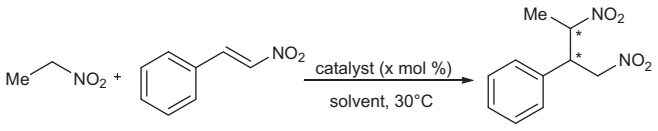
2.1. Optimization of the reaction conditions

Initially, all of the catalysts tested catalyzed the reactions in moderate to high ee values (50–81%) and satisfactory yields (76–96%) at 5 mol % catalyst loading in toluene (Table 1, entries 1–6). Catalysts **QD-2** and **Q-5** showed the highest catalytic activities, yielding the major *syn*-products with opposite absolute configurations,[11–13,15] that is, (2*R*,3*R*) for **QD-2** and (2*S*,3*S*) for **Q-5** (entries 1 and 4). For **QD-3** and **QD-4**, which have more hindered protecting groups at the 9-position, the dr and ee values decreased slightly (entries 2 and 3). Meanwhile, a longer reaction time was needed for **Q-6**, which has a benzoyl group at the 9-position (entry 5). For **QD-7**, the reaction resulted in a high yield but a lower ee value when thiourea was used as the hydrogen-bonding donor at the 6′-position (entry 6). These results suggest that the structures of the protecting group at the 9-position and the hydrogen-bonding donor at the 6′-position play important roles in achieving high enantioselectivity.

Further screening of the reaction conditions showed that the solvent significantly affected the enantioselectivity. Toluene appeared to be the optimal solvent in terms of the reaction time, yield, enantioselectivity and diastereoselectivity (entries 7–15). On the other hand, both the enantioselectivity and diastereoselectivity decreased in the absence of any organic solvent (entry 7). A decrease in temperature to 0 °C had no significant effect on the ee or dr values but decreased the activity (entry 16). At 2 mol % or even 0.5 mol % catalyst loading, the ee and dr values were comparable with those of 5 mol % loading, whereas a catalyst loading of 10 or 20 mol % reduced the diastereoselectivity (entries 17–21). Moreover, no oligomerization was observed in this study.[14]

The process of the **QD-2** catalyzed asymmetric Michael addition of nitroalkanes to nitroalkenes was also monitored (Table 2). The

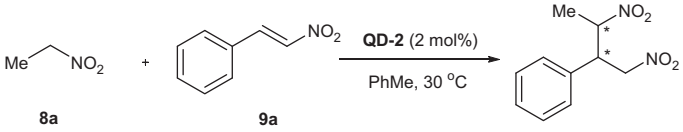
Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Catalyst loading (mol %)	Solvent	Time (h)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee of *syn*[d] (%)
1	**QD-2**	5	Toluene	48	82	66/34	81 (2*R*,3*R*)
2	**QD-3**	5	Toluene	48	85	69/31	78 (2*R*,3*R*)
3	**QD-4**	5	Toluene	48	78	72/28	77 (2*R*,3*R*)
4	**Q-5**	5	Toluene	48	80	66/34	81 (2*S*,3*S*)
5	**Q-6**	5	Toluene	72	76	60/40	80 (2*S*,3*S*)
6	**QD-7**	5	Toluene	24	96	66/34	50 (2*R*,3*R*)
7	**QD-2**	5	—	24	95	54/46	74 (2*R*,3*R*)
8	**QD-2**	5	DCE	24	78	59/41	78 (2*R*,3*R*)
9	**QD-2**	5	$CHCl_3$	24	76	58/42	76 (2*R*,3*R*)
10	**QD-2**	5	DCM	24	80	59/41	76 (2*R*,3*R*)
11	**QD-2**	5	THF	120	65	62/38	80 (2*R*,3*R*)
12	**QD-2**	5	MTBE	96	61	56/44	70 (2*R*,3*R*)
13	**QD-2**	5	Acetone	120	70	57/43	74 (2*R*,3*R*)
14	**QD-2**	5	^{i}PrOH	48	72	56/44	24 (2*R*,3*R*)
15	**QD-2**	5	DMF	48	60	58/42	5 (2*R*,3*R*)
16[e]	**QD-2**	5	Toluene	72	80	62/38	83 (2*R*,3*R*)
17	**QD-2**	2	Toluene	48	85	67/33	81 (2*R*,3*R*)
18	**QD-2**	1	Toluene	48	75	58/42	83 (2*R*,3*R*)
19	**QD-2**	0.5	Toluene	120	58	66/34	83 (2*R*,3*R*)
20	**QD-2**	10	Toluene	30	94	50/50	81 (2*R*,3*R*)
21	**QD-2**	20	Toluene	18	96	51/49	82 (2*R*,3*R*)

[a] Unless otherwise indicated, the reactions were performed with nitroethane (30 mmol, 30 equiv), *trans*-β-nitrostyrene (149 mg, 1 mmol), and the catalyst (5 mol %) in the solvent (2.5 mL).
[b] Isolated yields.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.
[e] Reaction at 0 °C.

Table 2
Michael addition of nitroethane to β-nitrostyrene in the presence of catalyst **QD-2**[a]



8a **9a** **10aa**

Entry	Time (h)	Yield (%)	dr (*syn*/*anti*)
1	2	15	77/23
2	6	38	75/25
3	12	60	72/28
4	24	80	69/31
5	48	85	67/33

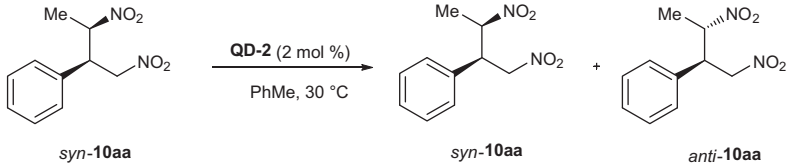
[a] The reaction was performed using nitroethane (30 mmol, 30 equiv), *trans*-β-nitrostyrene (149 mg, 1 mmol), and **QD-2** (2 mol %) in toluene (2.5 mL).

dr value was 77/23 during the first 2 h and was then significantly reduced to 67/33 after 48 h.

In addition, epimerization of *syn*-**10aa** was also investigated (Scheme 1). Almost no epimerization was observed in the first 2 h; however, 15% and 21% of the *anti*-product formed after 48 and 72 h, respectively. These results showed that both the inherent difficulty of controlling the diastereoselectivity and the epimerization of the *syn*-product caused the moderate dr value in the asymmetric Michael reaction.

2.2. Substrate scope and limitation

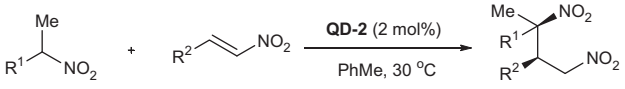
The scope of the asymmetric Michael reaction of nitroalkanes to nitroalkenes was then investigated. As shown in Table 3, a wide array of aromatic nitroalkenes reacted smoothly with nitromethane to afford the corresponding 1,3-dinitro compounds with high enantioselectivities (up to 94% ee). The electronic character of the substituent group on the phenyl had a marginal effect on the dr and ee values, but exhibited a significant effect on the reaction rate. Substrates with electron-withdrawing groups reacted faster than those with electron-donating groups (entries 2–10). Heteroaromatic nitroalkenes were also able to participate in the reaction: furanyl and thienyl nitroalkenes gave 80% and 94% ee, respectively (entries 11 and 12). α,β-Unsaturated nitroolefin **9n** was also a viable substrate (entry 14). Aliphatic nitroolefin **9m** proved to be quite inert in this catalytic system, affording low yield (20% even after 5 days) and moderate enantioselectivity (entry 13). The



time	*syn*/*anti*
2 h	97/3
24 h	89/11
48 h	85/15
72 h	79/21

Scheme 1. Epimerization of the *syn*-**10aa**.

Table 3
Michael addition of nitroalkanes to nitroalkenes in the presence of catalyst **QD-2**[a]



8 **9** **10**

Entry	R^1	R^2	Time (days)	Yield[b] (%)	dr[c] (*syn*/*anti*)	ee of *syn*[d] (%)
1	H **8a**	Phenyl **9a**	2	85	67/33	81
2	H **8a**	4-Bromophenyl **9b**	2	87	60/40	81
3	H **8a**	2-Chlorophenyl **9c**	2	83	55/45	80
4	H **8a**	3-Chlorophenyl **9d**	2	87	62/38	77
5	H **8a**	4-Chlorophenyl **9e**	2	82	60/40	82
6	H **8a**	2-Fluorophenyl **9f**	2	85	72/28	74
7	H **8a**	3-Fluorophenyl **9g**	2	80	57/43	83
8	H **8a**	4-Fluorophenyl **9h**	2	84	60/40	80
9	H **8a**	4-Methylphenyl **9i**	5	76	54/46	82
10	H **8a**	4-Methoxyphenyl **9j**	5	73	58/42	84
11	H **8a**	2-Furyl **9k**	3	80	60/40	80
12	H **8a**	2-Thienyl **9l**	3	82	60/40	94
13	H **8a**	*i*-Pr **9m**	5	20	52/48	79
14	H **8a**	Cinnamyl **9n**	2	80	60/40	65
15[e]	Me **8b**	Phenyl **9a**	4	60	–	83

[a] Unless otherwise indicated, the reactions were performed using nitroalkane (30 mmol, 30 equiv), nitroalkene (1 mmol), and **QD-2** (2 mol %) in PhMe (2.5 mL).
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] Determined by HPLC.
[e] With 20 mol % catalyst.

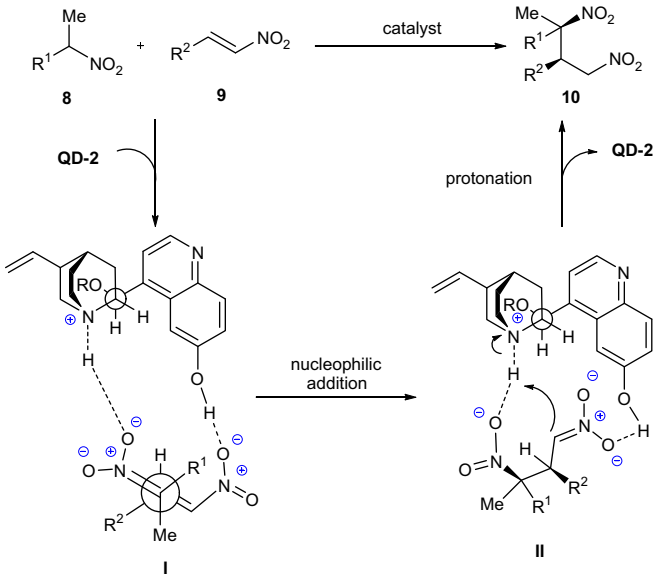


Figure 2. Possible mechanism for the asymmetric Michael reaction.

addition of sterically hindered 2-nitropropane to *trans*-β-nitrostyrene in the presence of 20 mol % **QD-2** gave 83% ee; however, the reaction was slow (entry 15).

2.3. Possible mechanism for the asymmetric Michael reaction

The possible mechanism for the cinchona alkaloid-catalyzed Michael reactions is proposed in Figure 2.[20,25] The chiral base first captures the α-proton of the nitroalkane to form an activated carbanion. Meanwhile, organocatalyst **QD-2** adopts a conformation which simultaneously activates and orientates the Michael donor and the acceptor by means of double hydrogen bond interactions (transition state **I**). After nucleophilic attack of the carbanion to the nitroalkene, transition state **II** forms and finally releases the chiral base to afford 1,3-dinitro compounds.

3. Conclusions

In conclusion, we have developed an effective asymmetric synthesis of optically active 1,3-dinitro compounds via the Michael addition of nitroalkanes to nitroalkenes, to afford the corresponding adducts with 72/28 dr and up to 94% ee. The catalytic system performs well with a broad variety of substrates, and the catalyst loading can be decreased to 2 mol % without compromising the asymmetric induction or the reaction rate. Further investigation on defining the scope and expanding the synthetic utility of this reaction system is currently in progress.

4. Experimental

4.1. General

Unless otherwise stated, commercial reagents purchased from Alfa Aesar, Acros, Aldrich or Shanghai Aladdin chemical companies were used without further purification. Purification of the reaction products was carried out by flash chromatography using Qing Dao Sea Chemical Reagent silica gel (200–300 mesh). ^{1}H NMR spectra were recorded on a Bruker Avance III spectrometer (400 MHz) and the spectra were referenced internally to the residual proton resonance in $CDCl_3$ (δ = 7.26 ppm), or with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. Chemical shifts are reported as parts per million (ppm) in the δ scale downfield from TMS. ^{13}C NMR spectra were recorded on a Bruker spectrometer with complete proton decoupling, and chemical shifts are reported in ppm from TMS with the solvent as the internal reference ($CDCl_3$, δ = 77.0 ppm). HPLC analyses were conducted on a Shimadzu 10A instrument using Daicel Chiralcel OD-H, Chiralpak AD-H or AS-H column (0.46 cm diameter × 25 cm length). Optical rotations were recorded on a Perkin–Elmer polarimeter (Model 341). Analytical TLC was performed using EM separations percolated silica gel 0.2 mm layer UV 254 fluorescent sheets.

4.2. Procedures for the preparation of the catalysts

4.2.1. (*S*)-(6-Hydroxyquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl acetate QD-2[26]

Under nitrogen, *O*-acetylquinidine[27] (1.06 g, 2.9 mmol) was dissolved in CH_2Cl_2 (20 mL) at −78 °C. Next, BBr_3 (1.6 mL, 12 mmol) in CH_2Cl_2 (15 mL) was added dropwise to the reaction flask and stirred for 1 h, then gradually warmed to room temperature and stirred overnight. Ammonia water (25%, 10 mL) was added dropwise into the mixture at 0 °C, and stirred for 15 min before adding water (10 mL), the water layer was separated and washed with CH_2Cl_2 (3 × 10 mL), the organic layer was combined and washed with saturated brine and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, purified by column chromatography (ethyl acetate/ammonia water 80:1, V/V) to give **QD-2** as a white solid (705 mg, 70% yield). $[\alpha]_D^{20} = +110.1$ (*c* 0.4, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 4.5 Hz, 1H), 7.96 (d, *J* = 9.1 Hz, 1H), 7.56 (d, *J* = 2.4 Hz, 2H, OH), 7.32–7.23 (m, 2H), 6.53 (d, *J* = 5.8 Hz, 1H), 6.03–5.94 (m, 1H), 5.10–5.06 (m, 2H), 3.30–3.24 (m, 1H), 3.00–2.93 (m, 2H), 2.81–2.71 (m, 2H), 2.31–2.27 (m, 1H), 2.10 (s, 3H), 1.97–1.86 (m, 1H), 1.80 (s, 1H), 1.54–1.47 (m, 2H), 1.42–1.34 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 156.3, 146.2, 143.5, 143.3, 139.9, 131.2, 127.2, 122.6, 118.5, 115.1, 105.6, 73.8, 58.5, 49.7, 49.0, 39.5, 27.8, 26.0, 22.7, 21.1.

4.2.2. (*S*)-(6-Hydroxyquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl propionate QD-3 [26]

QD-3 was prepared from *O*-propionylquinidine[28]according to the literature procedure and similar to **QD-2**, white solid, 50% yield for two steps. $[\alpha]_D^{20} = +99.0$ (*c* 0.4, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 4.5 Hz, 1H), 7.97 (d, *J* = 9.1 Hz, 1H), 7.55 (d, *J* = 2.5 Hz, 1H), 7.33–7.25 (m, 2H), 6.58 (d, *J* = 5.3 Hz, 1H), 6.07–5.92 (m, 2H), 5.14–5.05 (m, 2H), 3.32–3.22 (m, 1H), 3.00 (d, *J* = 9.7 Hz, 2H), 2.89–2.68 (m, 2H), 2.42 (q, *J* = 7.5 Hz, 2H), 2.29 (dd, *J* = 8.1, 16.2 Hz, 1H), 1.99–1.88 (m, 1H), 1.81 (s, 1H), 1.59–1.44 (m, 2H), 1.42–1.31 (m, 1H), 1.15 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.0, 156.4, 146.3, 143.6, 143.0, 139.7, 131.4, 126.9, 122.6, 117.8, 115.2, 104.8, 73.5, 58.3, 49.7, 49.0, 39.3, 27.8, 27.8, 25.8, 21.9, 9.0.

4.2.3. (*S*)-(6-Hydroxyquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl isobutyrate QD-4[26]

QD-4 was prepared from *O*-isobutyrylquinidine according to the literature procedure and similar to **QD-2**, white solid, 60% yield. $[\alpha]_D^{20} = +89.5$ (*c* 0.4, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, *J* = 4.5 Hz, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 2.5 Hz, 1H), 7.29 (d, *J* = 4.6 Hz, 1H), 7.22 (dd, *J* = 2.4, 9.1 Hz, 1H), 6.51 (d, *J* = 5.7 Hz, 1H), 6.00 (m, 2H), 5.15–5.01 (m, 2H), 3.25 (dd, *J* = 9.0, 14.9 Hz, 1H), 3.04–2.93 (m, 2H), 2.86–2.56 (m, 3H), 2.28 (q, *J* = 8.5 Hz, 1H), 1.95–1.86 (m, 1H), 1.81 (s, 1H), 1.50–1.33 (m, 3H), 1.18 (dd, *J* = 3.8, 7.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 156.1, 146.3, 143.6, 143.6, 139.8,

131.3, 127.2, 122.5, 118.3, 115.1, 105.5, 73.6, 58.6, 49.6, 49.1, 39.5, 34.2, 27.7, 26.0, 22.8, 18.9, 18.8.

4.2.4. (*R*)-(6-Hydroxyquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl acetate Q-5[26]

Q-5 was prepared from *O*-acetylquinine[27] according to the literature procedure and similar to **QD-2**, white solid, 58% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 4.5 Hz, 1H), 7.97 (d, J = 9.2 Hz, 1H), 7.55 (d, J = 2.6 Hz, 1H), 7.34–7.25 (m, 2H), 6.57 (d, J = 5.7 Hz, 1H), 6.05–5.96 (m, 2H), 5.13–5.08 (m, 2H), 3.34–3.26 (m, 1H), 3.05–2.91 (m, 2H), 2.83–2.69 (m, 2H), 2.32–2.26 (m, 1H), 2.12 (s, 3H), 1.98–1.85 (m, 1H), 1.82 (s, 1H), 1.57–1.45 (m, 2H), 1.40–1.32 (m, 1H).

4.2.5. (*R*)-(6-Hydroxyquinolin-4-yl)((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl benzoate Q-6[26,29]

Q-6 was prepared from *O*-benzoylquinine according to the literature procedure; white solid, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 4.5 Hz, 1H), 8.11 (d, J = 7.1 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.72 (d, J = 2.5 Hz, 1H), 7.61 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.36 (d, J = 4.5 Hz, 1H), 7.31 (dd, J = 2.5, 9.1 Hz, 1H), 6.87 (d, J = 4.0 Hz, 1H), 5.75 (ddd, J = 7.5, 10.3, 17.4 Hz, 1H), 5.02–4.92 (m, 2H), 3.44–3.34 (m, 1H), 3.30–3.20 (m, 1H), 3.13 (dd, J = 10.3, 13.7 Hz, 2H), 2.78–2.62 (m, 3H), 2.38–2.28 (m, 1H), 1.96–1.90 (m, 2H), 1.86–1.71 (m, 2H), 1.66–1.56 (m, 1H).

4.2.6. (*S*)-1-Benzhydryl-3-(4-((*S*)-benzyloxy((2*S*,4*S*,5*R*)-5-vinylquinuclidin-2-yl)methyl)quinolin-6-yl)thiourea QD-7[30]

Under nitrogen at room temperature, *O*-benzyl-6-aminoquinidine[31,32] (400 mg, 1 mmol) was dissolved in THF (10 mL), after which 3,5-bis(trifluoromethyl)phenyl isothiocyanate (298 mg, 1.1 mmol) was added into the solvent, and stirred for 24 h. The solvent was removed under reduced atmosphere and then purified by column chromatography (ethyl acetate/methanol/triethylamine 80:1:1, V/V/V) to give **QD-7** as a colorless solid (396 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, J = 4.4 Hz, 1H), 8.18 (s, 1H), 8.11 (d, J = 9.0 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.42 (s, 1H), 7.23–7.34 (m, 15H), 6.79–6.89 (m, 2H), 5.86 (m, 1H), 5.03 (br s, 1H), 4.99 (s, 1H), 4.96 (d, J = 5.3 Hz, 1H), 4.31 (d, J = 11.6 Hz, 1H), 4.16 (d, J = 11.5 Hz, 1H), 3.74 (t, J = 6.5 Hz, 1H), 3.09 (s, 1H), 3.00 (s, 1H), 2.69–2.77 (m, 2H), 2.54–2.62 (m, 1H), 1.93 (s, 1H), 1.81–1.88 (m, 1H), 1.73 (s, 1H), 1.43–1.47 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.6, 149.6, 146.4, 146.3, 141.0, 140.4, 137.5, 131.3, 128.8, 128.4, 127.9, 127.8, 127.7, 127.6, 126.9, 126.5, 114.6, 71.3, 68.0, 62.0, 60.1, 49.8, 39.9, 28.0, 26.3, 25.6. HRMS (ESI-TOF): m/z calcd for $C_{40}H_{40}N_4OS$ $[M+H]^+$ 625.3001; found: 625.3000.

4.3. Typical procedure for the Michael addition reaction

Nitroethane **8a** (2.2 mL, 30 mmol) was added to a vial containing catalyst **QD-2** (7 mg, 0.02 mmol) and *trans*-β-nitrostyrene **9a** (149 mg, 1 mmol) at 30 °C. TLC analysis indicated the completion of the reaction. The reaction mixture was concentrated under vacuum. The dr value was determined by ^{1}H NMR analysis of the residue, which was then purified by flash silica gel chromatography (ethyl acetate/hexane = 1:20 to 1:10) to afford the adduct *syn*-**10aa** (125 mg, 0.56 mmol) as a white solid and *anti*-**10aa** (62 mg, 0.28 mmol) as a clear oil in 85% total yield.

4.3.1. (2*R*,3*R*)-1,3-Dinitro-2-phenylbutane 10aa[11]

$[\alpha]_D^{20} = +4.9$ (c 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.32 (m, 3H), 7.17–7.14 (m, 2H), 5.00–4.90 (m, 2H), 4.84–4.79 (m, 1H), 4.05–4.00 (m, 1H), 1.58 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.5, 129.3, 129.1, 128.0, 84.0, 76.1, 47.4, 16.7. HPLC conditions: Daicel Chiralpak AS-H, *i*-PrOH/hexane 5:95, flow rate 1.0 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 32.5 min, t_{minor} (2*S*,3*S*) = 35.4 min.

4.3.2. (2*R*,3*R*)-1,3-Dinitro-2-(4-bromophenyl)butane 10ab[12]

$[\alpha]_D^{20} = +8.5$ (c 1.13, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.4 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 4.98–4.86 (m, 2H), 4.79 (dd, J = 8.4, 13.6 Hz, 1H), 3.99 (dd, J = 6.3, 14.5 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.5, 129.6, 123.3, 83.9, 76.0, 46.9, 16.8. HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 30:70, flow rate 0.8 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 16.8 min, t_{minor} (2*S*,3*S*) = 36.9 min.

4.3.3. (2*R*,3*R*)-1,3-Dinitro-2-(2-chlorophenyl)butane 10ac[12]

$[\alpha]_D^{20} = +12.0$ (c 1.12, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46–7.40 (m, 1H), 7.26–7.13 (m, 3H), 5.18–5.06 (m, 1H), 4.89 (dd, J = 1.2, 6.8 Hz, 2H), 4.75–4.67 (m, 1H), 1.59 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.5, 132.0, 130.8, 130.2, 128.0, 127.8, 84.1, 75.3, 43.1, 16.3. HPLC conditions: Daicel Chiralpak AD-H, *i*-PrOH/hexane 2:98, flow rate 0.5 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 45.1 min, t_{minor} (2*S*,3*S*) = 47.9 min.

4.3.4. (2*R*,3*R*)-1,3-Dinitro-2-(3-chlorophenyl)butane 10ad[12]

$[\alpha]_D^{20} = +8.0$ (c 0.20, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.30 (m, 2H), 7.17 (s, 1H), 7.05 (d, J = 7.3 Hz, 1H), 4.96–4.88 (m, 2H), 4.83–4.80 (m, 1H), 4.01 (dd, J = 6.4, 14.5 Hz, 1H), 1.60 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 135.1, 130.6, 129.4, 128.4, 126.0, 83.9, 75.8, 46.9, 16.8. HPLC conditions: Daicel Chiralpak AS-H, *i*-PrOH/hexane 10:90, flow rate 1.0 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 25.7 min, t_{minor} (2*S*,3*S*) = 30.0 min.

4.3.5. (2*R*,3*R*)-1,3-Dinitro-2-(4-chlorophenyl)butane 10ae[11]

$[\alpha]_D^{20} = +10.2$ (c 1.02, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.32 (m, 2H), 7.10 (d, J = 8.5 Hz, 2H), 4.98–4.85 (m, 2H), 4.79 (dd, J = 8.5, 13.6 Hz, 1H), 4.00 (dt, J = 6.3, 8.2 Hz, 1H), 1.59 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.3, 131.9, 129.6, 129.3, 83.9, 76.0, 46.9, 16.8. HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 30:70, flow rate 0.8 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 15.7 min, t_{minor} (2*S*,3*S*) = 26.9 min.

4.3.6. (2*R*,3*R*)-1,3-Dinitro-2-(2-fluorophenyl)butane 10af[11]

$[\alpha]_D^{20} = +20.2$ (c 1.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35–7.32 (m, 1H), 7.13–7.10 (m, 3H), 5.08–5.04 (m, 1H), 4.94–4.82 (m, 2H), 4.32 (dd, J = 7.2, 14.3 Hz, 1H), 1.62 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.0, 130.9, 129.7, 129.6, 125.0, 120.9, 120.8, 116.4, 116.2, 83.3, 75.1, 42.1, 17.0. HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 20:80, flow rate 0.8 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 17.3 min, t_{minor} (2*S*,3*S*) = 28.8 min.

4.3.7. (2*R*,3*R*)-1,3-Dinitro-2-(3-fluorophenyl)butane 10ag

$[\alpha]_D^{20} = +20.0$ (c 1.05, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.34 (m, 1H), 7.09–6.93 (m, 3H), 4.87–4.78 (m, 2H), 4.70–4.65(m, 1H), 4.07–4.01 (m, 1H), 1.44 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.1, 161.7, 136.1, 131.0, 123.7, 116.2, 115.3, 84.0, 75.9, 47.0, 16.8. Daicel Chiralpak AS-H, *i*-PrOH/hexane 10:90, flow rate 1.0 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 24.0 min, t_{minor} (2*S*,3*S*) = 27.1 min.

4.3.8. (2*R*,3*R*)-1,3-Dinitro-2-(4-fluorophenyl)butane 10ah[11]

$[\alpha]_D^{20} = +7.3$ (c 0.87, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16–7.13 (m, 2H), 7.08–7.03 (m, 2H), 4.99–4.86 (m, 2H), 4.79 (dd, J = 8.4, 13.6 Hz, 1H), 4.01 (dd, J = 6.3, 14.5 Hz, 1H), 1.60 (d, J = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 129.8, 116.5, 116.3, 84.0, 76.2, 46.8, 16.8. HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 30:70, flow rate 0.8 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 14.0 min, t_{minor} (2*S*,3*S*) = 17.2 min.

4.3.9. (2*R*,3*R*)-1,3-Dinitro-2-(4-methylphenyl)butane 10ai[11]

$[\alpha]_D^{20} = +11.9$ (*c* 1.27, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, *J* = 7.9 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 4.96–4.88 (m, 2H), 4.85–4.75 (m, 1H), 3.97 (m, 1H), 2.32 (s, 3H), 1.57 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 130.3, 130.0, 127.8, 84.1, 76.2, 47.1, 21.0, 16.7. HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 30:70, flow rate 0.8 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 15.5 min, t_{minor} (2*S*,3*S*) = 46.5 min.

4.3.10. (2*R*,3*R*)-1,3-Dinitro-2-(4-methoxyphenyl)butane 10aj[11]

$[\alpha]_D^{20} = +16.8$ (*c* 0.67, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.00–4.87 (m, 2H), 4.82–4.76 (m, 1H), 3.96 (dd, *J* = 6.6, 14.1 Hz, 1H), 3.79 (s, 3H), 1.58 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.0, 129.1, 125.1, 114.7, 84.1, 76.4, 55.2, 46.8, 16.7. HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 30:70, flow rate 0.8 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 18.2 min, t_{minor} (2*S*,3*S*) = 36.6 min.

4.3.11. (2*R*,3*R*)-1,3-Dinitro-2-(2-furyl)butane 10ak[11]

$[\alpha]_D^{20} = +17.1$ (*c* 0.87, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1H), 6.33 (s, 1H), 6.26 (d, *J* = 3.1 Hz, 1H), 4.98–4.79 (m, 3H), 4.25–4.20 (m, 1H), 1.60 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 143.5, 110.7, 109.6, 82.4, 74.2, 41.2, 16.3. HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 5:95, flow rate 0.8 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 40.6 min, t_{minor} (2*S*,3*S*) = 42.7 min.

4.3.12. (2*R*,3*R*)-1,3-Dinitro-2-(2-thienyl)butane 10al[16]

$[\alpha]_D^{20} = +20.2$ (*c* 1.05, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.27 (m, 1H), 6.98 (dd, *J* = 3.6, 5.1 Hz, 1H), 6.92 (d, *J* = 3.5 Hz, 1H), 4.98–4.91 (m, 2H), 4.84–4.79 (m, 1H), 4.34 (dt, *J* = 5.8, 7.9 Hz, 1H), 1.61 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 127.5, 127.3, 126.3, 84.0, 42.7, 16.7. HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 25:75, flow rate 1.0 mL/min, UV detection at 208 nm, t_{major} (2*R*,3*R*) = 15.3 min, t_{minor} (2*S*,3*S*) = 26.2 min.

4.3.13. (3*R*,4*R*)-2-Methyl-4-nitro-3-(nitromethyl)pentane 10am[15]

$[\alpha]_D^{20} = -2.1$ (*c* 0.2, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 4.79–4.72 (m, 2H), 4.49–4.44 (m, 2H), 2.88–2.86 (m, 1H), 1.60 (m, 3H), 1.56 (m, 6H). HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 10:90, flow rate 0.4 mL/min, UV detection at 210 nm, t_{major} (3*R*,4*R*) = 27.1 min, t_{minor} (3*S*,4*S*) = 26.1 min.

4.3.14. ((3*R*,4*R*,*E*)-(4-Nitro-3-(nitromethyl)pent-1-enyl)benzene 10an[15]

$[\alpha]_D^{20} = +31.3$ (*c* 0.4, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 7.34–7.30 (m, 5H), 6.67–6.60 (m, 1H), 5.94–5.86 (m, 1H), 4.84–4.72 (m, 2H), 4.61–4.55 (m, 1H), 3.60–3.49 (m, 1H), 1.64–1.62 (m, 3H). HPLC conditions: Daicel Chiralcel OD-H, *i*-PrOH/hexane 10:90, flow rate 1.0 mL/min, UV detection at 235 nm, t_{major} (3*R*,4*R*) = 32.8 min, t_{minor} (3*S*,4*S*) = 66.5 min.

4.3.15. (*S*)-1,3-Dinitro-3-methyl-2-phenylbutane 10ba[11]

^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.31 (m, 3H), 7.22–7.16 (m, 2H), 4.98 (dd, *J* = 11.1, 13.4 Hz, 1H), 4.83–4.77 (m, 1H), 4.15 (dd, *J* = 4.0, 11.0 Hz, 1H), 1.59 (d, *J* = 8.1 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.6, 129.1, 129.0, 128.9, 89.6, 75.9, 51.6, 26.2, 23.0. HPLC conditions: Daicel Chiralpak AD-H, *i*-PrOH/hexane 5:95, flow rate 0.7 mL/min, UV detection at 208 nm, t_{minor} (*R*) = 16.2 min, t_{major} (*S*) = 16.9 min.

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