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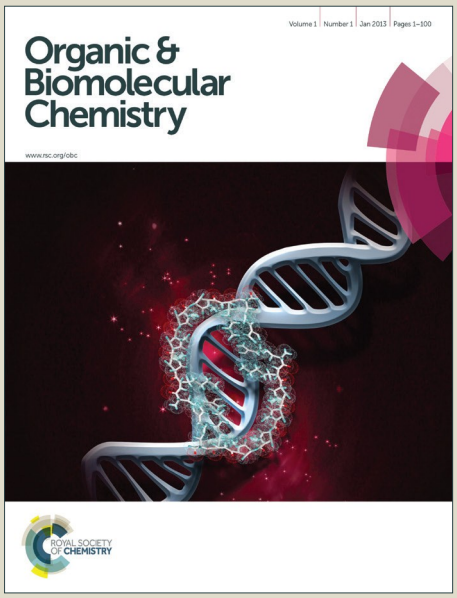

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Rawal's catalyst as an effective stimulant for the highly asymmetric Michael addition of β-keto esters to functionally rich nitro-olefins†

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A general approach to asymmetric synthesis of highly substituted dihydroquinolines was achieved through neighboring *ortho*-amino group engaged sequential Michael/amination/dehydration reactions on (*E*)-2-(2-nitrovinyl)anilines with cyclic and acyclic β-keto esters in the presence of a catalytic amount of Rawal's quinidine-N*H*-benzyl squaramide followed by TFA.

Recently organocatalytic domino/cascade reactions have emerged as powerful strategy for the complex molecular synthesis by employing simple and readily available precursors in a simple operational manner.[1] In this scenario, one of the important protocol for the C–C bond formation is asymmetric Michael reaction, which has been extensively used in cascade reactions.[2] Wherein, the Michael reaction of β-keto esters to nitro-olefins is a fully atom-economic transformation with prominent synthetic potential as the resulting functional groups will be in high demand.[3] To control the reactivity and selectivity of this Michael reaction, in 2003 Takemoto and co-workers identified the bifunctional thiourea–tertiary amine as an efficient catalyst.[4] A milestone report by Rawal's group showed that replacement of the thiourea function by a squaramide catalyst as the hydrogen-bond donor allows a dramatic decrease in the catalyst loading and also increase in the reaction rate/selectivity.[5,6] The pioneering work of Rawal's and other groups from the past few years has shown the importance of chiral hydrogen-bonding catalysis through squaramide catalyst.[5,6]

Nowadays, bio-mimetic one-pot synthesis of the highly functionalized chiral Michael adducts for synthetic applications are in high demand. Recently, we and others have reported the natural products inspired dihydrocoumarins synthesis through a Michael addition of 1,3-dicarbonyls to 2-(2-nitrovinyl)phenol and subsequent intramolecular hemiacetalization.[7] In this reaction, the *ortho*-hydroxyl group participates as neighboring group both during and after the reaction and makes this sequence as a powerful tool among the existing annulation methods. With this inspiration, herein we describe an unusual efficient neighboring *ortho*-amino group engaged asymmetric organocatalytic sequential one-pot reaction for the synthesis of drug-like chiral dihydroquinolines from simple substrates and catalysts by using sequential Michael/amination/dehydration reactions.

Hydroquinolines are versatile synthetic intermediates in organic synthesis and also prevalent unit in biological and pharmaceutical substances (Figure 1).[8] Even though numerous synthetic methods have been known for their synthesis, there is an urgent requirement to develop an efficient asymmetric protocol due to their many applications.[9]

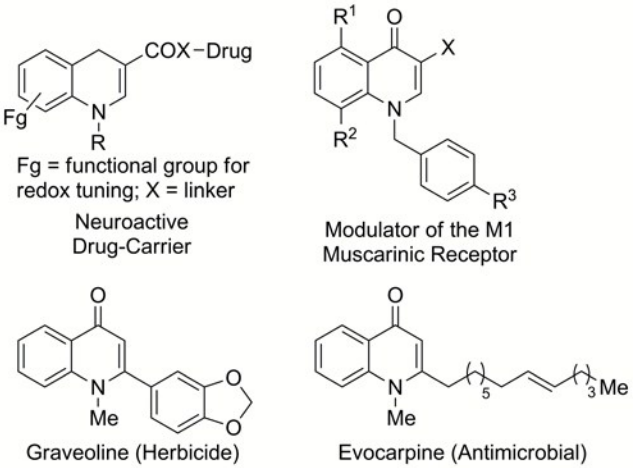

Figure 1 Biologically active molecules containing 1,4-dihydroquinoline.

Recently, we and Kim group independently reported the asymmetric synthesis of 2,3,4-trisubstituted 1,4-dihydroquinolines by the cascade Michael/amination/dehydration reaction of aldehydes or ketones with (*E*)-2-(2-nitrovinyl)anilines through enamine-catalysis with excellent selectivity.[10] However, there is no suitable asymmetric method to synthesise highly functionalized 1,4-dihydroquinolines in optically pure form from (*E*)-2-(2-nitrovinyl)anilines with β-keto esters through enolate-catalysis.[11] In continuation of our research interest in this area, we envisaged functionally rich (*E*)-2-(2-nitrovinyl)anilines and β-keto esters as the potential substrates for the newly designed Michael/amination/dehydration reaction sequence (Scheme 1).

To find the best catalytic conditions, we screened a number of emerging hydrogen-bond-donating organocatalysts for the reaction of *N*-Boc-(*E*)-2-(2-nitrovinyl)aniline **1a** with 1.3 equiv. of ethyl 2-oxocyclopentanecarboxylate **2a** (Table 1). Reaction of **1a** with 1.3 equiv. of **2a** under 10 mol% of quinine-*N*H-thiourea **3a**-catalysis in toluene at 25 °C for 4 h furnished the **4aa** in 70% yield with 58% *ee* and >99% *de* (Table 1, entry 1). The same reaction in DCM for 4 h furnished the product **4aa** with *ee* increased to 75% with 68% yield and >99% *de* (Table 1, entry 2). Reaction under the hydroquinine-*N*H-thiourea **3b**-catalysis furnished **4aa** with increased yield (82%) and no change in *ee* and *de* (Table 1, entry 3). With these moderate results, we moved to investigate this reaction with other set of hydrogen-bond-donating catalysts **3c-e** based on the chiral squaramide derivatives discovered by Rawal's group. Recently Rawal's squaramide catalysts have been found to be more powerful hydrogen-bond-donating catalysts compared to

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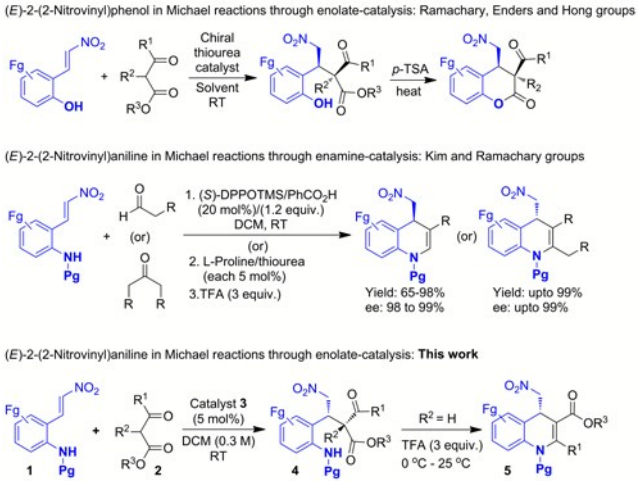
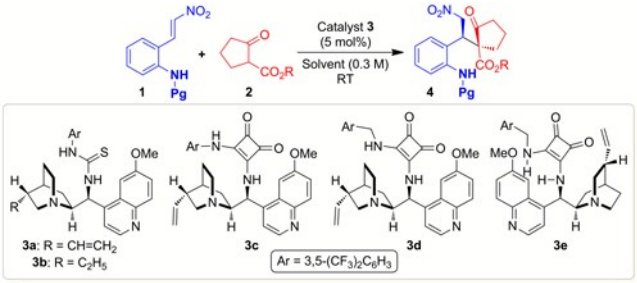
their corresponding thiourea analogues in both catalytic activity and selectivity.[5,6] Therefore, herein we shown interest to investigate Rawal's catalysts **3c-e** for the high asymmetric induction.



Scheme 1 Reaction design for the 1,4-dihydroquinoline synthesis.

Unfortunately, reaction of **1a** with **2a** under 5 mol% of quinine-*N*H-squaramide **3c** in DCM at 25 °C for 6 h gave the product **4aa** in 71% yield with poor *ee* (18%) and good *de* (Table 1, entry 4). After this poor selectivity, we shown interest to investigate the electronic and steric factors of *N*-aryl group in the squaramide catalyst, we used quinine-*N*H-benzyl squaramide catalyst **3d** for the high selectivity. Surprisingly, the Michael reaction of **1a** with **2a** under 5 mol% of **3d**-catalysis furnished the product (-)-**4aa** in 71% yield with 97% *ee* and >99% *de* within 5 h (Table 1, entry 5). This result is indicating that the presence of benzyl group in the squaramide catalyst has significant effect on the outcome of selectivity. In a similar manner, the Michael reaction of **1a** with **2a** under the 5 mol% of quinidine-*N*H-benzyl squaramide **3e**-catalysis furnished the opposite enantiomer (+)-**4aa** in 77% yield with 98% *ee* and >99% *de* within 5 h (Table 1, entry 6). Whereas 10 mol% of **3e**-catalysis furnished the product (+)-**4aa** in 77% yield with decreased *ee* of 83% (entry 7), which indicates that the catalyst loading has a significant effect on the selectivity of the reaction. Use of brine instead of DCM as solvent with 2 mol% of catalyst **3e** the aforesaid product was obtained in 48% yield with 91% *ee* and >99% *de* in 16 h (Table 1, entry 8). To obtain the highest selectivity of the product **4aa**, we thought of using sterically hindered isopropyl 2-oxocyclopentanecarboxylate **2b** with **1a** under **3d/3e**-catalysis. Surprisingly, the reaction of **1a** with **2b** under 5 mol% of **3e**-catalysis in DCM at RT for 6 h furnished the product (+)-**4ab** in 80% yield with >99% *ee* and *de* (Table 1, entry 10). Similar reaction under **3d**-catalysis furnished the opposite enantiomer (-)-**4ab** in 75% yield with >99% *ee* and *de* (Table 1, entry 11). To further investigate the reaction conditions, we carried out the Michael reactions of other *N*-protected-(*E*)-2-(2-nitrovinyl)anilines **1b**/**1c** with **2b** under **3d**- or **3e**-catalysis in DCM at RT. It has shown that other carbamate protecting groups (Cbz and CO_2Et) were tolerated and the desired products were obtained in moderate yields (42−65%) with excellent *ee*'s (96 to >99%) and *de*'s (97 to >99%) within 8 h (Table 1, entries 12-14). Finally we envisioned the optimized condition to be 25 °C in DCM under 5 mol% of Rawal's catalysts **3d** or **3e** to furnish the Michael adduct **4ab** in 75-80% yield with >99% *ee* and >99% *de* (Table 1, entry 10-11).

Table 1 Reaction optimization.[a]



Entry	Pg	R	Catalyst 3 (5 mol%)	Solvent (0.3 M)	Time (h)	Yield (%)[b]	ee (%)[c]	de (%)[c]
1[d]	**1a:** Boc	**2a:** Et	**3a**	Toluene	4	**4aa** (70)	58	>99
2[d]	**1a:** Boc	**2a:** Et	**3a**	DCM	4	**4aa** (68)	75	>99
3[d]	**1a:** Boc	**2a:** Et	**3b**	DCM	4	**4aa** (82)	74	>99
4	**1a:** Boc	**2a:** Et	**3c**	DCM	6	**4aa** (71)	18	>99
5	**1a:** Boc	**2a:** Et	**3d**	DCM	5	**4aa** (71)	97	>99
6	**1a:** Boc	**2a:** Et	**3e**	DCM	5	**4aa** (77)	-98	>99
7[d]	**1a:** Boc	**2a:** Et	**3e**	DCM	5	**4aa** (77)	-83	>99
8[e]	**1a:** Boc	**2a:** Et	**3e**	Brine	16	**4aa** (48)	-91	>99
9[d]	**1a:** Boc	**2b:** ^{i}Pr	**3e**	DCM	6	**4ab** (75)	-95	>99
10	**1a:** Boc	**2b:** ^{i}Pr	**3e**	DCM	6	**4ab** (80)	->99	>99
11	**1a:** Boc	**2b:** ^{i}Pr	**3d**	DCM	6	**4ab** (75)	>99	>99
12	**1b:** Cbz	**2b:** ^{i}Pr	**3e**	DCM	8	**4bb** (65)	->99	>99
13	**1b:** Cbz	**2b:** ^{i}Pr	**3d**	DCM	8	**4bb** (63)	98	97
14	**1c:** CO_2Et	**2b:** ^{i}Pr	**3e**	DCM	8	**4cb** (42)	-96	>99

[a] Unless otherwise mentioned, all reactions were carried out with **1** (0.2 mmol), **2** (0.26 mmol), catalyst **3** (5 mol%) in DCM (0.3 M) at rt. [b] Yield refers to the column purified product. [c] Ee and de was determined by CSP HPLC analysis. [d] 10 mol% of catalyst **3** was used. [e] Reaction performed with 2 mol% of **3e**.

With the optimized conditions in hand, the scope of the Rawal's quinidine-*N*H-benzyl squaramide **3e**-catalyzed asymmetric Michael reaction was investigated. A series of substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines **1d-g** were reacted with 1.3 equiv. of cyclic β-keto esters **2a-f** catalyzed by 5 mol% of **3e** at 25 °C in DCM for 8-96 h to furnish the highly substituted chiral Michael adducts **4db-af** in 40-95% yields with excellent *ee*'s and *de*'s (Table 2). Electronic and steric nature of the *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines were investigated with β-keto ester **2b**. Halogen substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines **1d-e** reacted well with **2b** and furnished the products (+)-**4db** and (+)-**4eb** in excellent yields (90 and 95%) and *ee*'s (99%) with good to moderate *de*'s (97 and 70%) within 8 h respectively. Methyl substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines **1f-g** gave the desired products (-)-**4fb** and (+)-**4gb** in moderate to good yields (40 and 70%) with excellent *ee*'s (>99%) and moderate *de*'s (47 and 88%) through **3e**-catalysis for 96 and 72 h, respectively. We also tested the other cyclic β-keto esters to investigate the generality of this asymmetric reaction. Methyl 2-oxocyclopentanecarboxylate **2c** with **1a** under the **3e**-catalysis furnished the product (-)-**4ac** in 81% yield with 94% *ee* and 95% *de* within 8 h. Intriguingly, six-membered cyclic β-keto ester **2d** gave the product (+)-**4ad** only in 40% yield with 94% *ee* and 84% *de* for 96 h; but simple ethyl 2-oxocyclohexanecarboxylate **2d'** gave the Michael product (+)-**4ad'** in 65% yield with >99% *ee* and >99% *de* for within 40 h (Table 2). Heterocyclic β-keto ester **2e** with **1a** under **3e**-catalysis furnished the product (+)-**4ae** in 60% yield with >99% *ee* and *de* for 24 h. In a similar manner, 2-acetylcyclopentanone **2f** with **1a** under **3e**-catalysis furnished the product (+)-**4af** in 62% yield with 94% *ee* and 79% *de* within 8 h.

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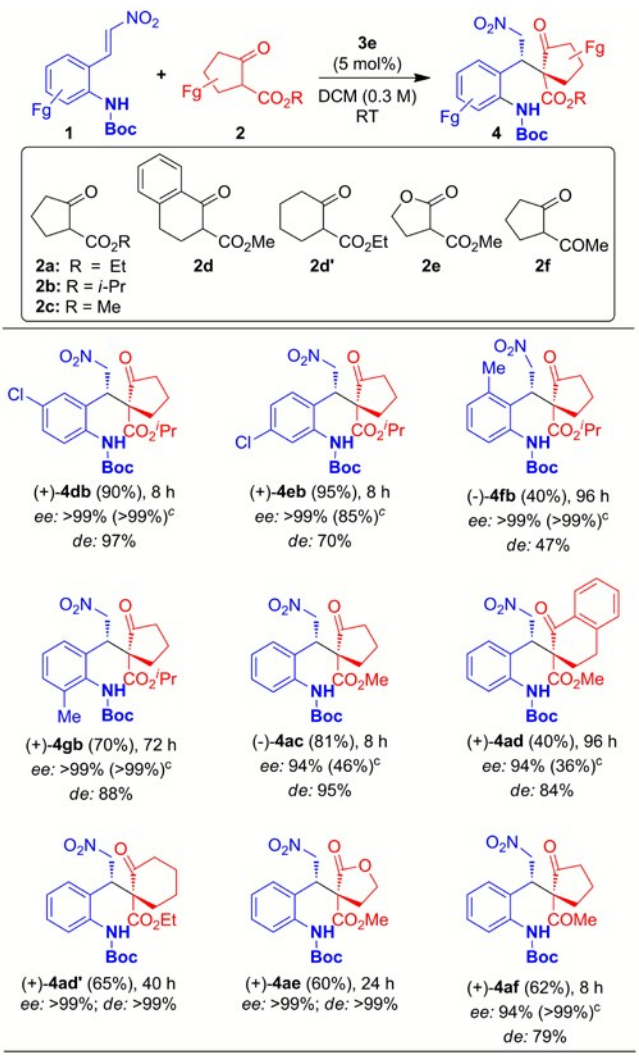
It was observed that compared to five membered cyclic β-keto esters, six-membered cyclic β-keto esters gave the corresponding products in low yield. The structure and absolute stereochemistry of the Michael products **4** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (+)-**4ae** as shown in Fig. S1 (Supporting Information-1).[12]

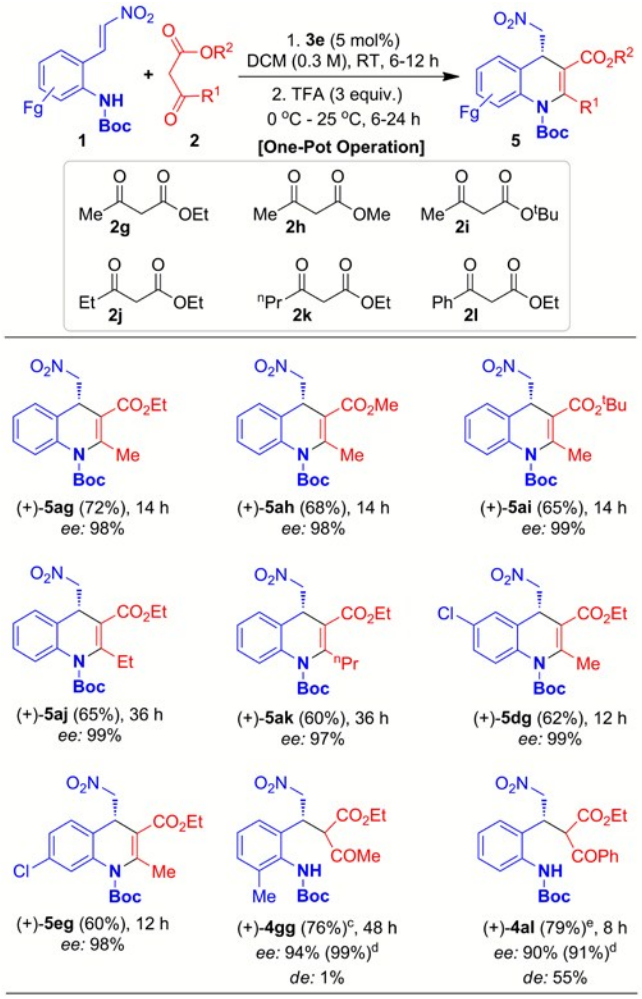
Table 2 Reaction scope.[a-c]



[a] Yield refers to the column purified product. [b] Ee and de were determined by CSP HPLC analysis. [c] In parenthesis values refers to minor ee.

In order to expand the reaction scope, we explored the utilization of different acyclic β-keto esters **2g-l**. First the reaction of **1a** with 1.3 equiv. of ethyl acetoacetate **2g** under the catalysis of **3e** at 25 °C for 8 h in DCM furnished the product **4ag** in 76% yield with 1:1 *dr*. For the clear understanding of selectivity and also for the HPLC separation, we transformed the product **4ag** in situ into easily separable and also very important 1,4-dihydroquinoline (+)-**5ag** in 72% yield with 98% *ee* through TFA-mediated cascade amination/dehydration in DCM at 0-25 °C for 6 h in one-pot manner (Table 3). We further investigated the substrate scope for Rawal's quinidine-*N*H-benzyl squaramide **3e**-catalyzed and TFA-promoted asymmetric Michael/amination/dehydration reaction sequence with **1a-g** and **2h-l** for the synthesis of chiral 1,4-dihydroquinolines (Table 3). Methyl and ^{t}butyl-3-oxobutanoates **2h-i** with **1a** under **3e**-catalysis in DCM followed by TFA-mediated one-pot amination/dehydration reaction generated the cyclised products (+)-**5ah-ai** in 68% and 65% yields with 98% and 99% *ee*, respectively (Table 3). Likewise, ethyl 3-oxopentanoate and 3-oxohexanoate **2j-k** generated the expected cyclised products (+)-**5aj** and (+)-**5ak** in 65% and 60% yields with excellent *ee*'s

Table 3 Reaction application.[a-e]



[a] Yield refers to the column purified product. [b] Ee and de were determined by CSP HPLC analysis. [c] Only Micheal product obtained. [d] In parenthesis values refers to minor *ee*. [e] Reaction of (+)-**4al** with TFA gave ethyl 2-phenylquinoline-3-carboxylate in 65% yield (see SI).

(99% and 97%) after 36 h respectively (Table 3). In the case of ethyl 3-oxo-3-phenylpropanoate **2l**, the Michael product (+)-**4al** was obtained in 79% yield with 90% *ee* and 55% *de* at 25 °C for 8 h; but when in-situ treatment of (+)-**4al** with TFA at 0-25 °C for 24 h furnished the unexpected by-product ethyl 2-phenylquinoline-3-carboxylate in 65% yield may be due to the electronic/steric hindrance of phenyl group (Table 3 and see Supporting Information-I). Reaction of substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)anilines **1d-e** with **2g** under **3e**-catalysis followed by in situ treatment with TFA furnished the cyclised products (+)-**5dg** and (+)-**5eg** in good yields (62 and 60%) with excellent *ee*'s (99 and 98%) at 25 °C for 12 h, respectively (Table 3). Surprisingly, the reaction of methyl substituted *N*-Boc-(*E*)-2-(2-nitrovinyl)aniline **1g** with **2g** under **3e**-catalysis followed by in situ treatment with

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TFA furnished the only Michael product (+)-**4gg** in 76% yield with 94/99% *ee* and 1:1 *dr* at 25 °C for 48 h without cyclization may be due to the steric hindrance of methyl groups (Table 3).[13] After these interesting results, TFA-mediated cascade amination/dehydration protocol was applied to the many of Table 2 compounds in DCM at 0-25 °C; for within 1 h compounds were decomposed.

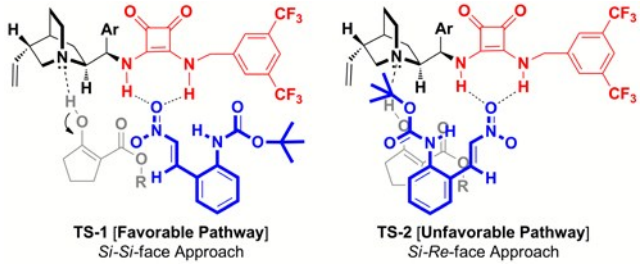
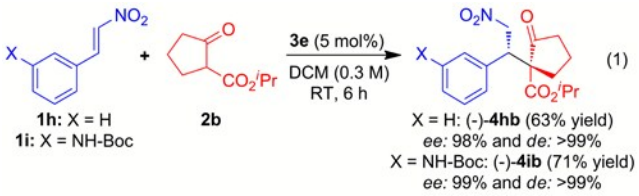


Figure 2 Proposed transition state for the asymmetric Michael reactions.

With controlled experimental data in hand, herein we firmly elucidate the mechanism of the asymmetric Michael reaction through double hydrogen-bonding assembly by **3e**-catalysis, and propose that the reaction most likely proceeds *via* **TS-1** mechanism (Figure 2). In the case of the addition of β-keto-esters **1** to substituted 2-(2-nitrovinyl)anilines **2** *via* Rawal's **3e**-catalysis, we can rationalize the observed stereochemistries through a favoured double hydrogen-bonding assembly transition state where the less hindered *si*-face of **2** approaches the *si*-face of the *in situ* generated enol as shown in **TS-1**. Outcome of decent selectivity and reactivity for the β-keto-ester **1** addition to the 2-(2-nitrovinyl)anilines **2** could be explained by soft involvement due to the steric hindrance of neighboring group Ar-**NHBoc** as shown in Figure 2. Fascinatingly, the Michael reaction of simple (*E*)-(2-nitrovinyl)benzene **1h** and *N*-Boc-(*E*)-3-(2-nitrovinyl)aniline **1i** with **2b** *via* **3e**-catalysis in DCM at 25 °C for 6 h furnished the expected products (-)-**4hb** in 63% yield with 98% *ee* and >99% *de*; and (-)-**4ib** in 71% yield with 99% *ee* and >99% *de* respectively as shown in eq. (1). This result gives evident for the fact that there is not much of neighboring *ortho*-amino group participation in the reaction pre-transition state and also Rawal's catalyst **3e** is sufficient enough to activating both the substrates in the pre-transition state along with steric hindrance of neighboring group Ar-**NHBoc** to control the selectivity.



In summary, we have developed Rawal's quinidine-*N*H-benzyl squaramide **3e**-catalyzed and TFA-promoted asymmetric sequential Michael/amination/dehydration reaction of *N*-protected-(*E*)-2-(2-nitrovinyl)anilines **1** with β-keto esters **2** for the synthesis of enantioenriched and highly functionalized 1,4-dihydroquinolines. Further work is in progress to utilize 1,4-dihydroquinoline derivatives for biological studies.

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11 During the preparation of this manuscript, Kim group reported asymmetric synthesis of 1,4-dihydroquinolines with lower selectivity (<90% *ee*) and more catalyst loading, see: H. Kim and S.-G. Kim, *Tetrahedron Lett*., 2015, **56**, 4819.

12 CCDC-1432348 for (**+**)-**4ae** contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or mailto:deposit@ccdc.cam.ac.uk. See supporting information for crystal structure.

13 For organocatalytic high-yielding synthesis of racemic products **4** and **5** from **1** and **2** through [Q + QD]-catalysis followed by TFA, see Table S1 and S2 in Supporting Information-I. We have also done racemic products **4** synthesis from **1** and **2** through DBU or DABCO-catalysis, but reaction conversions are very low even after 24 h at 25 °C.

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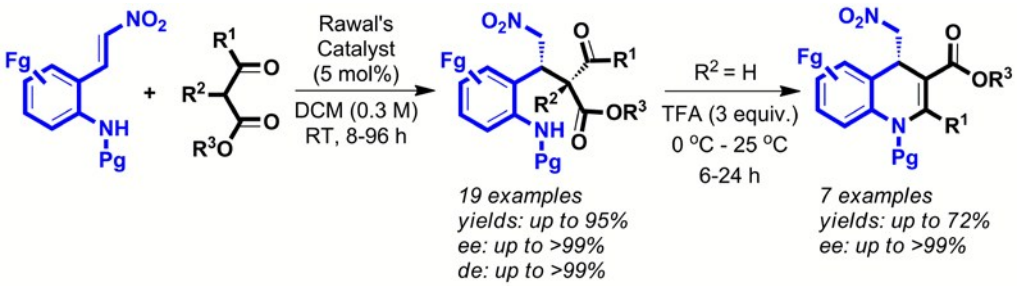

Short Statement

A general approach to the asymmetric synthesis of highly substituted dihydroquinolines was achieved through neighboring *ortho*-amino group engaged sequential Michael/amination/dehydration reactions on (*E*)-2-(2-nitrovinyl)anilines with cyclic and acyclic β-keto esters in the presence of a catalytic amount of Rawal's quinidine-N*H*-benzyl squaramide followed by TFA (see Scheme).