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Asymmetric synthesis of tetrahydroquinolines through supramolecular organocatalysis†

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Functionalized chiral tetrahydroquinolines were synthesized through supramolecular organocatalysis by using quinidine-N*H*-thiourea 3c/L-phenylalanine 4i followed by reductive amination from the simple substrates.

Tetrahydroquinolines are privileged structural moieties found in various natural and biologically active compounds. Some of them have shown a variety of potent biological activities such as antibacterial, antimalarial, antitumor, antiallergic, anticonvulsant, antioxidant and cardiovascular activity.[1] Especially, 2-methyl-1,2,3,4-tetrahydroquinoline is found in the human brain as an endogenous alkaloid. Functionalized chiral 2-alkyltetrahydroquinolines have attracted considerable attention from organic and medicinal chemists due to their many pharmaceutical applications (Fig. 1).

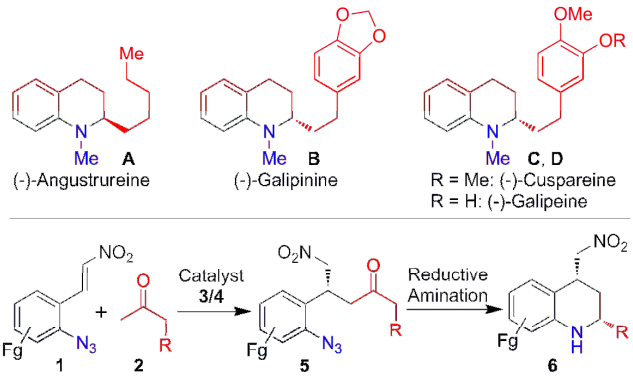
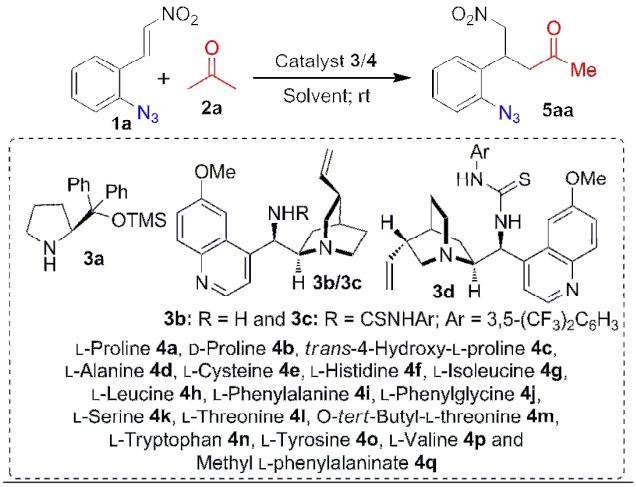


Fig. 1 Natural products with tetrahydroquinoline core structure and design plan for the asymmetric synthesis of this scaffold through supramolecular organocatalysis.

For the asymmetric synthesis of chiral tetrahydroquinolines, previous approaches mainly depend on the asymmetric hydrogenation of the corresponding hetero-aromatic compounds,[2] nucleophilic addition of cyclic imines,[3] or the Povarov reaction.[4] Even though a few organocatalytic reactions have been reported,[5] direct and efficient asymmetric methods for their preparation is still a challenging task. However to develop a diversity platform for the asymmetric synthesis of 2,4-disubstituted tetrahydroquinolines with high selectivity, we propose herein a synthetic plan based on the enamine induced Michael reaction as the first step (Fig. 1). The organocatalytic asymmetric Michael reaction of functionalized 1-azido-2-(2-nitrovinyl)benzene **1** with ketone **2** followed by reductive amination yields the expected product **6** (Fig. 1).

Table 1 Reaction preliminary optimization[a]



Entry	Catalyst 3/4 (each 5 mol%)	Solvent (0.3 M)	Time (h)	Yield (%)[b] 5aa	*ee* (%)[c] 5aa
1[d]	3a/$PhCO_2H$	DCM	84	40	43
2[e]	3b/$PhCO_2H$	DCM	96	23	18
3	3c/$PhCO_2H$	DCM	72		
4[f]	4a	DMSO	6	69	3
5[f]	4a	DCM	96	16	11
6	4i	DCM	72	–	–
7	3c/4a	C_6H_6	108	56	49
8	3d/4b	DCM	28	85	24
9	3c/4j	C_6H_6	144	27	94
10	3c/4j	DCM	72	17	95
11	3c/4i	$CH_3C_6H_5$	72	46	92
12	3c/4l	DCM	72	90	92
13	3c/4i	DMSO	72	52	6
14	3c/4q	DCM	72	13	11

[a] Unless stated otherwise, all reactions were carried out with **1a** (0.3 mmol), **2a** (4.2 mmol, 14 equiv.), catalysts **3** or **4** (5 mol%) in DCM at rt. [b] Yield refers to the column purified product. [c] Ee determined by CSP-HPLC analysis. [d] **3a**/$PhCO_2H$ (20 mol% each) was used. [e] **3b**/$PhCO_2H$ (10 mol% each) was used. [f] 20 mol% of **4a** was used.

Over the past few years, the organocatalytic asymmetric Michael reaction has become a viable tool for C-C bond formation with good selectivity under mild reaction conditions.[6] The standard organocatalysts for Michael reaction include proline derivatives or cinchona alkaloid-based primary amines and thioureas. To execute the hypothesis of the reaction design, first we propose the asymmetric Michael reaction, for which we have chosen 1-azido-2-(2-nitrovinyl)benzene **1a** and acetone **2a** as the model substrates with **3** and **4** as catalysts. Surprisingly, when we performed the

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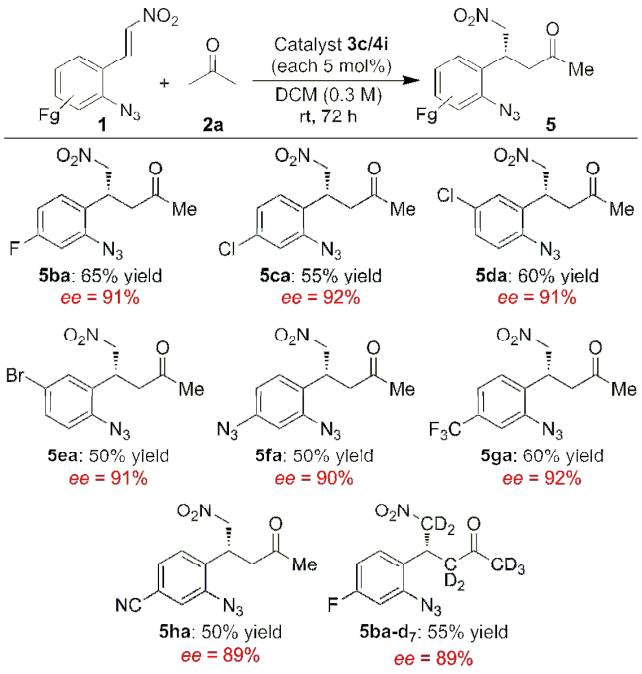
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, HRMS and HPLC) for all new compounds. See DOI: 10.1039/xxxxxxxx

Michael reaction of **1a** with 14 equiv. of **2a** under the standard reaction conditions, the product **5aa** was obtained in moderate to poor yield and *ee*'s (Table 1, entries 1-6). In order to ameliorate the yield and enantioselectivity, instead of screening new catalysts, we initiate of using the emerging chiral supramolecular organocatalysts,[7] which can be assembled *in situ* from the easily available simple organocatalysts **3** and **4** through weak interactions. As anticipated, treatment of **1a** and **2a** with Zhao's supramolecular organocatalyst (each 5 mol % of catalysts **3c** and **4a**)[7b] in benzene at 25 °C for 108 h furnished the expected keto azide **5aa** in moderate yield (56%) and promising *ee* (49%) (Table 1, entry 7).

Table 2 Scope of the asymmetric supramolecular-catalysis[a-b]

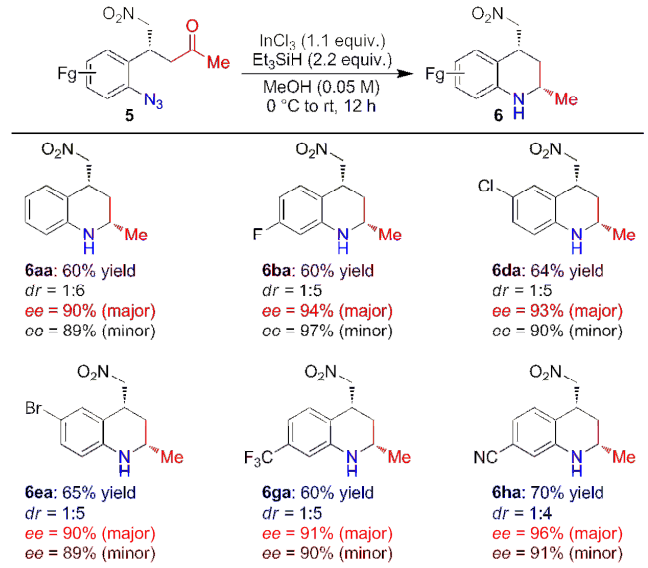


[a] Yield refers to the column-purified product. [b] Ee determined by CSP-HPLC analysis.

Recently, asymmetric supramolecular-organocatalysis has become an innovative tool for achieving high asymmetric induction and faster reaction rates from reactions involving highly functionalized starting materials, when compared to organocatalysis.[7] Disappointingly, when we performed the Michael reaction of **1a** and **2a** with known supramolecular assembly catalysts of Ramachary's **3d/4b**[7e] or Zhao's **3c/4j**,[7b] we turned out with either less yield or low *ee* (Table 1, entries 8-10). To overcome this problem, we screened different supramolecular organocatalysts assembled *in situ* from the library of organocatalysts **3** and **4** (Tables 1 and S1). After thorough investigation of the asymmetric Michael reaction of **1a** and **2a** under the catalysis of supramolecular assembly, *in situ* generated from **3c** or **3d** with sixteen amino acids **4a-p**; gave the interesting results that the amino acids L-cysteine **4e**, L-isoleucine **4g**, L-phenylglycine **4j**, O-*tert*-butyl-L-threonine **4m**, L-tryptophan **4n** or L-valine **4p** on combination with **3c** furnished the keto azide (–)-**5aa** in moderate to poor yields with high enantioselectivity (Table S1, see SI-1 for full detials). The same reaction under the combination of **3c** with the amino acid L-phenylalanine **4i** in DCM gave the keto azide (–)-**5aa** in 90% yield with 92% *ee* within 72 h as the best optimized condition (Table 1, entry 12). *Intriguingly, deviating from this optimized condition, by switching the solvent to DMSO (interactions arising from the solvent predominates), by using either* ***3c*** *or* ***4i*** *as the catalyst or by using the catalyst combination* ***3c/4q*** *(where in* ***4q*** *is methyl ester of* ***4i*** *and so does not have free-acid for weak interactions) was ineffective in promoting the Michael reaction (Table 1, entries 3, 6, 13 and 14).* These results clearly support our hypothesis of involvement of supramolecular assembly as catalyst.[7]

The principle of the supramolecular-organocatalysis was further extended by reacting a group of functionalized 1-azido-2-(2-nitrovinyl)benzenes **1b–h** with 14 equiv. of acetone **2a** each catalyzed by 5 mol % of **3c/4i** at 25 °C in DCM for 72 h (Table 2). All the substrates **1b-h** furnished the chiral keto azides **5ba-ha** in good yields and excellent *ee*'s, irrespective of the electronic factors of the substituents present. Treatment of **1b** with deuterated acetone **2a-d$_6$** furnished the expected chiral keto azide **5ba-d$_7$** in 55% yield with 89% *ee* without much alteration in the reaction rate (Table 2).

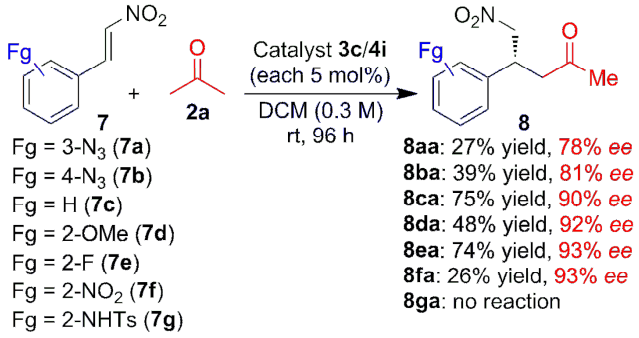
Table 3 Reductive amination of the chiral keto azides[a-c]



[a] Yield refers to the column-purified product. [b] Ee determined by CSP-HPLC analysis. [c] dr was determined based on ^{1}H NMR or HPLC analysis.

After synthesizing the optically pure keto azides **5**, we further transformed them into medicinally significant functionalized tetrahydroquinolines **6** through reductive amination by using the Bencivenni-Nanni protocol.[8] Thorough optimization of **5aa→6aa** through single step reductive amination or two steps aza-Wittig/hydrogenation proved that $InCl_3$-Et_3SiH in MeOH at 0-25 °C is the suitable condition to prepare the **6aa** in good yield with high *de*/*ee* (Tables S2 and S3, see SI-1 for full detials). Then we subjected the optically pure keto azide (–)-**5aa** to reductive amination conditions with triethylsilane and $InCl_3$ at 0-25 °C for 12 h.[8b] To our delight, the reductive amination product (–)-*syn*-**6aa** was isolated in 60% yield with 71% *de* and 90% *ee* (Table 3). The selective reductive amination strategy was demonstrated with five more substrates of **5** containing halogen, CF_3 and CN substituents to furnish the *syn*-tetrahydroquinolines **6** in good yields with high *de*/*ee* (Table 3). The amine compounds, *syn*-**6** are structural analogues of natural products **A**-**D**,[1] which is accentuating the

relevance of sequential Michael-reductive amination approach to synthesize these compounds. The structure and absolute stereochemistry of the keto azides **5** and reductive amination products *syn*-**6** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis of (–)-*syn*-**6ba** as shown in Fig. S1 (SI-1).[9]



Scheme 1 Controlled experiments to study the N_3 involvement in the pre-transition state (pre-TS).

Furthermore we performed a few controlled experiments to investigate the involvement of N_3, NO_2 and other active functional groups of the substrates and the catalysts in the pre-transition state of the Michael reaction (Scheme 1). *In addition to NO_2, N_3 also involves for the hydrogen bonding with N-H group of* ***3c****, due to this reason position of N_3 on the aryl is crucial for achieving the high rate and selectivity*. This statement was proven by obtaining very poor yields and *ee*'s of Michael products **8aa-8ba** for the longer reaction times from the reaction of **7a-7b** and **2a** with the **3c/4i**-catalysis (Scheme 1). To support this, we carried out the reaction of **2a** with N_3-free substrates **7c-f**, which gave better results compared to **7a-b** and this confirms that N_3 competes for hydrogen bonding with **3c** in addition to NO_2 (Scheme 1). Surprisingly, there is no reaction observed between **2a** and *ortho*-NHTs substrate **7g** under the optimized conditions (Scheme 1). It appears that a topological modification in the pre-transition state assembly by decreasing single directional hydrogen-bonding between *N*-H group of **3c** and *ortho*-N_3/NO_2 disturbs the supramolecular assembly and diminishes the rate, yield and *ee* of the reactions (Scheme 1). We gained some more evidence for the involvement of hypothetical pre-transition state supramolecular assembly, by careful investigation of the on-going reaction of **1a** and **2a** under the **3c/4i**- and **3c/4m**-catalysis using ESI-HRMS technique, which enabled us to identify the proposed catalytic pre-transition state intermediates (Fig. S2, see SI-1 for full details).[7]

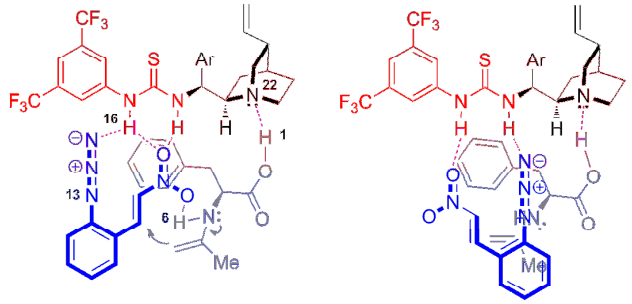
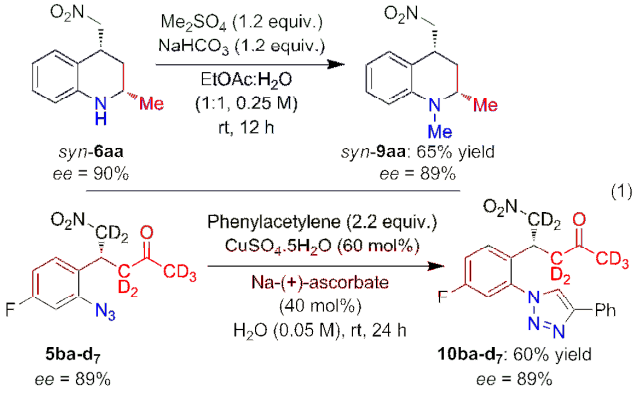


Fig. 2 Proposed reaction mechanism.

With controlled experimental data, herein we securely illustrate the mechanism of the asymmetric Michael reaction through conformationally flexible cyclic 22-membered pre-transition state supramolecular assembly by **3c/4i**-catalysis and the reaction most probably proceeds through the **TS-1** mechanism (Fig. 2). We emphasize five interactions between the substrates and the catalysts to support a cyclic 22-membered pre-transition state assembly (**TS-1**) to furnish the chiral keto azides **5** over the less stable **TS-2**. Based on our observations, (i) CO_2H group of L-**4i** undergoes hydrogen bonding with *tert*-amine group of **3c**, which brings the two catalysts closer to the reaction centre; (ii) *N*H groups of **3c** involves the hydrogen-bonding with both N_3 and NO_2 groups of **1a-h** to activate the electrophilic nature of olefin; (iii) primary amino group of L-**4i** forms enamine with acetone to activate the nucleophilic nature; (iv) finally NO_2 group of **1a-h** undergoes hydrogen-bonding with enamine N*H*, thus closing the mobile 22-membered supramolecular cyclic pre-transition state to control the enantioselectivity (Fig. 2).



With applications in mind, we explored the utilization of (–)-*syn*-**6aa** and (–)-**5ba-d$_7$** in the synthesis of functionalized drug-like compounds (+)-*syn*-**9aa** and (+)-**10ba-d$_7$** *via* simple *N*-methylation and a click reaction, respectively (eq. 1).[10] Compounds of the type (+)-*syn*-**9aa** and (+)-**10ba-d$_7$** are important molecules in medicinal chemistry,[1] which is emphasizing the value of the present catalytic approach to the chiral pharmaceuticals.

In summary, we have demonstrated a novel and efficient *in situ* generated chiral supramolecular assembly as the best catalyst than its synthons for the asymmetric Michael reaction of acetone with (*E*)-1-azido-2-(2-nitrovinyl)benzenes followed by reductive amination to furnish the medicinally important *syn*-2,4-disubstituted tetrahydroquinolines **6** with high yield, *ee*'s and *de*'s. With the help of the ESI-HRMS technique and controlled experiments, we have obtained strong evidence for the *in situ* formation of proposed catalytic supramolecular assembly from the organocatalysts. Readily *in situ* generated chiral supramolecular assembly catalysts would become promising future catalytic systems for more functionalized substrates than organocatalysts.

We thank DST (New Delhi) for financial support. KSS thank CSIR, New Delhi for her research fellowship.

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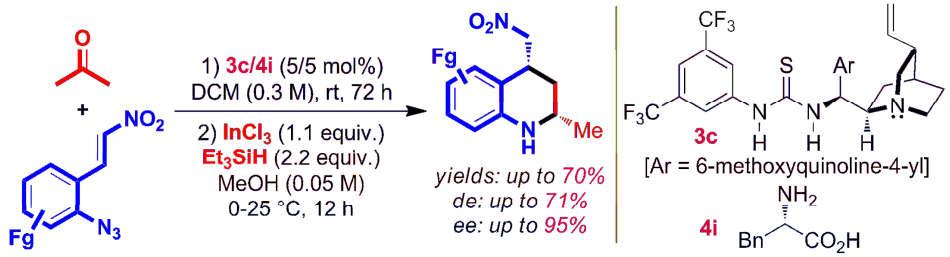

Short Statement

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