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Organocatalytic diastereoselective synthesis of chiral decalines through domino Claisen-Schmidt/Henry reaction†

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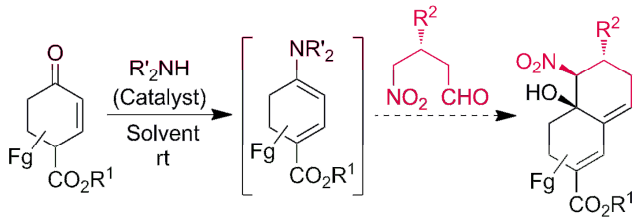
General and operative domino Claisen-Schmidt/Henry (CS/H) reaction has been revealed to obtain highly substituted chiral decalines in good yields with excellent *ee*'s and *de*'s by using push-pull enamine-catalysis.

The asymmetric synthesis of functionalized bicyclic carbon frameworks is always a challenging task in synthetic chemistry. Bicyclic carbon frameworks (decalines) found in a wide variety of polyterpenoid and steroid natural products with interesting biological activity.[1] Recently, organocatalytic domino processes involving iminium and enamine activation have become useful for the synthesis of bicyclic, tricyclic and spirocyclic molecules with high *ee*/*de*.[2] The domino reactions of Serebryakov 1-amino-1,3-butadiene,[3] Barbas 2-amino-1,3-butadiene,[4] Jørgensen/Chen trienamine[5] and Ramachary/Gouverneur aminoenyne[6] were well explored for the asymmetric synthesis of functionalized cyclohexanes. Although organocatalytic domino reactions were reported recently, the development of more efficient approaches in multi C-C bond formation with multiple stereogenic centers in a cascade manner is of significant interest.[7]

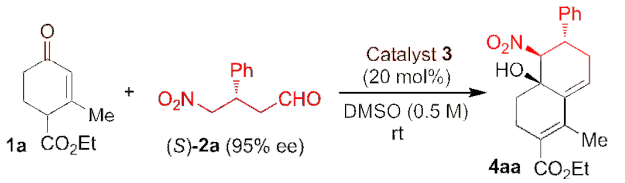


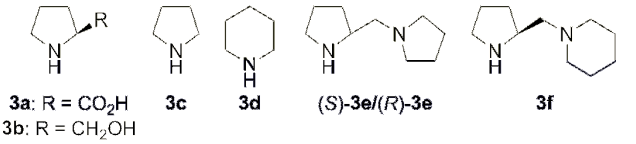
Scheme 1 Reaction design for the diastereoselective synthesis of chiral decalines through push-pull enamine-catalysis.

The Claisen-Schmidt reaction is one of the important C-C bond formation processes in organic chemistry which is able to provide α, β-unsaturated carbonyl compounds, which are important intermediates for the natural product synthesis.[8] The Henry (nitroaldol) reaction is another powerful C-C bond forming tool for the preparation of valuable synthetic intermediates such as nitro alcohols, which can be further transformed into a number of important nitrogen and oxygen-containing compounds.[9] Recently, Michael-Henry processes have been successfully demonstrated in the synthesis of substituted cyclic frameworks with multiple stereogenic centers.[10] However, to the best of our knowledge, there is no report involving a domino Claisen-Schmidt/Henry reaction strategy for the selective synthesis of bicyclic decalines with three contiguous stereocenters (Scheme 1).

In continuation to our interest in the development of organocatalytic domino asymmetric reactions through push-pull enamine- or dienamine-catalysis,[11] herein we have designed a diastereoselective approach to the substituted chiral decalines from commercially available enones and chiral γ-nitroaldehydes through domino Claisen-Schmidt/Henry (CS/H) reaction based on the push-pull enamine-catalysis (Scheme 1). Optically pure γ-nitroaldehydes (93-95% *ee*), which are used as starting materials in this study were obtained from the recent discovery of List or Hayashi protocol of (*S*)-α,α-diphenylprolinol trimethylsilyl ether [(*S*)-DPPOTMS]-mediated conjugate addition of acetaldehyde to β-nitrostyrenes or nitroalkanes to α,β-unsaturated aldehydes, respectively.[12,13]

Table 1 Reaction preliminary optimization[a-c]





Entry	Catalyst 3 (20 mol%)	Time (h)	Yield (%) of **4aa**	ee (%) of **4aa**
1	(*S*)-**3a**	24 h	-	-
2	(*S*)-**3b**	24 h	-	-
3	**3c**	24 h	15	n.d
4	**3d**	24 h	28	92
5	(*S*)-**3e**	5 h	64	94
6	(*S*)-**3f**	5 h	50	95
7*d*	(*S*)-**3e**	5 h	53	96
8*e*	(*S*)-**3e**	24 h	-	-
9*f*	(*S*)-**3e**	3 h	53	96
10*g*	(*S*)-**3e**	6 h	70	>99
11*g,h*	(*S*)-**3e**	5 h	50	96
12*g*	(*R*)-**3e**	5 h	75	94
13*g,i*	(*S*)-**3e**	4 h	72	-93
14*g,j*	(*S*)-**3e**	2 h	57	98

[a] Reactions were carried out in solvent (0.5 M) with 2.0 equiv. of **1a** relative to the (*S*)-**2a** in the presence of 20 mol % of catalyst **3**. [b] Yield refers to the column-purified product. [c] Ee determined by CSP-HPLC analysis. [d] DMF used as solvent. [e] $HClO_4$ (20 mol %) taken as co-catalyst. [f] 1.0 equiv. of **1a** was used. [g] 1.5 equiv. of (*S*)-**2a** was used. [h] Crude compound (*S*)-**2a** was used as such. [i] (*R*)-**2a** was used. [j] Reaction was performed at 70 °C.

For the reaction optimization, we screened a few simple organocatalysts for the reaction of enone **1a** with 0.5 to 1.5 equiv. of γ-nitroaldehyde (*S*)-**2a** (Table 1). Reaction of **1a** with 0.5 equiv.

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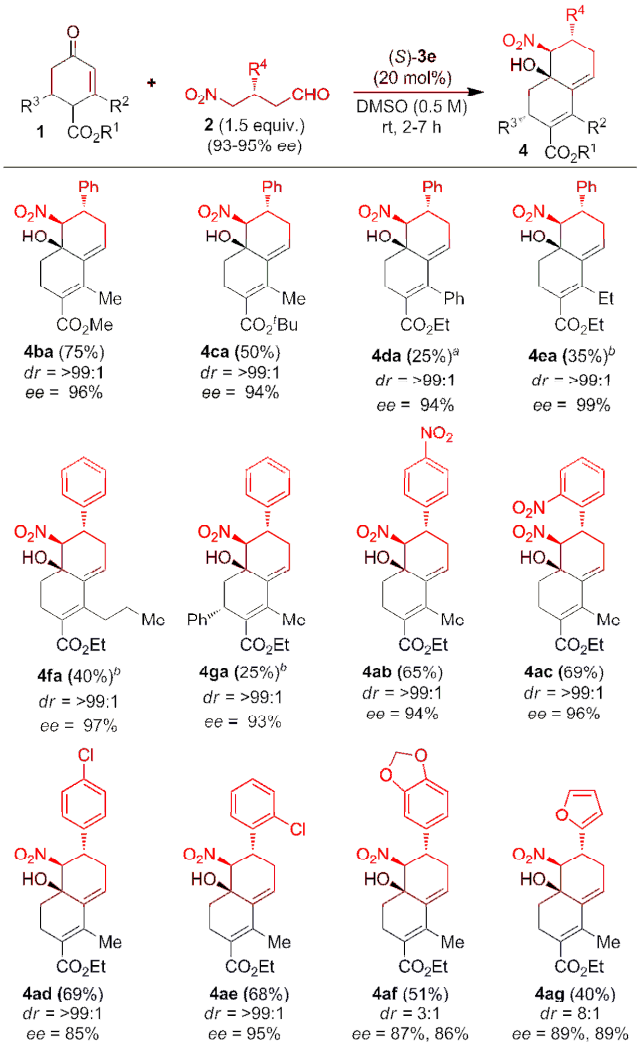
† Electronic supplementary information (ESI) available: Experimental procedures and analytical data (^{1}H NMR, ^{13}C NMR, HRMS and HPLC) for all new compounds. See DOI: 10.1039/xxxxxxxx

Table 2 Synthesis of chiral substituted decalines

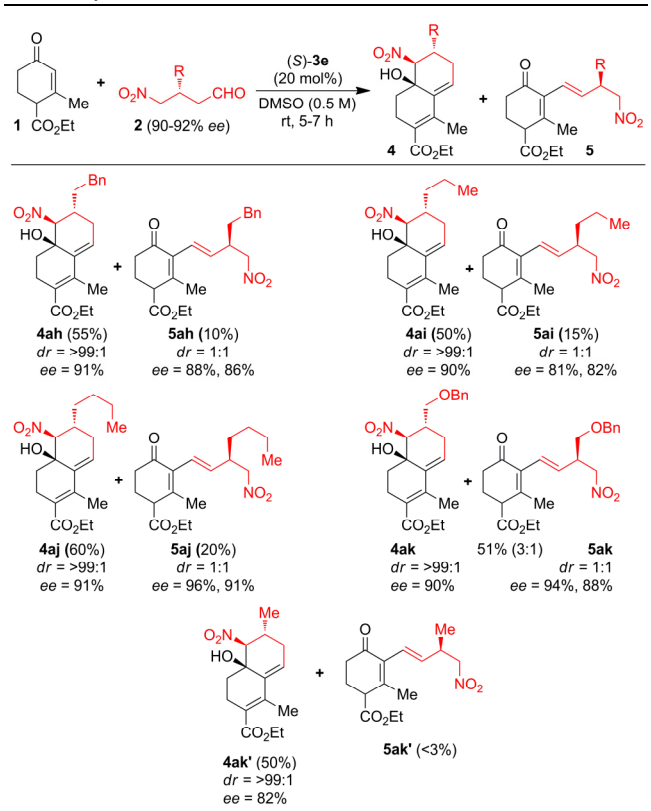


[a] Reaction performed at 50 °C for 70 h. [b] Reaction time was 24 h. All yields representing for the single isomer of **4**.

of (*S*)-**2a** in DMSO catalyzed by 20 mol% of L-proline **3a** or L-prolinol **3b** didn't furnished the expected product (Table 1, entries 1-2). Surprisingly, same reaction in the presence of pyrrolidine **3c**-catalysis furnished the product (-)-**4aa** in only 15% yield; but the same reaction under piperidine **3d**-catalysis gave the (-)-**4aa** in 28% yield with 92% *ee* and >99% *de* (Table 1, entries 3-4). To increase the CS/H reaction rate and yield, we tested the cascade reaction of **1a** with (*S*)-**2a** in the presence of more basic chiral diamine catalysts (*S*)-**3e**, (*R*)-**3e**, and (*S*)-**3f** in DMSO at 25-70 °C (Table 1, entries 5–14). Interestingly, domino reaction with 20 mol% of (*S*)-**3e** as catalyst furnished the single isomer of (-)-**4aa** in 64% yield with 94% *ee* at 25 °C for 5 h; but the same reaction catalyzed by (*S*)-**3f** furnished (-)-**4aa** in reduced yield (Table 1, entries 5-6). There was no further improvement by changing the solvent or by adding co-catalyst; but yield and *ee* of the reaction were increased to 70% yield and >99% *ee* by taking 1.5 equiv. of (*S*)-**2a** instead of 0.5 equiv. under the (*S*)-**3e**-catalysis in DMSO at rt (entries 7-10). Reaction of the crude chiral aldehyde (*S*)-**2a** (which is obtained from the quick work up of Hayashi method) with **1a** gave the product (-)-**4aa** with reduced yield and *ee* (Table 1, entry 11). To further understand the reaction kinetics, we carried out the reaction of **1a** and (*S*)-**2a** with (*R*)-**3e** as catalyst, which gave the same enantiomer of (-)-**4aa** in 75% yield with 94% *ee* (Table 1, entry 12). In another experiment, we performed the reaction with opposite enantiomer of γ-nitroaldehyde (*R*)-**2a** with **1a** under (*S*)-**3e**-catalysis to furnish the opposite enantiomer of decalin (+)-**4aa** in 72% yield with 93% *ee* (Table 1, entry 13). Surprisingly, there was no further improvement in the yield by changing the temperature from 25 °C to 70 °C (Table 1, entry 14); and there is no reaction observed under the *tert*-amine, DABCO-catalysis (result not shown in Table 1). After the preliminary studies, we considered the optimization conditions to be DMSO at 25 °C using 1.5 equiv. of (*S*)-**2a** and commercially available (*S*)-**3e** as catalyst (Table 1, entry 10).

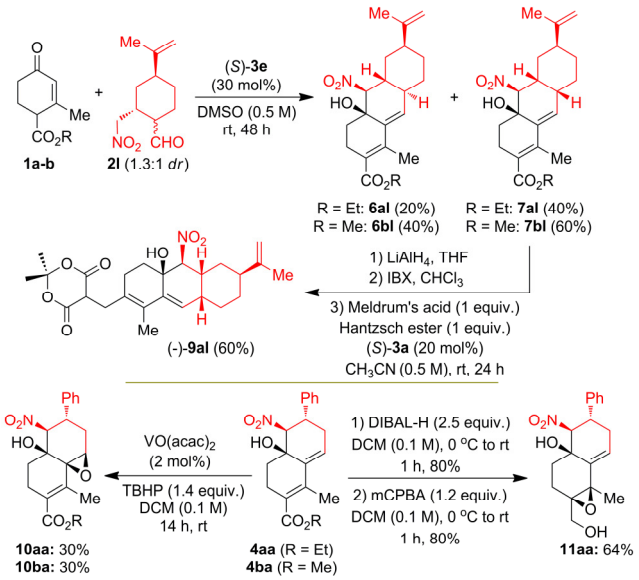
With the optimized conditions in hand, the scope and limitations of domino CS/H reaction were investigated by using functionalized enones **1a–g** and chiral γ-nitroaldehydes **2a–g** (Table 2). A variety of functionalized cyclic enones **1b-g** with freshly prepared chiral γ-nitroaldehyde **2a** delivered the chiral decalines **4ba-ga** in good to moderate yields with high *ee* and *de*'s (Table 2, entries 1-6). Decaline yields were reduced with increase in bulkiness of C-2 substitution of enone without effecting the *ee* and *de* values, for example C-2 substituted enones **1d-f** furnished the expected decalines **4da-4fa** in 25%, 35% and 40% yields with 94%, 99% and 97% *ee*'s and >99% *de* respectively (Table 2, entries 3-5).

Table 3 Synthesis of chiral substituted decalines and dienes[a-c]



[a] Reactions were carried out in solvent (0.5 M) with 1.5 equiv. of (*S*)-**2** relative to the **1** in the presence of 20 mol % of catalyst (*S*)-**3e**. [b] Yield refers to the column-purified product. [c] Ee determined by CSP-HPLC analysis; and dr was determined by CSP-HPLC and crude NMR analysis.

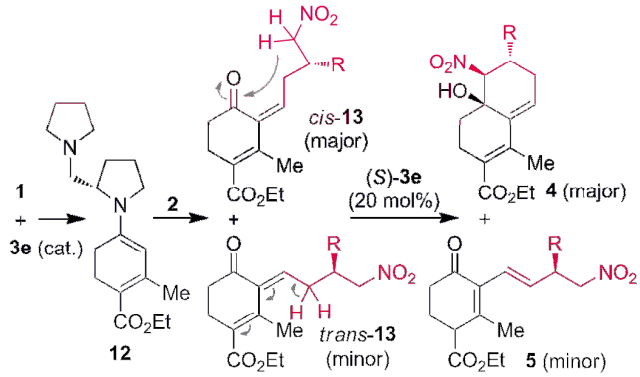
Surprisingly, the C2/C6-disubstituted enone **1g** gave only one isomer of domino CS/H product **4ga** in 25% yield with 93% *ee* and >99% *de* (Table 2, entry 6). The domino CS/H reaction of enone **1a** with γ-nitroaldehydes bearing electron-deficient aryl substituent's such as 4-nitrophenyl **2b**, 2-nitrophenyl **2c**, 4-chlorophenyl **2d** and 2-chlorophenyl **2e** gave the expected decalines **4ab-4ae** in good yields with high *ee* and *de*'s (Table 2, entries 7-10), whereas electron-rich aryl substituent such as 3,4-methylenedioxyphenyl **2f** and heteroaryl substituent such as furyl **2g** reduced the diastereoselctivity of decalines **4af-4ag** without effecting *ee*'s (Table 2, entries 11-12). The structure and absolute stereochemistry of the chiral CS/H products were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on (-)-**4aa** as shown in Figure S1 (see Supporting Information).[14]



Scheme 2 Applications of domino CS/H chiral products.

We further showed interest to screen β-alkyl-γ-nitroaldehydes **2h-k'** as substrates with **1a** to investigate the electronic factors on product formation (Table 3). A series of β-alkyl-γ-nitroaldehydes **2h-k'** were reacted with **1a** catalyzed by 20 mol% of (*S*)-**3e** at 25 °C for 5-7 h in DMSO. Surprisingly, in all these reactions along with CS/H products **4ah-ak'**, monocyclic chiral (*E*)-1,3-diene products **5ah-ak'** were isolated in minor quantities through Claisen-Schmidt/isomerization (CS/I) reaction (Table 3). The CS/H products **4ah-ak'** were furnished in good to excellent *ee*'s and *de*'s whereas the CS/I products **5ah-ak'** were furnished in good to excellent *ee*'s with 1:1 *dr*. Interestingly, formation of monocyclic chiral (*E*)-1,3-diene **5ak'** is very poor from the domino reaction of **1a** with simple (*R*)-3-methyl-4-nitrobutanal **2k'** under the (*S*)-**3e**-catalysis. These results suggesting that the sterically crowded β-alkyl group in **2h-k'** is responsible for the formation of major/minor isomers of CS intermediates, from which minor *trans*-isomer is converting into the CS/I product.

With applications in mind, we explored the utilization of CS/H products **4** in the synthesis of chiral terpenoid type compounds **6-11** *via* reduction, oxidation and organocatalytic reductive coupling (OrgRC) reactions (Scheme 2). Interestingly, CS/H reaction of **1a-b** with functionally rich chiral γ-nitroaldehyde (-)-**2l** in DMSO at 25 °C under (*S*)-**3e**-catalysis for 48 h furnished the terpenoid-type tricyclic products **6** and **7** in good yields with 1:1.5 to 1:2 *dr*. In both the cases *cis*-isomer **7** was formed in major compared to *trans*-isomer **6**. The OrgRC[15] reaction of the dienal **8al** (which is obtained after high-yielding ester reduction followed by oxidation of (-)-**7al**) with Meldrum's acid and Hantzsch ester in CH_3CN (0.5 M) at 25 °C for 24 h furnished the chiral terpenoid-type product (-)-**9al** in 60% yield. High-yielding reduction of chiral decaline (–)-**4aa** with 2.5 equiv. of DIBAL-H in dry DCM at 0-25 °C for 1.0 h furnished the allylic alcohol, which on oxidation with mCPBA furnished regioselectively single isomer of epoxide (–)-**11aa** in 64% overall yield (Scheme 2). Surprisingly, treatment of the chiral decalines (–)-**4aa** and (–)-**4ba** with 1.4 equiv. of TBHP under 2 mol% of $VO(acac)_2$ in DCM at 25 °C for 14 h furnished regioselectively single isomer of epoxides (–)-**10aa** and (–)-**10ba** in each 30% yield with >99% *ee*. The structure and regiochemistry of the products **6-11** were confirmed by NMR analysis and also finally confirmed by X-ray structure analysis on **7bl** as shown in Figure S2 (see SI).[14]



Scheme 3 Proposed reaction mechanism.

Even though additional studies are needed to securely elucidate the mechanism of CS/H and CS/I reactions through (*S*)-**3e**-catalysis, the domino reaction proceeds by stepwise manner between *in situ* generated push-pull enamines **12** with γ-nitroaldehydes **2** (Scheme 3). First, reaction of catalyst (*S*)-**3e** with **1a** generates chiral push–pull enamine **12** through iminium formation. The chiral γ-nitroaldehyde **2** reacts with the *in situ* generated **12** to furnish the Claisen-Schmidt intermediates **13** as the major [*cis*-**13**] and minor [*trans*-**13**] isomers due to the steric hindrance between diamine and β-aryl/alkyl groups. Further *in situ* treatment of **13** with diamine (*S*)-**3e**, major *cis*-**13** isomer transforms into the single isomer of decaline **4** *via* intramolecular Henry reaction. Based on the crystal structure studies, we can rationalize that the *re*-face of the nucleophilic carbon attacks the *si*-face of the electrophilic carbon in an intramolecular manner. The formation of chiral (*E*)-1,3-dienes **5** from minor *trans*-**13** isomer can be explained by using steric hindrance-induced (*S*)-**3e**-catalyzed isomerization (see full details in the Scheme S1, Supporting Information).

In summary, we have developed a domino Claisen-Schmidt/Henry process for the synthesis of terpenoid-type chiral decalines with three-contiguous stereocenters. This novel CS/H reaction proceeds in good yields with high enantio- and diastereoselectivity through push–pull enamine catalysis. Furthermore, we have demonstrated the application of chiral CS/H products in the synthesis of highly substituted terpenoid-type compounds.

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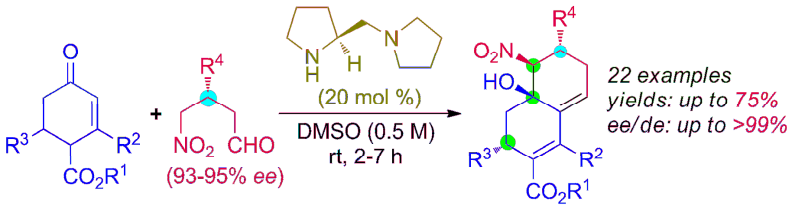
Graphical Abstract for Table of Contents:



Short Statement

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