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Direct organocatalytic in situ generation of novel push–pull dienamines: application in tandem Claisen–Schmidt/iso-aromatization reactions

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Dedicated to Professor A. Srikrishna for his many contributions to the area of sesquiterpene total synthesis

Abstract—A new, green, regioselective, one-step, tandem reaction of an aldehyde possessing a non-enolizable carbonyl function with a highly substituted cyclohex-2-enone, under amine catalysis afforded highly substituted phenols or 2-arylidenecyclohexanones, respectively. The yields and regioselectivities were good. Evidence for a pathway involving formation of novel push–pull dienamines is presented along with examples demonstrating the amenability of the process to combinatorial chemistry.

One of the major goals in organic chemistry is the catalytic assembly of simple and readily available precursor molecules into stereochemically complex products under green reaction conditions. In this regard, the development of tandem and multi-component reaction methodologies can provide expedient access to complex products from simple starting materials.[1] Recently, organocatalysis has emerged as a promising green synthetic tool for constructing C–C, C–O and C–N bonds in a single operation with high diastereo- and enantioselectivity in a tandem or multi-component process.[2] Typically in organocatalysis, structurally simple and stable chiral organoamines and amino acids facilitate iminium- and enamine-based transformations with carbonyl compounds and are used as catalysts in operationally simple and, in some cases, environmentally friendly tandem reactions.

As part of our program to engineer direct organocatalytic tandem or multi-component reactions, herein we report the first organocatalytic regioselective direct tandem Claisen–Schmidt/iso-aromatization reactions that produce highly substituted 2-arylidene cyclohexanones **4** and highly substituted phenols **5** from commercially available Hagemann's esters **1a**–**b**, aldehydes **2a**–**o** and amines **3** as shown in Scheme 1. Phenols **5** are attractive intermediates in the synthesis of natural products and in medicinal chemistry,[3] whilst 2-arylidene cyclohexanones **4** and analogues thereof have broad utility in pharmaceutical chemistry[4] and in organic synthesis. Hence, their preparation has continued to attract considerable synthetic interest.[5]

We envisioned that an amine would catalyze the tandem Claisen–Schmidt condensation[5a] of an aldehydes **2** with the push–pull 1-amino-1,3-butadiene[6] intermediate generated in situ from Hagemann's ester **1** and amine **3** to form the substituted 3-arylidene Hagemann's ester **4** in a highly regioselective manner, which then undergoes iso-aromatization to produce substituted phenols **5**.

We were pleased to find that the tandem reaction of Hagemann's ester **1a** and 4-nitrobenzaldehyde **2a** with a catalytic amount of (*S*)-1-(2-pyrrolidinyl-methyl)pyrrolidine **3b** in DMF at ambient temperature for 7 h furnished the tandem product **5aa** as a single isomer, in 75% yield (Table 1, entry 2). The same reaction, catalyzed by pyrrolidine **3c** at 25 °C for 2 h furnished the Claisen–Schmidt product **4aa** as a 1:1 mixture of *E*/*Z* isomers, in 60% yield and tandem product **5aa** in 5% yield (Table 1, entry 6). The regiochemistry of products **4aa** and **5aa** was established by NMR analysis and molecular mechanics (MMX) calculations.

Keywords: Amines; Hagemann's ester; Organocatalysis; Push–pull dienamine; Tandem reactions.
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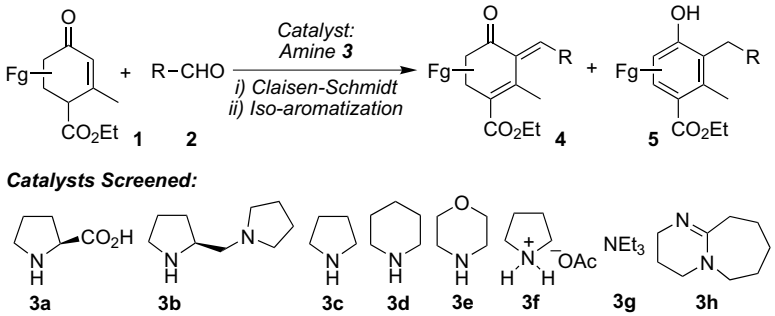
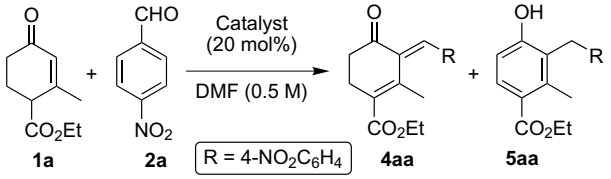


Scheme 1. Direct organocatalytic tandem Claisen–Schmidt/iso-aromatization reactions.

Table 1. Optimization of the direct organocatalytic tandem Claisen–Schmidt/iso-aromatization of **1a** and **2a**[a]



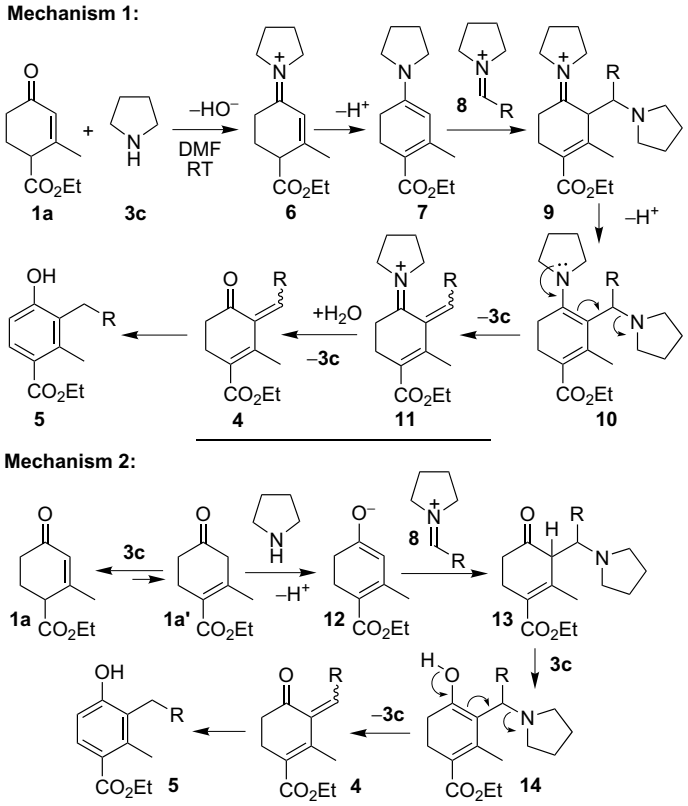
Entry	Catalyst	Temperature (°C)	Time (h)	Yield (%)[b]	
				4aa	**5aa**
1[c]	**3a**	25	12	—	—
2	**3b**	**25**	**7**	—	**75**
3	**3c**	25	6	—	65
4	**3c**	**25**	**12**	—	**75**
5[d]	**3c**	25	12	—	77
6[e]	**3c**	25	2	60	5
7	**3c**	60	2	—	61
8[f]	**3c**	25	23	—	65
9	**3d**	25	12	—	61
10[c]	**3e**	25	12	—	—
11	**3f**	25	12	—	30
12[c]	**3g**	25	12	—	—
13[c]	**3h**	25	12	—	—

[a] Experimental conditions: reactions were carried out in DMF (0.5 M) with the same proportions of Hagemann's ester **1a** and aldehyde **2a** in the presence of 20 mol % catalyst.
[b] Yield refers to the column-purified product.
[c] 70–85% of unreacted Hagemann's ester **1a** was isolated.
[d] 1.25 equiv of ester **1a** was used.
[e] 1:1 mixture of *E*/*Z* isomers were isolated.
[f] DMSO was used as the solvent.

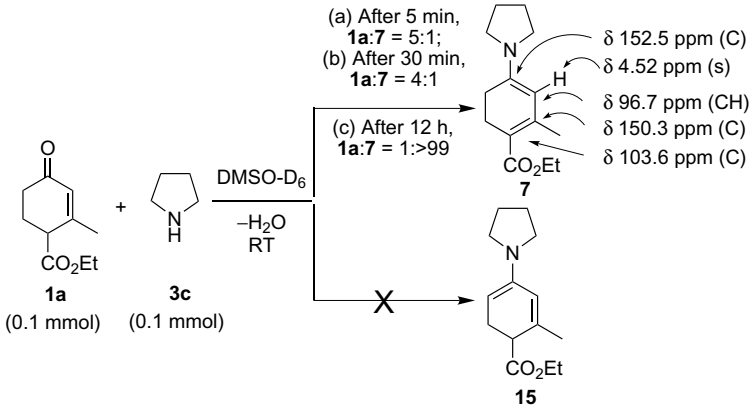
In the tandem Claisen–Schmidt/iso-aromatization reaction of ester **1a** and 4-nitrobenzaldehyde **2a** catalyzed directly by diamine **3b**, we found that the solvent had a significant effect on the rates and yields (Table 1). The results of this investigation indicated that the tandem Claisen–Schmidt/iso-aromatization reaction catalyzed by diamine **3b** and pyrrolidine **3c** produced the product **5aa** with good yields in aprotic dipolar solvents, DMF and DMSO (Table 1, entries 1–13) but did not furnish products **4aa** and **5aa** in protic polar solvents (H_2O, MeOH, EtOH, $CHCl_3$, CH_3CN and CH_2Cl_2), the aprotic polar solvent (THF) and in the ionic liquid [bmim]BF_4 (not presented in Table 1). The Claisen–Schmidt condensation is strongly solvent dependent. The first step, the formation of 1-amino-1,3-butadiene from keto ester **1a** and amine, and its addition to the carbonyl (or imine) group is facilitated in solvents of high polarity and the second step, 1,2-elimination, is inhibited by protic solvents. Thus, dipolar aprotic solvents such as DMF and DMSO are especially useful in Claisen–Schmidt condensations.[7]

Next, we screened several pyrrolidine-based catalysts monitoring the reaction yield and regioselectivity of the tandem reaction of Hagemann's ester **1a** and 4-nitrobenzaldehyde **2a** in DMF (Table 1). The amino acid, L-proline **3a** did not furnish the expected Claisen–Schmidt **4aa** or tandem **5aa** products (Table 1, entry 1). The structurally simple pyrrolidine **3c** catalyze the tandem reaction to produce **5aa** in 65% yield (Table 1, entry 3). At 60 °C, the same reaction with pyrrolidine **3c** furnished the tandem Claisen–Schmidt/iso-aromatization product **5aa** in 61% yield in reduced time (Table 1, entry 7). Piperidine **3d** also catalyzed the tandem reaction in good yield (Table 1, entry 9). The *tert*-amines triethylamine **3g** and DBU **3h** did not catalyzed the tandem reaction, which is strong evidence for intermediate enamine formation during these reactions. The optimal conditions involved pyrrolidine **3c** catalysis at 25 °C in DMF with equimolar quantities of **1a** and **2a**, which furnished the tandem product **5aa** in 75% yield (Table 1, entry 4).

Two possible reaction mechanisms for the regioselective synthesis of substituted phenol **5aa** and 3-arylidene Hagemann's ester **4aa** are illustrated in Scheme 2. First, reaction of the chiral (*S*)-1-(2-pyrrolidinyl-methyl)pyrrolidine **3b** or pyrrolidine **3c** with aldehyde **2** generates imine cation[8] **8**, an excellent electrophile that undergoes Mannich type reactions with the in situ generated push–pull dienamine **7** or dienolate **12** of Hagemann's ester **1a** to generate the Mannich products **9** and **13**, respectively. Retro-Mannich or a base induced elimination reaction of amines **10** and **14** under basic conditions would furnish *E*/*Z* mixtures of enone **4**. Iso-aromatization of the Claisen–Schmidt product **4** would then give phenol **5**. The formation of imine ion **8** and product **4** via Mannich and retro-Mannich reactions is consistent with our hypothesis that aldol products do not form in these reactions and formation of the highly reactive push–pull dienamine **7** was established in an NMR experiment as shown in Scheme 3. We favour mechanism 1 based on NMR studies.



Scheme 2. Proposed reaction mechanisms.

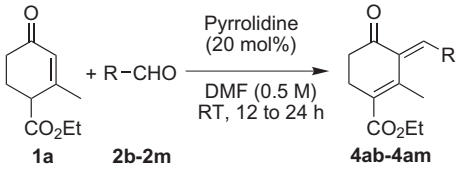


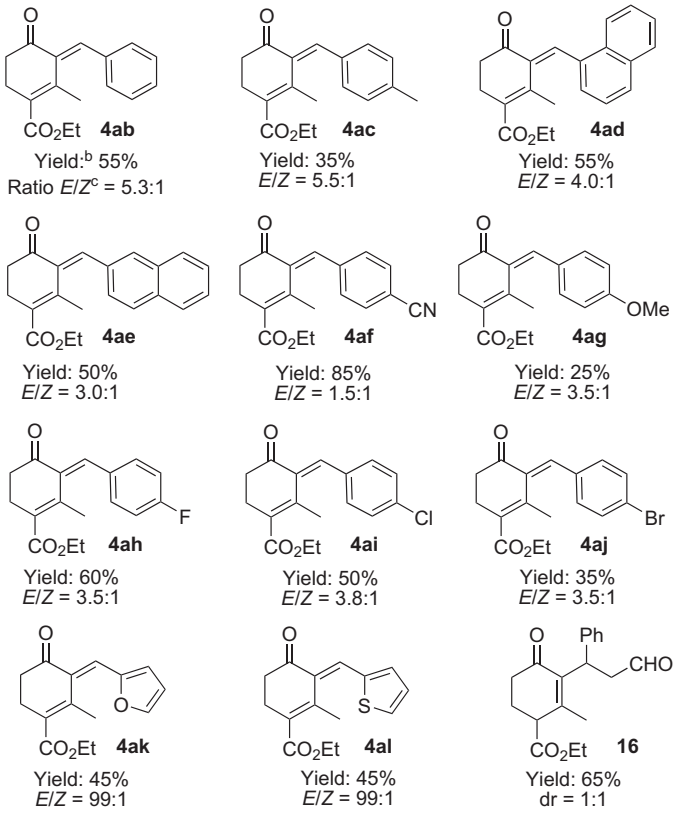
Scheme 3. NMR experiment for the in situ generation of push–pull dienamine **7**.

We explored further the scope of pyrrolidine **3c** catalyzed tandem Claisen–Schmidt/iso-aromatization reaction of Hagemann's ester **1a** with various aldehydes **2a**–**m** as shown in Table 2. Interestingly, in these reactions iso-aromatization did not take place and only the Claisen–Schmidt products, the 3-arylidene Hagemann's esters **4ab**–**al** were isolated in moderate to good yields and with stereoselectivities favouring the *E*-isomers. Reaction of **1a** with *trans*-cinnamaldehyde **2m** under pyrrolidine **3c** catalysis furnished the Michael product **16** in 65% yield in a 1:1 diastereomeric ratio, which is different from the other results may be due to the nature of **2m** as Michael acceptor.

The regioselective tandem Claisen–Schmidt/iso-aromatization reaction of Hagemann's esters **1a**–**b** with aldehydes **2a**–**o** in DMF at room temperature under diamine **3b** catalysis only furnished the expected tandem products in good yields when the aldehydes possessed electron withdrawing groups at the *para*-position (Table 3). The in situ generated push–pull dienamine of **1a** and **3b** reacted with 4-dimethylaminobenzaldehyde **2n** to

Table 2. Chemically diverse libraries of 3-arylidene-Hagemann's esters **4**[a]





[a] All reactions were carried out in DMF (0.5 M) with the same proportions of Hagemann's ester **1a** and aldehyde **2** in the presence of 20 mol % pyrrolidine.
[b] Yield refers to the column-purified product.
[c] *E*/*Z* ratio determined by NMR analysis.

furnish the push–pull enone **4an** in good yield. The highly conjugated enone **4ao** was produced in 75% yield with a 99:1 *E*/*Z* ratio (Table 3). Interestingly, reaction of **1a** with *trans*-cinnamaldehyde **2m** under diamine **3b** catalysis furnished the Claisen–Schmidt product **4am** in 75% yield with a 1:6 *E*/*Z* ratio. The regiochemistry was established based on a deuterium labelling experiment, NOE experiments and MMX calculations (see Supporting information). 2-Arylidenecyclohexanones, 2,6-bis(arylidene)-cyclohexanones and related compounds were evaluated for antitumour, anti-inflammatory, antineoplastic, cytotoxic activity and inhibition of mitochondrial function in yeast.[4] In addition, generation of molecular diversity about the 2-arylidenecyclohexanone scaffolds may allow for the identification of more potent species.

In summary, we have developed the first examples of amine-catalyzed direct tandem Claisen–Schmidt/iso-aromatization and Claisen–Schmidt reactions. This experimentally simple and environmentally friendly approach can be used to construct highly substituted enones and phenols in a regiospecific fashion. For the first time in organocatalysis, push–pull dienamines were generated in situ and applied in tandem reactions. Further work is in progress to utilize an asymmetric version of this process.

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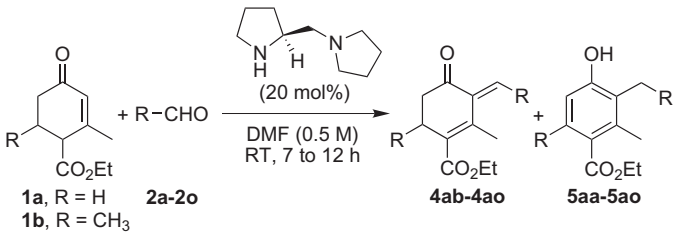
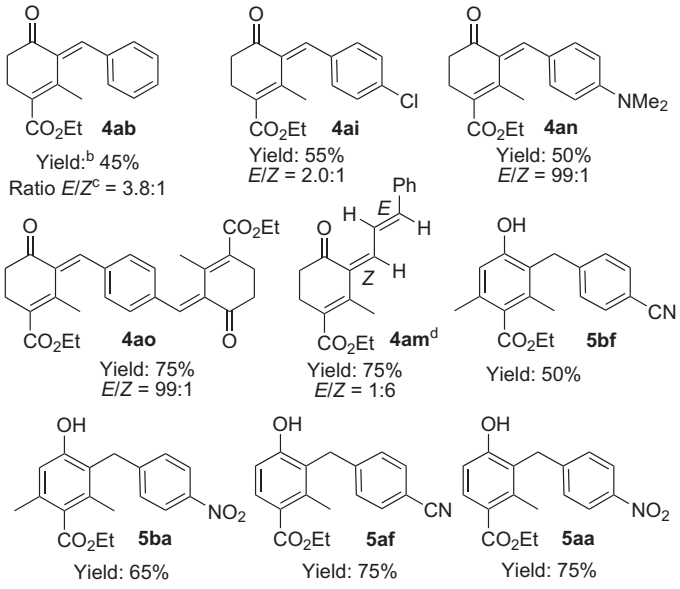
Table 3. Chemically diverse libraries of 3-arylidene-Hagemann's esters **4** and highly substituted phenols **5**[a]





[a] All reactions were carried out in DMF (0.5 M) with the same proportions of Hagemann's ester **1a** and aldehyde **2** in the presence of 20 mol % diamine **3b**.
[b] Yield refers to the column-purified product.
[c] *E*/*Z* ratio determined by NMR analysis.
[d] Reaction time was 1 h.

Supplementary data

Experimental procedures and analytical data for all new compounds. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.08.051.

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