Primary 1,2-diamine catalysis III: an unexpected domino reaction for the synthesis of multisubstituted cyclohexa-1,3-dienamines†

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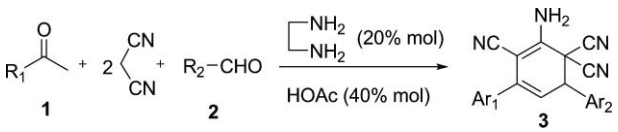
The first organocatalyzed multicomponent domino reactions of aryl ketones, aldehydes and malononitrile were carried out successfully to afford multisubstituted cyclohexa-1,3-dienamines in satisfactory yields.

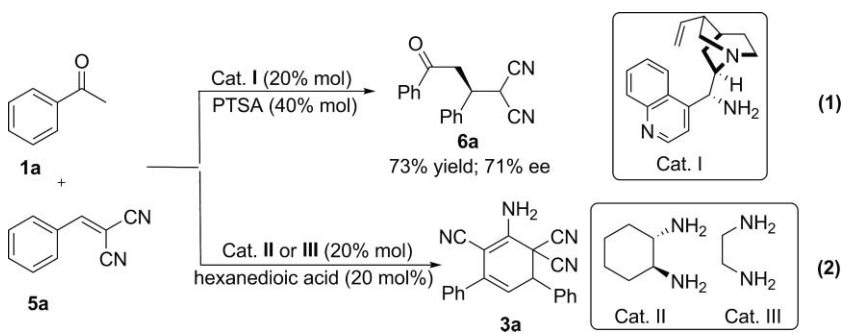
Creation of highly functionalized and diversified molecules[1] from simple starting materials while combining economic[2] and environmental aspects[3] is highly desirable in modern organic chemistry and still remains a great challenge.[4] From this perspective, organocatalyzed multicomponent reactions (MCRs) involving domino processes must be competent to come close to reaching this ideal goal. MCRs[5] meet the economic desires, for they can avoid time-consuming and costly processes for purification of various precursors and tedious steps of protection and deprotection of functional groups.[6] And organocatalyzed reactions are always environmentally friendly processes with the benefits of easy operation, ready availability, and low toxicity of catalysts.[7] Hence, domino reactions catalyzed by organocatalysts have emerged as a powerful tool in organic synthesis during the past few years.[8] Herein, we wish to report the first primary 1,2-diamine catalyzed three component domino reactions of aryl ketones, aldehydes and malononitrile for the construction of multifunctional useful molecules cyclohexa-1,3-dienamines **3** (Scheme 1).

Our original aim was to explore whether the chiral 1,2-diaminocyclohexane-hexanedioic acid system could catalyze the asymmetric Michael addition reactions of aryl ketones with alkylidenemalonitrile **5**, which has been reported by Chen's group using a chiral primary amine 9-amino-9-deoxyepicinchonine as catalyst in middle yields (48–85%) and enantioselectivities (71–81%) (Scheme 2, 1),[9] because we have used this catalytic system successfully in the asymmetric Michael addition reactions of chalcones with cyclopentanone[10a] and 2(5*H*)-furanones,[10b] respectively. However, it was surprising to find that under the chiral 1,2-diaminocyclohexane-hexanedioic acid catalyst, the reaction of acetophenone **1a** with alkylidenemalonitrile **5a** did not produce the expected asymmetric Michael addition product **6a**. On the contrary, a racemic cyclohexa-1,3-dienamine **3a** was obtained as the main product. Meanwhile, using ethanediamin-acetic acid as the catalyst also led to the same result (see ESI†).



Scheme 1 Multicomponent reactions of aryl ketones.

Compounds **3** belong to typical acceptor–donor–accept systems, which are the basis for artificial photosynthetic systems, materials presenting semiconducting or nonlinear optical properties and molecular electronic devices.[11] Both **3** and their aromatization products **4** are useful intermediates for building blocks for cyclophanes to create a large molecular cavity and host–guest complex.[12] In addition, their biaryl unit is represented in several types of compounds of current interest including natural products, polymers, advanced materials, liquid crystals, ligands and molecules of medicinal interest.[12,13] Therefore, numerous reports have described their synthesis.[11–14] However, most methods involved cumbersome procedures, costly reagents and low yields,[12] such as preformation of the precursors arylidenemalonoditriles **5** is always necessary. The reaction between malononitrile and α,β-unsaturated ketones could also gave compounds **4**, however the yields were very poor.[12,14c,15] Furthermore, compounds **3** are prone to aromatization by the elimination of hydrogen cyanide affording compounds **4**. In some instances the driving force of aromatization is so enhanced that the intermediate diaryl cyclohexadiene derivatives **3** cannot be isolated and the reaction affords only



Scheme 2 Reactions of acetophenone **1a** with alkylidenemalonitrile **5a**.

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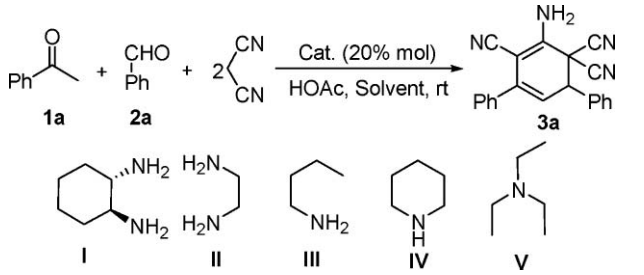
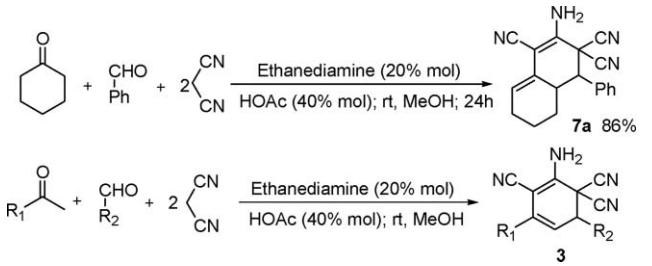
Table 1 Catalyst and solvent screening for the domino reactions



Entry	Cat.	Solvent	Time/h	**3a** Yield (%)[d]
1	—[a]	MeOH	72	trace
2[b]	II	MeOH	15	90
3[c]	III	MeOH	15	complex
4[c]	IV	MeOH	15	complex
5[c]	V	MeOH	15	complex
6[b]	II	$CHCl_3$	36	trace
7[b]	II	THF	36	complex
8[b]	II	DMSO	36	trace
9[b]	II	H_2O	36	—[e]

[a] No catalyst used; [b] The loading of HOAc is 40 mol%; [c] The loading of HOAc is 20 mol%; [d] Isolated yields of the corresponding product; [e] No product **3a** observed.

Table 2 Three component domino reactions of aryl ketones, aldehydes and malononitrile



Entry[a]	R_1	R_2	Time/h	Yield (%)[b]
1	Ph	Ph	15	**3a**, 90
2	Ph	2-ClPh	12	**3b**, 92
3	Ph	3-ClPh	12	**3c**, 95
4	Ph	4-MePh	10	**3d**, 89
5	Ph	$Me(CH_2)_9$	10	**3e**, 91
6	4-MePh	Ph	15	**3f**, 88
7	4-MePh	2-ClPh	18	**3g**, 86
8	4-MePh	3-ClPh	18	**3h**, 90
9	4-MePh	3-BrPh	14	**3i**, 96
10	3-ClPh	4-ClPh	13	**3j**, 93
11	3-ClPh	4-MePh	12	**3k**, 93
12	4-FPh	Ph	18	**3l**, 91
13	4-FPh	3-FPh	12	**3m**, 89
14	3,4-diClPh	Ph	12	**3n**, 95
15	3,4-diClPh	3-ClPh	12	**3o**, 95
16	3,4-diMeOPh	Ph	32	**3p**, 86

[a] All the reactions were conducted at room temperature; [b] Isolated yields of the corresponding products.

4.[14e] Just recently, Yan *et al.* reported a multicomponent domino reaction of malononitrile, benzaldehyde and ethyl α-bromoacetate (or chloroacetonitrile) in refluxing acetonitrile, affording 2,6-dicyanoanilines **4** in 31–53% yields.[16] However, only very few domino reactions are known for the synthesis of compounds **3** from alkyl ketones with moderate yields,[17] and unfortunately, aryl ketones employed in these one-pot multicomponent reactions are unprecedented.

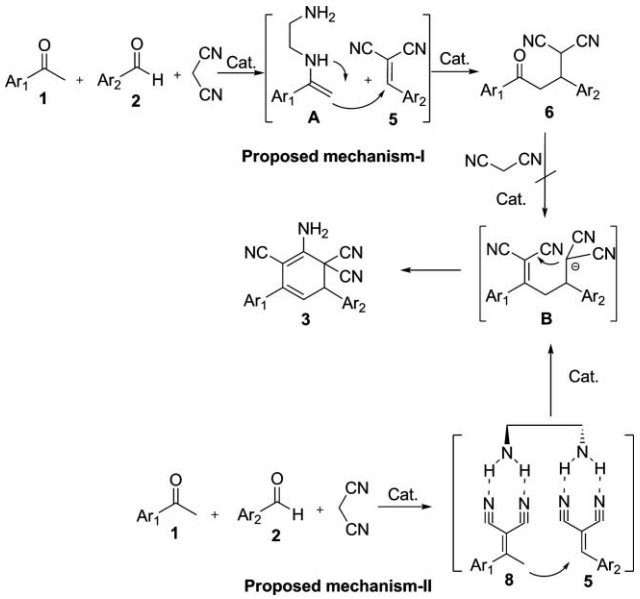
Inspired by the unexpected formation of **3a** and Yan's multicomponent domino reaction,[16] we reasoned that the synthesis of multisubstituted cyclohexa-1,3-dienamines **3** would be achieved through organocatalyzed multicomponent reactions of aryl ketones, aldehydes and malononitrile.

Therefore, the reaction of acetophenone **1a** with benzaldehyde **2a** and malononitrile was selected as the model reaction to examine various amine-acid catalysts and solvents. As listed in Table 1, except ethanediamine, all the other simple primary amine, secondary amine and tertiary amine catalysts gave unsatisfactory results, affording a complex mixture of at least four products (Table 1, entries 2–4). The screening of different solvents was also carried out using 20 mol% of ethanediamine and 40 mol% of acetic acid as catalyst at room temperature (Table 1, entries 1 and 5–8). Among the screened solvents, only the protic polar solvent MeOH gave the valuable result (Table 1, entry 1).

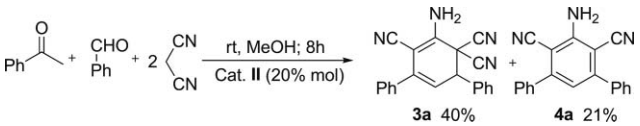
Subsequently, the substrate scope of aryl ketones and aldehydes was studied under the optimized reaction conditions (20 mol% of ethanediamine and 40 mol% of HOAc as the catalyst, methanol as solvent and the reactions were carried out at room temperature). Much to our delight, all the reactions were carried out smoothly in excellent yields (Table 2). The properties and position of the substituents on the aromatic ring for aryl ketones and aromatic aldehydes do not have obvious influence on the reaction rate and yields (Table 2, entries 2–4, 6–16). Meanwhile, alkyl aldehyde was also investigated giving the corresponding cyclohexa-1,3-dienamine derivatives in satisfactory yield (Table 2, entry 5). What is more exciting is that the pure products could be obtained by simple filtration and/or recrystallization after reaction (except **3e**, which is obtained as a colorless oil).

Two possible pathways (**I** and **II**) based on enamine and hydrogen bonding activation of substrates were proposed for the formation of compounds **3** as shown in Scheme 3. Inspired by Chen's work,[9] aryl ketone donors were proposed to be activated through enamine intermediate **A**, which then reacted with alkylidenemalonitrile **5** to form product **6**. Then under the catalytic system, **6** reacted with malononitrile to form the key intermediate **B**, which then transformed easily to **3** (mechanism-**I**). However, the proposed mechanism-**I** did not seem to make sense, for compound **6a** was not observed in this process monitored by TLC and the reaction of **6a** and malononitrile could not be facilitated under the catalytic system (Scheme 3). Excluding the enamine activation of substrates, the hydrogen bonding between primary amine[18] and cyano group might be a reasonable explanation (mechanism-**II**). For only the primary diamine catalyst could catalyze the reaction effectively, therefore, we proposed that both substrates **5** and **8** were linked together through hydrogen binding by the 1,2-diamine catalyst. Moreover, using the mechanism-**II**, we could also understand why the racemic product **3a** was obtained under the chiral 1,2-diaminocyclohexane-hexanedioic acid catalyst, because the long distance between the reacting centers and the chiral centers makes the steric effect unimportant.

In order to explore the action of acid additive, the domino reaction of **1a**, **2a** and malononitrile was carried out, using only 20 mol% ethanediamine as the catalyst (Scheme 4). Without



Scheme 3 Proposed mechanisms for the domino reaction.



Scheme 4 The domino reaction catalyzed only by ethanediamine.

acid additive, though the reaction still proceeded smoothly, the aromatization product **4a** appeared in 21% yield accompanied by an unidentified by-product after 8 h. Obviously, the acid additive HOAc in the reaction functioned to inhibit the elimination of HCN efficiently (the aromatization process).

In conclusion, primary 1,2-diamine was proven to be efficient in activating ketone substrates once more. The first organocatalyzed multicomponent domino reactions of aryl ketones, aldehydes and malononitrile were conducted to form multi-substituted cyclohexa-1,3-dienamines **3** in satisfactory results. The possible mechanisms were proposed.

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