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COMMUNICATION

Construction of highly functional α-amino nitriles *via* a novel multicomponent tandem organocatalytic reaction: a facile access to α-methylene γ-lactams†‡

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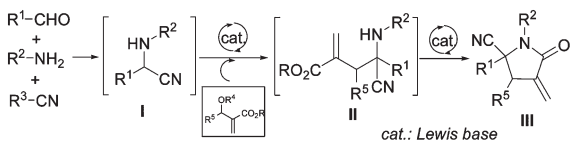
The first tertiary amine-catalyzed multicomponent tandem Strecker–allylic-alkylation (SAA) reaction has been developed, which provides a facile access to functionalized α-amino nitriles, which could be readily converted into α-methylene-γ-butyrolactams.

Compounds containing the α-methylene γ-lactam moiety, which are fairly common in nature,[1a] display a wide variety of biological activities[1] because they exhibit less cytotoxic activity than the corresponding α-alkylidene-γ-butyrolactones. In addition, a large variety of modulations by the nitrogen substitutions of α-methylene γ-lactam scaffolds may help to improve the pharmacological properties and decrease the toxicity, in contrast to their isosteric replacement α-methylene-γ-burtyrolactones for instance. Due to their excellent activities for potential drug candidates as well as their versatile synthetic potential, the construction of α-methylene γ-lactam skeletons has received much attention over several decades.[2]

Although a number of methods have been developed which mainly relied on metal reagents,[2c–i] an efficient synthetic route based on metal-free catalysis to access α-methylene-γ-butyrolactams, which contain quaternary carbon centers, from readily available chemicals is still undeveloped. α-Amino nitriles are exceptionally versatile intermediates in synthetic chemistry and also proposed as being prebiotic precursors to porphyrins, corrins and nicotinic acids.[3] α-Amino nitriles bearing an α-hydrogen have been widely used in the generation of multiple polyfunctional structures.[4] Interestingly, to the best of our knowledge, the construction of α-amino nitriles including densely functional quaternary carbon centers *via* a multicomponent tandem reaction with a metal-free catalyst is still unexploited.[5]

Recently, a Lewis base assisted Brønsted base catalysis strategy was been applied for direct allylic substitutions of Morita–Baylis–Hillman (MBH) adducts, which provided a powerful tool for preparing multifunctional compounds.[6] We recently reported a novel tandem cyanation–allylic-alkylation (CAA) reaction which provided a facile access to densely functionalized products containing *O*-substituted quaternary centers using amine catalysts.[10] Based on this work, we envisaged that an attractive multicomponent tandem reaction promoted by organocatalyst could be established by utilizing three-component Strecker reaction and Lewis base catalyzed allylic substitution reaction, which may deliver highly functional α-methylene γ-lactam skeletons. In this protocol, the α-amino nitrile **I** bearing an α-hydrogen is generated from aldehyde, amine and cyanation reagent *in situ*. Subsequently, the deprotonation of the acidic CH group of the α-amino nitrile by the oxygen-based anion generated *in situ* would occur, and C-selective allylic alkylation would follow to deliver highly functionalized α-amino nitrile **II**, which could be readily converted into α-methylene-γ-butyrolactams **III** separately or in one pot fashion. In this manner, a great pool of valuable densely functionalized α-amino nitriles and α-methylene-γ-butyrolactams containing quaternary carbon centers could be easily accessed. Meanwhile, the readily manipulated α-amino nitrile moiety and other functional groups of **II** or **III** and the application of robust and well-tested methodologies for the elaboration of the core structure of **II** may eventually result in the discovery of new bioactive compounds. Herein, we report a novel tandem organocatalytic Strecker–allylic-alkylation reaction (SAA) and Strecker–allylic-alkylation–cyclization reaction (SAAC) for the construction of highly functionalized α-amino nitriles and α-methylene-γ-butyrolactams (Scheme 1).

Our initial investigation was examined with MBH carbonate **2a** and preformed α-amino nitrile **1a** which can be prepared readily from Strecker reaction (benzaldehyde, aniline and TMSCN) in the presence of 20% DABCO (1,4-diazabicyclo [2.2.2]octane) (Table 1).[5b] A wide range of solvents were



Scheme 1 Strategy of tandem Strecker–allylic-alkylation–cyclization reaction for α-methylene-γ-butyrolactams.

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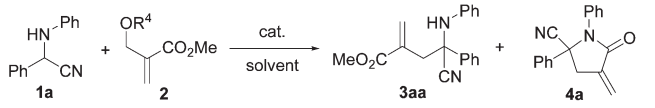
‡ Electronic supplementary information (ESI) available. See DOI: 10.1039/c2ob07112f

Table 1 Optimization of Lewis base catalyzed direct allylic alkylation of α-amino nitrile **1a** with MBH carbonate **2**[a]

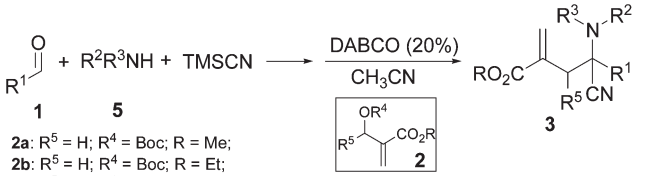


2a: R^4 = Boc; **2e**: R^4 = Ac;

Entry	Catalyst	Solvent	*t* (h)	Yield[b] (%)
1	DABCO	$PhCH_3$	4	52(**3aa**)
2	DABCO	DCM	9	50(**3aa**)
3	DABCO	THF	4	36(**3aa**)
4	DABCO	$CHCl_3$	20	40(**3aa**)
5	DABCO	1,4-Dioxane	15	62(**3aa**)
6	DABCO	*t*-BuOH	9	56(**3aa**)
7	DABCO	DMF	2	79(**3aa**); 5(**4a**)
8	DABCO	CH_3CN	3.5	32(**3aa**); 50(**4a**)
9[c]	DABCO	CH_3CN	14	93(**3aa**)
10[d]	DABCO	CH_3CN	22	35(**3aa**)
11	DMAP	CH_3CN	2.5	44(**3aa**); 50(**4a**)
12	Ph_3P	CH_3CN	2.5	50(**3aa**)

[a] Unless otherwise noted, reactions were performed with 0.3 mmol of **1a**, 0.45 mmol of **2a**, and 20 mol% of DABCO in 3.0 mL of solvent at 30 °C. [b] Isolated yield. [c] 4 Å molecular sieve was added and the reaction was performed at 0 °C. [d] MBH acetate **2e** (0.45 mmol) was employed.

Table 2 Synthesis of densely functionalized α-amino nitrile **1a** *via* multicomponent tandem reaction (SAA)[a]



2a: R^5 = H; R^4 = Boc; R = Me;
2b: R^5 = H; R^4 = Boc; R = Et;
2c: R^5 = H; R^4 = Boc; R = Bu^t;
2d: R^5 =Ph; R^4 = Boc; R = Me;

Entry	R^1	NR^2R^3(**5**)	**2**	**3**	*t* (h)	Yield[b] (%)
1	Ph	*N*HPh	**2a**	**3aa**	2.5	95
2	Ph	*N*H(C_6H_4Cl-*p*)	**2a**	**3ab**	2.5	85
3	Ph	*N*HBn	**2a**	**3ac**	4	77[c]
4	Ph	*N*HPMP	**2a**	**3ad**	2.5	96
5	Ph	*N*MeBn	**2b**	—	—	—[d]
6	Ph	*N*-Morpholinyl	**2a**	**3ae**	14	67
7	4-ClC_6H_4	*N*HPMP	**2a**	**3b**	1.5	70
8	4-MeC_6H_4	*N*HPMP	**2a**	**3c**	2	91
9	3-$MeOC_6H_4$	*N*HPMP	**2a**	**3d**	2	79
10	2-BrC_6H_4	*N*HPMP	**2a**	**3f**	3.5	78[c]
11	2-Naphyl	*N*HPMP	**2a**	**3g**	2	83
12	2-Furyl	*N*HPMP	**2a**	**3h**	2	76
13	Ph	*N*HPMP	**2b**	**3af**	2	95
14	Ph	*N*HPMP	**2c**	**3ag**	4	94
15	Ph	*N*HPh	**2d**	**3ah**	4	9

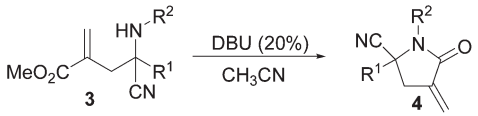
[a] Aldehydes (0.3 mmol), amine (1.05 equiv.) and TMSCN (1.1 equiv.) were stirred at 30 °C for 50 min. DABCO (20 mol%) and solvent were added. The mixture was stirred for the mentioned reaction times at 30 °C. [b] Isolated yield. [c] Based on ^{1}H NMR (see the ESI†). [d] No desired product was detected. PMP: *p*-methoxyphenyl.

screened. Although the substitution reactions took place in all screened solvents, the regioselectivity of this reaction showed strong solvent-dependence. Besides the desired product **3aa**, the *N*-alkylation and simultaneous *C*- and *N*-alkylation also were observed in less polar solvents.[7] The desired *C*-allylic alkylation proceeded well in polar solvents such as CH_3CN and DMF (Table 1, entries 7 and 8). While exploring the reaction conditions of this allylic alkylation reaction, α-methylene-γ-butyrolactam **4a** was isolated, which could be generated from desired product **3aa** in the presence of base (Table 1, entries 7, 8 and 11). Performing this reaction at 0 °C in the presence of molecule sieves can significantly increase the yield of **3aa** (Table 1, entry 9). MBH adduct **2e** can also react with **1a** to furnish **3aa**, albeit in low yield (Table 1, entry 10). Other Lewis bases such as DMAP and Ph_3P have also been tested. DMAP exhibited efficiency comparable with that of DABCO, while Ph_3P afforded allylic product in decreased yield (Table 1, entries 11 and 12).

With these preliminary results in hand, next we investigated the feasibility of the multicomponent tandem SAA reaction. Straightforwardly mixing benzaldehyde, aniline, TMSCN, DABCO (20%) and MBH adduct **2a** in one flask in CH_3CN resulted in the desired product **3aa** in low yield (44%) and side product formation. We hypothesized that the order of reagent mixing may be crucial in order to increase the production of **3**. Indeed, submitting benzaldehyde, aniline and TMSCN in one flask, and subsequently adding DABCO (20%), MBH adduct **2a** and the optimum solvent, readily furnished the desired product **3aa** in high yield with a trace amount of α-methylene-γ-butyrolactam **4a**. The scope and generality of this novel tandem SAA reaction was evaluated. Firstly, the reactions of different primary amines with benzaldehyde, TMSCN and MBH adduct **2a** were examined. Noteworthily, anilines with electron-withdrawing or -donating substituents at the *para*-position can be smoothly employed in SAA reaction to furnish **3** in good to high yield (Table 2, entries 1, 2 and 4). The electronic properties of the aromatic system of the amine component do not seem to influence the yield. *N*-Benzyl protected **3ac** also could be obtained in 77% yield when benzylamine was used (Table 2, entry 3). *N*-PMP and *N*-benzyl substitutions of **3** may provide a potential handle for further elaboration, due to their facile deprotection.[8] When a secondary amine such as *N*-methylbenzylamine was used, SAA reactions didn't provide desired product, while morpholine gave rise to **3ae** in moderate yield (Table 2, entry 6). A variety of aromatic and heteroaromatic aldehydes were evaluated next with *p*-anisidine as the amine component. Gratifyingly, the reactions took place efficiently in good to excellent yields for all studied aldehydes (Table 2, entries 7–12). An aromatic aldehyde with an *ortho*-substituent on the aryl group, which potentially causes steric hindrance effects, also gave good yield (Table 2, entry 10). When an aromatic aldehyde with an electron-withdrawing substituent was employed, a slight decrease in yield was observed (Table 2, entry 7). In addition, MBH adducts such as ethyl and *t*-butyl esters also were applied in the SAA reaction and both of them provided desired products **3** in high yield (Table 2, entries 13 and 14), while SAA reaction with MBH adduct **2d**, which may create adjacent quaternary and tertiary centers, gave desired product **3ah** in low yield (Table 2, entry 15).

We next focused our attention on the synthesis of highly functionalized α-methylene-γ-butyrolactams **4** based on SAA reaction. After several attempts at the cyclization of α-amino nitriles **3**, α-methylene-γ-butyrolactam **4a** could be readily synthesized from **3aa** in the presence of a catalytic amount of DBU (Table 3,

Table 3 Synthesis of densely functionalized α-methylene-γ-butyrolactams **4** from α-amino nitrile **3** catalyzed by Lewis base[a]

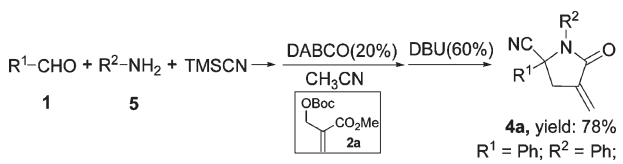


Entry	R^1	R^2	4	*t* (h)	Yield[b] (%)
1	Ph	Ph	**4a**	13	89
2	Ph	4-ClC_6H_4	**4b**	13	66
3	Ph	4-$MeOC_6H_4$	**4c**	18	92
4[c]	Ph	Bn	**4d**	56	52
5	4-ClC_6H_4	4-$MeOC_6H_4$	**4e**	13	82
6	4-MeC_6H_4	4-$MeOC_6H_4$	**4f**	18	81
7	3-$MeOC_6H_4$	4-$MeOC_6H_4$	**4g**	13	70
8	2-BrC_6H_4	4-$MeOC_6H_4$	**4h**	18	58
9	2-Naphthyl	4-$MeOC_6H_4$	**4i**	12	85
10	2-Furyl	4-$MeOC_6H_4$	**4j**	15	55

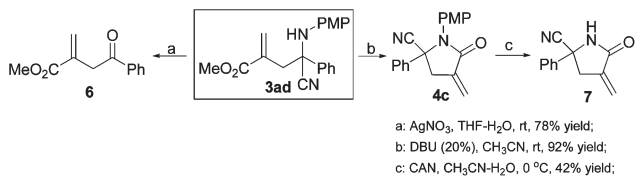
[a] Unless otherwise noted, reactions were performed with 0.2 mmol of **3** and 20 mol% of DBU in CH_3CN (2.0 mL) at 30 °C. [b] Isolated yield. [c] The reaction was performed with 0.2 mmol of **3** and 20 mol% of *p*-TsOH in toluene (2.0 mL) at 80 °C.

entry 1). It turned out that the electronic properties of the *N*-substituent of **3** seemed to influence the yield. When *N*-substitutions with neutral or electron-donating groups on **3** were employed, the cyclization reactions worked well and gave the products in high yields (Table 3, entries 1 and 3). Compound **3ab** with electron-withdrawing group afforded the product **4b** in moderate yield (Table 3, entry 2). The cyclization of *N*-benzyl substituted **3ac** gave a trace amount of **4d** in the presence of DBU (20%), while the treatment of **3ac** with *p*-TsOH (20%) in toluene at 80 °C furnished **4d** in 52% yield. A variety of above mentioned α-amino nitriles **3** can be employed for the cyclization successfully. Noteworthily, based on this, a novel multicomponent tandem SAAC reaction has also been developed. In this manner, α-methylene-γ-butyrolactam **4a** can be readily obtained from available aldehyde **1**, amine **5** and MBH adduct **2a** in a one-pot reaction (Scheme 2).[11]

Finally, the synthetic utilities of SAA products were illustrated. The treatment of **3ad** with a $AgNO_3$ in THF–H_2O solution afforded the β,γ-unsaturated ketone **6** in 78% yield



Scheme 2 Multicomponent tandem Strecker–allylic-alkylation–cyclization reaction (SAAC).



Scheme 3 Synthetic applications of the SAA substitution adduct.

(Scheme 3).[9] The deprotection of the *N*-PMP protecting group of α-methylene-γ-butyrolactam **4c** produced compound **7**, which may serve as an effective scaffold for a large variety of modulations by the *N*-substitution of α-methylene γ-lactams (Scheme 3).[8]

In conclusion, we have demonstrated an organocatalytic Strecker–allylic-alkylation reaction with aldehydes, amines and MBH adducts, which provided an efficient synthetic route for the preparation of densely functionalized α-amino nitriles bearing an *N*-substituted quaternary carbon center, which could be readily converted into α-methylene-γ-butyrolactams separately or in one-pot fashion. A number of aromatic aldehydes could be successfully applied to give multifunctional desired products. The potential synthetic applications of SAA products have also been displayed, which have potential utility in organic synthesis. Further studies on synthetic applications and asymmetric catalysis are ongoing in our laboratories and will be reported in due course.

Acknowledgements

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11 Under standard reaction conditions as mentioned in Table 1, direct allylic alkylation of α-amino nitrile **1a** with MBH carbonate **2a** provided **3aa** in 19% yield and **4a** in 55% yield in the presence of DBU (20%) after 3 hours. However, submitting benzaldehyde, aniline and TMSCN in one flask, subsequently adding DBU (20%), MBH adduct **2a** and CH_3CN (under standard reaction conditions as mentioned in Table 2), gave rise to α-methylene-γ-butyrolactam **4a** in 54% yield with small amount of unidentified substance after 25 hours.