RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2015, **5**, 26972

Received 21st January 2015
Accepted 6th March 2015

DOI: 10.1039/c5ra01254f

www.rsc.org/advances

Synthesis of functionalized γ-lactones *via* a three-component cascade reaction catalyzed by consecutive N-heterocyclic carbene systems†

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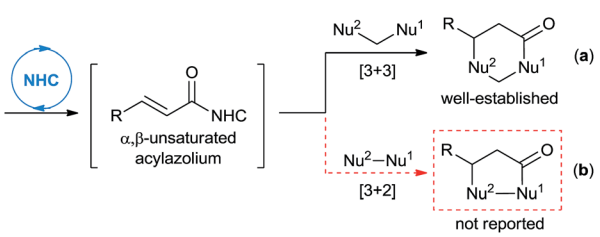
Two consecutive N-heterocyclic carbene (NHC) catalytic systems were combined in a one-pot cascade reaction for the assembly of aromatic aldehydes and 2-haloenals into a structurally complex γ-lactone backbone. To our knowledge, this is the first report of NHC-catalyzed [3 + 2] annulation of α,β-unsaturated acylazoliums with 1,2-bisnucleophiles.

N-Heterocyclic carbene (NHC) catalysis, an elegant organocatalytic method for forming new bonds, is used broadly in organic synthesis.[1] A number of NHC catalytic multicomponent cascade reactions have been developed, but most rely on a single catalyst, to perform continuous operations.[2]

Combining two catalytic bond-forming tactics into a single cascade reaction can offer unique synthetic opportunities, as it can allow unprecedented transformations that would be impossible in the presence of either catalyst on its own. NHC catalysis has been successfully integrated with transition metal catalysis,[3] Lewis acid catalysis[4] or aminocatalysis.[5] These combinations have opened up synthetic possibilities, but they are severely limited by self-quenching between NHCs and transition metals/Lewis acids and by mutual interference between NHCs and the acidic additive in aminocatalytic systems. Over the past decade, NHC-mediated HOMO/LUMO activation of carbonyl compounds at the ipso-, α-, β- or γ-position has become well established; these carbonyl compounds include aldehydes, ketones and esters, as well as their α,β unsaturated variants.[1] Despite these advances, few studies have explored the combination of two NHC-mediated activation modes in one multicomponent cascade reaction in a way that takes advantage of the inherent basicity and compatibility of both catalysts.

An efficient NHC-catalyzed activation mode that recently received immense attention is the generation of α,β-unsaturated acylazolium, which may be achieved from α,β-unsaturated acyl fluorides, enol esters, enals (under oxidative conditions), ynals, or 2-haloenals.[6–14] This reactive intermediate may serve as an analogue of 1,3-biselectrophiles and form the basis for novel domino reactions. In fact, the groups of Lupton,[6] Bode,[7] Studer,[8] Biju,[9] You,[10] Ye,[11] Yao,[12] Chi[13] and Xiao[14] have independently described NHC-catalyzed [3 + 3] annulation of α,β-unsaturated acylazoliums with 1,3-bisnucleophiles, leading to the formation of dihydropyranone or dihydropyridinone derivatives (Scheme 1, eqn (a)). To the best of our knowledge, the analogous [3 + 2] cycloaddition with 1,2-bisnucleophiles to synthesize five-membered heterocycles has not been reported (Scheme 1, eqn (b)).

As part of our ongoing investigations aimed at assembling multiple substrates into synthetically important cyclic molecules,[15] we envisaged a two-step organocatalytic relay cascade, beginning with NHC-catalyzed benzoin condensation,[16] as a way to synthesize functionalized γ-lactones (Scheme 2). Condensation of aldehyde **1** generates an α-hydroxyketone



Scheme 1 Annulation based on NHC-catalyzed generation of α,β-unsaturated acylazoliums.

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† Electronic supplementary information (ESI) available: Experimental procedures and characterization data for new compounds. CCDC 958885. For ESI and crystallographic data in CIF or other electronic formats see: DOI: 10.1039/c5ra01254f

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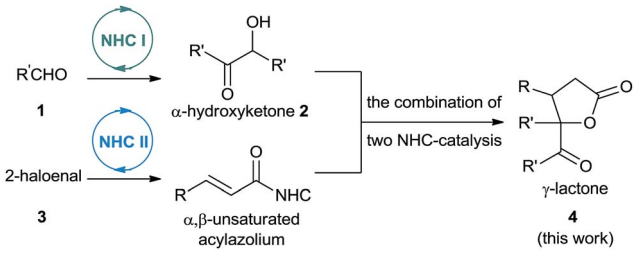
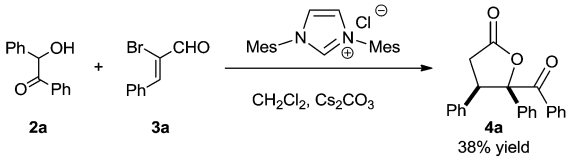


Scheme 2 Combination of two NHC catalytic cycles to construct γ-lactone bearing a quaternary carbon center.

intermediate **2**, which then serves as the 1,2-bisnucleophile in the second NHC catalytic cycle. Subsequent [3 + 2] cyclization between the NHC-generated α,β-unsaturated acylazolium with α-hydroxyketone affords the desired γ-lactone **4**. This approach, if successful, would provide an alternative method for preparing pharmacologically interesting γ-lactones or dihydrofuranones,[17] and it would broaden the applications of sequential dual catalysis.[18]

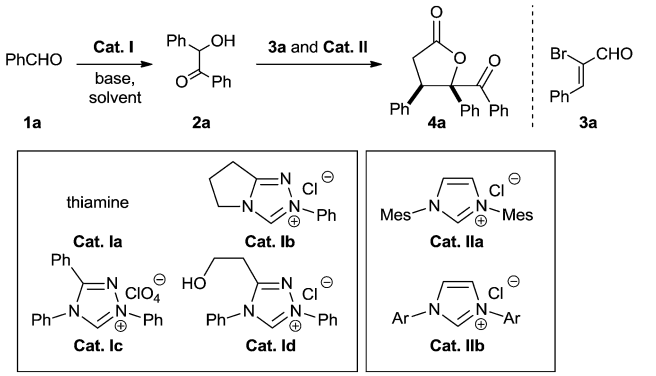
At the very first beginning, we wondered whether NHC-catalyzed [3 + 2] annulation of α,β-unsaturated acylazoliums with 1,2-bisnucleophiles could work. So we investigated the reaction of benzoin **2a** and α-bromo cinnamaldehyde **3a** in the presence of NHC precursor with cesium carbonate. Fortunately, we were able to isolate the desired **4a** product in moderate yield (Scheme 3). Since NHCs are known to catalyze benzoin condensation, we also wondered whether benzoin **2a** could be generated *in situ*. If successful, two sequential NHC catalytic systems could be combined.

To probe the feasibility of the proposed two-step cascade process, the preliminary experiment was carried out with precatalyst **Ia** and benzaldehyde **1a** to afford benzoin **2a** *in situ*, after which precatalyst **IIa** and α-bromocinnamic aldehyde **3a** were added in the reaction mixture. To our delight, by performing the reaction in dichloromethane with Cs_2CO_3, we were able to isolate the desired product with good diastereoselectivity, albeit in moderate yield (Table 1, entry 1). Screening various catalyst combinations (entries 1–5) showed **Id** and **IIa** to be the most promising catalyst pair for the reaction (entry 4). Different bases led to different yields, with DBU giving the best results (entries 6–10). Replacing dichloromethane with other solvents did not improve yield or diastereoselectivity (entries 10–13). We wondered whether one NHC catalyst could be used in both catalytic cycles. Performing the cascade reaction in the absence of precatalyst **Id** furnished only a trace amount of the desired product (entry 14), as did the reaction with only precatalyst **Id** (entry 15). At the same time, α-hydroxyketone **2a**



Scheme 3 NHC-catalyzed [3 + 2] annulation of benzoin and 2-bromoenal.

Table 1 Optimization of reaction conditions[a]



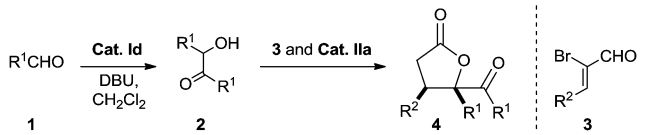
Entry	Cat. I	Cat. II	Base	Solvent	Yield[b] (%)	dr[c]
1	**Ia**	**IIa**	Cs_2CO_3	CH_2Cl_2	41	85 : 15
2	**Ib**	**IIa**	Cs_2CO_3	CH_2Cl_2	37	80 : 20
3	**Ic**	**IIa**	Cs_2CO_3	CH_2Cl_2	49	85 : 15
4	**Id**	**IIa**	Cs_2CO_3	CH_2Cl_2	59	88 : 12
5	**Id**	**IIb**	Cs_2CO_3	CH_2Cl_2	52	88 : 12
6	**Id**	**IIa**	K_2CO_3	CH_2Cl_2	59	86 : 14
7	**Id**	**IIa**	*t*BuOK	CH_2Cl_2	54	78 : 22
8	**Id**	**IIa**	TEA	CH_2Cl_2	39	85 : 15
9	**Id**	**IIa**	DABCO	CH_2Cl_2	46	82 : 18
10	**Id**	**IIa**	DBU	CH_2Cl_2	64	90 : 10
11	**Id**	**IIa**	DBU	Toluene	48	85 : 15
12	**Id**	**IIa**	DBU	MeCN	59	86 : 14
13	**Id**	**IIa**	DBU	THF	34	80 : 20
14	**IIa**	**IIa**	DBU	CH_2Cl_2	<10	n.d.
15	**Id**	**Id**	DBU	CH_2Cl_2	<10	n.d.

[a] Unless otherwise noted, reactions were performed with precatalyst **I** (0.1 mmol), base (0.3 mmol) and **1a** (1.6 mmol) in solvent (2 mL) at 50 °C for a specified reaction time until the sufficient benzoin **2a** was generated (monitored by TLC), after which precatalyst **II** (0.1 mmol) and **3a** (0.4 mmol) were added. [b] Isolated yield of pure diastereomer **4a**. [c] Based on ^{1}H NMR analysis of the crude reaction mixture. Mes = 2,4,6-$(CH_3)_3C_6H_2$; Ar = 2,6-$(CH_3CHCH_3)_2C_6H_3$.

was detected by ^{1}H NMR and HRMS of the crude reaction mixture (entry 15). These results suggest that different NHC catalysts are required in the two catalytic systems.

With the optimal reaction conditions in hand, we explored the substrate scope of the procedure (Table 2). Annulation of α-bromo cinnamaldehyde **3a** proceeded smoothly with a variety of aldehydes **1** to give moderate to high yield with good diastereoselectivity (entries 1–10). Most substituted aromatic aldehydes **1** bearing electron-withdrawing groups led to higher yield than those possessing electron-donating groups, and dr values for products varied in the trend *ortho* > *meta* and *para*. This implies that the substitution pattern on the phenyl rings affects the reaction to some extent. Heteroaryl aldehydes participated efficiently, giving even higher yields than aryl aldehydes but with slightly lower dr values (entries 9 and 10). We also evaluated the use of aliphatic aldehydes (such as octanal and 3-phenylpropanal) in the optimal reaction conditions, but no [3 + 2] annulation products were obtained.[19] To extend the scope of the reaction further, we explored other

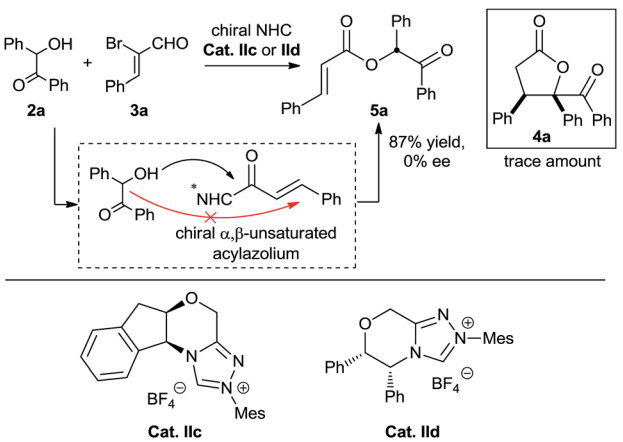
Table 2 Scope of the cascade reaction[a]



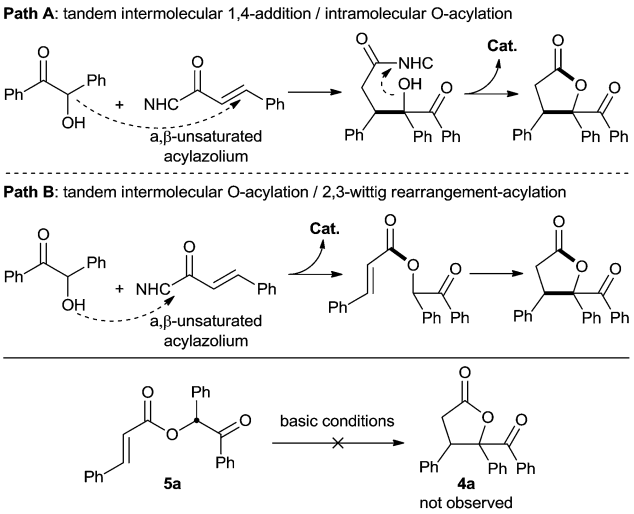
Entry	R^1	R^2	Product	Yield[b] (%)	dr[c]
1	Ph	Ph	**4a**	64	90 : 10
2	2-ClC_6H_4	Ph	**4b**	65	95 : 5
3	4-ClC_6H_4	Ph	**4c**	68	88 : 15
4	3-BrC_6H_4	Ph	**4d**	65	92 : 8
5	4-BrC_6H_4	Ph	**4e**	70	85 : 15
6	4-FC_6H_4	Ph	**4f**	65	87 : 13
7	2,4-$Cl_2C_6H_3$	Ph	**4g**	70	92 : 8
8	4-i-PrC_6H_4	Ph	**4h**	54	86 : 14
9	2-Furyl	Ph	**4i**	72	80 : 20
10	2-Thienyl	Ph	**4j**	71	75 : 25
11	Ph	2-ClC_6H_4	**4k**	60	92 : 8
12	Ph	4-ClC_6H_4	**4l**	61	86 : 14
13	Ph	4-BrC_6H_4	**4m**	66	85 : 15
14	Ph	2-FC_6H_4	**4n**	57	90 : 10
15	Ph	3-FC_6H_4	**4o**	61	85 : 15
16	Ph	4-FC_6H_4	**4p**	68	82 : 18
17	Ph	4-$NO_2C_6H_4$	**4q**	63	84 : 16
18	Ph	4-MeC_6H_4	**4r**	54	80 : 20
19	Ph	2-$OCH_3C_6H_4$	**4s**	50	87 : 13
20	Ph	2-Furyl	**4t**	35	80 : 20

[a] See entry 13 and footnote a in Table 1. [b] Isolated yield of pure diastereomer **4**. [c] Based on ^1H NMR analysis of the crude reaction mixture.

2-bromoenals **3**. The position and electronic properties of substituents on the aromatic ring of aryl-substituted 2-bromoenals did not significantly affect reaction efficiency (entries 11–19). The transformation was rather sluggish in the case of 2-bromo-3-furanylacrylaldehyde, and the corresponding γ-butyrolactone was afforded in only 35% yield after prolonged reaction time (entry 20). The relative configuration of **4a** was determined by X-ray crystallographic analysis.[20] Configurations



Scheme 4 Studies on the enantioselectivity of the annulation process.



Scheme 5 Two possible pathways for [3 + 2] annulation mediated by α,β-unsaturated acylazolium.

of the other dihydrofuranones were tentatively assigned by analogy.

We also performed experiments on the asymmetric version of this [3 + 2] annulation (Scheme 4). We envisioned that treatment of benzoin **2a** and 2-bromoenal **3a** in the presence of chiral triazolium salts **IIc** and **IId**, which has proven effective in many asymmetric [3 + 3] cycloadditions involving activation of α,β-unsaturated acylazolium, might furnish the desired chiral product. Unfortunately, numerous attempts were unsuccessful, with only the α,β-unsaturated ester product **5a** obtained in nearly quantitative yield. This linear product presumably formed *via* direct intermolecular O-acylation of the benzoin to the chiral α,β-unsaturated acylazolium intermediate (Scheme 4). Notably, the final product **5a** was a racemic mixture, suggesting no kinetic or dynamic kinetic resolution during the conversion.

Based on these results, we were puzzled by what the reaction mechanism might be. We reasoned that the γ-butyrolactone might form either by tandem 1,4-addition followed by intramolecular acylation (Scheme 5, path A) or by tandem intermolecular acylation followed by 2,3-wittig rearrangement-acylation (Scheme 4, path B). Importantly, the product **5a** (generated in Scheme 4) did not undergo cyclization under various alkaline conditions,[21] suggesting that pathway A is more reasonable to describe this α,β-unsaturated acylazolium-mediated [3 + 2] annulation.

Conclusions

In summary, we have developed a flexible and simple organocatalytic cascade reaction involving two sequential NHC catalytic cycles, and we have used it to assemble a functionalized γ-lactone (or dihydrofuranone) scaffold bearing a quaternary carbon center. Starting from aromatic aldehydes and 2-haloenals, we obtained the desired products in moderate to good yield with high diastereoselectivity. The present work is the first report of NHC-catalyzed [3 + 2] annulation of α,β-unsaturated

acylazoliums with 1,2-bisnucleophiles. Studies are under way in our laboratory to clarify the detailed reaction mechanism and explore whether this method can be applied to asymmetric domino reactions.

Acknowledgements

We are grateful for financial support from the National Natural Science Foundation of China (21302016 and 81303208), the Science & Technology Department of Sichuan Province (2014JQ0020) and the Foundation for the Author of National Excellent Doctoral Dissertation of PR China.

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19 The mixture of the aliphatic α-hydroxyketone and the aldol condensation product could be detected.

20 ESI.†

21 We screened Cs_2CO_3, K_2CO_3, *t*BuOK, TEA, DABCO and DBU.