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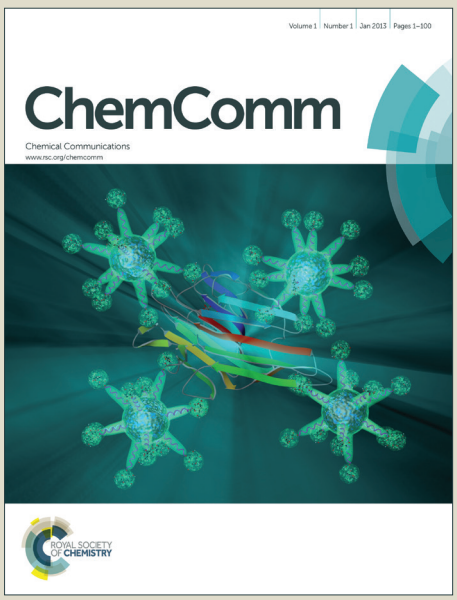

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N-Heterocyclic Carbene-Catalyzed [2 + 3] Cyclocondensation of α-Chloroaldehydes with Azomethine Imines

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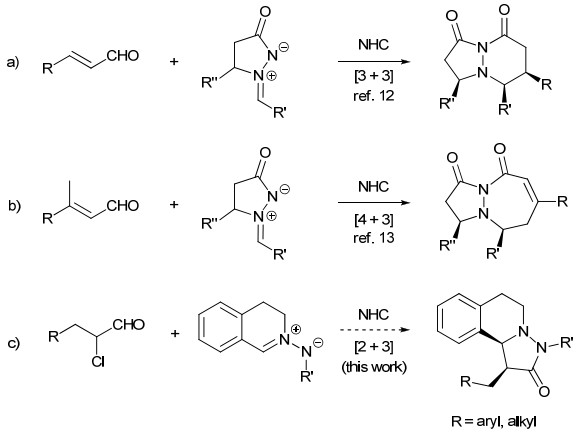
An N-heterocyclic carbene-catalyzed enantioselective [2 + 3] cyclocondensation of α-chloroaldehydes with azomethine imines was developed. The corresponding pyrazolidinones were obtained in good yields with moderate to good diastereoselectivities and excellent enantioselectivities.

Over the past decades, N-heterocyclic carbenes (NHCs) have been found to be efficient catalysts for a wide variety of reactions.[1] In addition to the classic NHC-catalyzed umpolung of aldehydes for the benzoin,[2] aza-benzoin[3] and Stetter reactions,[4] the NHC-catalyzed reactions were further applied to functionalized aldehydes,[5] ketenes,[6] carboxyl acid derivatives,[7] and others.[8]

1,3-Dipoles have been discovered and used as important reagents for more than 100 years.[9] The [2 + 3] cyclization of 1,3-dipoles and unsaturated bonds is a powerful approach to five-membered cyclic compounds.[10] Recently, the NHC-catalyzed cyclization reactions of 1,3-dipoles have been reported. Following the pioneering NHC-catalyzed cycloaddition of enals with carbonyl compounds,[11] Scheidt et al. reported the first NHC-catalyzed [3 + 3] cycloaddition of enals with azomethine imines (Scheme 1, reaction a).[12] Chi et al. reported the NHC catalyzed [4 + 3] cycloaddition of enals with azomethine imines (Scheme 1, reaction b).[13] Meanwhile, the NHC-catalyzed reactions of α-haloaldehydes have been explored by Rovis et al.,[5b] and well established by several other groups.[14] We envision that the in situ generated azolium enloate from α-chloroaldehydes may also react with 1,3-dipoles to give five-membered compounds. In this paper, we disclose the NHC catalyzed [2 + 3] cyclocondensation of α-chloroaldehydes with azomethine imines to give pyrazolidinones[15] (Scheme 1, reaction c). While our work was in progress, Studer et al. reported the chiral amines catalyzed cyclocondensation of mixed anhydrides from carboxylic acids with azomethine imines.[16] It should be noted that only β-aryl carboxylic acids were employed in Studer's work, while both β-aryl and β-alkyl α-chloroaldehydes worked well in our reaction.

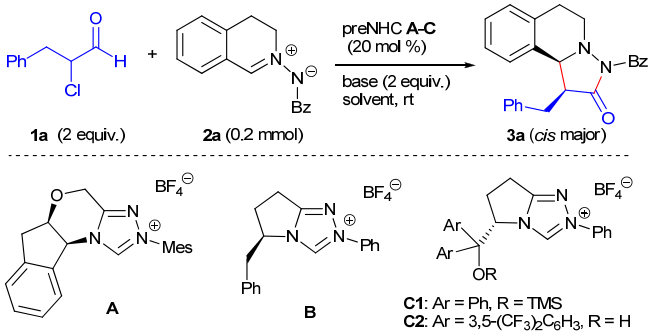
Initially, the reaction of α-chloroaldehyde **1a** and *N*-benzoyl azomethine imine **2a** was investigated under NHC catalysis (Table 1). We were encouraged to find that the reaction catalyzed by the modified Rovis' NHC **A'**,[17] generated in situ from the triazolium salt



Scheme 1 NHC-catalyzed [n + 3] (n = 2,3,4) cyclization reactions of functionalized aldehydes with azomethine imines

A in the presence of triethylamine as the base, afforded the desired [2 + 3] cycloadduct **3a** in 36% yield, with 2:1 dr and 95% ee (entry 1). The yield was improved to 55% with 6:1 dr and 98% ee when using diisopropylethylamine as the base (entry 2), while only trace of the cycloadduct was observed using Cs_2CO_3 as the base (entry 3). The reaction catalyzed by NHC **B'** derived from L-pyroglutamic acid gave the cycloadduct in 60% yield but with reversed diastereoselectivity (entry 4).[18] Unexpectedly, both NHC **C1'** with bulkyl trimethylsilyl[6a, 19] and bifunctional NHC **C2'** with a free hydroxyl group[6h, 19b, 20] did not work for the reaction (entries 5 and 6). Solvent screening revealed that the reaction went best in toluene than in acetonitrile and 1,4-dioxane (entries 7-9). Several additives such as Lewis acids[21] and molecular sieves[7a, 22] were also tested for the reaction, which benefited somewhat to the diastereoselectivities but resulted in slightly decreased yields (entries 10-12). Further attempt to improve the yield was made by alternation of the reaction temperature (entries 13-14). Although there is no significant change for the reaction with $Sc(OTf)_3$ as the additive at rt or 40 °C (entry 11 *vs* 13), the yield could be improved to 82% with good diastereo- and excellent enantioselectivity when the reaction was carried out using 4Å MS as the additive at 40 °C. (entry 7 *vs* 12 *vs* 14).

Table 1 Reaction optimization

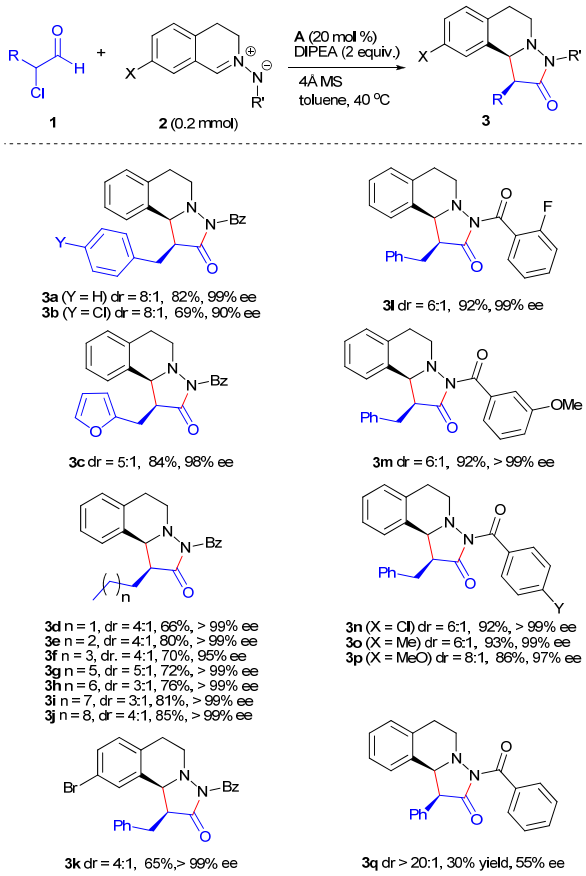


entry	cat.	base	solvent	yield[a] (%)	dr[b]	ee[c] (%)
1	**A**	Et_3N	THF	36	2:1	95
2	**A**	DIPEA	THF	55	6:1	98
3	**A**	Cs_2CO_3	THF	trace	/	/
4	**B**	DIPEA	THF	60	1:4	58[d]
5	**C1**	DIPEA	THF	trace	/	/
6	**C2**	DIPEA	THF	trace	/	/
7	**A**	DIPEA	toluene	61	4:1	99
8	**A**	DIPEA	CH_3CN	28	1:1	/
9	**A**	DIPEA	1,4-dioxane	trace	/	/
10[e]	**A**	DIPEA	THF	52	10:1	99
11[f]	**A**	DIPEA	THF	55	6:1	98
12[g]	**A**	DIPEA	THF	50	8:1	99
13[e,h]	**A**	DIPEA	THF	54	12:1	99
14[g,h]	**A**	DIPEA	toluene	82	8:1	99

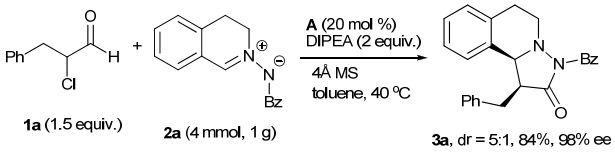
[a]Isolated yield. [b]Diastereomeric ratio of *cis*/*trans*, determined by ^{1}H NMR (400 MHz) of the unpurified reaction mixture. [c]The ee value of *cis*-isomer **3**, determined by HPLC using a chiral stationary phase. [d]The ee value of *trans*-isomer **3**. [e] 20 mol % of $Sc(OTf)_3$ was added. [f] 20 mol % of $Mg(OTf)_2$ was added. [g] 100 mg 4Å MS was added. [h] The reaction was conducted at 40 °C.

With the optimized reaction conditions in hand, the scope of the reaction was then briefly investigated (Scheme 2). It was found that both β-aryl and β-heteroaryl α-chloroaldehydes worked well for the reaction, giving the desired cycloadducts **3a-c** in good yields with good diastereo- and highly enantioselectivities. More importantly, various alkyl α-chloroaldehydes worked well for the reaction, affording the cycloadducts **3d-3j** in good to high yields with excellent enantioselectivities. The scope of azomethine imines was also examined. The reaction of the azomethine imine of 7-bromo-3,4-dihydroisoquinoline gave the cycloadduct **3k** in 65% yield with 4:1 dr and > 99% ee. The reaction of azomethine imines with various *N*-arylcarbonyl groups went smoothly to afford the cycloadduct **3l-3p** in high yields with excellent enantioselectivities. It should be noted that the reaction of α-chlorophenylacetaldehyde with azomethine imine also worked but gave the desired cycloadduct **3q** in decreased yield and enantioselectivity.

The reaction could be scaled up without apparent loss of yield and stereoselectivity. For example, the desired pyrazolidinone **3a** could be obtained in 84% yield with 5:1 dr and 98% ee when the reaction was scaled up with 1 gram of azomethine imine **2a** and 1.5 equiv. of α-chloroaldehyde **1a** using 10 mol % of triazolium **A** as the pre-catalyst (Scheme 3).



Scheme 2 Reaction scope



Scheme 3 Gram-scale reaction

The absolute configuration of cycloadduct **3k** was determined by the X-ray analysis of its single crystal (Figure 1).

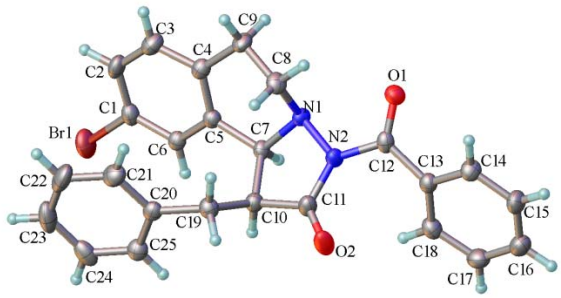
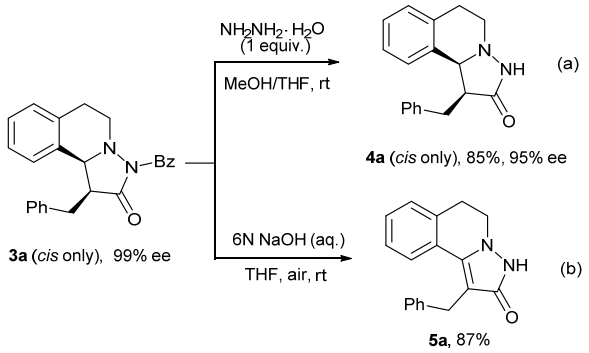


Figure 1 X-ray crystal structure of compound **3k**

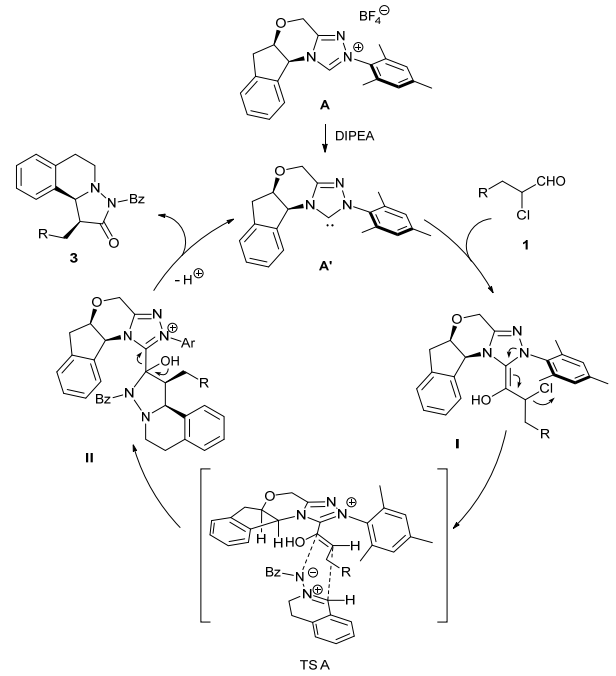
Removal of the benzoyl protective group of cycloadduct **3a** und hydrazine gave the pyrazolidinone **4a** in high yield with hig enantiopurity (Scheme 4, reaction a). Unexpectedly, th corresponding pyrazolone **5a** was obtained *via* dehydro-aromatization when the debenzoylation reaction was carried o

under atmosphere in the presence of sodium hydroxide as the base (Scheme 4, reaction b).



Scheme 4 Chemical transformations of pyrazolidinone

A plausible catalytic cycle for the NHC catalyzed [2 + 3] cyclocondensation of α-chloroaldehydes and azomethine imines is depicted in Scheme 5. The active catalyst, NHC **A'**, is generated from the triazolium in the presence of the base. The addition of NHC to the α-chloroaldehyde **1a** gives the corresponding Breslow intermediate **I**, which is decomposed to afford the azolium enol *via* removal of the leaving group in the presence of base. The [2 + 3] cycloaddition of enol and azomethine imine *via* the favored *endo*-transition state (TS A) gives the adduct **II** with *cis*-selectivity. The elimination of the NHC catalyst from adduct **II** affords the pyrazolidinone **3a** as the final product.



Scheme 5 Plausible catalytic cycle and stereochemical mode

Conclusions

In conclusion, we have developed an NHC catalyzed enantioselective [2 + 3] cyclocondensation of α-chloroaldehydes with azomethine imines. The desired pyrazolidinones were obtained in good to high yields, with moderate to good diastereoselectivities and excellent enantioselectivities. Other related NHC-catalyzed cycloaddition reactions with 1,3-dipoles are underway in our laboratory.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data, CCDC 1048523 for compound **3k** see DOI: 10.1039/c000000x/

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