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Article *in* Advanced Synthesis & Catalysis · April 2013

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Enantioselective N-Heterocyclic Carbene-Catalyzed Annulations of 2-Bromoenals with 1,3-Dicarbonyl Compounds and Enamines *via* Chiral α,β-Unsaturated Acylazoliums

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Received: March 14, 2013; Published online: ■■ ■■, 0000

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201300219.

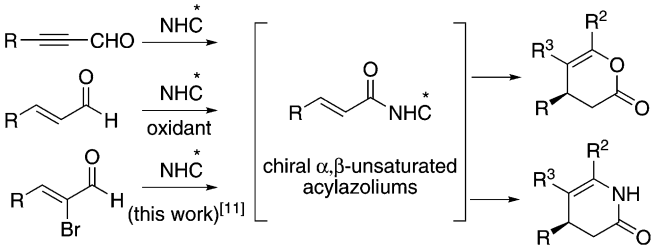
Abstract: The N-heterocyclic carbene (NHC)-catalyzed generation of chiral α,β-unsaturated acylazoliums from 2-bromoenals followed by their interception with 1,3-dicarbonyl compounds or enamines, the formal [3+3] annulation reaction, is reported. The reaction results in the enantioselective synthesis of synthetically and medicinally important dihydropyranones and dihydropyridinones, and tolerates a wide range of functional groups. It is noteworthy that the reaction takes place under mild reaction conditions utilizing relatively low catalyst loadings. In addition, based on DFT calculations, a mechanistic scenario involving the attack of the nucleophile from below the plane of the α,β-unsaturated acylazoliums, and the mode of enantioinduction is presented.

Keywords: acylazoliums; annulation reactions; asymmetric catalysis; N-heterocyclic carbenes; organocatalysis

Introduction

N-Heterocyclic carbenes (NHCs) have found widespread applications as versatile organocatalysts for a variety of carbon-carbon and carbon-heteroatom bond-forming reactions.[1] In this context, NHC-catalyzed reactions of enals with electrophiles *via* the generation of the homoenolate equivalents allow the facile preparation of diverse ranges of annulated products.[2] One of the important modes of action of NHCs is the generation of α,β-unsaturated acylazoliums, which has recently received great attention.[3] The four important methods for the generation of α,β-unsaturated acylazoliums include (i) the reaction of α,β-unsaturated enol esters or acyl fluorides with NHCs,[4] (ii) treatment of enals with NHCs followed by stoichiometric oxidation of the generated Breslow intermediate,[5] (iii) reaction of ynals with NHCs[6] and more recently (iv) the reaction of 2-bromoenals with NHCs.[7] Recently, Yao and co-workers developed the NHC-catalyzed reaction of 2-bromoenals with 1,3-dinucleophilic reagents leading to racemic dihydropyranone derivatives.[7a] Interestingly, however, the generation of chiral α,β-unsaturated acylazoliums from 2-bromoenals and their subsequent reactivity as a Michael acceptor in asymmetric catalysis is less explored.

Recently, Xiao and co-workers reported the chiral NHC-catalyzed annulation of α,β-unsaturated acylazoliums generated from ynals and enals with 1,3-dicarbonyl compounds leading to the formation of dihydropyranones (Scheme 1).[8] Independent investigations by You and co-workers demonstrated the Mi-



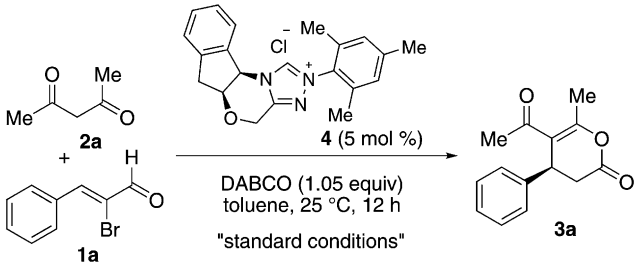
Scheme 1. NHC-catalyzed synthesis of dihydropyranones and dihydropyridinones *via* chiral α,β-unsaturated acylazoliums.

chael addition of 1,3-dicarbonyl compounds to α,β-unsaturated acylazoliums using a camphor-derived triazolium pre-catalyst.[9] In addition, Bode and co-workers uncovered the enantioselective synthesis of dihydropyridinones utilizing the NHC-catalyzed aza-Claisen reaction.[10] Moreover, NHC-catalyzed enantioselective synthesis of dihydropyranones was recently demonstrated by Ye and co-workers.[11] However, a general method for the synthesis of both dihydropyranones and dihydropyridinones from a common precursor is highly desirable given the fact that these compounds are useful intermediates in organic synthesis and are medicinally important.[12] Herein, we report the enantioselective synthesis of dihydropyranones and unprotected dihydropyridinones by the reaction of 2-bromoenals with 1,3-dicarbonyl compounds or enamines. It is noteworthy that the reaction takes place without the aid of external oxidants under mild reaction conditions and relatively low catalyst loadings. Interestingly, 2-bromoenals are very stable to air compared to corresponding enals, which make their handling easy.[13]

Results and Discussion

The present study was initiated with the treatment of α-bromocinnamaldehyde (**1a**) and acetylacetone (**2a**) with the triazolium salt **4** originally developed by Bode et al.[14] and 1.05 equiv. of DABCO (1,4-diazabicyclo[2.2.2]octane) as the base. To our delight, a facile reaction occurred leading to the formation of dihydropyranone derivative **3a** in 62% yield (based on ^{1}H NMR spectroscopy) and 88% *ee*. (Table 1, entry 1). The optimization studies revealed that decreasing or increasing the reaction temperature was not beneficial (entries 2 and 3). Among the various solvents screened, THF and 1,4-dioxane resulted in reduced selectivity (entries 4 and 5), whereas non-polar solvents including xylene and mesitylene furnished comparable results (entries 6 and 7). An exten-

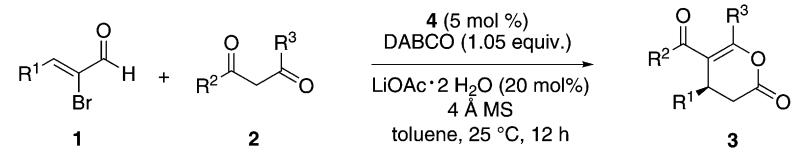
Table 1. Optimization of the reaction conditions.



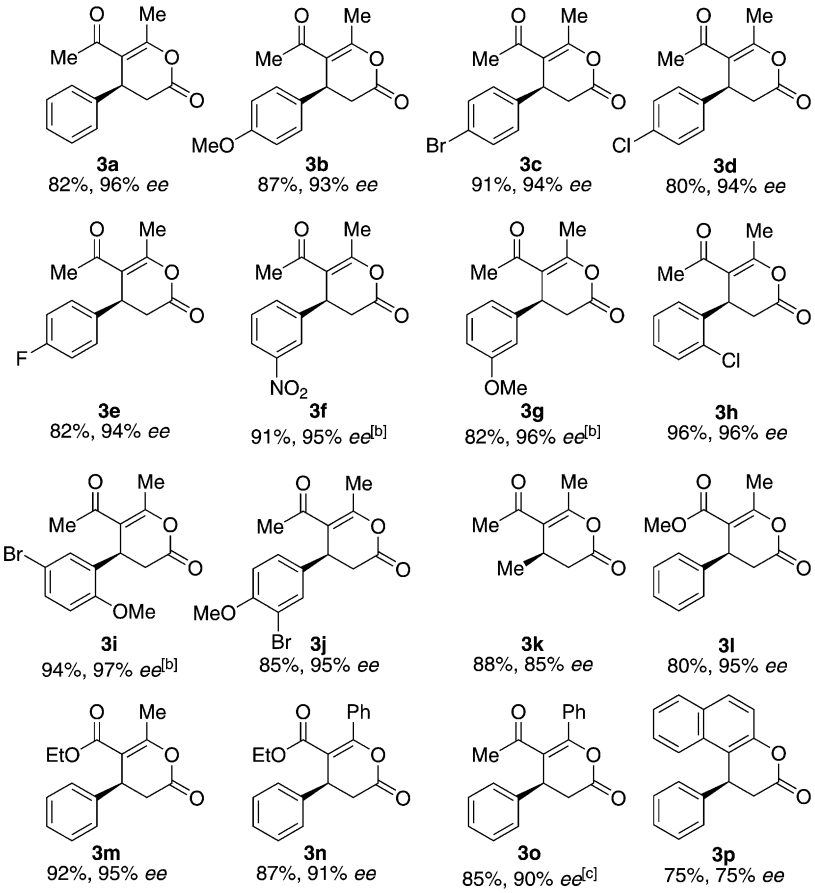
Entry	Variation of the standard conditions[a]	Yield of **3a** [%][b]	*ee* of **3a** [%][c]
1	none	62	88
2	reaction run at 0 °C	51	86
3	reaction run at 40 °C	58	85
4	THF instead of toluene	70	60
5	1,4-dioxane instead of toluene	50	80
6	xylene instead of toluene	61	87
7	mesitylene instead of toluene	61	88
8	DMAP instead of DABCO	80	82
9	Et_3N instead of DABCO	66	63
10[d]	DBU instead of DABCO	54	10
11[d]	KO-*t*-Bu instead of DABCO	35	37
12	Na_2CO_3 instead of DABCO	40	82
13	LiOAc·2 H_2O instead of DABCO	25	90
14	**20 mol % LiOAc·2 H_2O, 4 Å MS**	**85 (82)**	**96**
15	20 mol% Li_2CO_3 and 4 Å MS	59	80
16	20 mol% LiBr and 4 Å MS	40	80
17	20 mol% NaOAc and 4 Å MS	79	79
18	20 mol% AcOH and 4 Å MS	53	86

[a] *Standard conditions:* **1a** (0.25 mmol), **2a** (0.25 mmol), **4** (5 mol%), DABCO (1.05 equiv.), toluene (1.0 mL), 25 °C and 12 h.
[b] The yields were determined by ^{1}H NMR analysis of crude products using CH_2Br_2 as the internal standard. Isolated yield in parentheses.
[c] Determined by HPLC analysis on a chiral column.
[d] Reaction carried out using 10 mol% of **4** and 1.10 equiv. of DABCO.

Table 2. Substrate scope for the enantioselective synthesis of dihydropyranones.[a]



1 2 3



[a] *General reaction conditions:* **1** (0.50 mmol), **2** (0.50 mmol), **4** (5.0 mol%), DABCO (1.05 equiv.) $LiOAc{\cdot}2H_2O$ (20 mol%), and 4 Å MS (100 mg) in toluene (2.0 mL) at 25 °C for 12 h.

[b] Reaction run on 0.25-mmol scale.

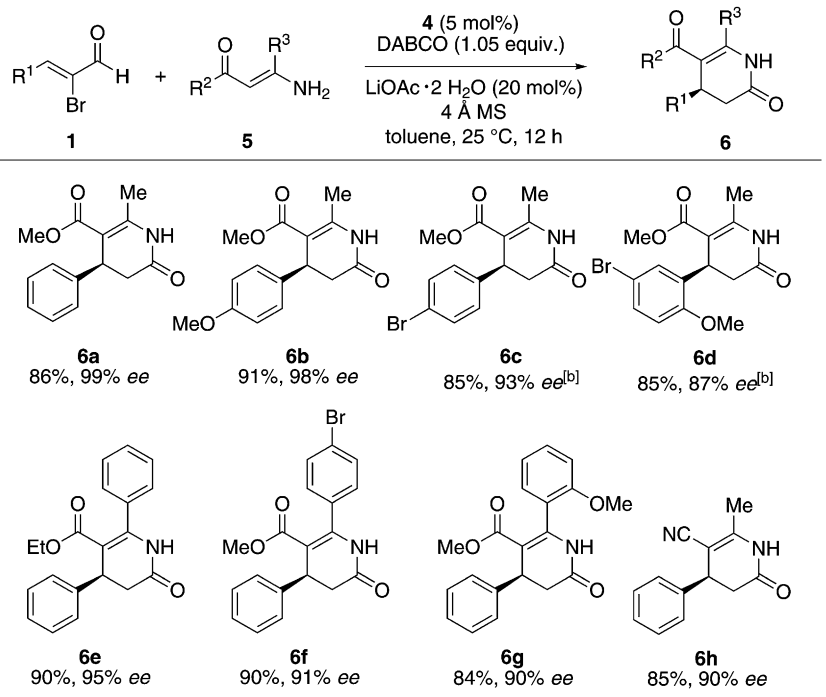
[c] < 5% of the other regioisomer was also formed.

sive base screening revealed that DMAP returned comparable results (entry 8), but other bases such as Et_3N, DBU, KO-*t*-Bu, and Na_2CO_3 afforded reduced reactivity and selectivity (entries 9–12). Interestingly, when the reaction was carried out using $LiOAc{\cdot}2H_2O$ as the base, the selectivity was improved to 90%, but the yield of the product was substantially reduced to 25% yield (entry 13). At this stage, we thought of using a combination of two bases. Delightfully, the reaction carried out using a combination of 1.05 equiv. DABCO and 20 mol% $LiOAc{\cdot}2H_2O$, the desired product was formed in 82% isolated yield and 96% *ee* (entry 14).[15]

Thus, the combination of two bases was essential for better reactivity and selectivity. To shed light on the role of lithium source, the reaction was carried out using other lithium sources such as Li_2CO_3 and LiBr as additives, but these reactions returned inferior results (entries 15 and 16). Additionally, the reactions carried out using NaOAc and AcOH as additives were also not promising (entries 17 and 18). These experiments rule out the possibility of any Lewis acid activation by the lithium source as well as any counterion effect induced by the acetate anions.[16] Furthermore, lowering the amount of catalyst below 5 mol% resulted in reduced yield of the product (not shown).

With these optimized reaction conditions in hand, we then examined the substrate scope of this annulation reaction (Table 2). First, we evaluated various 2-bromoenals. The unsubstituted parent system worked

Table 3. Substrate scope for the enantioselective synthesis of dihydropyridinones.[a]

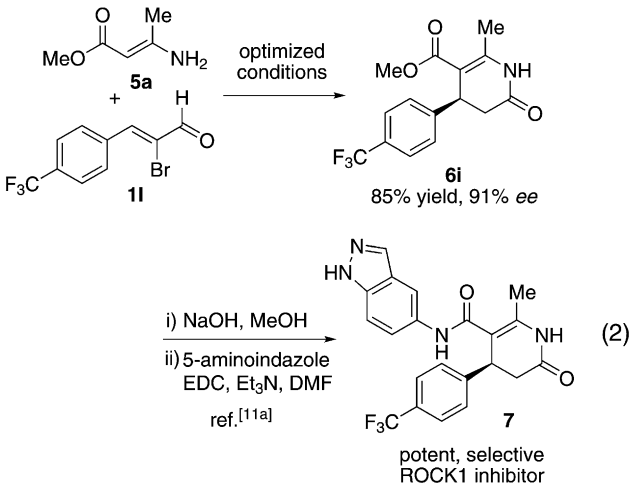


[a] *General reaction conditions:* **1** (0.50 mmol), **2** (0.50 mmol), **4** (5.0 mol%), DABCO (1.05 equiv.) LiOAc·2 H_2O (20 mol%), and 4 Å MS (100 mg) in toluene (2.0 mL) at 25 °C for 12 h.

[b] Reaction run on 0.25-mmol scale.

well, and electron-donating and electron-withdrawing groups at the 4-position of the aromatic ring were well tolerated, leading to dihydropyranones in good yields and with excellent *ee* values over 90% in all cases (**3a–3e**). Moreover, substitution at position 3 as well as position 2 of the benzene ring of **1** as well as disubstitution resulted in the smooth conversion to the product (**3f–3j**) in good yield and high enantioselectivity. Interestingly, halides such as bromide in position 4 or 3 (**3c**, **3i**, **3j**) or chloride in position 4 or 2 (**3d**, **3h**) were well tolerated, and the corresponding products could undergo further functionalization by traditional cross-coupling reactions for the construction of more complex molecules. Additionally, challenging aliphatic aldehydes such as (*Z*)-2-bromobut-2-enal also furnished good yield and moderate enantioselectivity of the desired products, further expanding the scope of this annulation reaction (**3k**). Furthermore, we evaluated the scope of the reaction with various 1,3-dicarbonyl compounds. The β-keto esters as well as unsymmetrical β-diketones underwent efficient annulation leading to the formation of the dihydropyranone derivatives in good yields and enantioselectivity (**3l–3o**). Interestingly, β-naphthol can also be used as a coupling partner affording chiral benzochromen-3-one **3p** in moderate yield and selectivity.[17] In all cases, the absolute configuration of the major enantiomer was assigned as *S* by comparison with optical rotations of compounds described previously.[8,9,12]

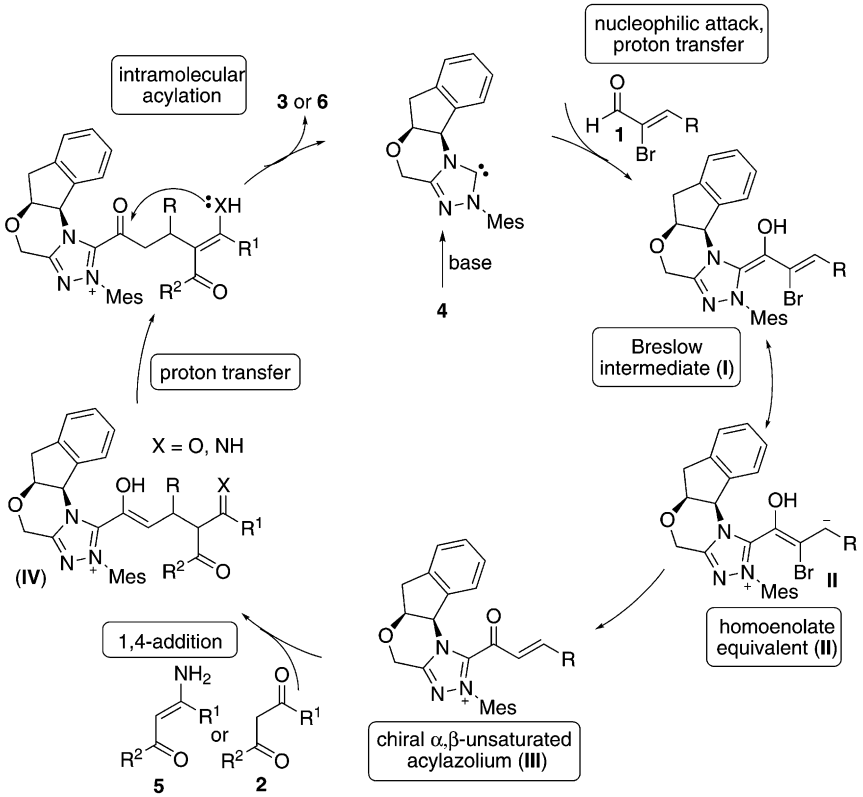
Inspired by these interesting results, we then focused our attention on another class of nucleophiles, the primary vinylogous amides with the objective to synthesize nitrogen heterocycles. Delightfully, treatment of 2-bromoenal **1a** with the enamine **5a** under the optimized reaction conditions afforded the dihydropyridinone derivative **6a** in 86% yield and 99% *ee* (Table 3). It is noteworthy that no nitrogen protecting group was employed for this annulation and the reaction delivered the medicinally and synthetically valuable dihydropyridinones. Intriguingly, the competing amide-bond formation was not observed under the optimized reaction conditions.[7b] Substitution at the benzene ring of 2-bromoenal **1** was well tolerated leading to the product formation in good yield and excellent *ee* values (**6b–6d**). In addition, a number of stable, unprotected and substituted enamines underwent smooth annulation reaction to afford the desired products (**6e–6g**). Moreover, the unprotected enamine containing a cyano group was well tolerated leading to the expected product **6h** in 84% yield and 90% *ee*.



To demonstrate the synthetic utility of our method and to show the versatility of dihydropyridinones **6**, following the optimized conditions, we have synthesized the trifluoromethyl-substituted dihydropyridinone **6i** starting from the 2-bromoenal **1l** and enamine **5a** in 85% yield and 91% *ee*. The product **6i** could be easily converted to the potent and selective ROCK1 inhibitor **7** in two steps [Eq. (1)].[12a]

The mechanistic rationale for this NHC-catalyzed annulation is shown in Scheme 2. The reaction is likely initiated by the 1,2-addition of the NHC generated from **4** to 2-bromoenal **1**,[18] followed by proton transfer to generate the nucleophilic Breslow intermediate **I**[19] and the homoenolate equivalent **II**. Rapid debromination of **II** generates the key α,β-unsaturated acylazolium intermediate **III**.[15,20] Nucleophilic addition of either **2** or **5** to the Michael acceptor **III** in a 1,4-fashion[21] delivers the enol intermediate **IV**, which undergoes proton transfer and intramolecular acylation to afford the final product.[22]

To shed light on the mechanism as well as the induction of enantioselectivity in the present reaction,[23] high level quantum chemical calculations have been done using density functional theory (DFT), employing the TZVP^2/PBE^3 approach with Turbomole 6.4.[15,24] The initial focus of the computational study was on the addition of the substrate **2a** to the chiral α,β-unsaturated acylazolium (**III**).[25] As shown in Figure 1, this can occur through two approaches: from above the plane containing the triazolium moiety (pathway a), and from below the plane (pathway b). The calculated energiess of the two complexes **IVa** and **IVb** thus formed indicate that pathway b is energetically preferred in comparison to pathway a, by 4.0 kcal mol^{-1}. This is due to the fact that nucleophilic attack from below the plane containing the triazolium moiety can lead to a favorable hydrogen bonding interaction between the enolic and carbonyl moieties,



Scheme 2. Proposed mechanism of the NHC-catalyzed annulation of 2-bromoenals.

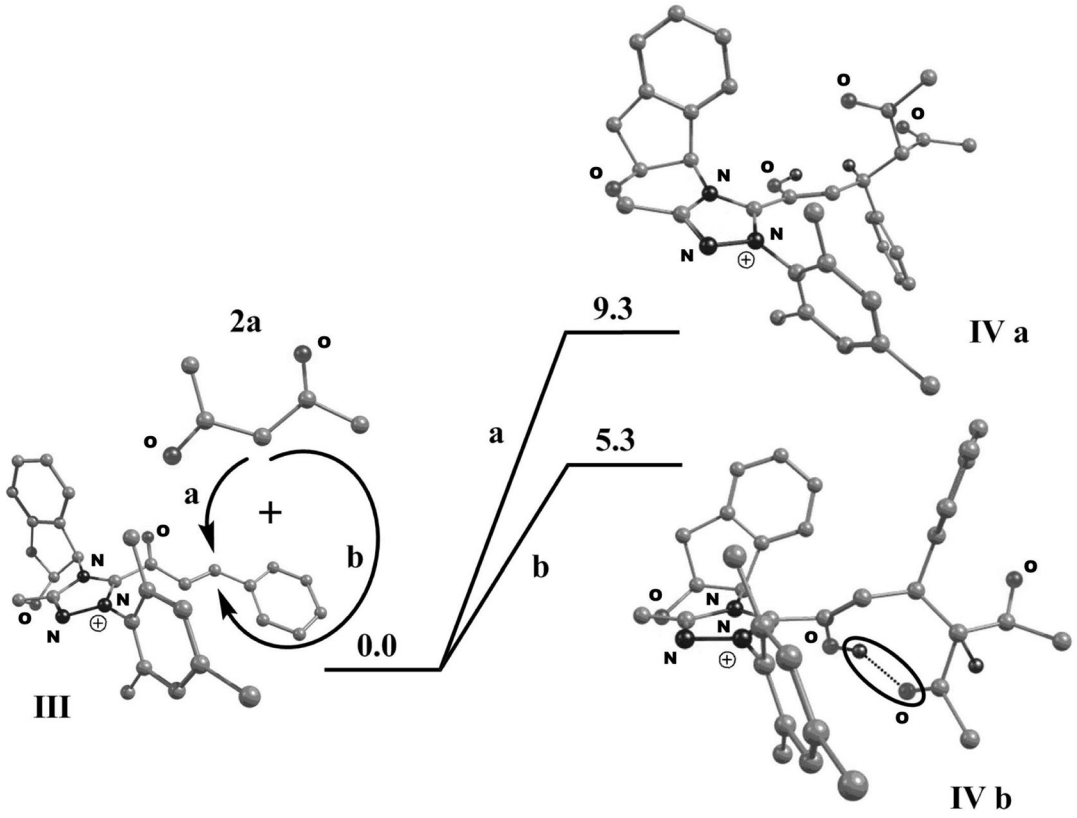


Figure 1. Two possible pathways for the approach of acetylacetone **2a** towards **III** leading to two different intermediates **IVa** and **IVb**; intermediate **IVb** is stabilized by intramolecular hydrogen bonding (encircled in the figure); all structures shown are fully optimized geometries obtained from DFT; hydrogen atoms are omitted for the purpose of clarity – only the hydrogen taking part in hydrogen bonding is shown; the reported energies are in kcal mol^{-1}.

a possibility that does not exist in the case of the approach from above the plane. The hydrogen bonding O–H distance is found to be 1.69 Å, while the O–H–O angle is found to be 154.7°, both values falling in the range of typical hydrogen bonding interactions.

Subsequent steps leading to the formation of **3a** are delineated in Figure 2. The complex **IVb** can undergo enol-keto, and keto-enol transformations to yield the intermediate **V**. The energy for such a conversion has been calculated to be endergonic by 12.5 kcal mol^{-1}. At this point, the cationic species **V** can be converted to the neutral species **VI** through the abstraction of the proton by the acetate anion released from the lithium acetate, in solution. This is found to be a highly favorable process, being exothermic by −41.8 kcal mol^{-1}. This also indicates the role of lithium acetate in the catalytic process, and the calculations seems to indicate that DABCO is ineffective for the proton abstraction process, the energy for its proton abstraction has been found to be endothermic by 20.7 kcal mol^{-1}. This is due to the fact that the proton abstraction by DABCO involves the conversion of the neutral DABCO species to the cation (DABCO)(H)$^+$, a less favorable process than the conversion of the anionic acetate species to acetic acid. Calculations also indicate that the use of LiOAc·2 H_2O base in place of LiOAc (thus generating the acetate dihydrate anion) would also be effective, though slightly less, the proton abstraction in this case being exothermic by −22.6 kcal mol^{-1}. The neutral complex **VI** thus formed can then undergo intramolecular acylation to give rise to **4** and **3a**.This step has been calculated to be exergonic by −25.5 kcal mol^{-1}. The fact that this step is entropically favorable, converting the single intermediate species **VI** to two moieties **4** and **3a**, helps to explain its exergonicity. Therefore, taken together, the conversion of **IV** to **4** and **3a** is favorably exothermic by −54.8 kcal mol^{-1} (considered for the case of the lithium acetate base). This therefore helps to explain why product **3a** is formed in high yield and high enantioselectivity.

Conclusions

In conclusion, we have developed the NHC-organocatalyzed annulation of 2-bromoenals with readily available 1,3-dicarbonyl compounds or enamines proceed-

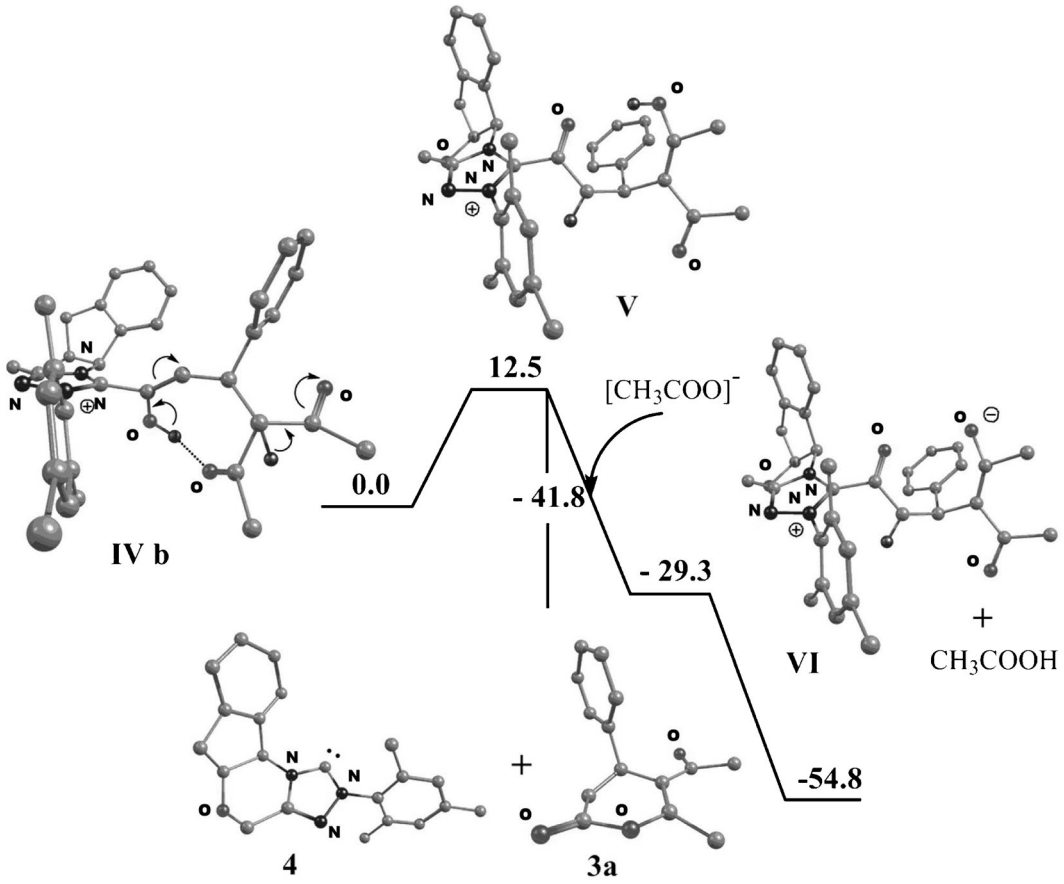


Figure 2. The steps converting the intermediate **IVb** to **4** and **3a**; all values reported are in kcal mol^{-1}.

ing *via* the chiral α,β-unsaturated acylazolium intermediates. The reaction furnished an enantioselective synthesis of dihydropyranones and dihydropyridinones, which takes place without the use of external oxidants, under mild conditions with broad substrate scope. Moreover, based on DFT calculations, we have provided a reasonable rationalization for the mechanistic scenario and the mode of enantioinduction. Further studies on the application of chiral α,β-unsaturated acylazolium in various carbon-carbon and carbon-heteroatom bond-forming reactions are ongoing in our laboratory.

Experimental Section

Procedure for the Enantioselective Synthesis of Dihydropyranones

To a flame-dried screw-capped test tube equipped with a magnetic stir bar were added triazolium salt **4** (9.1 mg, 0.025 mmol), and DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), followed by activated, powdered 4 Å molecular sieves (100 mg). Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (2.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C for 10 min. To this mixture was added the 2-bromoenal **1** (0.50 mmol) followed by 1,3-dicarbonyl compound **2** (0.5 mmol). Then the reaction mixture was stirred at 25 °C for 12 h. When the reaction is complete, the solvent was evaporated and the crude residue was purified by flash column chromatography on silica gel (20% EtOAc-petroleum ether) to afford the corresponding dihydropyranones.

Data of compound 3a:[8a,9] R_f (petroleum ether/EtOAc = 60/40): 0.60; 96% *ee*, $[\alpha]_D^{25}$: +103.20 (*c* 0.1, $CHCl_3$); HPLC (Chiralcel OJ-H, 95:05 petroleum ether/EtOH, 1.0 mL min^{-1}): major: 35.3 min, minor: 41.5 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 3H), 7.15 (d, J = 7.1 Hz, 2H), 4.15 (apparent doublet, J = 6.1 Hz, 1H), 3.00 (dd, J_1 = 7.1 Hz, J_2 = 15.6 Hz, 1H,), 2.86 (dd, J_1 = 2.6 Hz, J_2 = 15.6 Hz, 1H), 2.43 (s, 3H) 2.12 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.11, 165.76, 160.44, 139.83, 129.61, 128.12, 126.81, 117.43, 39.02, 37.33, 29.93, 19.24; HR-MS: m/z = 231.1020 $[M+H]^+$, calculated for $C_{14}H_{15}O_3$: 231.1016; FT-IR: ν = 2924, 2857, 1733, 1699, 1358, 1255, 1176, 1149, 1030, 943, 764, 702 cm^{-1}.

General Procedure for the Enantioselective Synthesis of Dihydropyridinones

To a flame-dried screw-capped test tube equipped with a magnetic stir bar were charged triazolium salt **4** (9.1 mg,

0.025 mmol), and DABCO (58.8 mg, 0.525 mmol), lithium acetate dihydrate (10.2 mg, 0.10 mmol), and activated, powdered 4 Å molecular sieves (100 mg) were added. Then the screw-capped tube was evacuated and backfilled with argon. To this mixture was added toluene (2.0 mL) under argon atmosphere and mixture was kept stirring at 25 °C for 10 min. To this mixture was added the 2-bromoenal **1** (0.50 mmol) followed by enamine derivative **5** (0.5 mmol). Then the reaction mixture was stirred at 25 °C for 12 h. When the reaction was complete, the solvent was evaporated and the crude residue was purified by flash column chromatography (20% EtOAc-petroleum ether) on silica gel to afford the corresponding dihydropyridinones.

Data of compound 6a:[10a] R_f (petroleum ether/EtOAc = 60/40): 0.46; 99% *ee*, $[\alpha]_D^{25}$: +120.04 (*c* 0.1, $CHCl_3$); HPLC (Chiralcel OJ-H, 70:30 petroleum ether/IPA, 0.5 mL min^{-1}): minor: 15.9 min, major: 27.0 min; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.76 (bs, 1H), 7.32–7.29 (m, 2H), 7.25–7.19 (m, 3H), 4.29 (apparent doublet, J = 7.9 Hz, 1H), 3.67 (s, 3H), 2.98 (dd, J_1 = 7.9 Hz, J_2 = 16.2 Hz, 1H), 2.74 (d, J = 16.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.53, 167.47, 146.47, 141.95, 128.90, 127.1, 126.7, 107.0, 51.54, 38.26, 37.84, 19.15; HR-MS: *m/z* = 246.1124 $[M+H]^+$, calculated for $C_{14}H_{16}O_3N$: 246.1125; FT-IR: ν = 3242, 3027, 2925, 2854, 1694, 1455, 1367, 1286, 1202, 1091, 1031, 789, 764, 697, 648, 467 cm^{-1}.

Acknowledgements

We are grateful to Mrs. Sunita Kunte (CSIR-NCL) for skillful technical assistance with the HPLC analysis. This work was supported by CSIR-NCL (start-up grant to ATB, MLP022426) and CSIR-New Delhi (Network project-ORIGIN, CSC0108) as well as CSIR-OSDD (HCP0001). SRY, AB, and AP thank CSIR-New Delhi for the award of Junior Research Fellowship. We thank Dr. P. R. Rajamohanan for the NMR spectra and Ms. B. Santhakumari for the HR-MS data. MM and KV wish to thank the Center of Excellence for Scientific Computing (COESC) for computational facilities, as well as the Multi-Scale simulation and Modeling project - MSM - for financial assistance.

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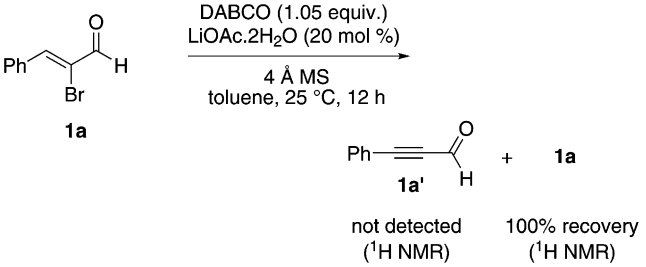

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