Synthetic Methods

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Highly Enantioselective γ-Amination by N-Heterocyclic Carbene Catalyzed [4+2] Annulation of Oxidized Enals and Azodicarboxylates**

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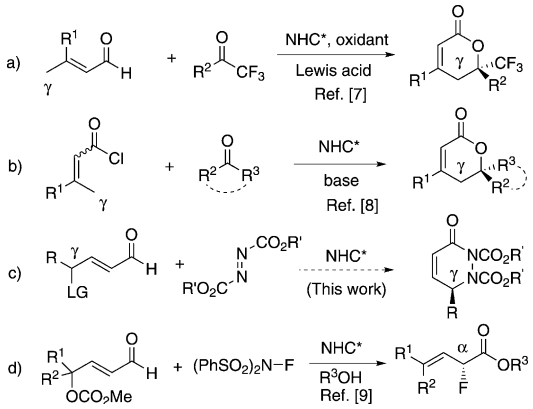
N-heterocyclic carbene (NHC) catalysis has been developed extensively for various chemical transformations over the past decade.[1,2] In 2004, Bode et al. and Glorius et al. independently reported the pioneering NHC-catalyzed [3+2] annulation reaction of enals by β-addition through an a^3-d^3 umpolung approach.[3] Since then, a series of NHC-catalyzed [3+*n*] annulation of enals has been realized for the synthesis of a range of hetero- and carbocyclic compounds.[4,5] The NHC-catalyzed [2+4] annulation of enals by α addition was also established.[6]

In 2012, Chi et al. reported a pioneering oxidative NHC-catalyzed [4+2] annulation of enals with trifluoromethyl ketones by γ addition (Scheme 1 a).[7] In 2011, we reported an NHC-catalyzed [4+2] annulation of α,β-unsaturated acyl chlorides with activated ketones (Scheme 1 b).[8] We envisioned that the addition of an NHC to enals having a γ leaving group may generate a dienolate intermediate, which would then react with an azodicarboxylate to give the [4+2] annulation product (Scheme 1 c). While our work was in progress, Sun et al. reported an NHC-catalyzed α fluorination of preoxidized enals (Scheme 1 d).[9] It is interesting that only γ amination and not α amination is observed in our reaction.

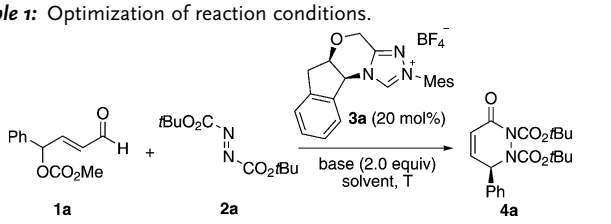
The catalytic asymmetric amination of carbonyl compounds provides an efficient way to amino acids.[10] However, the enantioselective approaches to γ-amino acid derivatives are still very limited.[11,12] Recently, we reported a cinchona-alkaloid-catalyzed [4+2] annulation of α,β-unsaturated acyl chlorides and azodicarboxylates.[13] The reaction worked well for the synthesis of various γ-amino acids but not for γ-aryl ones because of the difficulty in the preparation of γ-aryl-α,β-unsaturated acyl chlorides.

Initially, the model reaction of the enal **1a**, having a γ leaving group, and di-*tert*-butyl azodicarboxylate (DTBAD; **2a**) was investigated under NHC catalysis (Table 1). We were pleased to find that the reaction catalyzed



Scheme 1. NHC-catalyzed [4+2] annulation through γ addition (a–c) and related α fluorination (d).

Table 1: Optimization of reaction conditions.



Entry	**1a**/**2a**	Base	Solvent, *T*	Yield [%][a]	*ee* [%][b]
1	1.5:1	NaOAc	CH_2Cl_2, RT	33	99
2	1.5:1	NaOAc	CH_2Cl_2, 30 °C	44	99
3	1.5:1	NaOAc	CH_2Cl_2, reflux	41	99
4	1.5:1	NaOAc	CH_3CN, RT	trace	–
5	1.5:1	NaOAc	toluene, RT	41	96
6	1.5:1	NaOAc	THF, RT	60	99
7	1:1.5	NaOAc	THF, RT	53	99
8	1:1.5	K_2CO_3	THF, RT	81	99
9	1:1.1	K_2CO_3	THF, RT	82	99

[a] Yield of isolated product. [b] Determined by HPLC using a chiral stationary phase. Mes = 2,4,6-trimethylphenyl, THF = tetrahydrofuran.

by the NHC **3a′**,[6b,14] generated in situ from the chiral azolium **3a** in the presence of sodium acetate, furnished the desired [4+2] annulation product **4a** in 33% yield with 99% *ee* (entry 1). After optimization (entries 2–9), the yield was improved to 82% with 99% *ee* when the reaction was carried out with K_2CO_3 as the base in THF (entry 9).

With these optimized reaction conditions in hand, the scope of enals was briefly investigated (Scheme 2). Both

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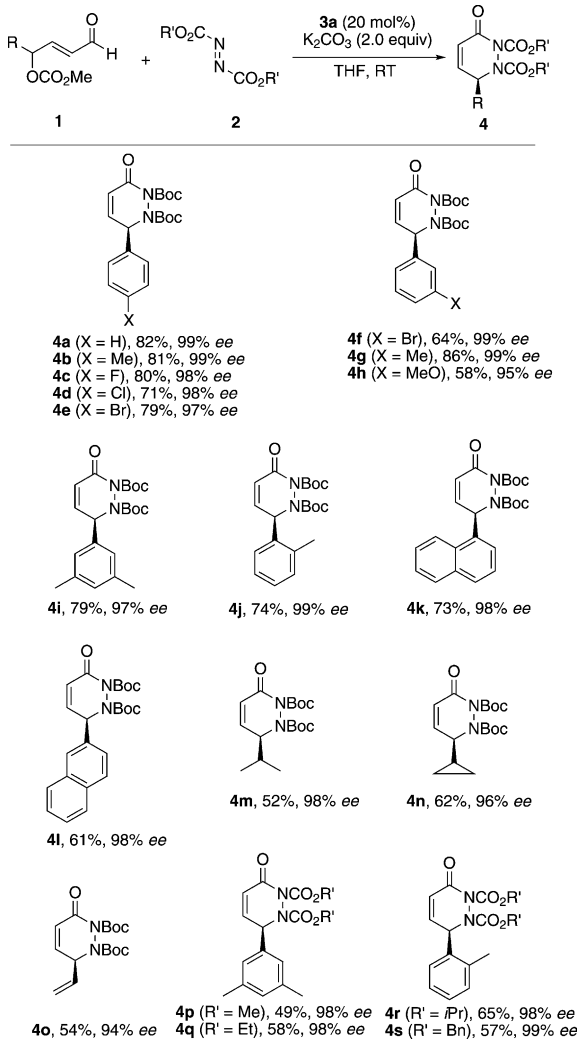
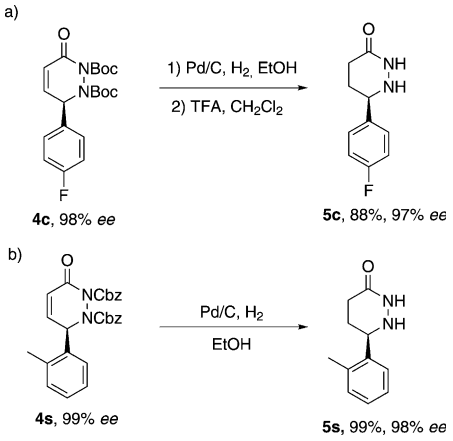


Scheme 2. Reaction scope. Boc = *tert*-butoxycarbonyl.

electron-donating (4-MeC_6H_4) and electron-withdrawing (4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4) groups on aromatic enals were tolerated and give the desired annulation products **4b–e** in good yields with excellent enantioselectivities. Aromatic enals with a *meta* substituent (3-BrC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$) also worked well (**4f–h**). The *ortho*-substituted (2-MeC_6H_4) or *meta*,*meta*-disubstituted (3,5-$Me_2C_6H_3$) aryl substrates showed no negative effect on the reaction (**4i** and **4j**). The reactions of the enals with γ-1-naphthyl or 2-naphthyl substrates gave the corresponding dihydropyridazinones (**4k** and **4l**) in good yields with excellent enantioselectivities. It is noteworthy that aliphatic enals worked as well to give the desired annulation products (**4m** and **4n**) in moderate to good yields with high enantioselectivities. In addition, an enal with a γ-vinyl group gave the annulation product **4o** in 54% yield with 94% *ee*. The reaction with various alkyl azodicarboxylates (**2b–d**; R′ = Me, Et, *i*Pr, Bn) were also successful, and the desired annulation products **4p–s** were obtained in 49–65% yields with excellent enantioselectivities.

The *R* configuration of **4d** having a γ-aryl group was determined by the X-ray analysis of its crystal.[15] The *S* configuration of the compounds **4m–o** with a γ-alkyl or alkenyl group was assigned by the comparison of its optical rotation with those reported in the literature.[13a]

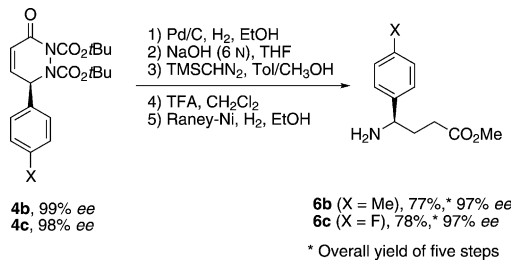
The resulting dihydropyridazinones are structurally interesting and afford many possible chemical transformations.[16] Tetrahydropyridazinone is an important pharmacological motif in many bioactive compounds, such as a 5-lipoxygenase inhibitor.[17] The tetrahydropyridazinone **5c** could be easily obtained in high yield from **4c** by hydrogenation with Pd/C and subsequent removal of the N-Boc group (Scheme 3a). The hydrogenation and deprotection could be carried out at the same time for the N-Cbz annulation product **4s**, thus giving the tetrahydropyridazinone **5s** in quantitative yield with high enantiopurity (Scheme 3b).



Scheme 3. Synthesis of tetrahydropyridazinones. Cbz = benzyloxycarbonyl. TFA = trifluoroacetic acid.

The synthesis of alkyl γ-amino acids from the γ-alkyl cycloadduct **4** has been demonstrated in our previous publication.[13a] As expected, this process also worked well for the γ-aryl cycloadducts **4b** and **4c**, thus giving the desired γ-amino esters **6b** and **6c**, respectively, in high overall yields without erosion of enantiopurities (Scheme 4).

A plausible catalytic cycle is depicted in Figure 1. The addition of in situ generated NHC to enals gives the vinyl Breslow intermediate **A**, which decomposes to the azolium dienol **B** by removal of the γ leaving group. The γ addition of the dienol to the azodicarboxylate affords the acyl azolium adduct **C**[18] with subsequent cyclization to afford the final annulation product **4** and regenerate the NHC catalyst.



Scheme 4. Synthesis of γ-amino esters. TMS = trimethylsilyl.

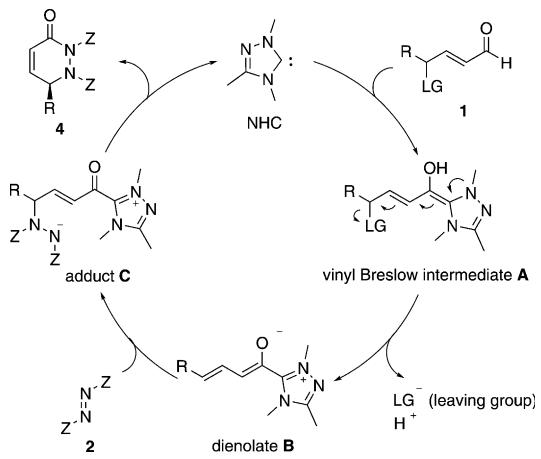


Figure 1. Plausible catalytic cycle.

In summary, the NHC-catalyzed [4+2] annulation of enals, having a γ leaving group, and azodicarboxylates was developed, thus giving the corresponding dihydropyridazinones in good yields with excellent enantioselectivities. The reaction worked well for γ-aryl, alkyl, and alkenyl enal derivatives. Highly enantiopure tetrahydropyridazinones and γ-amino acid derivatives could be easily prepared by subsequent transformations of the resulting dihydropyridazinones. The readily available substrates,[19] broad reaction scope, excellent enantioselectivity, and mild reaction conditions[20] make this γ-amination process potentially useful for the synthesis of γ-amino acids and their derivatives. Other related NHC-catalyzed reactions of γ functionalized of enals are underway in our laboratory.

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