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Enantioselective [4 + 2] cycloaddition of ketenes and 1-azadienes catalyzed by N-heterocyclic carbenes†

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Optically active highly functionalized 3,4-dihydropyridin-2-ones were synthesized by N-heterocyclic carbene-catalyzed [4 + 2] enantioselective cycloaddition of ketenes and 1-azadienes.

The hetero-Diels–Alder (HDA) reaction is one of the most powerful methods for the construction of six-membered heterocycles, which are widely presented in many natural and unnatural bioactive compounds.[1] In 1989, Boger *et al.* successfully employed *N*-sulfonyl 1-azadienes for the HDA reaction with vinyl ethers.[2] Several decades later, the HDA reaction of 1-azadienes has been developed as an efficient approach to a wide variety of N-heterocycles.[3] However, the catalytic enantioselective HDA reactions of 1-azadienes are very limited so far.

In 2006, Bode *et al.* reported an enantioselective HDA reaction of 1-azadienes, in which the enolates, generated *in situ* from enals and the nucleophilic catalyst of N-heterocyclic carbenes, acted as the dienophile for the DA reaction.[4] In 2007 Arrayás and Carretero *et al.* developed the enantioselective HDA reaction of 1-azadienes with vinyl ethers catalyzed by a nickel complex with chiral ligand.[5] In 2008, Chen *et al.* successfully applied the aminocatalysis to the HDA reactions of 1-azadienes with aldehydes.[6]

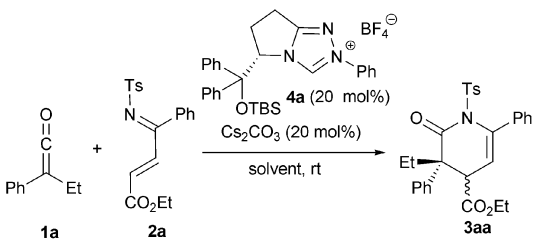
During the past decades, N-heterocyclic carbenes (NHCs) were found to be efficient catalysts for a wide variety of reactions.[7,8] In 2008, We and Smith *et al.* independently reported a series of NHC-catalyzed cycloaddition of ketenes, involving the enolates generated by the addition of NHC to ketenes.[9,10] Latterly, we reported an NHC-catalyzed enantioselective [4 + 2] cycloaddition of ketenes and oxodienes.[11] We conjecture that the enolate generated *in situ* from the ketene may be able to react with 1-azadienes in a inverse-electron-demand DA mode to afford 3,4-dihydropyridin-2-ones.[12,13]

Initially, we found that NHC **4a′**, generated freshly from its precursor **4a** in the presence of Cs_2CO_3, could catalyze the cycloaddition reaction of phenyl ethyl ketene **1a** and 1-azadiene **2a** in toluene to give the corresponding dihydropyridinone **3aa** in 67% yield with 4 : 1 diastereoselectivity and 71% ee (Scheme 1). It is interesting that the diastereoselectivity was improved dramatically (*trans* : *cis* > 20 : 1) albeit with some loss of enantioselectivity when DME was used as the solvent. The better solubility of Cs_2CO_3 in DME may facilitate the epimerization of the *cis*-**3aa** to *trans*-**3aa**. Thus, DME was added after the completion of the reaction in toluene, giving the cycloadduct **3aa** as nearly pure *trans*-isomer without erosion of enantioselectivity.

A series of NHC precursors were then tested for the model reaction (Table 1). The NHC precursors **4a–f**, derived from L-pyroglutamic acid,[9,14] were first tested. The NHCs **4a′** and **4b′** with either TBS or TMS group gave similar results (entries 1 and 2). NHC **4c′** with *N*-4-methoxylphenyl group gave the best yield and selectivity, while NHC **4d′** with *N*-2-isopropylphenyl group is inferior to NHC **4c′** (entries 4 and 5). The NHCs **4e′** and **4f′** with a free hydroxy group showed decreased or reversed enantioselectivity (entries 6 and 7).[9c] The Rovis' tetracyclic NHCs **5a′** and **5b′** derived from aminoindanol and You's bis-NHC **6′** also worked in the reaction (entries 8–10).[15,16]

It is surprising that better yields and enantioselectivities were observed when excess Cs_2CO_3 was used, which may be due to the facilitation of the formation of the NHCs (entries 11 and 12). Further optimization of solvents showed that benzene is the best choice, in which high yield and 91% ee were achieved (entries 13–18).

A variety of ketenes were then tested for the NHC-catalyzed reaction with 1-azadiene **2a** (Table 2). Aryl(alkyl)ketenes **1b–1e** with either electron-withdrawing group (Ar^1 = 4-ClC_6H_4, 4-BrC_6H_4) or electron-donating group (Ar^1 = 4-MeC_6H_4, 4-$MeOC_6H_4$) worked well to give the cycloadducts **3** in good



Scheme 1

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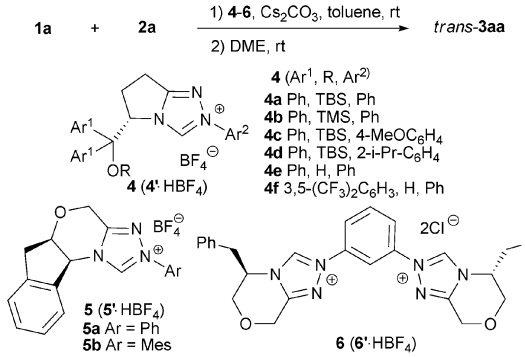
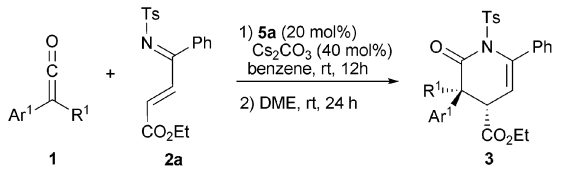
Table 1 Screening of NHCs and optimization of reaction conditions



Entry	**4–6** (mol%)	Cs_2CO_3 (mol%)	Solvent	Yield[a] (%)	ee[b,c] (%)
1	**4a** (20)	20	Toluene	68	71
2	**4b** (20)	20	Toluene	69	72
3	**4c** (20)	20	Toluene	71	74
4	**4d** (20)	20	Toluene	59	60
5	**4e** (20)	20	Toluene	30	37
6	**4f** (20)	20	Toluene	37	−67
8	**5a** (20)	20	Toluene	15	−60
9	**5b** (20)	20	Toluene	38	−45
10	**6** (20)	20	Toluene	47	57
11	**4a** (20)	40	Toluene	72	75
12	**5a** (20)	40	Toluene	73	−86
13	**5a** (20)	40	THF	47	−72
14	**5a** (20)	40	DME	37	−46
15	**5a** (20)	40	Et_2O	Trace	—
16	**5a** (20)	40	DCM	61	−66
17	**5a** (20)	40	Xylene	55	−72
18	**5a** (20)	40	Benzene	87	−91

[a] Isolated yield of the pure *trans*-isomer, and *trans* : *cis* > 20 : 1 for all the entries. [b] Determined by chiral HPLC. [c] The minus ee value indicates a reversed enantioselectivity. DME = 1,2-dimethoxylethane.

Table 2 Variation of ketenes



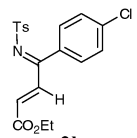
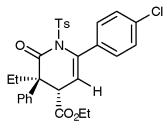
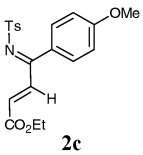
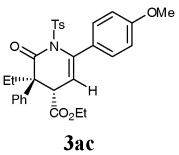
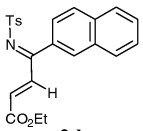
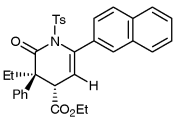
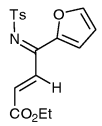
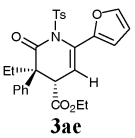
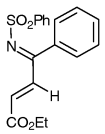
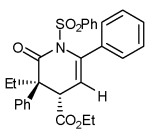
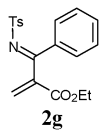
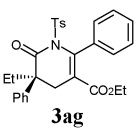
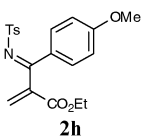
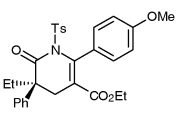
Entry	**1** (Ar^1, R^1)	**3**	Yield[a] (%)	ee (%)[b]
1	**1a** Ph, Et	**3aa**	87	91
2	**1b** 4-ClC_6H_4, Et	**3ba**	88	91
3	**1c** 4-BrC_6H_4, Et	**3ca**	87	92
4	**1d** 4-MeC_6H_4, Et	**3da**	84	90
5	**1e** 4-$MeOC_6H_4$, Et	**3ea**	87	83
6	**1f** 3-ClC_6H_4, Et	**3fa**	78	93
7	**1g** 2-ClC_6H_4, Et	**3ga**	Trace	/
8	**1h** Ph, *n*-Pr	**3ha**	87	87
9	**1i** Ph, *n*-Bu	**3ia**	81	93

[a] Isolated yield of pure *trans*-isomer. [b] Determined by chiral HPLC.

yields with high enantioselectivities (entries 2–5). Ketene **1f** with 3-chlorophenyl also worked well, while ketene **1g** with 2-chlorophenyl failed (entries 6 and 7). The reaction of ketenes with other alkyl groups (R = *n*-Pr, *n*-Bu) afforded the cycloadducts in high yields with high enantioselectivities (entries 8 and 9).

The scope of 1-azadienes was also briefly explored (Table 3). Both azadienes with an electron-withdrawing group (**2b**, Ar^2 = 4-ClC_6H_4) and with an electron-donating group (**2c**, Ar^2 = 4-$MeOC_6H_4$) reacted smoothly (entries 1 and 2). Azadiene **2d** with β-naphthyl group and azadiene **2e** with 2-furyl group also worked well (entries 3 and 4). *N*-Phenylsulfonyl azadiene **2f** showed similar reactivity with *N*-tosylate azadiene **2a** (entry 5). It is interesting that when the ethoxycarbonyl group moved from 4- to 3-position in the 1-azadienes, the tetracyclic NHC **5b′** catalyzed reaction of 3-ethoxycarbonyl-1-azadienes (**2g** and **2h**) gave the cycloadducts in good yields but with very low enantioselectivities, while the corresponding reaction catalyzed by bicyclic NHC

Table 3 Variation of 1-azadienes

Entry	**2**	**3**	Yield[a] (%)	ee (%)[b]
1	 **2b**	 **3ab**	81	88
2	 **2c**	 **3ac**	87	86
3	 **2d**	 **3ad**	82	91
4	 **2e**	 **3ae**	88	83
5	 **2f**	 **3af**	81	87
6	 **2g**	 **3ag**	71 (72)[c]	7(−68)[c]
7	 **2h**	 **3ah**	61 (58)[c]	3(−52)[c]

[a] Isolated yields of pure *trans*-isomer. [b] Determined by chiral HPLC. [c] The result of reactions catalyzed by NHC **4b′** is shown in parenthesis.

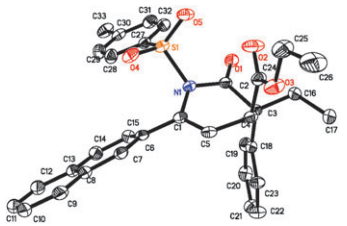


Fig. 1 X-Ray crystal structure of dihydropyridinone **3ad**.

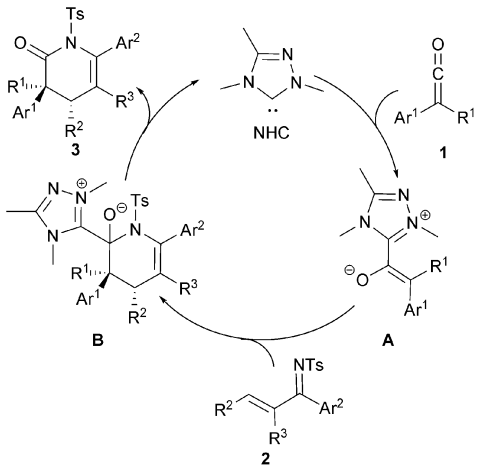


Fig. 2 Possible catalytic cycle.

4b′ afforded much better enantioselectivities for these two 3-substituted-1-azadienes (entries 6 and 7).

The structure of dihydropyridinone **3ad** was unambiguously established by X-ray crystallographic analysis (Fig. 1) (ESI†).

One possible catalytic cycle of the NHC-catalyzed cycloaddition of ketenes and 1-azadienes is shown in Fig. 2. The nucleophilic addition of NHC to ketenes gives enolate **A**, which reacts with 1-azadienes **2** in an inverse-electron-demand Diels–Alder reaction mode to afford the adduct **B**. The fragmentation of adduct **B** gives the final dihydropyridinone **3** and regenerates the NHC catalyst.

In conclusion, the enantioselective synthesis of highly substituted 3,4-dihydropyridin-2-ones was realized by the chiral N-heterocyclic carbene-catalyzed cycloaddition of ketenes and 1-azadienes. To the best of our knowledge, this is the first example of the catalytic enantioselective [4 + 2] cycloaddition reaction of ketenes and 1-azadienes. The highly functionalized 3,4-dihydropyridin-2-ones may find potential usage in organic synthesis.

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