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Stereoselective Synthesis of γ-Butyrolactones *via* Organocatalytic Annulations of Enals and Keto Esters

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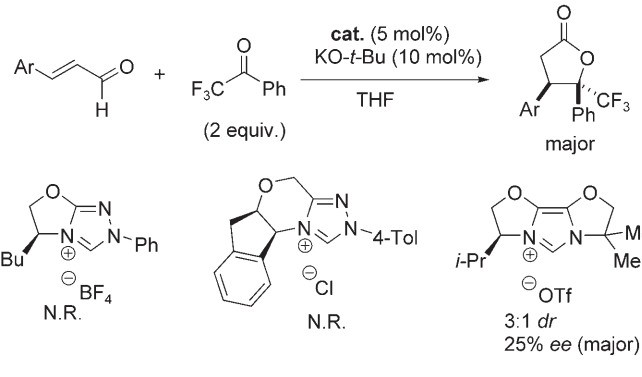
Abstract: 4,5,5-Trisubstituted γ-butyrolactones bearing two stereocenters including one quaternary carbon center have been synthesized in excellent yields *via* N-heterocyclic carbene-catalyzed annulations of enals and ketoesters. Chiral N-heterocyclic carbenes were used to tune the diastereoselectivity up to an 83/17 *cis*/*trans* ratio and the enantioselectivity up to 78% *ee* (*trans* isomer).

Keywords: lactones; N-heterocyclic carbenes; organocatalysis; stereoselectivity; umpolung

Introduction

N-Heterocyclic carbene (NHC)-catalyzed umpolung reactions of aldehydes have become an intense research area recently, providing an unconventional access to some important target molecules.[1,2] The most studied reactions include the reaction of the Breslow intermediate with electrophilic reagents such as aromatic aldehydes, namely the benzoin reaction,[3] and α,β-unsaturated ketones or esters, namely the Stetter reaction.[4] Recently, versatile electrophilic reagents such as ketones,[5] aziridines[6] and nitroalkenes[7] have also been recognized as suitable acceptors for acyl anions during the umpolung. In addition, extended umpolung reactions involving the use of functionalized aldehydes have also received considerable attention and witnessed significant progress in the past several years.[8] Among the recent redox-type umpolung reactions, Bode et al. and Glorius et al. introduced the concept of "conjugate umpolung", generating the homoenolate by the reaction of NHC with enals.[9a,b] These two groups together with Nair's and Scheidt's groups have demonstrated that these homoenolates undergo annulation with simple aldehydes, ketones, and imines, providing efficient syntheses of γ-butyrolactones and γ-lactams.[9,10] As interesting as these reactions are, however, the stereoselective control of these reactions has been a great challenge. Glorius and co-workers have shown that only 25% *ee* could be obtained for the reaction of enals with trifluoromethyl phenyl ketone in the presence of a chiral imidazolium salt (Scheme 1).[9a] Annulations of enals and imines recently reported by Bode et al. also gave the γ-lactam product with low enantioselectivity (24% *ee*).[9l]

In our continuing endeavors to develop novel N-heterocyclic carbenes and extend their applications in organocatalytic reactions,[11] we envisioned that keto esters might be suitable electrophilic partners in the "conjugate umpolung" reaction to afford 4,5,5-trisubstituted γ-butyrolactones bearing two stereocenters including one quaternary carbon center. Notably, Glorius and co-workers have used keto esters as the electrophilic partners in the NHC-catalyzed annulation with enals.[10a,b] However, diastereoselectivities of the



Scheme 1. Enantioselective synthesis of γ-butyrolactones from enals and trifluoromethyl phenyl ketone.

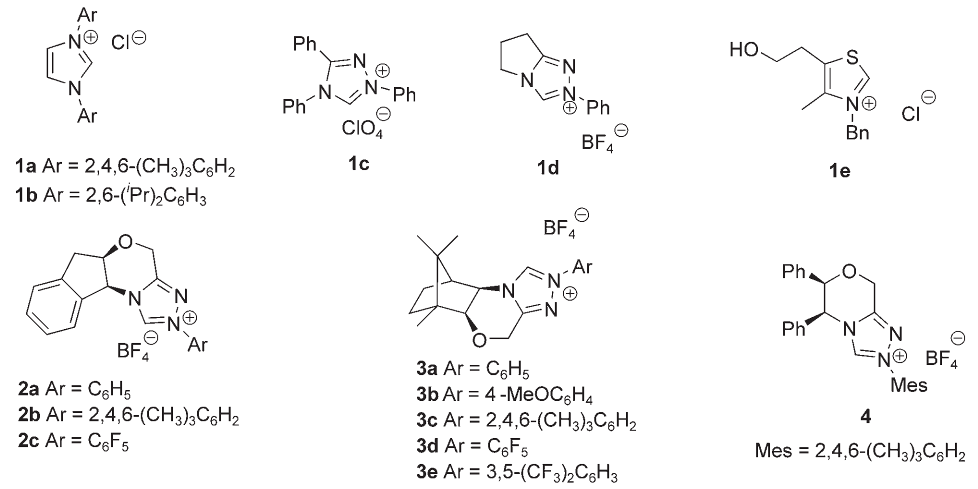


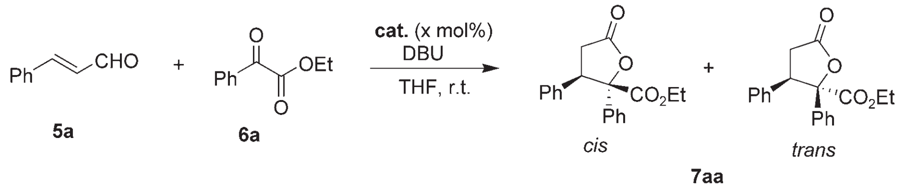
Figure 1. Structures of several NHC precursors.

products are generally low and their asymmetric version has not been explored. Having tested various chiral NHCs, including those developed in this laboratory, we found that both the diastereoselectivities and enantioselectivites of this annulation could be well tuned. In this paper, we report the details of our study.

Results and Discussion

Our studies began with an initial examination of different readily available NHC precursors (Figure 1) for the annulation of cinnamaldehyde **5a** and keto ester **6a**. The results are summarized in Table 1. In the presence of 15 mol% of DBU, both imidazolium

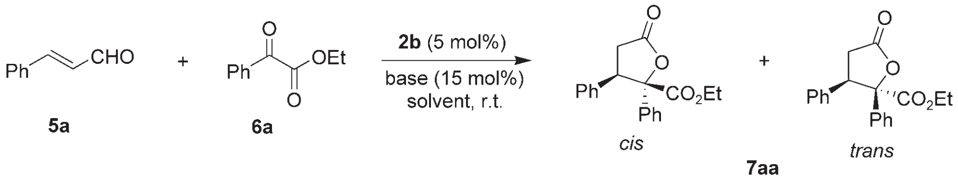
Table 1. Different NHC catalysts for annulations of enal **5a** and keto ester **6a**.[a]



Entry	Catalyst	x [mol%]	Time [h]	Yield [%][b]	*cis*:*trans*[c]	*ee* [%][d]
1	**1a**	15	4	88	55:45	–
2	**1b**	15	6	65	61:39	–
3	**1c**	15	24	N.R.[f]	–	–
4	**1d**	15	24	56	50:50	–
5	**1e**	15	24	N.R.	–	–
6	**2a**	15	2	53	65:35	48/33
7	**2b**	15	4	85	81:19	14/14
8	**2c**	15	24	<5	–	–
9	**3a**	15	24	<5	–	–
10[e]	**3b**	15	24	N.R.	–	–
11	**3c**	15	11	86	50:50	43/13
12	**3d**	15	24	N.R.	–	–
13	**3e**	15	24	N.R.	–	–
14	**4**	15	12	74	40:60	55/78
15	**2b**	5	4	80	81:19	13/15

[a] *Reaction conditions:* **5a**/**6a**/DBU = 1/1.2/0.15, 0.1 M of **5a** in THF at 25 °C.
[b] Isolated yields.
[c] Determined by ^{1}H NMR.
[d] Determined by chiral HPLC (Chiralpak AD-H).
[e] The self-condensation of **5a** was observed.
[f] No reaction.

Table 2. Optimizing the conditions for the annulation of enal **5a** and keto ester **6a**.[a]



Entry	Solvent	Base	Time [h]	Yield [%][b]	*cis*:*trans*[c]	*ee* [%][d]
1	THF	DBU	4	80	81:19	13/15
2	EtOAc	DBU	3	82	78:22	3/6
3	*t*-BuOH	DBU	8	86	67:33	27/30
4	DMF	DBU	8	97	67:33	10/3
5	CH_2Cl_2	DBU	48	55	67:33	–
6	toluene	DBU	12	70	82:18	23/25
7	THF	*t*-BuOK	36	20	–	–
8	THF	LiHMDS	48	24	–	–
9	THF	DIEA[e]	48	N.R.	–	–

[a] *Reaction conditions:* 5**a**/**6a**/**2b**/base = 1/1.2/0.05/0.15, 0.1 M of 5**a** in solvent at 25 °C.

[b] Isolated yields.

[c] Determined by ^{1}H NMR.

[d] Determined by chiral HPLC (Chiralpak AD-H).

[e] Diisopropylethylamine.

salts **1a** and **1b** (15 mol%) are capable of catalyzing the reaction to give γ-butyrolactone **7aa** in an 88% yield and a 65% yield, respectively (entries 1 and 2, Table 1). Unfortunately, the diastereoselectivity of the product in either case is not satisfying. The reaction did not proceed with triazolium salt **1c** but worked well with triazolium salt **1d**, however, the diastereoselectivity remained poor (entries 3 and 4, Table 1). The reaction with thiazolium salt **1e** failed to give any annulation product (entry 5, Table 1).

We next examined several chiral N-heterocyclic carbenes for the enantioselective and diastereoselective formation of 4,5,5-trisubstituted γ-butyrolactones. The reaction with 15 mol% of **2a** gave **7aa** in 53% yield and 65/35 *cis*/*trans* ratio with 48% *ee* and 33% *ee* for the *cis* and *trans* isomers, respectively (entry 6, Table 1). In the presence of **2b**, the desired product was obtained in a much higher yield of 85% and an increased *cis*/*trans* ratio of 81/19. Unfortunately, the *ee*s of the products were decreased (entry 7, Table 1). The catalyst derived from **2c** was found to be not suitable for the reaction (entry 8, Table 1). Another series of chiral triazolium salts **3a–e**, recently developed in our group, were also tested in this reaction.[11c] The NHC derived from **3c** could efficiently catalyze the reaction but with poor *cis*/*trans* ratio and only moderate *ee*s of the products were obtained (entries 9–13, Table 1).

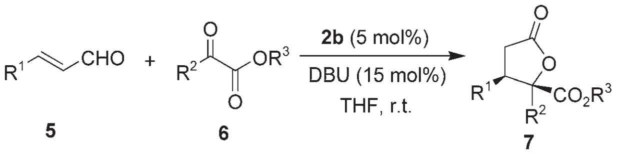
Interestingly, the reaction with triazolium salt **4**, developed by Scheidt and co-workers,[9j] could give the annulation product **7aa** with a *cis*/*trans* ratio of 40:60 and an improved enantioselectivity of 78% *ee* (*trans* isomer) (entry 14, Table 1). Although the overall results are still unsatisfying, this represents the highest *ee* for the NHC-catalyzed annulation of enals with simple aldehydes, ketones, or imines.[9a,l]

Since no catalyst gives both satisfying diastereoselectivity and enantioselectivity, we decide to simply tune the diastereoselectivity of the annulation reaction with the readily available NHCs. With NHC catalyst derived from **2b**, the reaction proceeded well even with 5 mol% of the catalyst, retaining the same level of yield and selectivity (entry 15, Table 1).

As summarized in Table 2, different solvents and bases have been examined for the reaction. Several common solvents such as EtOAc, *t*-BuOH, DMF, toluene all led to the formation of the γ-butyrolactone **7aa** in good to excellent yields, except for CH_2Cl_2. However, the diastereoselectivity was decreased compared with that in THF (entries 1–5, Table 2). The yield decreased in toluene due to the self-condensation of **5a**, while the diastereoselectivity remained at the same level as in THF (entry 6, Table 2). When *t*-BuOH was used, the *ee* was slightly improved but remained unpractical. Poor yields were obtained for the reaction with several bases such as *t*-BuOK, LiHMDS, and DIEA (entries 7–9, Table 2).

Above all, reaction with 5 mol% of **2b** in THF gave the best diastereoselectivity, and these conditions were used to examine the substrate scope for this reaction. The results are summarized in Table 3. Since

Table 3. Annulations of enals and keto esters catalyzed by **2b**.[a]



Entry	**5**, R^1	**6**, R^2, R^3	**7**, Yield [%][b]	*cis*:*trans*[c]
1	**5a**, Ph	**6a**, Ph, Et	**7aa**, 80	81:19
2	**5a**, Ph	**6b**, Ph, Me	**7ab**, 98	81:19
3	**5a**, Ph	**6c**, Ph, Bn	**7ac**, 90	75:25
4	**5a**, Ph	**6d**, 4-MeOC$_6$H$_4$, Et	**7ad**, 90	83:17
5	**5a**, Ph	**6e**, 4-FC$_6$H$_4$, Et	**7ae**, 80	73:27
6	**5a**, Ph	**6f**, 4-ClC$_6$H$_4$, Et	**7af**, 95	75:25
7	**5a**, Ph	**6g**, 3-MeC$_6$H$_4$, Et	**7ag**, 89	82:18
8	**5a**, Ph	**6h**, 2-thienyl, Et	**7ah**, 93	77:23
9	**5a**, Ph	**6i**, *c*-C$_6$H$_{11}$, Me	**7ai**, 80	67:33
10	**5a**, Ph	**6j**, Me, Et	**7aj**, 79	72:28
11	**5a**, Ph	**6k**, CF$_3$, Et	**7ak**, 94	55:45
12	**5a**, Ph	**6l**, 2-MeC$_6$H$_4$, Et	N.R.	-
13	**5a**, Ph	**6m**, 1-naphthyl, Et	N.R.	-
14	**5b**, 4-MeC$_6$H$_4$	**6b**, Ph, Me	**7bb**, 92	81:19
15	**5c**, 4-NO$_2$C$_6$H$_4$	**6b**, Ph, Me	**7cb**, 45	79:21
16	**5d**, 2-furyl	**6b**, Ph, Me	**7db**, 78	77:23
17	**5e**, *n*-C$_3$H$_7$	**6b**, Ph, Me	**7eb**, 80	75:25

[a] *Reaction conditions:* **5a**/**6a**/**2b**/DBU = 1/1.2/0.05/0.15, 0.1 M of **5a** in THF at 25 °C.

[b] Isolated yields.

[c] Determined by ^{1}H NMR.

the enantioselectivity for the reaction was not practical, only the *dr* values of the products were reported.

Various α,β-unsaturated aldehydes and ketoesters were examined, and all keto esters were easily accessed by reaction of the corresponding Grignard reagents with dialkyl oxalates.[12]

This methodology was found to be quite general for both enals and keto esters. Keto esters bearing different ester groups such as methyl ester (**6b**) and benzyl ester (**6c**) underwent the reaction smoothly, affording the γ-butyrolactone products in excellent yields with similar *dr* values (entries 2 and 3, Table 3). Aryl keto esters **6d–g** having different substituents on the phenyl ring such as 4-MeO, 4-F, 4-Cl, 3-Me were well tolerated in the reaction with cinnamaldehyde **5a** to afford the desired annulation products (entries 4–7, Table 3). The methodology was also suitable for heteroaryl keto ester **6h** and aliphatic keto esters **6i–k** with relatively lower *dr* values (entries 8–10, Table 3). Reaction of cinnamaldehyde **5a** with ethyl 3,3,3-trifluoro-2-oxopropanoate **6k** could lead to a trifluoromethyl-containing γ-butyrolactone in excellent yield (94%) but with a poor *dr* value (entry 11, Table 3). For 2-methylphenyl and 1-naphthyl keto esters **6l–m**, the reaction did not proceed, probably due to the steric hindrance (entries 12 and 13, Table 3). Various enals have also been tested under these optimized conditions and were found to be well tolerated (entries 14–17, Table 3).

The relative stereochemistry of the cyclization product was unambiguously determined. As shown in Figure 2, an X-ray analysis of the major isomer of **7db** disclosed that the major isomer is the *cis* isomer.[14]

Conclusions

In summary, we have developed N-heterocyclic carbene-catalyzed annulations of enals and keto esters, providing a facile synthesis of 4,5,5-trisubstituted γ-butyrolactones bearing two stereocenters including one quaternary carbon center. Chiral N-heterocyclic carbenes were used to tune the diastereoselectivity up to 83/17 (*cis*/*trans*) and for one substrate the enantioselectivity could be tuned up to 78% *ee* (*trans* isomer). The reaction features an organocatalytic approach, broad substrate scope, mild reaction conditions, and high yields. Further studies for improvement of the diastereoselectivity and enantioselectivity of the reaction and application of the methodology in organic synthesis are currently underway.

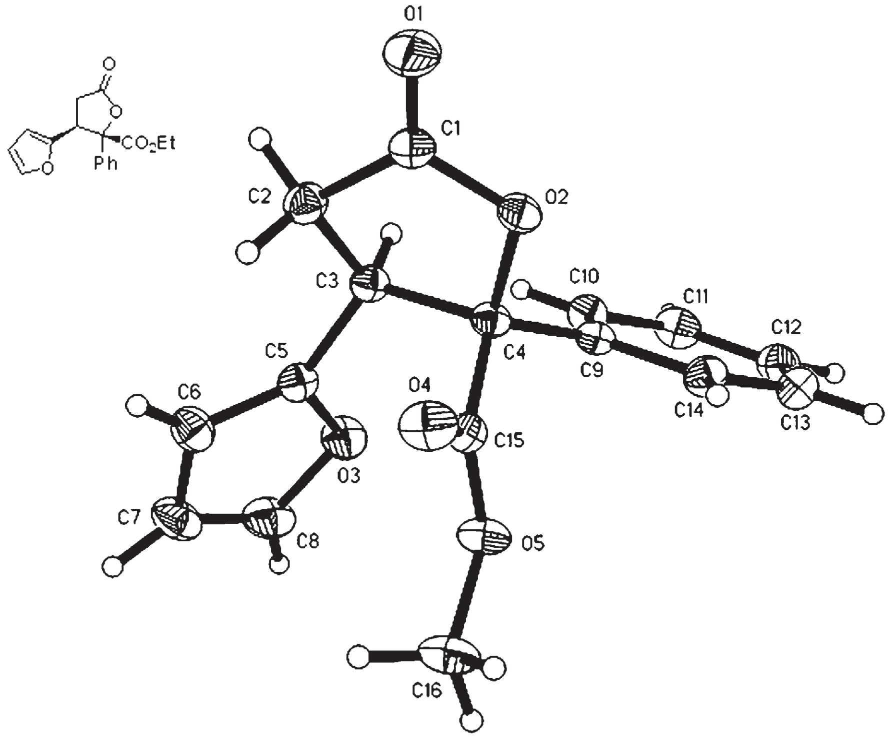


Figure 2. X-ray crystal structure of major isomer of γ-butyrolactone **7db**.

Experimental Section

General Considerations

Please see the Supporting Information for the general remarks about the equipment used, the spectroscopic and analytical data for all compounds.

Typical Procedure for the NHC-Catalyzed Annulations of Enals with Keto Esters: Preparation of γ-Butyrolactone 7aa (Table 3, entry 1)

To a dry flask filled with argon were added cinnamaldehyde **5a** (26.4 mg, 0.20 mmol), keto ester **6a** (42.8 mg, 0.24 mmol), triazolium salt **2d** (4.2 mg, 0.01 mmol) and THF (2 mL). After stirring for 5 min, DBU (4 μL, 0.03 mmol) was added. The reaction mixture was stirred at room temperature. After the reaction was complete (the disappearance of **5a**, monitored by TLC), the solvent was removed and the residue was purified by silica gel column chromatography (hexane/EtOAc = 15/1) to afford product **7aa** as a mixture of diastereomers (*cis/trans*: 81/19), white solid, yield: 80%.

Acknowledgements

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[14] CCDC 685521 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.