

Organocatalytic Enantioselective Synthesis of Nitrogen-Substituted Dihydropyran-2-ones, a Key Synthetic Intermediate of 1 β -Methylcarbapenems

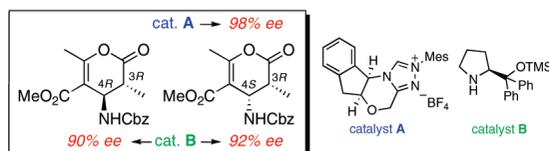
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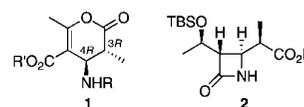
ABSTRACT



Organocatalytic enantioselective cycloadditions providing nitrogen-substituted dihydropyran-2-ones were developed in two catalytic systems. The (3*R*,4*R*)-product was a versatile intermediate in the synthesis of 1 β -methylcarbapenem antibiotics.

Enantioselective assembly of contiguous stereogenic centers remains a great challenge in organic synthesis. The task is rendered more rigorous when multiple stereocenters are involved in target molecules such as natural products and drug candidates. For instance, optically active (3*R*,4*R*)-4-amino-3,6-dimethyl-2-oxo-3,4-dihydro-2*H*-pyran-5-carboxylate (**1**), a precursor of 1 β -methylazetidinone (**2**), is a versatile intermediate in the synthesis of 1 β -methylcarbapenem antibiotics.¹ Cycloaddition is a promising approach to this molecule.² Turner et al. first reported an inverse-electron-demand hetero-Diels–Alder reaction between 2-acylamino-methylene-3-oxobutanoic acid derivatives (e.g., **4**) and a ketene acetal under thermal conditions to provide substituted

dihydropyranones.^{2a} Although they successfully constructed dihydropyranone structures, separation of the undesired diastereomers was unavoidably required. Interestingly, they found that protection of the carboxylic acid moiety as an amide was crucial to obtain the 3,4-*trans* isomer selectively. No chiral induction, however, was observed when chiral amide derivatives were subjected to cycloaddition. About 10 years later, Nakai et al. reported the Lewis acid promoted version of the cycloaddition reaction.^{2b} Despite the high 3,4-*trans* diastereoselectivity, less than 26% ee of asymmetric induction was realized by use of chiral aluminum, titanium, or borane complexes. We therefore considered that high enantiocontrol was a critical component for the efficient preparation of **1**. Herein, we wish to report the first organocatalytic enantioselective synthesis of **1**.



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(1) For a review on the synthesis of 1 β -methylcarbapenem antibiotics, see: Berks, A. H. *Tetrahedron* **1996**, *52*, 331–375.

(2) (a) Bayles, R.; Flynn, A. P.; Galt, R. H. B.; Kirby, S.; Turner, R. W. *Tetrahedron Lett.* **1988**, *48*, 6341–6344. (b) Nishiuchi, M.; Honda, K.; Nakai, T. *Chem. Lett.* **1996**, 321–322.

Recently, a chiral *N*-heterocyclic carbene (NHC) catalyzed, enantioselective oxodiene Diels–Alder reaction was reported by Bode et al.^{3,4} The reaction efficiently provided a wide range of 3,4-*cis*-dihydropyranones with high levels of diastereo- and enantioselectivity. The high stereoselectivity was explained by the transition state in which β -substituted enones approach the *Z*-enolates in *endo* fashion (Figure 1,

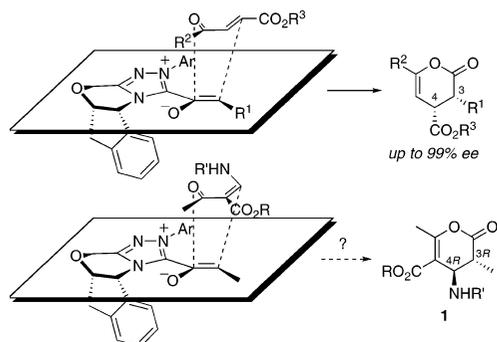


Figure 1. Stereochemical models for *endo* cycloaddition. Bode's result (top) and the proposed model for this study (bottom).

top). Therefore, we envisioned that *endo* cycloaddition between α,β -disubstituted enones and the *Z*-enolate would generate the 3,4-*trans* stereoisomers **1** predominantly (Figure 1, bottom). In addition, the cycloaddition reaction with an amino-containing oxodiene was performed to expand this methodology to complex molecules.

Hence, we prepared various substrates **4a–f** in a single step from the corresponding alkoxyethyleneacetoacetates (Table 1).^{5,6} All substrates have a *trans* configuration with respect to the ester and amino groups as supported by NMR data.⁷ The highly volatile and labile 2-chloropropanal

required an elaborate preparation method from *n*-propanal and *N*-chlorosuccinimide (NCS).⁸ After many attempts, we found that chlorination was successful in CCl_4 , and the succinimide formed was easily separated by filtration of the reaction mixture. The ^1H NMR spectrum of the filtrate showed 98% conversion to 2-chloropropanal with no contamination of succinimide. The racemic 2-chloropropanal thus obtained was subjected as a CCl_4 solution to the cycloaddition reaction with **4a–f** in the presence of 5 mol % of chiral NHC ligand **3**.^{4,9,10} Remarkably, tetrasubstituted 3,4-dihydropyran-2-ones were obtained in adequate yields with high enantiomeric excesses. To our surprise, *cis*-isomers **5a–f** predominated over *trans*-isomers **1a–f** in all cases. The enantiomeric excesses of **5d–f** were greater than 97% ee, reaching >99% ee after a single recrystallization. This stereochemical outcome was unexpected since *endo* approach of the *E*-oxodiene from the less hindered face of the *Z*-enolate should lead to the *trans*-lactone **1** (cf. Figure 1). This led us to consider the possibility of olefin isomerization under the cycloaddition conditions. To this end, the reaction was stopped prior to completion, and the recovered products were analyzed by NMR spectroscopy. However, no isomeric oxodiene was detected, which implied that *E*-oxodiene was the actual reactant in the cycloaddition.^{11,12}

In consideration of the above experiments and parallel studies, the stereochemical mode of cycloaddition was reconsidered. The *R*-configuration at C3 is rationalized by a

(3) For a review on *N*-heterocyclic carbenes as organocatalysts, see: Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606–5655.

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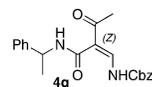
(7) Saito, S.; Uedo, E.; Kato, Y.; Murakami, Y.; Ishikawa, T. *Synlett* **1996**, 1103–1105.

(8) (a) Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108–4109. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790–4791. (c) Recently, α -chloroaldehyde bisulfite salts were identified as potential alternatives (see ref 4c).

(9) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Org. Chem.* **2005**, *70*, 5725–5728.

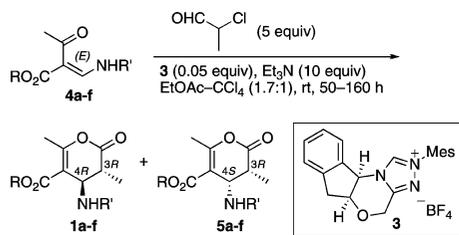
(10) We initially performed the reaction with 0.5 mol % of the catalyst according to the original procedure. However, no 3,4-dihydropyran-2-ones were obtained, presumably due to the low reactivity of the amino-containing oxodienes.

(11) We further explored the influence of olefin geometry on the stereoselectivity by carrying out the reaction with *Z*-oxodiene **4g**^{2a} where α -phenethylamide was incorporated as a carboxylic acid protecting group. In contrast, cycloaddition did not take place, and **4g** was recovered unchanged. This is probably due to the inherent inertness of the trisubstituted *Z*-oxodiene arising from the bulkiness of the amide portion or strong hydrogen bonding between the amide proton and the carbonyl oxygen, causing an *s-cis* conformation which is disfavored for cycloaddition.



(12) The influence of olefin geometry will become more apparent if the *Z*-isomers of **4a–f** are submitted to cycloaddition. However, in our hands, those isomers could not be synthesized. We therefore do not exclude the case that isomerization occurs to generate the *Z*-isomer, which reacts rapidly with the catalytically generated enolate, leading to the observed stereochemistry.

Table 1. Chiral NHC-Catalyzed Asymmetric Cycloaddition



entry	4	R	R'	yield ^a (%)	ratio (1:5) ^b	ee for 5 ^{c-e} (%)	[α] _D for 5 ^f (deg)
1	4a	Et	Ac	40	1:5	N.D.	–97
2	4b	Et	Cbz	65	1:5	N.D.	–74
3	4c	Et	Boc	65	1:7	N.D.	–86
4	4d	Me	Ac	62	1:4	97 (>99)	–95
5	4e	Me	Cbz	80	1:12	98 (>99)	–89
6	4f	Me	Boc	70	1:9	98 (>99)	–79

^a Isolated yield. ^b Determined by NMR analysis. ^c N.D.: not determined. ^d Determined by chiral-phase HPLC analysis. ^e The number in parentheses refers to the ee value after recrystallization from hexane/ethyl acetate. ^f After recrystallization.

selective addition of oxodiene from the sterically less congested *Si* face of the *Z*-enolate.⁴ The *endo* approach resulting in the *trans*-isomer **1** was blocked by a severe steric interaction between the bulky carbamate group (or acetyl-amino group) of the oxodiene and the triazolium moiety of the dienophile (cf. Figure 1, bottom). Such an interaction seems unlikely in the *exo* transition state where other steric interactions might increase (Figure S1, Supporting Information). We therefore supposed that the concerted transition states as shown in Figure 1 and S1 (Supporting Information) did not fully explain the observed stereochemical outcome. Alternatively, a two-step process consisting of Michael addition followed by ring closure might be involved in the present cycloaddition. By taking the steric environment into consideration, it is likely that Michael addition progresses through a conformation in which the β -hydrogen of the enone turns in the same direction as the bulky triazonium moiety (Figure 2, A). As a consequence, *cis*-lactones **5a–f** were

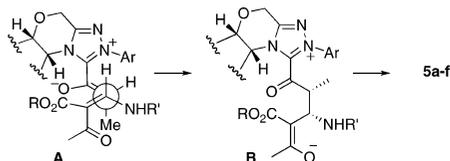


Figure 2. Stepwise reaction course leading to *cis*-isomers **5a–f**.

generated through the sterically defined Michael adduct **B**. Although we cannot fully exclude the concerted pathway, it is evident that this work provides vital information on the mechanism of the NHC-catalyzed cyclization reaction.

Despite the excellent enantioselectivity achieved by employing the chiral NHC ligand, the undesired diastereoselectivity forced us to investigate alternative cycloaddition methods. Recently, pyrrolidine derivatives such as diarylprolinol ethers have emerged as potentially general organocatalysts¹³ and cycloaddition reactions have been achieved with good diastereo- and enantioselectivities.¹⁴ However, these organocatalytic cycloadditions are limited to highly electron-deficient acceptors, and acceptors containing amino groups are still unknown. Therefore, we examined the organocatalytic cycloaddition reaction between oxodienes **4a–f** and *n*-propanal to produce dihydropyranones with a 4-amino group.

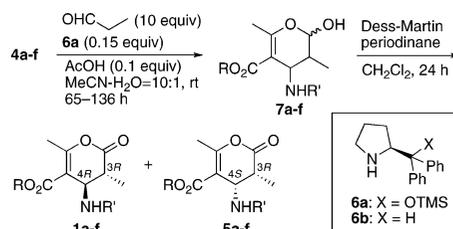
According to the conditions developed by Chen et al.,^{14d} *E*-oxodienes **4a–f** were treated with *n*-propanal in the

(13) For reviews on diarylprolinol ethers as organocatalysts, see: (a) List, B. *Chem. Commun.* **2006**, 819–824. (b) Marigo, M.; Jørgensen, K. A. *Chem. Commun.* **2006**, 2001–2011. (c) Guillena, G.; Ramón, D. J. *Tetrahedron: Asymmetry* **2006**, *17*, 1465–1492. (d) Palomo, C.; Mielgo, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 7876–7880.

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presence of a catalytic amount of AcOH (10 mol %) and α,α -diphenylprolinol trimethylsilyl ether **6a** (15 mol %) in $\text{CH}_3\text{CN}-\text{H}_2\text{O}$ (10:1) at room temperature (Table 2). The

Table 2. Asymmetric Cycloaddition Catalyzed by Diphenylprolinol Derivatives (**6a** and **6b**)



entry	4	R	R'	yield ^a (%)	ratio (1:5) ^b	ee for 1 ^{c,d} (%)	ee for 5 ^{c,d} (%)
1	4a	Et	Ac	54	1:1.7	N.D.	N.D.
2	4b	Et	Cbz	59	1:1.3	N.D.	N.D.
3	4c	Et	Boc	38	1:1.7	N.D.	N.D.
4	4d	Me	Ac	54	1:1.3	73	>99
5	4e	Me	Cbz	64	1:1.4	90	92
6 ^e	4e	Me	Cbz	54	1:1.1	52	32
7	4f	Me	Boc	22	1:1.4	85	79

^a Isolated yield for two steps. ^b Determined by ¹H NMR analysis. ^c For ethyl esters, ee values were not determined since two diastereomers were inseparable. ^d Determined by chiral-phase HPLC analysis. ^e **6b** was used instead of **6a** as an enamine catalyst.

cycloaddition products **7a–f** were obtained as a mixture of four inseparable diastereomers, which were oxidized as a mixture by Dess–Martin reagent to afford diastereomeric lactones (**5a–f** and **1a–f**) in moderate to good yields for two steps. Notably, in contrast with the results obtained by NHC-catalyzed cycloaddition, the diastereoselectivity was rather modest, and the desired 3,4-*trans*-dihydropyranones **1** were obtained with good enantiomeric excesses. Among the substrates tested, Cbz-protected methyl ester **4e** showed the best properties and the two diastereomers could be separated by flash column chromatography (entry 5). While the diastereoselectivity is still unsatisfactory, this is the first example of enantioselective assembly of nitrogen-substituted 3,4-*trans*-dihydropyranones by cycloaddition. Pyrrolidine catalyst **6b**, which does not contain a trimethylsilyl ether group, effected cycloaddition as well, but the enantioselectivity was considerably decreased (entry 6). Recently, in a related system Ma and co-workers succeeded in enantioselective synthesis of tetrasubstituted dihydropyranones lacking the *N*-substituent with high *trans* selectivity.^{14c} Interestingly, they observed that diastereoselectivity of the product was independent of the olefin geometry of the starting oxodienes; *E*→*Z* isomerization occurred first, and the reaction progressed from the *Z*-configuration even if the isomerically pure *E*-oxodiene was used. In our case, however, *E*→*Z* isomerizations of oxodienes **4a–f** were not observed as evidenced by the recovery of the unchanged starting materials. It is of

interest that such a difference in reactivity arises by the presence or absence of the nitrogen substituent.¹⁵

It can be rationalized that the configuration at C3 of the product is controlled by the steric hindrance of the substituent α to the pyrrolidine nitrogen. This forces the approach of electrophiles to the *Re* face of the enamine, thus affording the product of *3R*-configuration.¹³ The formation of *cis*-isomers **5a–f** is reasonably explained by a synclinal transition state, in which there are favorable electrostatic interactions between the enamine nitrogen and the carbonyl group (Figure 3, top). This arrangement¹⁶ widely accounts for the

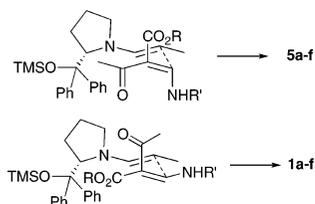


Figure 3. Synclinal models leading to *cis*-isomers **5a–f** (top) and *trans*-isomers **1a–f** (bottom).

prominent *syn* selectivity of the enamine-catalyzed reactions.^{13,14,17} However, when the amino substituent is attached to the β -position of the enone, such electrostatic interactions are weakened due to the resonance effect by the amino group. As a result, the reaction proceeds through either the conformation which has the carbamate (or acetylamino) group in the least hindered position (Figure 3, bottom) or, alternatively, the anti-periplanar transition state,¹⁶ where the amino substituent is away from the pyrrolidine ring to avoid steric hindrance (Figure S2, Supporting Information). Thus, comparable amounts of *trans*-isomers **1a–f** were produced along with *cis*-isomers **5a–f** with good enantioselectivity.¹⁸

With optically active *trans*- δ -lactone **1e** in hand, we then undertook the synthesis of *all-trans*-substituted tetrahydropyranone **9**, a valuable intermediate of 1β -methylcarbapenem

(15) Amide-containing Z-oxodiene **4g** was again unreactive in the enamine-catalyzed conditions.

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(17) For selected examples of *syn*-selective Michael additions with diarylprolinol ether catalysts, see: (a) Hayashi, Y.; Gotoh, H.; Hayashi, T.; Shoji, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4212–4215. (b) Ender, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 467–469. (c) Hayashi, Y.; Okano, T.; Aratake, S.; Hazeldard, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 4922–4925. (d) Zhu, S.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 545–548.

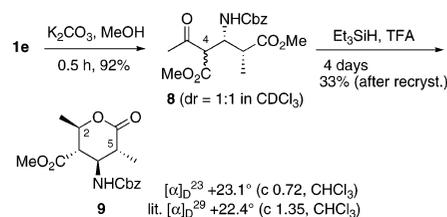
(18) A concerted mechanism as proposed by Jørgensen et al. for the addition of aldehyde to enones cannot be ruled out.^{14a}

(19) (a) Bayles, R.; Flynn, A. P.; Galt, R. H. B.; Kirby, S.; Turner, R. W. *Tetrahedron Lett.* **1988**, *29*, 6345–6348. (b) Hatanaka, M. *Tetrahedron Lett.* **1987**, *28*, 83–86. (c) Udodong, U. E.; Fraser-Reid, B. *J. Org. Chem.* **1988**, *53*, 2131–2132.

(20) Detailed NMR analysis indicated that two of the products were not lactones, but acyclic reduction products, namely precursors of lactone.

antibiotics (Scheme 1).^{2,19} Methanolysis of **1e** with K_2CO_3 afforded acyclic ketone **8** as an approximately 1:1 diaster-

Scheme 1. Synthesis of *All-Trans*-Substituted Tetrahydropyranone



omeric mixture at C4. The ketone **8** was then treated with excess Et_3SiH and TFA for 4 days to undergo reduction and spontaneous lactonization.^{19a} In the crude NMR spectrum, four possible diastereomers were detected in a ratio of 12:4:3:1²⁰ with the *all-trans* isomer **9** as the major product. After separation by silica gel chromatography and recrystallization, the major isomer **9** was isolated as colorless needles in 33% yield. The absolute configuration of **9** was determined to be *2R,3S,4R,5R* by comparison of the specific optical rotation with the value reported in the literature.^{19b}

In conclusion, we have achieved an enantioselective synthesis of 3,4,5,6-tetrasubstituted 3,4-dihydropyran-2-ones bearing a nitrogen substituent at C4 by means of organocatalytic cycloadditions. Our investigation proved that chiral triazonium salt **3** gave rise to excellent asymmetric induction with high *3,4-cis* stereoselectivity, while application of diphenylprolinol silylether **6a** resulted in a mixture of *cis* and *trans* isomers with good enantioselectivities. To the best of our knowledge, this is the first example using the organocatalytic reaction to construct the four contiguous asymmetric centers of 1β -methylcarbapenem skeletons. We believe that the present investigation will become not only an important guideline for developing new enantioselective routes to carbapenems and related biologically active molecules but also good examples to address their reaction mechanisms.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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