JACS Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

pubs.acs.org/jacsau

Letter

One-Step Asymmetric Construction of 1,4-Stereocenters via Tandem Mannich-Isomerization Reactions Mediated by a Dual-Functional Betaine Catalyst

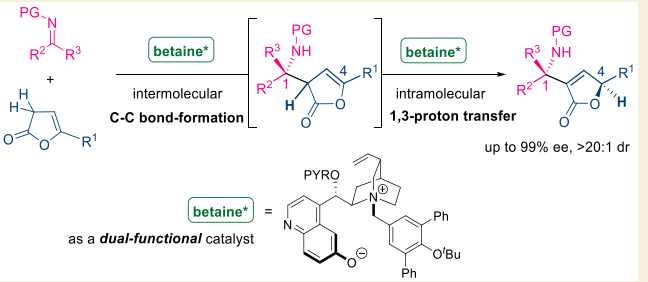
Yu Deng, Xiaohuo Shi, Guangfa Shi, Xingyu Lu, Jisheng Luo,* and Li Deng*

Cite This: *JACS Au* 2022, 2, 2678–2685

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The construction of chiral motifs containing nonadjacent stereocenters stands out as a major challenge as they are usually constructed in separate steps utilizing different chiral catalysts. Therefore, the development of new strategies to streamline the construction of such complex motifs has become a major focus of asymmetric synthesis. We report here an unprecedented asymmetric tandem Mannich-isomerization reaction that allows the direct construction of 1,4-stereocenters in a highly stereoselective manner. This asymmetric transformation demonstrated the potential of a tandem nucleophilic addition-isomerization reaction as a broadly useful strategy for the efficient construction of 1,4-stereocenters. Notably, this tandem reaction was mediated by a single chiral betaine as a dual-functional catalyst, promoting first an enantioselective intermolecular C−C bond forming reaction and next a stereoselective intramolecular 1,3-proton transfer reaction.

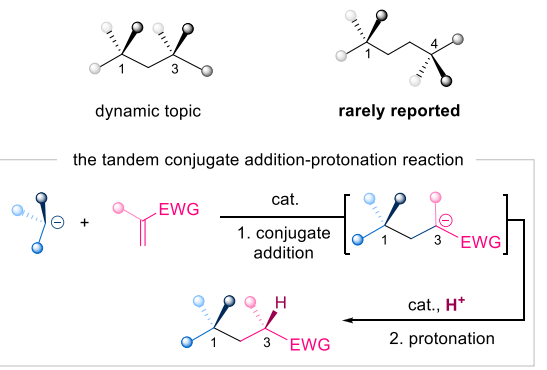


KEYWORDS: *asymmetric tandem reaction, remote stereocenters, Mannich reaction, dual-functional catalysis, butenolide, betaine catalyst.*

Modern organic synthesis concerns not only building complex molecular structures but also accomplishing these tasks in dramatically improved efficiency.[1−4] The development of new strategies to streamline the construction of complex motifs, which requires lengthy synthetic sequences by existing methods, has become a major focus. In the context of asymmetric synthesis, the construction of chiral motifs containing nonadjacent stereocenters stands out as a major challenge as they are usually constructed in separate steps utilizing different chiral catalysts.[5−8] Ideally, such chiral motifs could be constructed by a singular catalyst promoted tandem reaction. Indeed, the development of such tandem reactions for the construction of 1,3-stereocenters has been intensively pursued in recent years.[9−21] In particular, the catalytic asymmetric tandem conjugate addition-protonation reaction as a versatile streamline strategy to directly generate chiral motifs with 1,3-stereocenters from achiral starting materials attracts substantial attention (Scheme 1).[9] In contrast, the one-step construction of 1,4-stereocenters remains underexplored.

In 2021, Jiang and co-workers reported a tandem reductive coupling-protonation reaction using a photocatalyst and a chiral phosphoric acid catalyst, affording ε-oxo azaarenes bearing two benzylic 1,4-stereocenters (Scheme 2A).[22] Very recently, Wang and co-workers disclosed a tandem hydroalkylation-reduction reaction enabled by the combination of a chiral copper catalyst and a chiral ruthenium catalyst fulfilling the generation of 1,4-stereocenters.[23] Lundgren and co-workers developed a tandem arylation-allylation reaction catalyzed by a chiral ruthenium catalyst, yielding homoallylic alcohols bearing 1,4-stereocenters.[24] We envisaged that the 1,4-stereocenters could be constructed via a tandem addition-

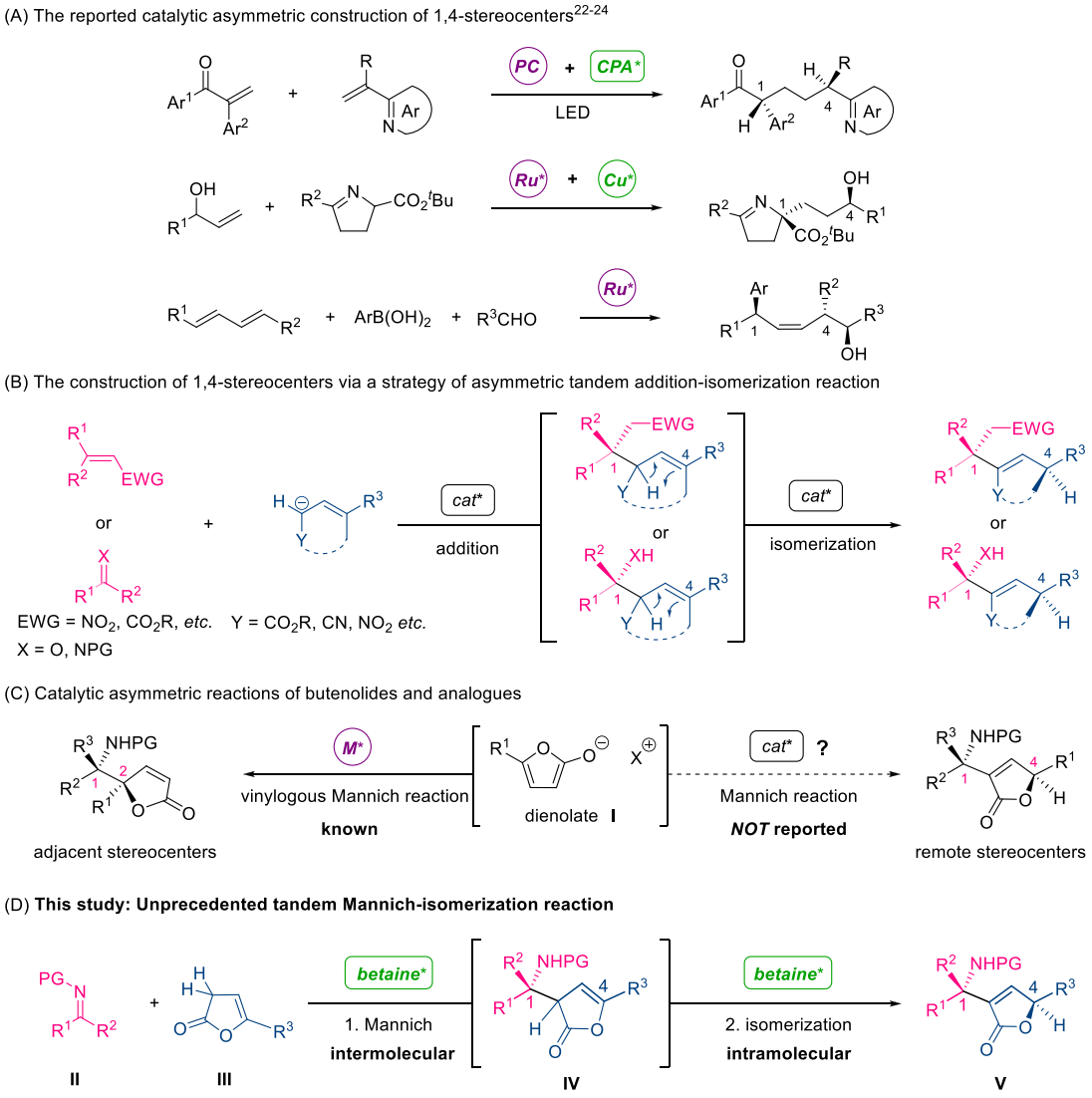
Scheme 1. Nonadjacent Stereocenters



Received: August 25, 2022
Revised: November 7, 2022
Accepted: November 8, 2022
Published: November 23, 2022

https://doi.org/10.1021/jacsau.2c00465
JACS Au 2022, 2, 2678−2685

Scheme 2. Direct Construction of 1,4-Stereocenters



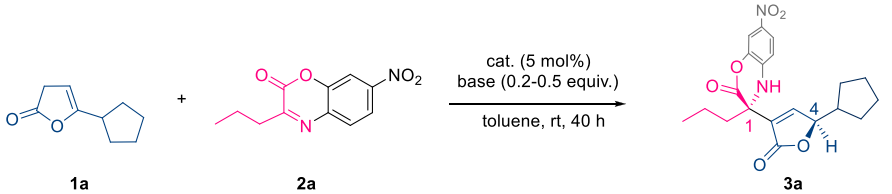
isomerization reaction (Scheme 2B). Specifically, the initial enantioselective addition reaction of allyl-type carbanion generates the C1 stereocenter followed by the stereoselective olefin isomerization reaction that generates the remote C4 stereocenter. In principle, various electrophiles could be employed in the nucleophilic addition reaction, such as carbonyl, imine, and a broad range of Michael acceptors. Thus, this tandem addition-isomerization reaction could serve as a broadly applicable strategy for the efficient construction of 1,4-stereocenters.

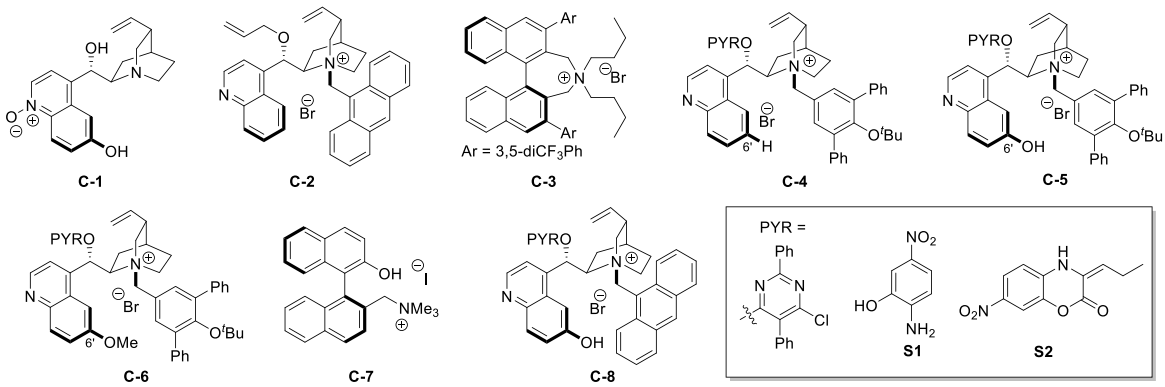
To demonstrate that the one-step construction of a 1,4-stereocenter could be realized via a strategy of catalytic asymmetric addition-isomerization tandem reaction, a Mannich reaction of butenolides was examined. Chiral amino butenolides are structural motifs embedded in a wide range of biologically active natural products.[25−28] Moreover, the amino butenolides were frequently presented with the amino stereocenter and the butenolide stereocenter in either 1,2- or 1,4-relationship. Accordingly, considerable efforts have been devoted to the development of asymmetric methods for the construction of these motifs.[29] Particularly, using metal-based chiral Lewis acids as catalysts, various asymmetric vinylogous Mannich reactions have been developed, yielding chiral amino butenolides with 1,2-stereocenters (Scheme 2C).[30−46] However, efficient constructions of amino butenolides with remote 1,4-stereocenters remains an unmet challenge.

In principle, one could envision that such a challenge could be overcame by the development of an asymmetric tandem reaction with a Mannich reaction of butenolides and imines followed by a stereoselective 1,3-proton transfer reaction (Scheme 2D). Ideally, this tandem asymmetric reaction could be realized by a single dual-functional catalyst. To realize this proposed tandem reaction, there were significant challenges. First, the required catalytic asymmetric Mannich reaction remains unknown. Second, although an efficient chiral catalyst for the asymmetric isomerization of butenolides by 1,3-proton transfer has been reported,[47] the realization of the postulated tandem asymmetric reaction required a unique chiral catalyst, which could not only promote 1,3-proton transfer but also promote first the intermolecular C−C bond-forming Mannich reaction and next the intramolecular 1,3-proton transfer reaction. This is particularly daunting, given that the starting material butenolide **III** is sterically much more accessible than

https://doi.org/10.1021/jacsau.2c00465
JACS Au 2022, 2, 2678−2685

Table 1. Investigation of Reaction Conditions[a]





entry	cat.	base	solvent	time	conversion	yield[b]	dr[c]	ee[d]
1[e]	**C-1**		toluene	40 h	12%	nd	nd	nd
2[f]	**C-2**	KOH	toluene	40 h	71%	33%	70:30	8%
3[f]	**C-3**	KOH	toluene	40 h	47%	8%	65:35	−12%
4[f]	**C-4**	KOH	toluene	40 h	63%	19%	68:32	5%
5[e,f]	TBAB	KOH	toluene	40 h	80%	nd	nd	nd
6[f]	**C-5**	KOH	toluene	40 h	>95%	43%	83:17	85%
7[f]	**C-6**	KOH	toluene	40 h	75%	13%	72:28	12%
8[e,f]	**C-7**	KOH	toluene	40 h	9%	nd	nd	nd
9[f]	**C-8**	KOH	toluene	40 h	82%	25%	50:50	72%
10[g]	**C-5**	K_2CO_3	toluene	40 h	>95%	64%	77:23	90%
11[h]	**C-5**	$NaHCO_3$	toluene	16 h	>95%	65%	86:14	98%
12[h,i]	**C-5**	$NaHCO_3$	CPME	3 h	>95%	75%	88:12	98%

[a] **1a** (0.15 mmol), **2a** (0.10 mmol), catalyst (5 mol %), base, 1.0 mL solvent. [b] NMR yields were determined by ^{1}H NMR analysis (see the Supporting Information for details). [c] dr values were determined by ^{1}H NMR analysis. [d] ee values were determined by chiral HPLC analysis. [e] nd = not determined since there was no detectable amount of desired product **3a**. [f] aq. KOH (50 wt %, 0.2 equiv). [g] aq. K_2CO_3 (33 wt %, 0.2 equiv). [h] aq. $NaHCO_3$ (50 g/L, 0.5 equiv). [i] CPME = cyclopentyl methyl ether.

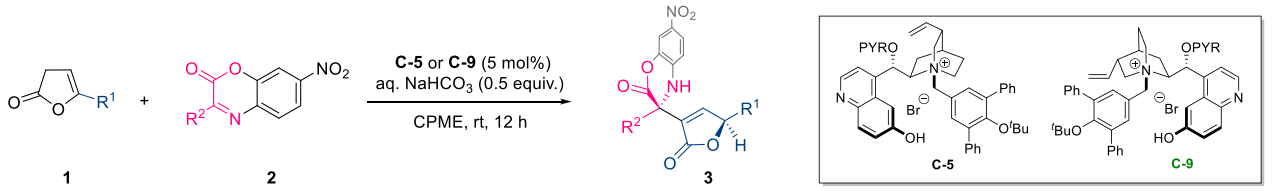
the intermediate butenolides **IV** toward isomerization via a 1,3-proton transfer reaction.

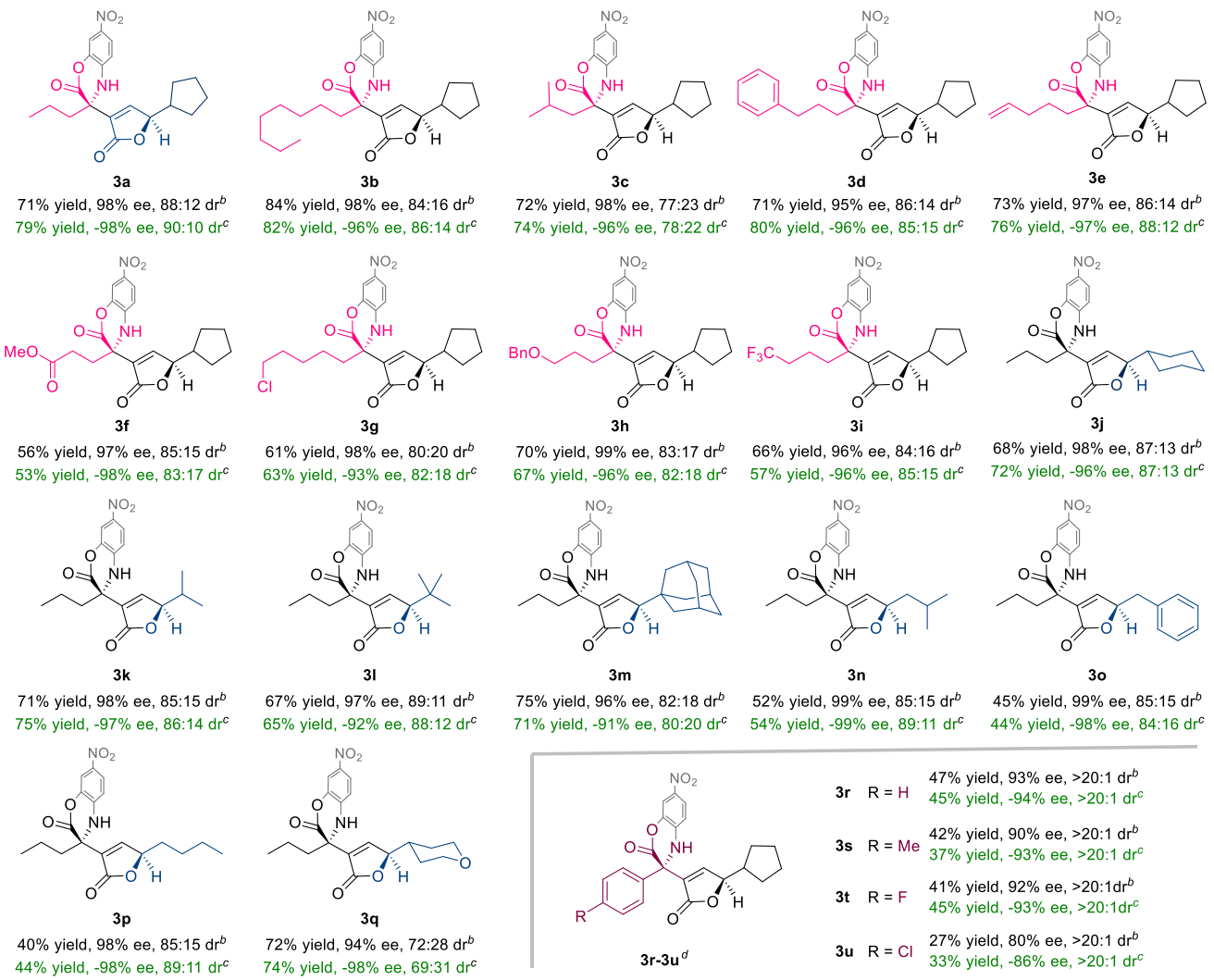
Several years ago, we discovered that 6′-OH cinchona alkaloid **C-1** promoted isomerization of β,γ-unsaturated butenolide via 1,3-proton transfer to generate optical active γ-substituted α,β-unsaturated butenolide.[47] This reaction presumably proceeded through dienol analogue of dienolate **I** (Scheme 2C). We postulated that dienolate **I** might be intercepted by an imine electrophile to realize the elusive asymmetric Mannich reaction. Following this postulation, we examined the reaction of butenolide **1a** and imine **2a**.[33] However, the desired amino butenolide **3a** was not detected (Table 1, entry 1). Further catalyst screening studies showed that these well-known phase transfer catalysts such as Corey catalyst (**C-2**),[48] Maruoka catalyst (**C-3**),[49] and cinchonium catalyst **C-4** afforded detectable amount of the desired product **3a** (Table 1, entries 2−4). However, the major product in these reactions was still the isomerization product while **3a** was formed as a minor product and in poor dr and ee. Moreover, the reaction with the achiral ammonium salt TBAB afforded a uncharacterizable complex mixture (Table 1, entry 5). We next investigated betaine **C-5** as a catalyst. To our delight, **3a** was formed as the major product and in significantly improved enantioselectivity and diastereoselectivity (Table 1, entry 6). To identify the structural features of **C-5** that are responsible for its activity and stereoselectivity, we examined catalysts **C-6** bearing a 6′-OMe group. Catalyst **C-6** (Table 1, entry 7) afforded product **3a** in much lower yield, dr (70:30), and ee (10%). These results clearly demonstrated that the presence of 6′-OH was critical to **C-5** as an efficient dual-functional catalyst for the tandem Mannich-isomerization reaction. Notably, the binaphthalene-betaine catalyst **C-7** (Table 1, entry 8) was found to be inactive.[50] On the other hand, betaine catalyst **C-8**, which contained an anthracen-9-ylmethyl group (Table 1, entry 9), afforded **3a** albeit in drastically reduced yield and stereoselectivities. These results demonstrated that betaine catalyst **C-5** is uniquely effective in promoting the asymmetric tandem Mannich-isomerization reaction.

Although **3a** could be obtained in good stereoselectivities with catalyst **C-5** (Table 1, entry 6), the yield of **3a** was moderate and needed further improvement. Upon careful analysis of the crude reaction mixture, except for an isomerized

https://doi.org/10.1021/jacsau.2c00465
JACS Au 2022, 2, 2678−2685

Table 2. Substrate Scope[a]





[a]**1** (0.30 mmol), **2** (0.20 mmol), **C-5** or **C-9** (5 mol %), aq. $NaHCO_3$ (50 g/L, 160 μL, 0.5 equiv), CPME (2.0 mL) at rt, 12 h. [b]Data for **C-5** catalyzed reactions; yields were yields of the isolated products; ee and dr values were determined by HPLC and ^{1}H NMR analysis, respectively. [c]Data for **C-9** catalyzed reactions are reported as green words. [d]20 mol % catalyst was used.

side product, amine **S1** and enamine **S2** were also detected (Table 1).[51] These two side products were presumably generated from the hydrolysis and tautomerization of the imine **2a**, respectively. We next found that these side reactions could be suppressed by replacing potassium hydroxide with a weaker base. Improved yield (64%) and ee value (90%) were obtained with potassium carbonate as the base (Table 1, entry 10). The reaction could proceed with even sodium bicarbonate (Table 1, entry 11), leading to significantly higher diastereoselectivity (86:14 dr) and enantioselectivity (98% ee). Solvent screening indicated that the reaction occurred much faster in ether solvents. In cyclopentyl methyl ether (Table 1, entry 12), the reaction went to completion in 3 h without compromising the stereoselectivity to furnish **3a** in 75% yield.

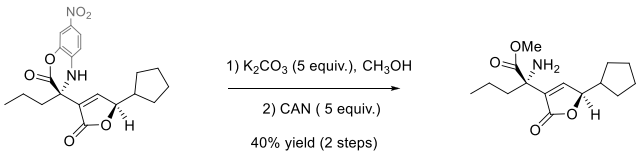
With the optimized condition, we investigated the substrate scope (Table 2). Catalyst **C-5** presented consistent high activity and selectivities to afford the desired products (**3a**–**3i**) with a range of alkylated ketimines in high enantioselectivities (96–98% ee), useful diastereoselectivities (77:23–88:12 dr) and yields (56–84%). Notably, the presence of long linear (**3b**) and β-branched (**3c**) aliphatic groups did not compromise either reactivity or stereoselectivity. The reaction readily tolerates various functional groups in the ketimines, including olefin (**3e**), ester (**3f**), halides (**3g**, **3i**), and ether (**3h**). We next examined the scope of γ-substituted β,γ-unsaturated butenolides. With butenolides bearing α-branched substituents, the reactions proceeded efficiently toward the desired products (**3a**, **3j**-**3m**) in high stereoselectivities and

https://doi.org/10.1021/jacsau.2c00465
JACS Au 2022, 2, 2678–2685

67−75% yields. Notably, even bulky groups such as *t*-butyl (**3l**) and adamantyl (**3m**) were well accepted by the reaction. Butenolides with less hindered *β*-branched and linear substituents were converted into **3** (**3n**−**3p**) in high stereoselectivities (98−99% ee, 85:15 dr) and moderate yields (40−52%). A good reactivity (72% yield) and ee value (94%) but lower diastereomeric ratio (72:28) were observed in the formation of product **3q** containing a heterocyclic group. We examined the reaction of *γ*-phenyl-*β*,*γ*-unsaturated butenolide with imine **2a**, which furnished a mixture of unidentifiable products. As listed in Table 2, catalyst **C-9**, a pseudoenantiomer of **C-5**, could catalyze the reaction in a similar efficiency (data in green).[52] Various aryl ketimines could also be employed in this tandem reaction. Reactions went to completion with an increased loading of 20 mol % catalyst, to afford the products (**3r-u**) in 80−94% ee, greater than 20:1 dr and moderate yields.

As illustrated in Scheme 3, product **3a** could be converted into amino butenolide **5**. The 2-morpholinone ring in **3a** underwent alcoholysis under the basic condition, while the butenolide ring remained intact. Then the *N*-aryl group was removed oxidatively by cerium ammonium nitrate (CAN) to afford the amino butanolide **5a** as a pure diastereomer in 98% ee and with 40% yield over two steps.

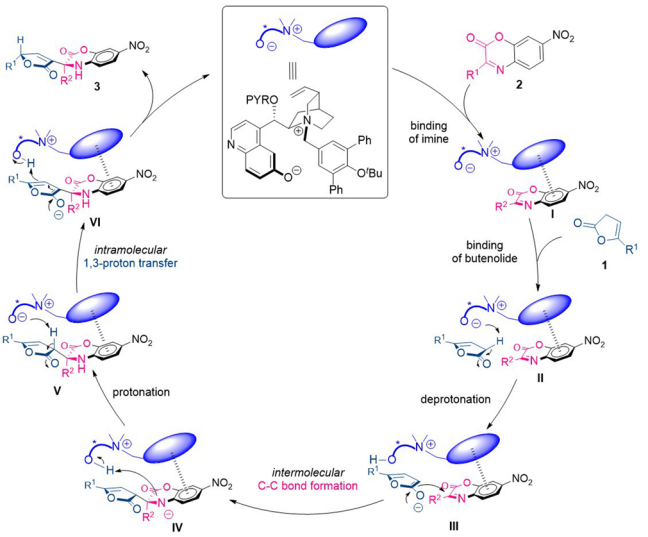
Scheme 3. Product Derivatization



To test the impact of replacing nitro group with other groups, ketimines bearing different *N*-aryl groups (**2A**−**D**) were investigated (Table 3). By replacing the nitro group with carboxylate or trifluoromethyl group, products (**3A,B**) were obtained in significantly decreased stereoselectivities. Meanwhile, catalyst **C-5** was inactive for the reactions of *N*-*para*-bromophenyl ketimine (**2C**) and *N*-phenyl ketimine (**2D**). These results indicated that the presence of *N*-*para*-nitrophenyl group has a positive impact on the stereoselectivities on both the Mannich reaction and isomerization reaction.

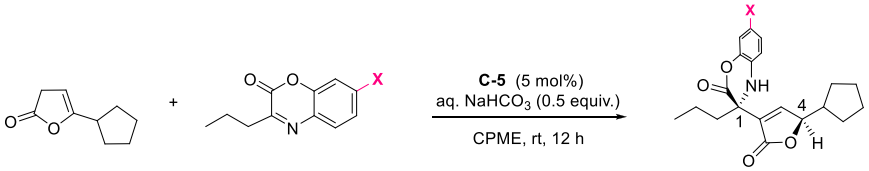
A proposed catalytic cycle is illustrated in Scheme 4. Presumably, the betaine interacts with imine **2** to form complex **I**. Next, butenolide **1** was deprotonated by the phenoxide of the betaine catalyst then underwent asymmetric Mannich reaction to afford intermediate **V**. Then, the Mannich product underwent stereoselective isomerization to deliver product **3**. In this proposed mechanism the putative dienolate and ketimine were postulated to be brought into proximity in complex **III**, which provided a rational for the catalyst to promote the intermolecular Mannich reaction first then the intramolecular isomerization.

Scheme 4. Proposed Catalytic Cycle



In summary, we realized an unprecedented organocatalytic asymmetric tandem Mannich-isomerization reaction of butenolides and ketimines, affording chiral amino butenolides with 1,4-stereocenters in excellent to good enantioselectivities. This asymmetric transformation demonstrated that the catalytic asymmetric tandem addition-isomerization reaction could provide an attractive strategy for the direct formation of 1,4-stereocenters from achiral starting materials. To our knowledge, this is the first documentation of betaines as an efficient chiral dual-functional catalyst. Notably, this dual-functional betaine promoted first an intermolecular C−C bond forming reaction and next an intramolecular 1,3-proton transfer reaction.

Table 3. Investigation of *N*-Aryl Imines



entry	substrate	X	conversion (%)	product	ee	dr
1	**2a**	NO_2	> 95	**3a**	98%	88:12
2	**2A**	CO_2Me	> 95	**3A**	80%	60:40
3	**2B**	CF_3	> 95	**3B**	78%	66:34
4	**2C**	Br	< 5	**3C**	\	\
5	**2D**	H	< 5	**3D**	\	\

https://doi.org/10.1021/jacsau.2c00465
JACS Au 2022, 2, 2678−2685

METHODS

General Procedure for the Tandem Mannich-Isomerization Reactions

To a 20 mL vial equipped with a stir bar, imine **2** (0.20 mmol, 1.0 equiv) and catalyst (5 mol % for **3a−q** or 20 mol % for **3r−u**) were added, followed by addition of CPME (2 mL). After complete dissolution, butenolide **1** (0.30 mmol, 1.5 equiv) and aqueous $NaHCO_3$ (50 g/L, 160 μL, 0.5 equiv) were added successively. After stirring for 12 h at rt, the reaction was quenched by the addition of water (1 mL). The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (2 mL × 3). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under vacuum to give the crude product, which was analyzed by ^{1}H NMR technique to determine the dr ratio. The crude product was subjected to flash chromatography on silica gel (hexanes/dichloromethane/acetonitrile: 60:30:10) to afford the desired products as a pair of diastereomers.

Other detailed experiment procedures are included in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.2c00465.

Experimental procedures, HRMS, IR, NMR, and HPLC (SFC) data for all new compounds, structure analysis and absolute configuration determination of product **3q** (NMR and ECD studies) (PDF)

AUTHOR INFORMATION

Corresponding Authors

Jisheng Luo − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science, Westlake University, Hangzhou 310024 Zhejiang Province, China;* orcid.org/0000-0001-8571-5619; Email: luojisheng@westlake.edu.cn

Li Deng − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science, Westlake University, Hangzhou 310024 Zhejiang Province, China;* orcid.org/0000-0003-2233-0222; Email: dengli@westlake.edu.cn

Authors

Yu Deng − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science, Westlake University, Hangzhou 310024 Zhejiang Province, China; Department of Chemistry, Brandeis University, Waltham, Massachusetts 02454-9110, United States*

Xiaohuo Shi − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, School of Science, Instrumentation and Service Center for Molecular Sciences, Westlake University, Hangzhou 310024 Zhejiang Province, China*

Guangfa Shi − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, Department of Chemistry, School of Science, Westlake University, Hangzhou 310024 Zhejiang Province, China*

Xingyu Lu − *Key Laboratory of Precise Synthesis of Functional Molecules of Zhejiang Province, School of Science, Instrumentation and Service Center for Molecular Sciences, Westlake University, Hangzhou 310024 Zhejiang Province, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacsau.2c00465

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Funding

This project was supported by Foundation of Westlake University and the Leading Innovative and Entrepreneur Team Introduction Program of Zhejiang (2020R01004) and Natural Science Foundation of China (U22A20389).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors thank Dr. Yinjuan Chen and Dr. Zhong Chen from Instrumentation and Service Center for Molecular Sciences at Westlake University for the measurement of HRMS, IR and ECD spectra.

REFERENCES

(1) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; John Wiley & Sons, 1995; pp 1−464.

(2) Corey, E. J. The Logic of Chemical Synthesis: Multistep Synthesis of Complex Carbogenic Molecules (Nobel Lecture). *Angew. Chem., Int. Ed.* **1991**, *30*, 455−465.

(3) Gaich, T.; Baran, P. S. Aiming for the ideal synthesis. *J. Org. Chem.* **2010**, *75* (14), 4657−4673.

(4) Qiu, F. Strategic efficiency—The new thrust for synthetic organic chemists. *Can. J. Chem.* **2008**, *6*, 903−906.

(5) Taylor, M. S.; Jacobsen, E. N. Asymmetric Catalysis in Complex Target Synthesis. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5368−5373.

(6) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. Asymmetric Synthesis of Active Pharmaceutical Ingredients. *Proc. Natl. Acad. Sci. U. S. A.* **2006**, *106*, 2734−2793.

(7) Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H. *Comprehensive Asymmetric Catalysis*; Springer: Berlin/Heidelberg, 1999; pp 1−1856.

(8) Carreira, E. M.; Yamamoto, H. *Comprehensive Chirality*; Elsevier, 2012; pp 1−5648.

(9) Wang, Y.; Liu, X.; Deng, L. Dual-function Cinchona Alkaloid Catalysis: Catalytic Asymmetric Tandem Conjugate Addition-Protonation for the Direct Creation of Nonadjacent Stereocenters. *J. Am. Chem. Soc.* **2006**, *128*, 3928−3930.

(10) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. Control of Diastereoselectivity in Tandem Asymmetric Reactions Generating Nonadjacent Stereocenters with Bifunctional Catalysis by Cinchona Alkaloids. *J. Am. Chem. Soc.* **2007**, *129*, 768−769.

(11) Tsubogo, T.; Saito, S.; Seki, K.; Yamashita, Y.; Kobayashi, S. Development of Catalytic Asymmetric 1,4-Addition and [3 + 2] Cycloaddition Reactions Using Chiral Calcium Complexes. *J. Am. Chem. Soc.* **2008**, *130*, 13321−13332.

(12) Li, X.; Luo, S.; Cheng, J. P. Asymmetric Conjugate Addition of Oxindoles to 2-Chloroacrylonitrile: A Highly Effective Organocatalytic Strategy for Simultaneous Construction of 1, 3-Nonadjacent Stereocenters Leading to Chiral Pyrroloindolines. *Chem.—Eur. J.* **2010**, *16*, 14290−14294.

(13) Duan, S. W.; An, J.; Chen, J. R.; Xiao, W. J. Facile Synthesis of Enantioenriched Cγ-Tetrasubstituted α-Amino Acid Derivatives via an Asymmetric Nucleophilic Addition/Protonation Cascade. *Org. Lett.* **2011**, *13*, 2290−2293.

(14) Zhu, B.; Lee, R.; Li, J.; Ye, X.; Hong, S. N.; Qiu, S.; Coote, M. L.; Jiang, Z. Chemoselective Switch in the Asymmetric Organo-

catalysis of 5*H*-Oxazol-4-ones and N-Itaconimides: Addition-Protonation or [4 + 2] Cycloaddition. *Angew. Chem., Int. Ed.* **2016**, *55*, 1299−1303.
(15) Li, Z.; Hu, B.; Wu, Y.; Fei, C.; Deng, L. Control of Chemoselectivity in Asymmetric Tandem Reactions: Direct Synthesis of Chiral Amines Bearing Nonadjacent Stereocenters. *Proc. Natl. Acad. Sci. U. S. A.* **2018**, *115*, 1730−1735.
(16) Zhang, X.; Liu, L.; López-Andarias, J.; Wang, C.; Sakai, N.; Matile, S. Anion-π catalysis: focus on nonadjacent stereocenters. *Helv. Chim. Acta* **2018**, *101*, No. e1700288.
(17) Davis, C. R.; Luvaga, I. K.; Ready, J. M. Enantioselective Allylation of Alkenyl Boronates Promotes a 1,2-Metalate Rearrangement with 1,3-Diastereocontrol. *J. Am. Chem. Soc.* **2021**, *143*, 4921−4927.
(18) Trost, B. M.; Zell, D.; Hohn, C.; Mata, G.; Maruniak, A. Enantio- and Diastereoselective Synthesis of Chiral Allenes by Palladium-Catalyzed Asymmetric [3 + 2] Cycloaddition Reactions. *Angew. Chem., Int. Ed.* **2018**, *57*, 12916−12920.
(19) Trost, B. M.; Schultz, J. E.; Chang, T.; Maduabum, M. R. Chemo-, Regio-, Diastereo-, and Enantioselective Palladium Allylic Alkylation of 1,3-Dioxaboroles as Synthetic Equivalents of alpha-Hydroxyketones. *J. Am. Chem. Soc.* **2019**, *141*, 9521−9526.
(20) Yang, S. Q.; Wang, Y. F.; Zhao, W. C.; Lin, G. Q.; He, Z. T. Stereodivergent Synthesis of Tertiary Fluoride-tethered Allenes via Copper and Palladium Dual Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 7285−7291.
(21) Zhang, J.; Huo, X.; Xiao, J.; Zhao, L.; Ma, S.; Zhang, W. Enantio- and Diastereodivergent Construction of 1,3-Nonadjacent Stereocenters Bearing Axial and Central Chirality through Synergistic Pd/Cu Catalysis. *J. Am. Chem. Soc.* **2021**, *143*, 12622−12632.
(22) Kong, M.; Tan, Y.; Zhao, X.; Qiao, B.; Tan, C. H.; Cao, S.; Jiang, Z. Catalytic Reductive Cross Coupling and Enantioselective Protonation of Olefins to Construct Remote Stereocenters for Azaarenes. *J. Am. Chem. Soc.* **2021**, *143*, 4024−4031.
(23) Chang, X.; Cheng, X.; Liu, X. T.; Fu, C.; Wang, W. Y.; Wang, C. J. Stereodivergent Construction of 1, 4-Nonadjacent Stereocenters via Hydroalkylation of Racemic Allylic Alcohols Enabled by Copper/Ruthenium Relay Catalysis. *Angew. Chem., Int. Ed.* **2022**, DOI: 10.1002/anie.202206517.
(24) Cooze, C. J. C.; McNutt, W.; Schoetz, M. D.; Sosunovych, B.; Grigoryan, S.; Lundgren, R. J. Diastereo-, Enantio-, and Z-Selective alpha,delta-Difunctionalization of Electron-Deficient Dienes Initiated by Rh-Catalyzed Conjugate Addition. *J. Am. Chem. Soc.* **2021**, *143*, 10770−10777.
(25) Ye, Y.; Qin, G.; Xu, R. Alkaloids of Stemona *Japonica*. *J. Nat. Prod.* **1994**, *57*, 665−669.
(26) Zhao, B.; Wang, Y.; Zhang, D.; Huang, X.; Bai, L.; Yan, Y.; Chen, J.; Lu, T.; Wang, Y.; Zhang, Q.; Ye, W. Virosaines A and B, Two New Birdcage-Shaped Securinega Alkaloids with an Unprecedented Skeleton from *Flueggea virosa*. *Org. Lett.* **2012**, *14*, 3096−3099.
(27) Ohsaki, A.; Nagaoka, T.; Yoneda, K.; Kishida, A. Secu'amamines E−G, New Alkaloids from Securinega Suffruticosa var. Amamiensis. *Tetrahedron Lett.* **2009**, *50*, 6965−6967.
(28) Kate, A. S.; Pearson, J. K.; Ramanathan, B.; Richard, K.; Kerr, R. G. Isolation, Biomimetic Synthesis, and Cytotoxic Activity of Bis(pseudopterane) Amines. *J. Nat. Prod.* **2009**, *72*, 1331−1334.
(29) Mao, B.; Fananas-Mastral, M.; Feringa, B. L. Catalytic Asymmetric Synthesis of Butenolides and Butyrolactones. *Chem. Rev.* **2017**, *117*, 10502−10566.
(30) Martin, S. E.; Lopez, O. D. Vinylogous Mannich Reactions. Catalytic, Asymmetric Additions of Triisopropylsilyloxyfurans to Aldimines. *Tetrahedron Lett.* **1999**, *40*, 8949−8953.
(31) Carswell, E. L.; Snapper, M. L.; Hoveyda, A. H. A Highly Efficient and Practical Method for Catalytic Asymmetric Vinylogous Mannich (AVM) Reactions. *Angew. Chem., Int. Ed.* **2006**, *45*, 7230−7233.
(32) Yamaguchi, A.; Matsunaga, S.; Shibasaki, M. Direct Catalytic Asymmetric Mannich-Type Reactions of γ-Butenolides: Effectiveness of Brønsted Acid in Chiral Metal Catalysis. *Org. Lett.* **2008**, *10*, 2319−2322.
(33) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. Ag-Catalyzed Diastereo- and Enantioselective Vinylogous Mannich Reactions of α-Ketoimine Esters. Development of a Method and Investigation of its Mechanism. *J. Am. Chem. Soc.* **2009**, *131*, 570−576.
(34) Hermange, P.; Dau, M. E. T. H.; Retailleau, P.; Dodd, R. H. Highly Diastereoselective Three-Component Vinylogous Mannich Reaction between Isoquinolines, Acyl/Sulfonyl Chlorides, and Silyloxyfurans. *Org. Lett.* **2009**, *11*, 4044−4047.
(35) Zhou, L.; Lin, L.; Ji, J.; Xie, M.; Liu, X.; Feng, X. Catalytic Asymmetric Vinylogous Mannich-type (AVM) Reaction of Non-activated α-Angelica Lactone. *Org. Lett.* **2011**, *13*, 3056−3059.
(36) Ruan, S.; Luo, J.; Du, Y.; Huang, P. Asymmetric Vinylogous Mannich Reactions: A Versatile Approach to Functionalized Heterocycles. *Org. Lett.* **2011**, *13*, 4938−4941.
(37) Guo, Y. L.; Bai, J. F.; Peng, L.; Wang, L. L.; Jia, L. N.; Luo, X. Y.; Tian, F.; Xu, X. Y.; Wang, L. X. Direct Asymmetric Vinylogous Mannich Reaction of 3,4-Dihalofuran-2(5H)-one with Aldimine Catalyzed by Quinine. *J. Org. Chem.* **2012**, *77*, 8338−8343.
(38) Hayashi, M.; Sano, M.; Funahashi, Y.; Nakamura, S. Cinchona Alkaloid Amide/copper(II) Catalyzed Diastereo- and Enantioselective Vinylogous Mannich Reaction of Ketimines with Siloxyfurans. *Angew. Chem., Int. Ed.* **2013**, *52*, 5557−5560.
(39) Yin, L.; Takada, H.; Kumagai, N.; Shibasaki, M. Direct Catalytic Asymmetric Vinylogous Mannich-type Reaction of γ-Butenolides with Ketimines. *Angew. Chem., Int. Ed.* **2013**, *52*, 7310−7313.
(40) Rao, V. U.; Jadhav, A. P.; Garad, D.; Singh, R. P. Asymmetric Vinylogous Mannich Reaction of Silyloxy Furans with *N*-tert-Butanesulfinyl Ketimines. *Org. Lett.* **2014**, *16*, 648−651.
(41) Guo, Y.; Zhang, Y.; Qi, L.; Tian, F.; Wang, L. Organocatalytic Direct Asymmetric Vinylogous Mannich Reaction of γ-Butenolides with Isatin-derived Ketimines. *RSC Adv.* **2014**, *4*, 27286−27289.
(42) Nakamura, S.; Yamaji, R.; Hayashi, M. Direct Enantioselective Vinylogous Mannich Reaction of Ketimines with γ-Butenolide by Using Cinchona Alkaloid Amide/Zinc(II) Catalysts. *Chem.—Eur. J.* **2015**, *21*, 9615−9618.
(43) Trost, B. M.; Gnanamani, E.; Tracy, J. S.; Kalnmals, C. A. Zn-ProPhenol Catalyzed Enantio- and Diastereoselective Direct Vinylogous Mannich Reactions between α,β- and β,γ-Butenolides and Aldimines. *J. Am. Chem. Soc.* **2017**, *139*, 18198−18201.
(44) Trost, B. M.; Hung, C. J.; Scharf, M. J. Direct Catalytic Asymmetric Vinylogous Additions of α,β- and β,γ-Butenolides to Polyfluorinated Alkynyl Ketimines. *Angew. Chem., Int. Ed.* **2018**, *57*, 11408−11412.
(45) Wang, Z. H.; You, Y.; Chen, Y. Z.; Xu, X. Y.; Yuan, W. C. An Asymmetric Organocatalytic Vinylogous Mannich Reaction of 3-Methyl-5-arylfuran-2(3H)-ones with *N*-(2-Pyridinesulfonyl) Imines: Enantioselective Synthesis of δ-Amino γ,γ-Disubstituted Butenolides. *Org. Biomol. Chem.* **2018**, *16*, 1636−1640.
(46) Feng, M.; Mosiagin, I.; Kaiser, D.; Maryasin, B.; Maulide, N. Deployment of Sulfinimines in Charge-Accelerated Sulfonium Rearrangement Enables a Surrogate Asymmetric Mannich reaction. *J. Am. Chem. Soc.* **2022**, *144*, 13044−13049.
(47) Wu, Y.; Singh, R. P.; Deng, L. Asymmetric Olefin Isomerization of Butenolides via Proton Transfer Catalysis by an Organic Molecule. *J. Am. Chem. Soc.* **2011**, *133*, 12458−12461.
(48) Corey, E. J.; Xu, F.; Noe, M. C. A Rational Approach to Catalytic Enantioselective Enolate Alkylation Using a Structurally Rigidified and Defined Chiral Quaternary Ammonium Salt under Phase Transfer Conditions. *J. Am. Chem. Soc.* **1997**, *119*, 12414−12415.
(49) Kitamura, M.; Shirakawa, S.; Maruoka, K. Powerful Chiral Phase-Transfer Catalysts for the Asymmetric Synthesis of α-Alkyl- and α,α-Dialkyl-α-Amino Acids. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549−1551.
(50) Uraguchi, D.; Koshimoto, K.; Ooi, T. Chiral Ammonium Betaines: A Bifunctional Organic Base Catalyst for Asymmetric

https://doi.org/10.1021/jacsau.2c00465
JACS Au 2022, 2, 2678−2685

Mannich-Type Reaction of *a*-Nitrocarboxylates. *J. Am. Chem. Soc.* **2008**, *130*, 10878−10879.
(51) Hydrolyzed product **S1** and a trace amount of tautomerized product **S2** were observed through ^{1}H NMR spectrum.
(52) Hu, B.; Bezpalko, M. W.; Fei, C.; Dickie, D. A.; Foxman, B. M.; Deng, L. Origin of and a Solution for Uneven Efficiency by Cinchona Alkaloid-Derived, Pseudoenantiomeric Catalysts for Asymmetric Reactions. *J. Am. Chem. Soc.* **2018**, *140*, 13913−13920.

https://doi.org/10.1021/jacsau.2c00465
JACS Au 2022, 2, 2678−2685