ChemCatChem

The European Society Journal for Catalysis

Chemistry Europe

European Chemical Societies Publishing

Supported by GECATS GERMAN CATALYSIS SOCIETY

Accepted Article

Title: Asymmetric Synthesis of Multi-substituted Prolines via a Catalytic 1,3-Dipolar Cycloaddition Using a Monocationic ZnIIOAc Complex of a Chiral Bisamidine Ligand, Naph-diPIM-dioxo-R

Authors: I. N. Chaithanya Kiran, Kazuki Fujita, Shinji Tanaka, and Masato Kitamura

To be cited as: *ChemCatChem* 10.1002/cctc.202001202

Link to VoR: https://doi.org/10.1002/cctc.202001202

WILEY-VCH

Asymmetric Synthesis of Multi-substituted Prolines via a Catalytic 1,3-Dipolar Cycloaddition Using a Monocationic $Zn^{II}OAc$ Complex of a Chiral Bisamidine Ligand, Naph-diPIM-dioxo-R

I. N. Chaithanya Kiran,[b] Kazuki Fujita,[a] Shinji Tanaka,[b] and Masato Kitamura*[a]

[a] Mr. K. Fujita, Prof. Dr. M. Kitamura
Graduate School of Pharmaceutical Sciences
Nagoya University
Chikusa, Nagoya 464-8601, Japan
E-mail: kitamura@ps.nagoya-u.ac.jp

[b] Dr. I. N. C. Kiran, Dr. S. Tanaka
Research Center for Materials Science
Nagoya University
Chikusa, Nagoya 464-8602, Japan

Supporting information for this article is given via a link at the end of the document.

Abstract: A monocationic zinc acetate complex of chiral bisamidine-type bidentate ligand (*R*)- or (*S*)-Naph-diPIM-dioxo-*i*Pr (**L**$_R$ or **L**$_S$) catalyzes a 1,3-dipolar cycloaddition between tridentate-type imino esters and acrylates in the absence of an external base to give the corresponding multi-substituted prolines with high reactivity, diastero-/enantio-/regio-selectivity, productivity, and broad generality. An anionic acetate ligand of the Lewis acidic Zn complex acts as a Brønsted base to facilitate a smooth intramolecular deprotonation to generate an imino *N*,*O*-*cis*-Zn enolate. The oxygen atoms of two dioxolanes of the **L**$_R$/**L**$_S$ ligand form a C_2 chiral scaffold that coordinates the Zn enolate via a non-bonding n-π^* interaction. This view is supported by the lack of enantioselectivity obtained with an sp^2N-based Ph-BOX ligand that has no oxygen atom in the reaction site.

As shown in Figure 1, multi-substituted proline is an important basic skeleton contained in various bioactive compounds[1] such as GW873082X (3082),[2] salinosporamide A,[3] disibetaine,[4] gracilamine,[5] kitecephalin,[6] and stephasidine A.[7] It is also the core structure of some chiral organic catalysts[8] and chiral ligands.[9] The development of an efficient method to construct such chiral multi-substituted prolines should provide a powerful tool for not only pharmaceutical investigations and industrial applications but also for the design and synthesis of chiral catalysts and ligands. Among the many methods available to construct the proline skeleton, the catalytic asymmetric 1,3-dipolar cycloaddition (1,3-DC) between imino ester **1** and acrylate **2** is an ideal strategy from the viewpoints of atom efficiency and substrate availability.[10] This process has been used in the industrial-scale synthesis of a chiral precursor of GW873082X using a Ag–dihydroquinine complex.[11] However, there are still problems in terms of reactivity, multi-stereoselectivity at C(2)–C(5) and reaction conditions requiring low temperature, molecular sieves (MS), and extra base in most cases. Matched/mismatched problems that have arisen with chiral α-substituted α-imino ester **1** have also not been solved. To address these issues, we aimed to design a new asymmetric 1,3-DC catalyst that has high reactivity, multi-selectivity, and low catalyst loading without the use of an external base in both the matched and mismatched systems.

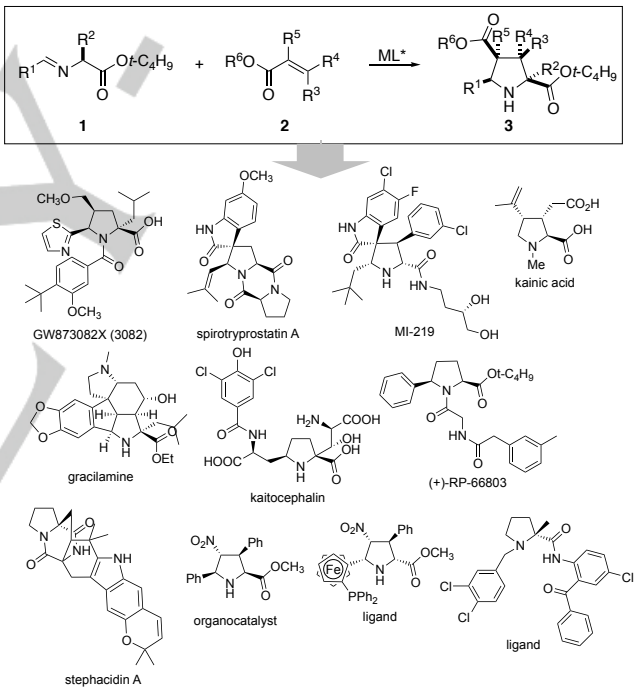


Figure 1. Multi-substituted prolines and the most efficient catalytic approach.

Figure 2 illustrates our conceptual catalyst, which is a monocationic octahedral (O_h) divalent metal complex of a bisamidine-type bidentate ligand, (*R*)- or (*S*)-Naph-diPIM-dioxo-*i*Pr (**L**$_R$ or **L**$_S$).[12] The bite angle of Naph-diPIM is close to 90° and geometrically fits well with the O_h complex. The highly planar and rigid core skeleton with two highly σ-donating amidine units fixed to the same side firmly capture the central metal M. An extended π-conjugated system showing a pyridine-level π-accepting ability also stabilizes the transition metal complexes. The 5,5,6,6,5,5 ring system of the chiral ligand, which fuses two dioxolane rings up and down at both ends in a C_2 manner, provides a wider reaction site than Ph-BOX-[13] and bipyridine-type ligands. In order to reduce the number of

stereoisomers of the O_h $[M^{II}(\mathbf{L}_R \text{ or } \mathbf{L}_S)]^+Y^-$ complex as much as possible, the imino ester **1** is designed to facilitate tridentate coordination. In the catalyst/**1** complex, the α-proton of **1** is intramolecularly abstracted by the action of anionic ligand X to generate the corresponding *N*,*O*-*cis*-M^{II} enolate, which reacts with acrylate to generate a pyrrolidine M^{II} amide and HX. The rate of deprotonation should be significantly affected by the chirality of **1**, creating a matched/mismatched issue. Protonation furnishes the proline product **3**, regenerating the catalyst. The Brønsted base/Lewis acid bifunctional synergistic effect of $[M^{II}X(\mathbf{L}_R \text{ or } \mathbf{L}_S)]^+Y^-$ allows the 1,3-DC to proceed smoothly under nearly neutral conditions in the absence of an external base. We expected i) that an attractive non-bonding n-$\pi^*_{C=N}$ interaction[14,15] between the *N*,*O*-*cis*-M^{II} enolate and the lone pair n orbital of the dioxolane oxygen atom of $\mathbf{L}_R$ would determine the location of the enolate and ii) that the direction of the acrylate approach would be determined by the steric circumstances created by the spatially opened quadrants in the *N*,*O*-*cis*-$M^{II}\mathbf{L}_R$ enolate complex.

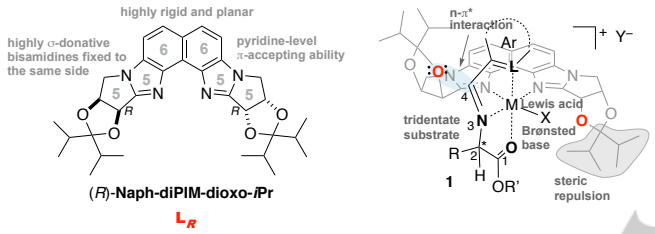


Figure 2. Our basic concept for realization of the catalytic 1,3-DC.

Complex $[M^{II}X(\mathbf{L}_R \text{ or } \mathbf{L}_S)]^+Y^-$ would be generated by mixing $M^{II}X_2(\mathbf{L}_R \text{ or } \mathbf{L}_S)$ with a stronger acid HY than HX.[16] Considering that X must be basic enough to deprotonate the α-proton of **1** and the need for Y to have low coordination to give a monocationic complex, $M^{II}(OAc)_2(\mathbf{L}_R \text{ or } \mathbf{L}_S)$ and triflic acid (HOTf) were selected and various divalent metals were screened. Finally, we found that $[Zn^{II}OAc(\mathbf{L}_R \text{ or } \mathbf{L}_S)]^+(OTf)^-$ exhibited high reactivity and selectivity in the reaction of thiazol-1-yl (Tz) α-imino ester **1a** (R^1 = Tz; R^2 = *i*-C_4H_9) and methyl acrylate (**2a**, R^3 = R^4 = R^5 = H; R^6 = CH_3) under the standard conditions of [**1a**] = [**2a**] = 1000 mM, [catalyst] = 1 mM (0.1 mol%), CH_3CN, 50 °C, and 6 h. Table 1 shows the screening results of Zn^{II} complexes. $Zn(OAc)_2/\mathbf{L}_S$ gave 52% of **3a** with a 13:87 2*R*/2*S* ratio (entry 1). No diastereomeric isomers were observed. Addition of one mol amount of HOTf to Zn^{II} led to a dramatic improvement of reactivity and enantioselectivity, furnishing **3a** with 2:98 er in 97% yield (entry 2). Replacement of $\mathbf{L}_S$ with $\mathbf{L}_R$ resulted in even higher reactivity and selectivity (entry 3), indicating that the (*S*)-**1a**/$\mathbf{L}_R$ is a matched case and (*S*)-**1a**/$\mathbf{L}_S$ is a mismatched case. $[Zn^{II}OAc]^+(OTf)^-$, which was prepared by disproportionation of $Zn(OAc)_2$ and $Zn(OTf)_2$,[17] was also usable (entry 4). This is advantageous because no HOAc is generated in the reaction system. Instead of HOTf, HBarf could be used, but relatively less acidic additives like methanesulfonic acid (HOMs) and trifluoroacetic acid (TFA) were less effective (entries 5–8). CH_3CN was the best solvent, and CH_2Cl_2 and THF could be used (entries 9, 10). Reaction in DMA, toluene, or *t*-BuOH was slow, and enantioselectivity was deteriorated (entries 11–13). No enantioselectivity was observed in CH_3NO_2 (entry 14). The Ph-BOX[13] ligand showed relatively high reactivity but little enantioselectivity (entry 15).

Table 1. Screening of the Conditions in the Reaction of **1a** (R^1 = Tz; R^2 = *i*-C_4H_9) and **2a** (R^3 = R^4 = R^5 = H; R^6 = CH_3) to **3a**.[a]

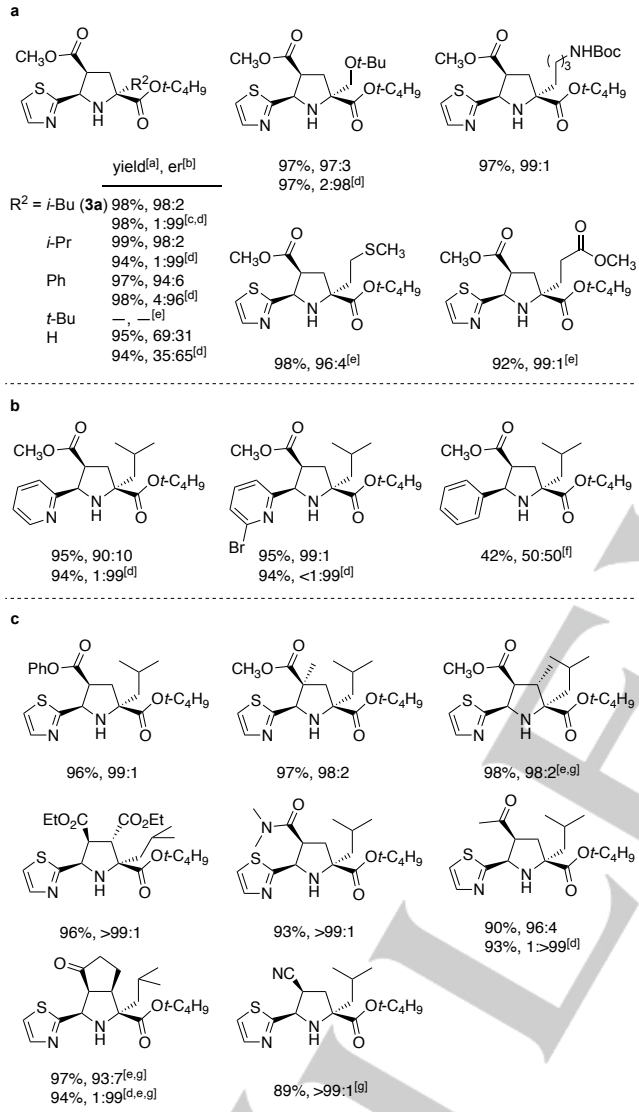
Entry	Catalyst	Solvent	Time, h	% Yield[b]	2*R*:2*S*[c]
1	$Zn(OAc)_2/\mathbf{L}_S$	CH_3CN	6	52	13:87
2	$Zn(OAc)_2/\mathbf{L}_S$/HOTf	CH_3CN	6 (0.25)	97 (43)	2:98
3	$Zn(OAc)_2/\mathbf{L}_R$/HOTf	CH_3CN	6 (0.25)	98 (65)	>99:1
4	$[ZnOAc]^+(OTf)^-/\mathbf{L}_R$	CH_3CN	6 (0.25)	98 (65)	>99:1
5[d]	$Zn(OAc)_2/\mathbf{L}_S$/HOTf	CH_3CN	4	70	2:98
6[d]	$Zn(OAc)_2/\mathbf{L}_S$/HBarf	CH_3CN	4	66	5:95
7[d]	$Zn(OAc)_2/\mathbf{L}_S$/HOMs	CH_3CN	4	19	12:88
8[d]	$Zn(OAc)_2/\mathbf{L}_S$/TFA	CH_3CN	4	22	16:84
9[d]	$Zn(OAc)_2/\mathbf{L}_S$/HOTf	CH_2Cl_2	48 (4)	98 (44)	4:96 (4:96)
10[d]	$Zn(OAc)_2/\mathbf{L}_S$/HOTf	THF	120 (4)	98 (38)	4:96 (3:97)
11[d]	$Zn(OAc)_2/\mathbf{L}_S$/HOTf	DMA	120 (4)	79 (7)	11:89 (—)
12[d]	$Zn(OAc)_2/\mathbf{L}_S$/HOTf	Toluene	120 (4)	98 (14)	12:88 (14:86)
13[d]	$Zn(OAc)_2/\mathbf{L}_S$/HOTf	*t*-C_4H_9OH	48 (4)	98 (74)	22:78 (25:75)
14[d]	$Zn(OAc)_2/\mathbf{L}_S$/HOTf	CH_3NO_2	120 (4)	31 (3)	48:52 (—)
15[d]	$Zn(OAc)_2$/(*S*)-Ph-BOX/HOTf	CH_3CN	6	92	55:45

[a] Conditions: [(*S*)-**1a**] = [**2a**] = 1000 mM, [catalyst] = 1 mM (0.1 mol%). [b] ^{1}H-NMR analysis. [c] HPLC analysis. [d] [catalyst] = 0.5 mM (0.05 mol%).

The substrate scope was investigated in the mismatched (*S*)-**1**/$\mathbf{L}_S$ system, and the results are shown in Table 2a–c. The isobutyl group of **1a** could be replaced with an isopropyl or phenyl group without significant loss of reactivity and selectivity. The *tert*-leucine-derived imino ester showed no reactivity. The less sterically encumbered, non-substituted imino ester of glycine decreased enantioselectivity. Serine-, lysine-, methionine-, or glutamic acid-derived **1** were also usable (a). A pyridin-2-yl or 2-bromopyridin-6-yl group could be used instead of the Tz group, but a phenyl group significantly diminished enantioselectivity (b). These results suggest that tridentate **1** is essential for attaining high selectivity. Among them, the Tz group is advantageous in terms of three characteristics: i) high metal coordination ability of the sp^2N atom; ii) high functional group convertibility as a masked formyl group;[18] and iii) it is a well-known structural motif of pharmaceuticals for expression of bioactivity.[19] Various polarophiles **2** could be used (c). The methyl ester of **2a** could be replaced with a phenyl ester. With

α-methylacrylate, a quaternary stereogenic carbon center could be controlled, and four continuous stereogenic centers were installed with (*E*)-crotonate. Diethyl fumarate also gave the nearly enantiomerically pure 1,3-DC adduct. In addition to esters, *N*,*N*-dimethyl amide, methyl ketone, a cyclic enone, and nitrile were successfully employed.

Table 2. Generality of the [Zn^{II}OAc(**L*R*** or **L*S***)]$^+$(OTf)$^-$-catalyzed 1,3-DC of α-Substituted α-Imino Esters **1** and Acrylate Derivatives **2**.



Conditions: [**1**] = 1000 mM (0.1 mmol), [**2**] = 1000 mM (0.1 mmol), [[ZnOAc**L*S***]$^+$(OTf)$^-$] = 1 mM, CH_3CN, 50 °C, 9 h. [a] Isolated yield. [b] HPLC analysis. [c] 15-g scale. [d] [ZnOAc**L*R***]$^+$(OTf)$^-$, 6 h. [e] 1 mol% catalyst. [f] 24 h. [g] 80 °C, 60 h.

Figure 3 illustrates the supposed catalytic cycle explaining the high enantioselectivity attained in both the matched and mismatched cases of the present asymmetric 1,3-DC of **1a** with **2a** using [Zn^{II}OAc**L*R***]$^+$(OTf)$^-$ (*R* cat). First, *R* cat is generated in situ by the reaction of $Zn(OAc)_2$, **L*R***, and HOTf (ESI analysis (positive, Nebulizer 0.4 atm, 180 °C) 667.2552). In the (*S*)-**1a**/*R* cat matched system (left cycle), *R* cat captures (*S*)-**1a** as a tridentate ligand to generate **A$_{23,syn}$**. Here, suffix "23" and "syn" indicate that (*S*)-**1a** coordinates to a monocationinc Zn metal in the 2nd–3rd quadrant side with the α proton of **1a** (C_1(2)H) and ZnOAc at the front side in a syn manner. The (*S*)-**1a**/*R* cat complex **A$_{23,syn}$** is stabilized by a non-bonding attractive interaction between the n orbital of the dioxolane oxygen atom and the π* orbital of the TzC=N group. The C_1(2)H is intramolecularly abstracted by the Brønsted basic C=O oxygen atom of ZnOAc to generate *N*,*O*-*cis*-Zn enolate **B$_{23}$** by liberation of HOAc. **B$_{23}$** would adopt an O_h geometry with coordination of S_{sol}, which is most probably HOAc or CH_3CN. Methyl acrylate (**2a**) approaches enolate **B$_{23}$** on the spatially opened 1st–4th quadrant side to generate **C$_{23}$** after C_1(2)–C_2(3) and C_2(2)–C_1(4) bond formations in an endo manner. With this dipolar/dipolarophile combination, C_1(2) and C_1(4) act as the nucleophilic and electrophilic carbons, respectively, controlling the regioselectivity. The Zn amide **C$_{23}$** is then protonated by HOAc intermolecularly or intramolecularly via a coordination of HOAc to Zn^+ (S_{sol} = AcOH), regenerating the chain carrier [Zn^{II}OAc**L*R***]$^+$(OTf)$^-$ by liberation of (2*R*)-*endo*-**3a**. In the (*S*)-**1a**/*R* cat matched system, **A$_{23,syn}$** is a productive species that can smoothly move to the Zn enolate **B$_{23}$**, which is also stabilized by an n-π* interaction in the 2nd quadrant and can be in equilibrium with **B$_{14}$**. 1,3-Dipolar **B$_{14}$** is destabilized by a steric repulsion between the R substituent at C_1(2) and the di-*i*Pr-substituted-dioxolane ring of **L*R*** in the 4th quadrant and has no n-π* attractive interaction. Therefore, contribution of **B$_{23}$** to the reaction with **2a** is far higher than that of **B$_{14}$** (k^3 >> k_{inv}), leading to a predominant production of (2*R*)-*endo*-**3a** via a **TS$_{23,endo}$** transition state. The endo approach is thought to be preferred over the exo approach giving (2*R*)-*exo*-**3a** probably due to an electrostatic interaction of the C=O oxygen atom of **2a** with the monocationic Zn atom or due to a so-called endo rule via a secondary orbital interaction in a concerted mechanism. A lower enantioselectivity with a smaller substituent R^2 such as H can be explained with the view of Figure 3; with a smaller R, the contribution of **B$_{14}$** would be increased because the degree of steric repulsion in the 4th quadrant decreases.

The enantiomeric substrate, (*R*)-**1a**, also reacts with [Zn^{II}OAc**L*R***]$^+$(OTf)$^-$ in a similar way to the case of (*S*)-**1a** to give **A$_{23,anti}$**, which can be also stabilized by an n-π* interaction in the 2nd quadrant. However, **A$_{23,anti}$** is non-productive for **B$_{23}$** generation because ZnOAc cannot abstract the C_1(2)H in an intramolecular manner. Complex **A$_{14,syn}$** with a C_1(2)H/ZnOAc syn location (right cycle) is productive but destabilized by a steric repulsion in the 4th quadrant; therefore, a quick isomerization to the stable **B$_{23}$** occurs by flipping the face of the enolate from the 1st–4th quadrant side to the 2nd–3rd quadrant side, entering the left cycle and furnishing (2*R*)-*endo*-**3a**. This view can explain the high enantioselectivity obtained even in the mismatched combination but with generation of a small amount of (2*S*)-*endo*-**3a**. Although the equilibrium between **B$_{14}$** and **B$_{23}$** lies far to the **B$_{23}$** side (K_{inv} >> 1), **B$_{14}$** must be generated in the mismatched system. In the balance of the inversion rate k_{inv} and the reaction rate k^3 of **B$_{14}$** with **2a**, the enantioselectivity would be determined.

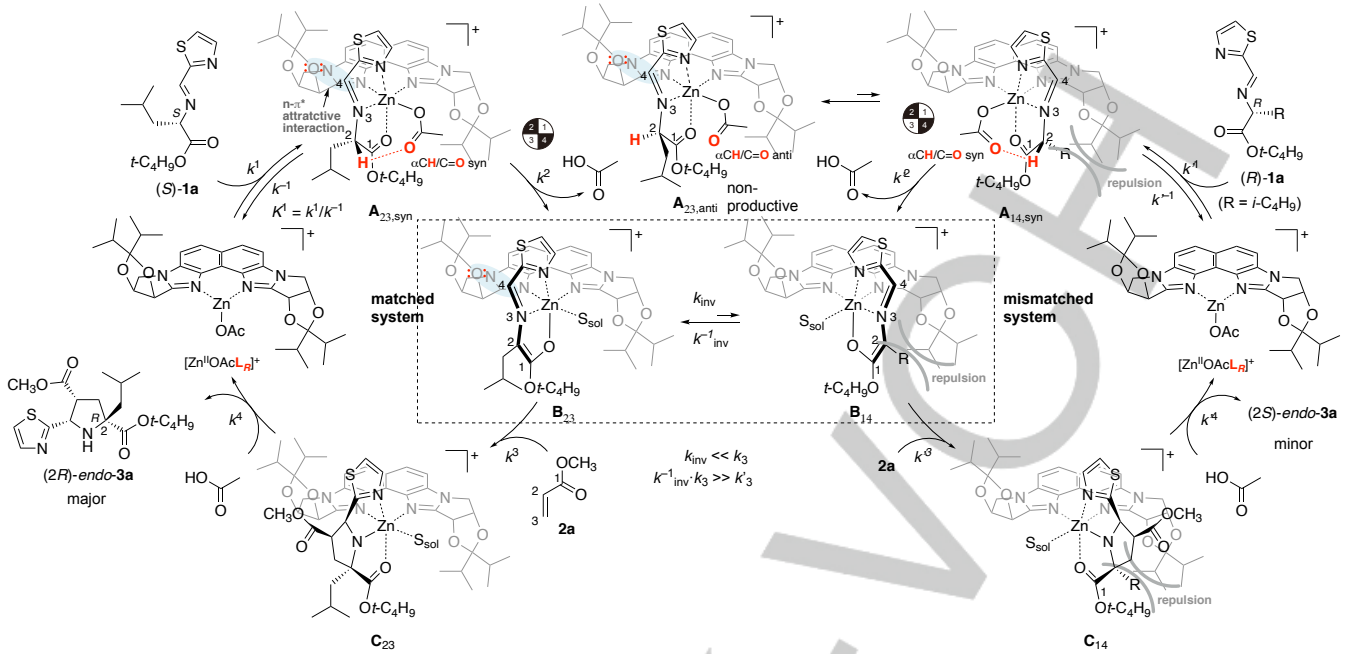


Figure 3. Supposed reaction pathways in the (*S*)-**1a**/*R* cat matched and (*R*)-**1a**/*R* cat mismatched systems. In the reaction of the mismatched system, (*S*)-**1a** and *S* cat were used for substrate availability.

In summary, we have established a new efficient catalytic system for the asymmetric 1,3-DC reaction, which is accelerated by a monocationic zinc acetate complex of $\mathbf{L}_R$ or $\mathbf{L}_S$. Various chiral multi-substituted prolines could be prepared in high yields even with 0.1 mol% catalyst under nearly neutral conditions. This method will help pharmaceutical investigations based on a structure-activity relationship study and industrial production. No use of an external base is necessary to enhance the utility in terms of isolation efficiency of the basic pyrrolidine product. $[Zn^{II}OAc(\mathbf{L}_R \text{ or } \mathbf{L}_S)]^+(OTf)^-$ acts as a Brønsted base/Lewis acid synergistic catalyst to facilitate generation of an *N*,*O*-*cis*-Zn enolate. Another important characteristic is an attractive non-bonding n-$\pi^*_{C=N}$ interaction, which is the origin of the high enantioselectivity in the lower reactive mismatched system. Further investigation on the mechanisms is ongoing.

Procedures for the substrate syntheses and the asymmetric allylation and physical data of all new compounds (PDF)

Acknowledgements

This work was aided by JSPS KAKENHI (Grant Number JP18H04250), an Advanced Catalytic Transformation program for Carbon utilization (ACT-C; Grant Number JPMJCR12YC) from Japan Science and Technology Agency (JST), the Platform Project for Supporting Drug Discovery and Life Science Research funded by Japan Agency for Medical Research and Development (AMED; Grant Number JP18am0101099), and The Sumitomo Foundation.

Keywords: 1,3-Dipolar cycloaddition • prolines • HCV inhibitor • GW873082X • Brønsted base/Lewis acid catalyst

[1] a) J. Janet, Z. Kamenik, R. Gazak, S. Kadlcik, L. Najmanova, *Nat. Prod. Rep.* **2018**, *35*, 257-289; b) A. B. Mauger, *J. Nat. Prod.* **1996**, *59*, 1205-1211.

[2] a) G. Burton, T. W. Ku, T. J. Carr, T. Kiesow, R. T. Sarisky, J. Lin-Goerke, A. Baker, D. L. Earnshaw, G. A. Hofmann, R. M. Keenan, D. Dhanak, *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1553-1556. b) G. Barton, T. W. Ku, T. J. Carr, T. Kiesow, R. T. Sarisky, J. Lin-Goerke, G. A. Hofmann, M. J. Slater, D. Haigh, D. Dhanak, V. K. Johnson, N. R. Parry, P. Thommes, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1930-1933. c) M. J. Slater, E. M. Amphlett, D. M. Andrews, G. Bravi, G. Burton, A. G. Cheasty, J. A. Corfield, M. R. Ellis, R. H. Fenwick, S. Fernandes, R. Guidetti, D. Haigh, C. D. Hartley, P. D. Howes, D. L. Jackson, R. L. Jarvest, V. L. H. Lovegrove, K. J. Medhurst, N. R. Parry, H. Price, P. Shah, O. M. P. Singh, R. Stocker, P. Thommes, C. Wilkinson, A. Wonacott, *J. Med. Chem.* **2007**, *50*, 897-900. d) C. Nájera, J. M. Sansano, *Org. Biomol. Chem.* **2009**, *7*, 4567-4581. e) R. Haudecoeur, M. Peuchmaur, A. Ahmed-Belkacem, J.-M. Pawlotsky, A. Boumendjel, *Med. Res. Rev.* **2013**, *33*, 934-984.

[3] R. H. Feling, G. O. Buchanan, T. J. Mincer, C. A. Kauffman, P. R. Jensen, W. Fenical, *Angew. Chem. Int. Ed.* **2003**, *42*, 355-357.

[4] a) R. Sakai, C. Oiwa, K. Takaishi, H. Kamiya, M. Tagawa, *Tetrahedron Lett.* **1999**, *40*, 6941-6944; b) R. Sakai, K. Suzuki, K. Shimamoto, H. Kamiya, *J. Org. Chem.* **2004**, *69*, 1180-1185.

[5] N. Ünver, G. i. Kaya, *Turk. J. Chem.* **2005**, *29*, 547-553.

[6] K. Shin-ya, J.-S. Kim, K. Furihata, Y. Hayakawa, H. Seto, *Tetrahedron Lett.* **1997**, *38*, 7079-7082.

[7] J. Qian-Cutrone, S. Huang, Y.-Z. Shu, D. Vas, C. Fairchild, A. Menendez, K. Krampitz, R. Dalterio, S. E. Klohr, Q. Gao, *J. Am. Chem. Soc.* **2002**, *124*, 14556-14557.

[8] R. Ruiz-Olalla, M. G. Retamosa, F. P. Cossío, *J. Org. Chem.* **2015**, *80*, 5588-5599.

[9] a) E. Conde, D. Bello, A. Cózar, M. Sánchez, M. A. Vázquez, F. P. Cossío, *Chem. Sci.* **2012**, *3*, 1486-1491; b) S. Zhou, S. Wang, J. Wang, Y. Nian, P. Peng, V. A. Soloshonok, H. Liu, *Eur. J. Org. Chem.* **2018**, 1821-1832.

[10] Review of 1,3-DC a) K. V. Gothelf, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 863-909. b) G. Pandey, P. Banerjee, S. R. Gadre, *Chem. Rev.* **2006**, *106*, 4484-4517. c) L. M. Stanley, M. P. Sibi, *Chem. Rev.* **2008**, *108*, 2887-2902. d) A Moyano, R. Rios, *Chem. Rev.* **2011**, *111*, 4703-4832.

e) J. Adrio, J. C. Carretero, *Chem. Commun.* **2011**, *47*, 6784-6794. f) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296-1310. g) J. Adrio, J. C. Carretero, *Chem. Commun.* **2014**, *50*, 12434-12446. h) T. Hashimoto, K. Maruoka, *Chem. Rev.* **2015**, *115*, 5366-5412. i) B. Bdiri, B.-J. Zhao, Z.-M Zhou, *Tetrahedron: Asymmetry* **2017**, *28*, 876-899. j) X. Fang, C.-J. Wang, *Org. Biomol. Chem.* **2018**, *16*, 2591-2601. k) J. Adrio, J. C. Carretero, *Chem. Commun.* **2019**, *55*, 11979-11991.

[11] A. A. Agbodjan, B. E. Cooley, R. C. B. Copley, J. A. Corfield, R. C. Flanagan, B. N. Glover, R. Guidetti, D. Haigh, P. D. Howes, M. M. Jackson, R. T. Matsuoka, K. J. Medhurst, A. Millar, M. J. Sharp, M. J. Slater, J. F. Toczko, S. Xie, *J. Org. Chem.* **2008**, *73*, 3094-3102.

[12] Naph-diPIM-dioxo-*i*Pr: 2,2,13,13-tetraisopropyl-3a,11a,14a,16b-tetrahydrobis(1,3-dioxolano[4',5':3,4]pyrrolo)[1,2-*a*:1',2'-*a*]naphtho[1,2-*d*:8,7-*d*']diimidazole. For the first use of this ligand for asymmetric catalysis, see: a) K. Miyata, H. Kutsuna, S. Kawakami, M. Kitamura, *Angew. Chem. Int. Ed.* **2011**, *50*, 4649-4653. Reviews: b) K. Miyata, M. Kitamura, *Synthesis* **2012**, *44*, 2138-2146. c) M. Kitamura, K. Miyata, T. Seki, N. Vatmurge, S. Tanaka, *Pure Appl. Chem.* **2013**, *85*, 1121-1132.

[13] E. J. Corey, N. Imai, H.-Y. Zhang, *J. Am. Chem. Soc.* **1991**, *113*, 728-729.

[14] Reports of the importance of n-π^* interaction in M$\mathbf{L}_{\boldsymbol{R}}$-catalyzed reaction: a) K. Morimoto, T. P. Le, S. K. Manna, I. N. C. Kiran, S. Tanaka, M. Kitamura, *Chem. - Asian J.* **2019**, *14*, 3283-3290. b) T. P. Le, K. Higashita, S. Tanaka, M. Yoshimura, M. Kitamura, *Org. Lett.* **2018**, *20*, 7149-7153. c) T. P. Le, S. Tanaka, M. Yoshimura, M. Kitamura, *Bull. Chem. Soc. Jpn.* **2020**, in press (doi: 10.1246/bcsj.20200172).

[15] For the first report of n-π^* interaction, see: a) H. B. Burgi, J. D. Dunitz, E. Shefter, *J. Am. Chem. Soc.* **1973**, *95*, 5065-5067. b) Reviews: R. W. Newberry, R. T. Raines, *Acc. Chem. Res.* **2017**, *50*, 1838-1846. c) J. Echeverría, *Chem. Commun.* **2018**, *54*, 3061-3064.

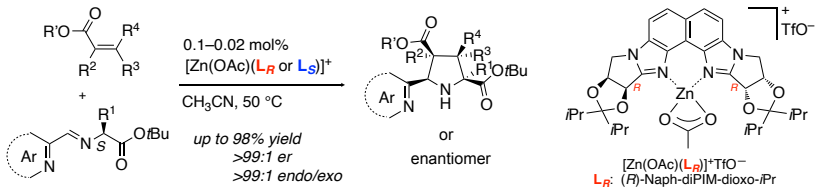
[16] Some examples for preparation of cationic metal complexes using acid/base principle: a) H. Lee, J. Y. Bae, O.-S. Kwon, S. J. Kim, S. D. Lee, H. S. Kim, *J. Organomet. Chem.* **2004**, *689*, 1816-1820. b) M. Bortoluzzi, G. Paolucci, G. Annibale, B. Pitteri, *Inorg. Chem. Commun.* **2010**, *13*, 945-948. c) J. Coetzee, D. L. Dodds, J. Klankermayer, S. Brosinski, W. Leitner, A. M. Z. Slawin, D. J. Cole-Hamilton, *Chem. - Eur. J.* **2013**, *19*, 11039-11050. d) A. G. D. Crisci, K. Chung, A. G. Oliver, D. Solis-Ibarra, R. M. Waymouth, *Organometallics* **2013**, *32*, 2257-2266. e) Z. F. Shi, J. M. Li, K. H. He, Y. M. Jiang, *Russ. J. Coor. Chem.* **2012**, *38*, 614-619.

[17] For example, see: D. C. Powers, D. Benitez, E. Tkatchouk, W. A. Goddard III, T. Ritter. *J. Am. Chem. Soc.* **2010**, *132*, 14092-14103.

[18] A. Dondoni, *Org. Biomol. Chem.* **2010**, *8*, 3366-3385.

[19] a) Z. Xu, T. Ye, Thiazoline and Thiazole and Their Derivatives. In *Heterocycles in Natural Product Synthesis*; K. C. Majumdar, S. K. Chattopadhyay, Eds.; Wiley-VCH: Weinheim, 2011; pp 459–505. b) M. Vinícius, M. Souza, *J. Sulfur Chem.* **2005**, *26*, 429-449. c) D. Davyt, G. Serra, *Mar. Drugs* **2010**, *8*, 2755-2780. d) A Rouf, C. Tanyeli, *Eur. J. Med. Chem*. **2015**, *97*, 911-927. e) S. Kumar, R. Aggarwal, *Mini-Rev. Org. Chem*. **2019**, *16*, 26-34.

Entry for the Table of Contents



A highly efficient catalytic asymmetric 1,3-dipolar cycloaddition was realized between tridentate α-imino esters and acrylates to furnish various multi-substituted prolines. A Brønsted base/Lewis acid synergistic effect of [Zn^{II}OAc(**L*R*** or **L*S***)]$^{+}$(OTf)$^{-}$ facilitates an intramolecular deprotonation to generate an *N*,*O*-*cis*-Zn enolate, which is attracted in the catalyst to the dioxo-*i*Pr side via an n-$\pi^{*}_{C=N}$ interaction to realize high selectivity.