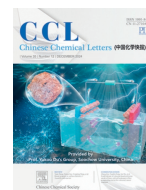




Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: [www.elsevier.com/locate/ccllet](http://www.elsevier.com/locate/ccllet)

# Palladium-catalyzed enantioselective decarboxylation of vinyl cyclic carbamates: Generation of amide-based aza-1,3-dipoles and application to asymmetric 1,3-dipolar cycloaddition

Xiaohui Fu<sup>a,b,c</sup>, Yanping Zhang<sup>b</sup>, Juan Liao<sup>a,b,c</sup>, Zhen-Hua Wang<sup>b</sup>, Yong You<sup>b</sup>, Jian-Qiang Zhao<sup>b</sup>, Mingqiang Zhou<sup>a,b,c</sup>, Wei-Cheng Yuan<sup>a,b,c,\*</sup>

<sup>a</sup> National Engineering Research Center of Chiral Drugs, Chengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, China

<sup>b</sup> Innovation Research Center of Chiral Drugs, Institute for Advanced Study, Chengdu University, Chengdu 610106, China

<sup>c</sup> University of Chinese Academy of Sciences, Beijing 100049, China

## ARTICLE INFO

### Article history:

Received 20 August 2023

Revised 20 February 2024

Accepted 27 February 2024

Available online 1 March 2024

### Keywords:

Cycloaddition

Palladium

Enantioselectivity

Asymmetric catalysis

Decarboxylation

## ABSTRACT

The catalytic asymmetric dipolar cycloaddition reaction is efficient for the construction of various chiral valuable carbo- and heterocycles. Thus, the design and exploration of new dipoles and the subsequent control of their reactivity for various stereoselective cycloadditions are significant aspects of modern organic synthesis. Herein, we have developed a series of vinyl cyclic carbamates containing an oxazolidinone-2,4-dione fragment and used them as reactive precursors for *in situ* generation of amide-based aza- $\pi$ -allylpalladium 1,3-dipoles, which could be applied to asymmetric decarboxylative 1,3-dipolar cycloaddition with different types of dipolarophiles containing C=C, C=N, and C=O double bonds. This strategy provides an opportunity for the synthesis of previously unusual structures, such as highly functionalized optically pure pyrrolidin-2-ones, imidazolidin-4-ones, and oxazolidin-4-ones. This protocol also has significant features including wide substrate scope, mild reaction conditions, simple operation, and good to excellent results (70 examples, up to 99% yield, >20:1 *dr* and 99% *ee*). This unique method significantly expands the reaction range of the amide-based aza- $\pi$ -allylpalladium 1,3-dipoles compared to the precedents.

© 2024 Published by Elsevier B.V. on behalf of Chinese Chemical Society and Institute of Materia Medica, Chinese Academy of Medical Sciences.

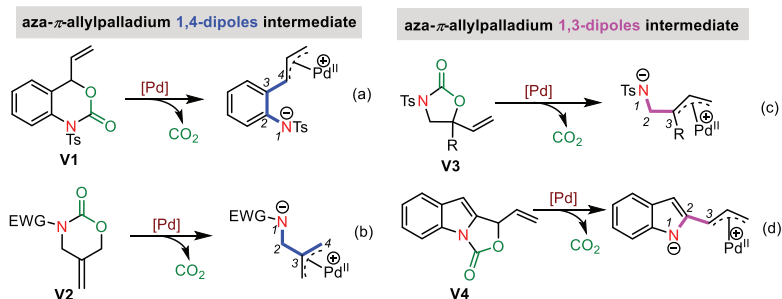
Catalytic asymmetric dipolar cycloaddition reaction is considered to be one of the most powerful and widely used strategies for the construction of chiral carbo- and heterocyclic compounds with elaborate ring frameworks [1–3]. In this research area, an important aspect is the design and exploration of effective dipole intermediates, which should have high reactivity and facilitate the control of reaction stereoselectivity in the asymmetric transformations. Actually, chiral transition-metal catalysts acting on reaction substrates to generate appropriate metal-containing zwitterionic dipoles for sequential asymmetric dipolar cycloaddition represents a remarkable advance in modern organic synthesis, and a number of elegant synthetic methods have been developed [4–8]. Despite this fact, the growing demand for structurally diverse three-dimensional cyclic scaffolds in the field of medicinal chemistry still inspires synthetic chemists to develop new and practical methods for complementing the existing approaches [9].

Therefore, the design and development of novel precursors to produce metal-mediated highly active dipole intermediates for new reaction discovery is still highly desirable.

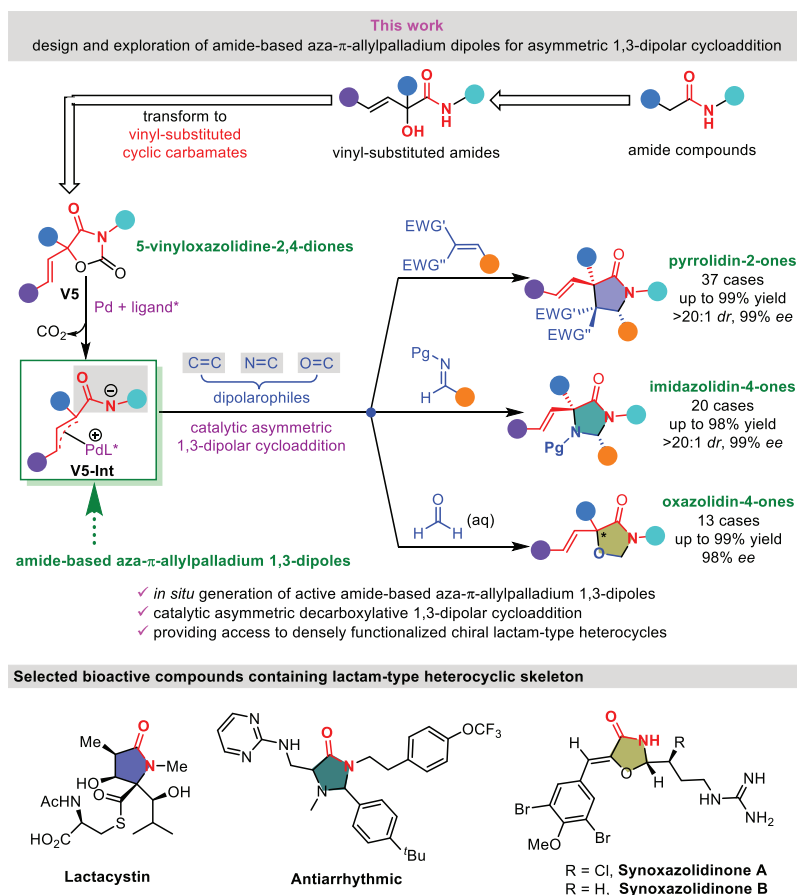
Transition metal-catalyzed asymmetric decarboxylation of cyclic carbonates/carbamates, leading to the *in situ* formation of active metal-containing zwitterionic intermediates for the construction of chiral cyclic structures, has become a research hotspot in organic synthetic chemistry [10–18]. In particular, the palladium-mediated decarboxylation of vinyl-substituted cyclic carbamates, which gives rise to aza- $\pi$ -allylpalladium 1,*n*-zwitterionic dipoles containing a nucleophilic nitrogen anion and a ligand ligated  $\pi$ -allylpalladium cation counterpart, has been widely applied in asymmetric dipolar cycloaddition to access nitrogen-containing heterocycles [19–23]. In fact, to date, only very few vinyl cyclic carbamates have been used as aza- $\pi$ -allylpalladium 1,4- or 1,3-dipole precursors for asymmetric reactions *via* a decarboxylation process. For example, the vinyl benzoxazinanes **VI** were first reported as aza- $\pi$ -allylpalladium 1,4-dipole precursors for enantioselective decarboxylative [4+2] cycloaddition by Tunge (Scheme 1a) [24–30]. Another type of aza- $\pi$ -allylpalladium 1,4-dipoles generated from

\* Corresponding author.

E-mail address: [yuanwc@cioc.ac.cn](mailto:yuanwc@cioc.ac.cn) (W.-C. Yuan).



**Scheme 1.** Palladium-catalyzed decarboxylation of vinyl cyclic carbamates for generating aza- $\pi$ -allylpalladium 1, $n$ -dipoles.



**Scheme 2.** Design and exploration of amide-based aza- $\pi$ -allylpalladium dipole precursors for asymmetric 1,3-dipolar cycloaddition, and the selected bioactive compounds containing lactam-type heterocyclic skeleton.

cyclic vinyl carbamates **V2** for asymmetric transformations were reported by Harrity's and our group, respectively (Scheme 1b) [31–33]. In addition, Ooi and co-workers realized the first Pd-catalyzed asymmetric decarboxylative cycloaddition of vinyl oxazolidinones **V3**, which acted as highly reactive aza- $\pi$ -allylpalladium 1,3-dipoles precursors (Scheme 1c) [34,35]. Moreover, Shi's and Deng's group independently discovered that the vinyl indoloxazolidinones **V4** could be used as indolyl-based Pd-allyl zwitterionic species precursors for asymmetric cycloaddition (Scheme 1d) [36,37].

Inspired by the precedents mentioned above, and as a continuation of our interest in catalytic asymmetric decarboxylative cycloaddition of cyclic carbonates/carbamates [33,38–44], we envisioned that introducing a vinyl motif at the  $\alpha$ -position of amide compounds and then converting them into vinyl-substituted cyclic carbamates **V5**, which should undergo a decarboxylation process

in the presence of a palladium catalyst thus leading to the formation of active amide-based aza- $\pi$ -allylpalladium 1,3-dipoles **V5-Int** (Scheme 2). If successful, we speculated that the *in situ* generated amide-based aza- $\pi$ -allylpalladium 1,3-dipoles would be applied to asymmetric 1,3-dipolar cycloadditions with various dipolarophiles including C=C, C=N, and C=O double bonds. Indeed, we have successfully synthesized a series of 5-vinylloxazolidine-2,4-diones **V5** acting as reactive precursors of aza- $\pi$ -allylpalladium 1,3-dipoles and further realized enantioselective cycloaddition reactions by a catalytic system consisting of a readily available phosphoramidite ligand and Pd(0) catalyst [45,46], affording highly functionalized optically active pyrrolidin-2-ones, imidazolidin-4-ones, and oxazolidin-4-ones (Scheme 2). Notably, due to the existence of the nucleophilic amide anion site in the *in situ* generated 1,3-dipole intermediates **V5-Int**, this would provide an efficient access to previously unknown structural opportunities, such as highly

**Table 1**  
Optimization of reaction conditions.<sup>a</sup>

Entry	L1-4	Solvent	x/y	Yield (%) <sup>b</sup>	<i>dr</i> <sup>c</sup>	<i>ee</i> (%) <sup>c</sup> - <b>3a</b>	<i>ee</i> (%) <sup>c</sup> - <b>3a'</b>
1	<b>L1</b>	CH <sub>2</sub> Cl <sub>2</sub>	5/20	95	1.7:1	-9	-24
2	<b>L2</b>	CH <sub>2</sub> Cl <sub>2</sub>	5/20	98	1.2:1	90	75
3	<b>L3</b>	CH <sub>2</sub> Cl <sub>2</sub>	5/20	20	1.8:1	-59	-61
4	<b>L4</b>	CH <sub>2</sub> Cl <sub>2</sub>	5/20	42	1.5:1	17	33
5	<b>L2</b>	CH <sub>2</sub> Cl <sub>2</sub>	5/15	96	1.1:1	89	79
6	<b>L2</b>	CH <sub>2</sub> Cl <sub>2</sub>	5/10	37	1.2:1	34	30
7	<b>L2</b>	DME	5/20	92	1.1:1	89	97
8	<b>L2</b>	Acetone	5/20	62	1.2:1	96	90
9	<b>L2</b>	EtOAc	5/20	95	1.1:1	93	97
10 <sup>d</sup>	<b>L2</b>	EtOAc	5/20	96	1.0:1	96	97
11 <sup>d</sup>	<b>L2</b>	EtOAc	2.5/10	94	1.2:1	95	98

<sup>a</sup> Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (x mol%), ligand (y mol%) in 1.0 mL solvent at 35 °C for 72 h under argon atmosphere.

<sup>b</sup> Isolated yields of two diastereoisomers.

<sup>c</sup> Diastereoisomeric ratio (*dr*) and *ee* values were determined by HPLC using chiral column.

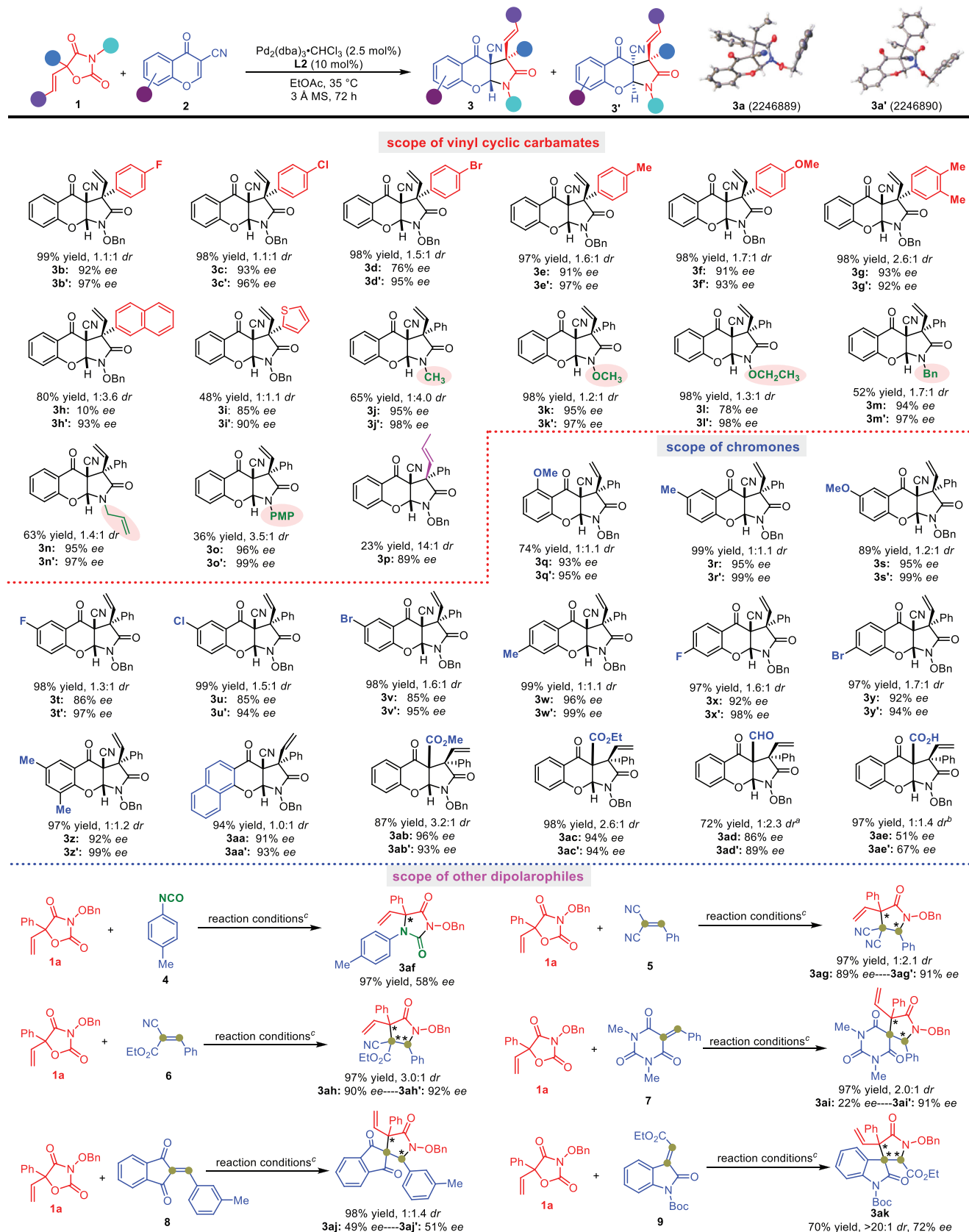
<sup>d</sup> 3 Å molecular sieves (30 mg) was used. DME = 1,2-Dimethoxyethane.

functionalized lactam-type heterocyclic skeletons, which are ubiquitous ring systems in many bioactive compounds and are a fundamental unit of important candidates in pharmaceutical research (Scheme 2, bottom) [47–50]. More importantly, this unique strategy not only is complementary to the well-established palladium-mediated dipolar cycloadditions but also significantly expands the reaction range of the amide-based aza- $\pi$ -allylpalladium 1,3-dipoles compared to the precedents [45,46]. Herein, we hope to report the results from this study.

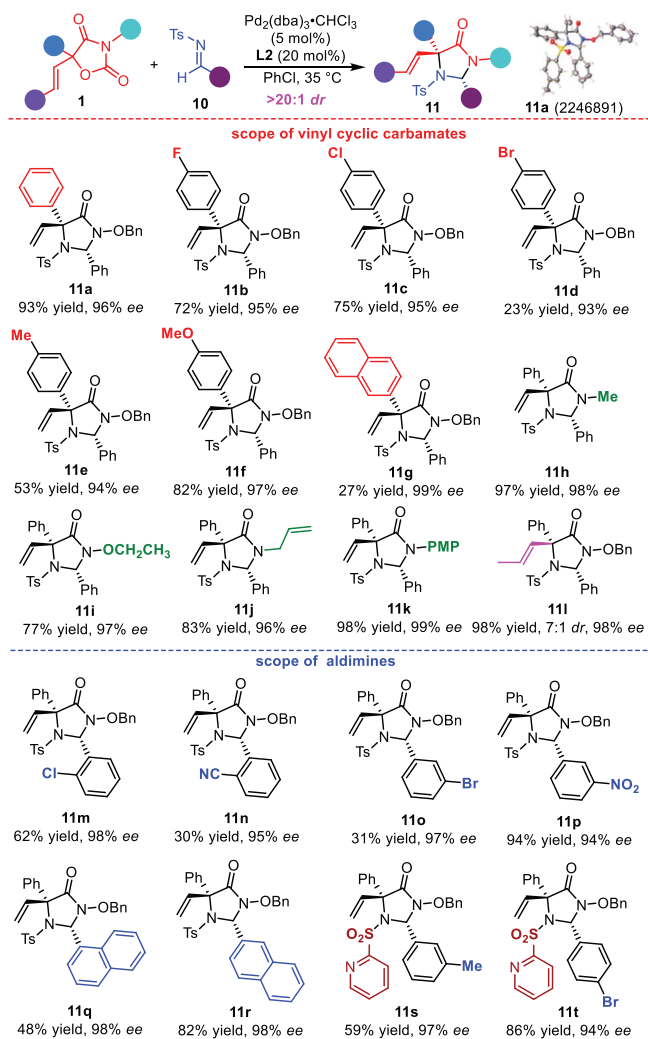
We started our study with the model reaction of 5-vinylloxazolidine-2,4-dione **1a** and 3-cyanochromone **2a** in CH<sub>2</sub>Cl<sub>2</sub>. As shown in Table 1, Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> was used as a precatalyst to investigate the chiral phosphoramidite ligands **L1–4** (entries 1–4). It was found that the readily available (*R<sub>a</sub>,S,S*)-Feringa ligand **L2** gave relatively satisfactory results for the cycloadducts in 98% yield with 1.2:1 *dr* and 90% *ee*/75% *ee* for the two diastereoisomers **3a** and **3a'** (entry 2). Fortunately, the two diastereoisomers could be isolated by column chromatography. And then, changing the ratio of precatalyst to **L2** showed a detrimental effect on the enantioselectivities (entries 5 and 6). Solvent screening revealed that ethyl acetate afforded the best *ee* values for the two diastereoisomers (entry 9). The addition of 3 Å molecular sieves slightly improved the *ee* values to 96% *ee* and 97% *ee* (entry 10). To our delight, the reaction also proceeded smoothly with a reduced catalyst loading, providing 94% yield with 1.2:1 *dr* and 95% *ee* and 98% *ee* (entry 11).

With the optimal reaction conditions in hand, a series of 5-vinylloxazolidine-2,4-diones and 3-cyanochromones were tested to evaluate the generality of the Pd-catalyzed asymmetric decarboxylative 1,3-dipolar cycloaddition. As shown in Scheme 3, the 5-vinylloxazolidine-2,4-diones bearing either electron-withdrawing or electron-donating substituent on the benzene ring, such as F-, Cl-, Br-, Me-, or MeO- group, reacted smoothly with **2a** to generate the corresponding products **3b/b'–3f/f'** in excellent yields with very high *ee* values. Likewise, the doubly substituted phenyl group is tolerated under the reaction conditions to give the products **3g** and **3g'** in 98% yield with 2.6:1 *dr* and 93% *ee*/92% *ee*. In addition, the vinyl cyclic carbamates bearing naphthyl and thiophen

moieties were also compatible well with the developed reaction conditions, thus giving the cycloadducts **3h/h'** and **3i/i'** with acceptable results. Moreover, it was found that the reactivity and stereoselectivity were hardly affected by the incorporation of different substituents on the nitrogen atom of the amide group, such as Me-, MeO-, EtO-, Bn-, allyl-, and PMP-substituents, the desired products **3j/j'–3o/o'** could be smoothly obtained in good to excellent yields with good diastereoselectivities and excellent enantioselectivities. Notably, non-terminal alkenyl-substituted cyclic carbamate could also be used for the cycloaddition reaction, affording **3p** in 23% yield with 14:1 *dr* and 89% *ee*. Although the catalytic system is less effective for the reactivity of substrate containing a non-terminal double bond, the results further proved that the reaction undergoes the palladium-catalyzed asymmetric decarboxylation to form aza- $\pi$ -allylpalladium dipole intermediates for the nucleophilic attack the unsaturated electrophiles and the subsequent intramolecular nucleophilic cyclization. On the other hand, 3-cyanochromones bearing different steric and electronic natures could react well with **1a** to furnish the desired products **3q/q'–3y/y'** in good to excellent yields with moderate diastereoselectivities and excellent enantioselectivities. In the case of 3-cyano-6,8-dimethyl chromone as a dipolarophile, the reaction with **1a** proceeded smoothly under the catalytic system to furnish products **3z** and **3z'** in 97% yield with 1:1.2 *dr* and 92% *ee*/99% *ee*. The reaction of **1a** with 3-cyanobenzochromone also performed well to generate corresponding cyclic products **3aa** and **3aa'** in high yield (94%) with high enantioselectivity (91% *ee*/93% *ee*) and 1:1 diastereoselectivity. Replacing the cyano group of the chromone with another electron-withdrawing group, such as ester, formyl, or carboxyl group, was also allowed for the occurrence of the 1,3-dipolar cycloaddition reaction, as shown by products **3ab/ab'–3ae/ae'**. It should be pointed out that the formyl (CHO) group and the carboxyl (CO<sub>2</sub>H) group in products **3ad/ad'** and **3ae/ae'** were eliminated. Furthermore, the palladium-catalyzed asymmetric decarboxylative cycloaddition reaction of **1a** with other unsaturated electrophiles was also examined. The reaction of **1a** with isocyanate **4** proceeded smoothly and furnished chiral imidazolidine-



**Scheme 3.** Substrate scope for vinyl cyclic carbamates and diverse dipolarophiles containing C=C double bond. Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (2.5 mol%), **L2** (10 mol%), and 3 Å MS (30 mg) in 1.0 mL EtOAc at 35 °C for 72 h under argon atmosphere. <sup>a</sup> The formyl (CHO) group was eliminated in the product. <sup>b</sup> The carboxyl (CO<sub>2</sub>H) group was eliminated in the product. <sup>c</sup> Reaction conditions: **1a** (0.1 mmol), **4–9** (0.12 mmol), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (5 mol%), **L2** (20 mol%) in 1.0 mL CH<sub>2</sub>Cl<sub>2</sub> at 35 °C for 168 h under argon atmosphere.



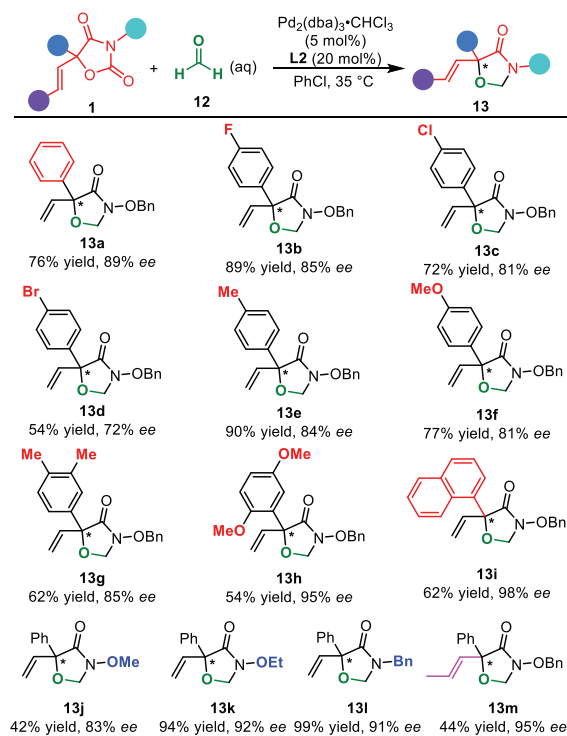
**Scheme 4.** Substrate scope for vinyl cyclic carbamates and imines. Reaction conditions: **1** (0.1 mmol), **10** (0.12 mmol), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (5 mol%), **L2** (20 mol%) in 1.0 mL PhCl at 35 °C for 168 h under argon atmosphere.

2,4-dione **3af** in 97% yield with 58% *ee*. Nevertheless, it was also found that some other acceptors bearing different electron-withdrawing groups, such as malononitrile (**5**), nitrile acetate (**6**), barbiturate (**7**), 1*H*-indene-1,3(2*H*)-dione (**8**), and oxindole (**9**), were also suitable in the developed catalytic system to give the desired cycloadducts with moderate to good results. In particular, the spirooxindole product **3ak** could be obtained with >20:1 *dr* and 72% *ee*. Notably, the two diastereoisomers **3** and **3'** in Scheme 3 could be isolated by column chromatography. The absolute configurations of products (*S,S,R*)-**3a** and (*S,R,S*)-**3a'** were unambiguously confirmed by X-ray crystallography, and assigned to all of other products by analogy.

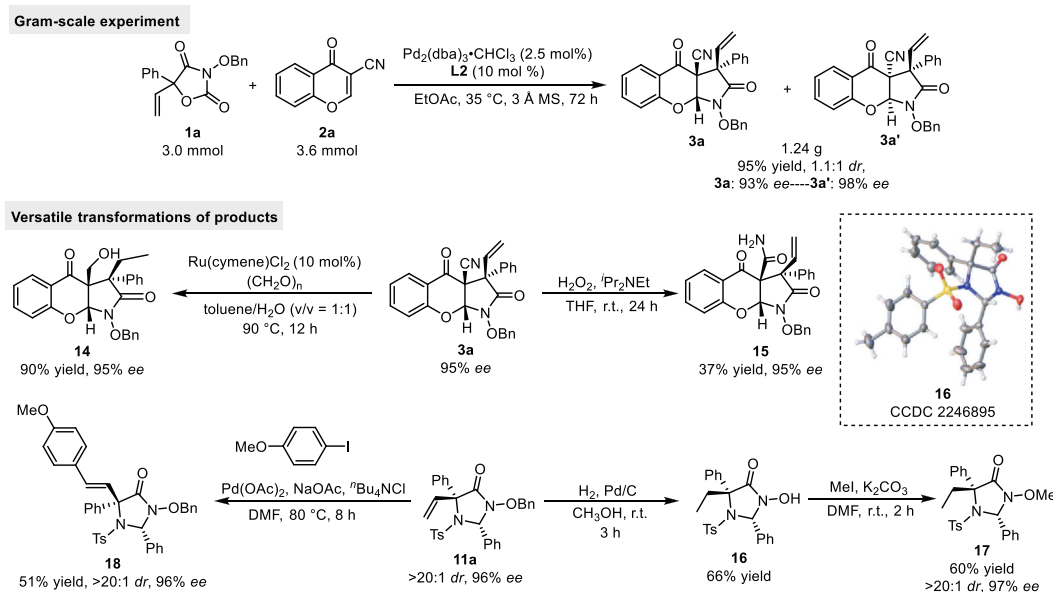
To our surprise, the catalytic system developed above could be successfully extended to imines as dipolarophiles. As shown in Scheme 4, at first, the reaction of **1a** with (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide (**10a**) in chlorobenzene as solution proceeded well, thereby delivering the cycloadduct **11a** in 93% yield with >20:1 *dr* and 96% *ee*. Nevertheless, different vinyl cyclic carbamates **1** bearing a variation of substituents including electron-withdrawing as well as electron-donating functionalities on the aryl moiety could also undergo decarboxylation for 1,3-dipolar cycloaddition with **10a**, providing the corresponding chiral imidazolidin-4-one products **11b-g** in 23–82% yield with 93%–99% *ee*. 5-Vinylloxazolidine-2,4-diones bearing different pro-

tecting groups (Me-, EtO-, allyl-, and PMP-) at the nitrogen atom were well tolerated in the reaction conditions to give the cycloadducts **11h-k** in good yields (77%–98%) with excellent enantioselectivities (96%–99% *ee*). In addition, the non-terminal alkenyl-substituted cyclic carbamate could react with **10a** to produce **11l** in 98% yield with 7:1 *dr* and 98% *ee*. On the other hand, imines **10** derived from arylaldehydes bearing different substitution patterns and electronic properties could react well with **1a** under the standard conditions, affording products **11m-p** in moderate to good yields with high to excellent *ee* values. In the case of imine derived from 1-naphthaldehyde, the cycloaddition reaction gave product **11q** in 48% yield with >20:1 *dr* and 98% *ee*, but the imine from 2-naphthaldehyde was able to produce the corresponding cycloadduct **11r** in 82% yield with >20:1 *dr* and 98% *ee*. The results of this pair of examples indicate that the steric hindrance of the aldimines has an obvious influence on the reactivity of the cycloaddition. Moreover, the pyridin-2-ylsulfonyl group was also compatible with the catalytic system, as shown by the products **11s** and **11t**. The absolute configuration of (*R,S*)-**11a** was unambiguously confirmed by X-ray crystallography, and assuming a common reaction pathway, the configuration of the other cycloadducts **11** was assigned by analogy. Notably, all products except **11l** could be obtained in >20:1 diastereoselectivity through the asymmetric decarboxylative 1,3-dipolar cycloaddition reaction.

More excitingly, we also found that the formaldehyde (37% aqueous solution) **12**, an abundant feedstock and a reactive one carbon electrophile, could be used for the palladium-catalyzed decarboxylative 1,3-dipolar cycloaddition with vinyl cyclic carbamates **1** under the developed catalytic system. As shown in Scheme 5, a series of 5-vinylloxazolidine-2,4-diones with different substitution patterns and electronic properties performed well, affording the oxazolidin-4-one products **13a-i** in 54%–90% yield with 72%–98% *ee*. In addition, the reaction conditions were also effective for



**Scheme 5.** Substrate scope for vinyl cyclic carbamates and formaldehyde. Reaction conditions: **1** (0.1 mmol), **12** (1.0 mmol, 37% aqueous solution), Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> (5 mol%), **L2** (20 mol%) in 1.0 mL PhCl at 35 °C for 168 h under argon atmosphere.



**Scheme 6.** Gram-scale experiment and transformations of products.

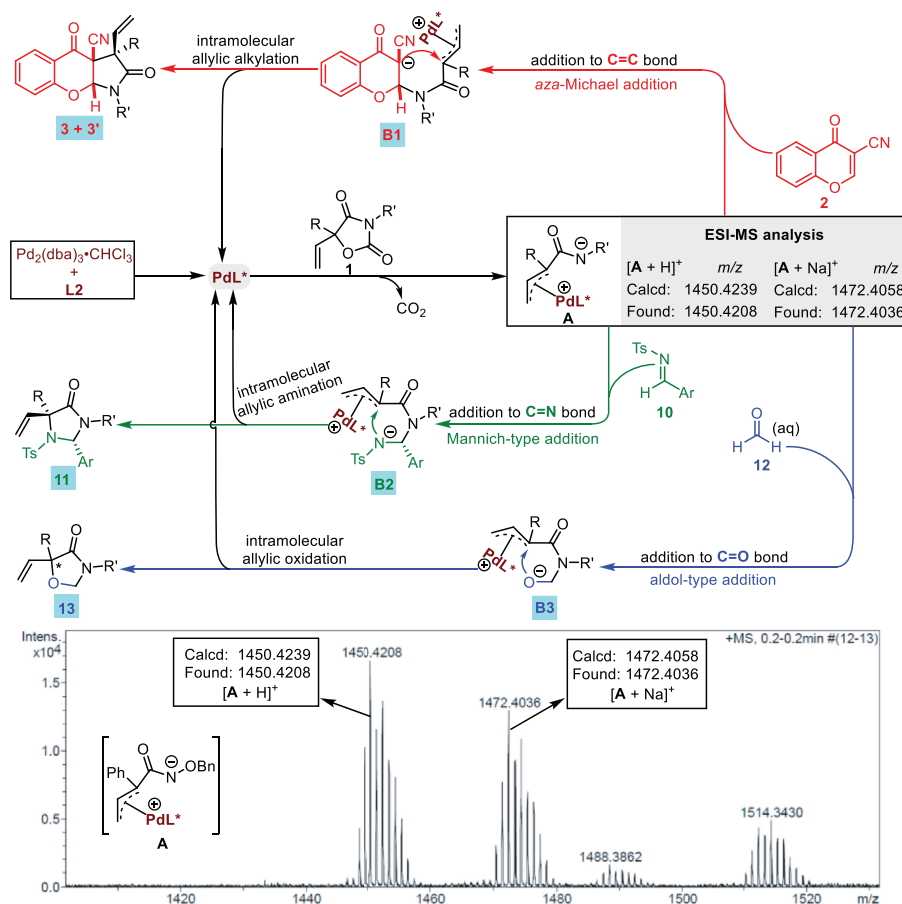
the *N*-OMe, *N*-OEt, and *N*-Bn substituted 5-vinylloxazolidine-2,4-diones, thus delivering the corresponding products **13j–l** in moderate to high yields (42%–99%) with 83%–92% *ee*. Furthermore, non-terminal alkenyl-substituted cyclic carbamate could also react with formaldehyde to afford product **13m** in 44% yield with 95% *ee* under the standard reaction conditions.

To investigate the synthetic applications of the Pd-catalyzed asymmetric decarboxylative 1,3-dipolar cycloaddition of 5-vinylloxazolidine-2,4-diones, we performed the gram-scale experiment and the versatile derivatizations of the products. As shown in Scheme 6, the reaction of **1a** and **2a** could be scaled up to 3.0 mmol for **1a** and proceeded smoothly under the standard conditions, affording the products **3a** and **3a'** in 95% yield with 1.1:1 *dr* and 93% *ee*/98% *ee* (Scheme 6, top). Luckily, the diastereoisomers **3a** and **3a'** could be readily separated by flash column chromatography on silica gel. And then, a variety of synthetic transformations of the products were explored. At first, under Ru-catalyzed reductive conditions, **3a** was readily converted to compound **14** in 90% yield with 95% *ee* in the presence of paraformaldehyde with a mixture of toluene and water as solvent. In addition, the nitrile group of **3a** was hydrolyzed to the amide group by using a 10-fold molar excess of 30% aqueous H<sub>2</sub>O<sub>2</sub> in THF at room temperature, resulting in the formation of **15** in 37% yield without deterioration of enantiomeric purity. On the other hand, we also found that product **11a** could be sequentially transformed into compounds **16** and **17** in good yields without loss of the diastereo- and enantioselectivities. Moreover, the Pd-catalyzed Heck coupling reaction of **11a** with 1-iodo-4-methoxybenzene occurred smoothly in DMF at 80 °C, leading to the generation of **18** in 51% yield with >20:1 *dr* and 96% *ee*. The structure of **16** was unambiguously assigned by X-ray crystallography.

Taking into account the previous related reports [26,36,37,51–53] and reconciling them with the results of our study, a possible reaction mechanism was proposed and outlined in Scheme 7. The chiral PdL\* complex from Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and ligand **L2** activates vinyl cyclic carbamates **1** through an oxidative addition and decarboxylation process to release CO<sub>2</sub> and generate a Pd-containing amide-based zwitterionic intermediate **A**, which could be detected with the help of ESI-HRMS analysis and characterized by peaks at *m/z* 1450.4208 as the [A + H]<sup>+</sup> species and at *m/z* 1472.4036 as the [A + Na]<sup>+</sup> species. This observation clearly demonstrates that not

only the *in situ* formation of aza- $\pi$ -allylpalladium 1,3-dipoles **A** in the catalytic system, but also the chiral palladium complex ligated 1,3-dipole intermediate **A** is critical for the asymmetric 1,3-dipolar cycloaddition. And then, the nucleophilic nitrogen anion site of intermediate **A** attacks the dipolarophiles **2** (C=C double bond), **10** (C=N double bond), and **12** (C=O double bond) via aza-Michael addition, Mannich-type addition, and aldol-type addition to form intermediates **B1**, **B2**, and **B3**, respectively. These intermediates then undergo independently intramolecular allylic alkylation (**B1**), intramolecular allylic amination (**B2**), and intramolecular allylic oxidation (**B3**) for the cyclization to generate their corresponding optically pure cycloadducts pyrrolidin-2-ones **3 + 3'**, imidazolidin-4-ones **11**, and oxazolidin-4-ones **13**, along with releasing the palladium catalyst into the next catalytic cycle.

In conclusion, we have successfully developed a series of vinyl cyclic carbamates containing an oxazolidine-2,4-dione fragment, which could be used as reactive precursors for the *in situ* generation of amide-based aza- $\pi$ -allylpalladium 1,3-dipoles via decarboxylation process with a palladium catalyst. This type of amide-based aza- $\pi$ -allylpalladium 1,3-dipoles could be used for asymmetric decarboxylative 1,3-dipolar cycloaddition with different types of dipolarophiles including C=C, C=N, and C=O double bonds. A catalytic system consisting of a readily available chiral phosphoramidite ligand and a Pd(0) catalyst displays high efficiency and excellent stereocontrol in the cycloaddition reactions. This strategy provides an opportunity for the synthesis of previously unusual structures, such as highly functionalized optically pure pyrrolidin-2-ones, imidazolidin-4-ones, and oxazolidin-4-ones. This protocol also has significant features including wide substrate scope, mild reaction conditions, simple operation, and good to excellent results (70 examples, up to 99% yield, >20:1 *dr* and 99% *ee*). The synthetic utility of the developed asymmetric decarboxylative 1,3-dipolar cycloaddition was showcased by gram-scale experiment and versatile derivatizations of the products. This unique strategy significantly expands the reaction range of the amide-based aza- $\pi$ -allylpalladium 1,3-dipoles compared to the precedents. Further applications of amide-based aza- $\pi$ -allylpalladium 1,3-dipoles in diverse asymmetric cycloaddition reactions and in the synthesis of biologically active compounds are currently underway.



Scheme 7. Proposed reaction mechanism and ESI-MS analysis.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### Acknowledgments

We are grateful for the National Natural Science Foundation of China (Nos. 22271027, 22171029, 21901024, 21871252, 21801024, and 21801026), the Sichuan Science and Technology Program (No. 2021YFS0315), and the Talent Program of Chengdu University (Nos. 2081919035 and 2081921038).

### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ccl.2024.109688.

### References

- S. Kobayashi, K.A. Jorgensen, *Cycloaddition Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2001.
- L.M. Harwood, R.J. Vickers, A. Padwa, W.H. Pearson, *Org. Proc. Res. Dev.* 8 (2004) 293–300.
- T. Hashimoto, K. Maruoka, *Chem. Rev.* 115 (2015) 5366–5412.
- B.D.W. Allen, C.P. Lakeland, J.P.A. Harrity, *Chem. Eur. J.* 23 (2017) 13830–13857.
- N. De, E.J. Yoo, *ACS Catal.* 8 (2018) 48–58.
- T.R. Li, Y.N. Wang, W.J. Xiao, L.Q. Lu, *Tetrahedron Lett.* 59 (2018) 1521–1530.
- J. Wang, S.A. Blaszczyk, X. Li, W. Tang, *Chem. Rev.* 121 (2021) 110–139.
- M.M. Zhang, B.L. Qu, B. Shi, et al., *Chem. Soc. Rev.* 51 (2022) 4146–4174.
- R.D. Taylor, M. MacCoss, A.D.G. Lawson, *J. Med. Chem.* 57 (2014) 5845–5859.
- J.D. Weaver, A. Recio III, A.J. Grenning, J.A. Tunge, *Chem. Rev.* 111 (2011) 1846–1913.
- R. Shintani, *Bull. Chem. Soc. Jpn.* 85 (2012) 931–939.
- A. Khan, Y.J. Zhang, *Synlett* 26 (2015) 853–860.
- W. Guo, J.E. Gómez, À. Cristófol, et al., *Angew. Chem. Int. Ed.* 57 (2018) 13735–13747.
- J. Zhang, Y. Chen, Y. Liu, et al., *Chin. J. Org. Chem.* 42 (2022) 3051–3101.
- Y. You, Y.P. Zhang, Z.H. Wang, et al., *Chem. Commun.* 59 (2023) 7483–7505.
- Zuo, W. Guo, *Synlett* 33 (2022) 903–906.
- B. Yan, W. Guo, *Synthesis* 54 (2022) 1964–1976.
- T. Liu, Y. Fang, L. Zuo, et al., *Org. Chem. Front.* 8 (2021) 1902–1909.
- L. Zuo, T. Liu, X. Chang, W. Guo, *Molecules* 24 (2019) 3930–3945.
- Q.Z. Li, Y. Liu, T. Qi, et al., *Org. Biomol. Chem.* 18 (2020) 3638–3648.
- B. Niu, Y. Wei, M. Shi, *Org. Chem. Front.* 8 (2021) 3475–3501.
- Y. Tian, M. Duan, K. Dong, et al., *Adv. Synth. Catal.* 363 (2021) 4461–4474.
- Y. You, Y.P. Zhang, Z.H. Wang, et al., *ChemCatChem* 14 (2022) 1–34.
- C. Wang, J.A. Tunge, *Org. Lett.* 8 (2006) 3211–3214.
- C. Wang, J.A. Tunge, *J. Am. Chem. Soc.* 130 (2008) 8118–8119.
- T.R. Li, F. Tan, D.Q. Shi, et al., *Nat. Commun.* 5 (2014) 5500–5510.
- C. Guo, D. Janssen-Müller, M. Fleige, et al., *J. Am. Chem. Soc.* 139 (2017) 4443–4451.
- M.M. Li, Y. Wei, L.Q. Lu, et al., *J. Am. Chem. Soc.* 139 (2017) 14707–14713.
- C. Guo, M. Fleige, C.G. Daniliuc, et al., *J. Am. Chem. Soc.* 138 (2016) 7840–7843.
- L.A. Leth, F. Glaus, E.A. Bitsch, et al., *Angew. Chem. Int. Ed.* 55 (2016) 15272–15276.
- B.D.W. Allen, M.J. Connolly, J.P.A. Harrity, *Chem. Eur. J.* 22 (2016) 13000–13003.
- J. Han, L. Hoteite, J.P.A. Harrity, *Chem. Eur. J.* 28 (2022) 1–6.
- S.P. Yuan, Y.P. Zhang, M.Q. Zhou, et al., *Org. Lett.* 24 (2022) 8348–8353.
- K. Ohmatsu, N. Imagawa, T. Ooi, *Nat. Chem.* 6 (2014) 47–51.
- K. Ohmatsu, S. Kawai, N. Imagawa, T. Ooi, *ACS Catal.* 4 (2014) 4304–4306.
- Q.Q. Hang, Y.C. Zhang, G.J. Me, et al., *Chin. J. Chem.* 38 (2020) 1612–1618.
- F. Tian, W.L. Yang, J.Z. Zhang, et al., *Sci. China Chem.* 64 (2021) 34–40.
- T.T. Li, Y. You, Z.H. Wang, et al., *Org. Lett.* 24 (2022) 5120–5125.
- Y. You, Q. Li, Y.P. Zhang, et al., *ChemCatChem* 14 (2022) e202101887.
- Y. You, T.T. Li, J.Q. Zhao, et al., *Org. Lett.* 24 (2022) 7671–7676.
- J.Q. Zhao, H.W. Rao, Z.H. Wang, et al., *Org. Chem. Front.* 9 (2022) 6172–6178.
- T. Wang, Y. You, B.D. Cui, et al., *Org. Lett.* 25 (2023) 1274–1279.
- Y. You, G.Y. Gan, S.Y. Duan, et al., *Org. Chem. Front.* 10 (2023) 5421–5427.

- [44] Y.P. Zhang, Y. You, J.Q. Yin, et al., *Eur. J. Org. Chem.* (2023) e202300728.
- [45] K. Li, S. Zhen, Y. Wu, et al., *Chem. Sci.* 14 (2023) 3024–3029.
- [46] A. Scuille, N. Casaretto, A. Archambeau, *J. Org. Chem.* 88 (2023) 9941–9945.
- [47] S. Omura, T. Fujimoto, H. Tanaka, et al., *Antibiot* 44 (1991) 113–116.
- [48] S. Flohr, S. Stengelin, M. Gossel, T.D.E. Klabunde, Patent, WO2004072076 (A1), 2004.
- [49] M. Tadesse, M.B. Strom, K. Stensvag, et al., *Org. Lett.* 12 (2010) 4752–4755.
- [50] J. Caruano, G.G. Muccioli, R. Robiette, *Org. Biomol. Chem.* 14 (2016) 10134–10156.
- [51] A. Khan, R. Zheng, J. Xing, et al., *Angew. Chem. Int. Ed.* 53 (2014) 6439–6442.
- [52] L. Yang, A. Khan, L.Y. Jin, et al., *Org. Lett.* 17 (2015) 6230–6233.
- [53] A. Khan, C. Zhao, Y.J. Zhang, *Chem. Commun.* 54 (2018) 4708–4711.