Asymmetric Catalysis Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2022,** *61,* e202205516
International Edition: doi.org/10.1002/anie.202205516
German Edition: doi.org/10.1002/ange.202205516

Zinc-Catalyzed Enantioselective [3+2] Cycloaddition of Azomethine Ylides Using Planar Chiral [2.2]Paracyclophane-Imidazoline N,O-ligands

*Sundaravel Vivek Kumar and Patrick J. Guiry**

Abstract: We present a facile synthetic route toward a novel series of imidazolinyl-[2.2]paracyclophanol (UCD-Imphanol) ligands possessing central and planar chirality. Both sets of diastereomeric ligands were successfully purified by column chromatography. The preliminary application of this family of ligands showed excellent activities in the asymmetric Zn-catalyzed azomethine ylide cycloaddition. Enantioenriched pyrrolidines, in a substrate scope of 20 examples, were accessed in high levels of *endo*/*exo* ratios (up to >99/1) and enantioselectivities (up to >99 % ee) with excellent yields (up to 99 %) by using (S,S,S_P)-UCD-Imphanol/(S,S,R_P)-UCD-Imphanol, respectively.

Introduction

Planar chiral paracyclophanes have attracted widespread attention because of their unique structural and electronic features and have been extensively utilized in bio-/material sciences and asymmetric catalysis.[1] However, their asymmetric catalytic applications have been less explored compared to planar chiral metallocenes due to the significant challenges associated with the separation of enantiopure cyclophanes.[1a,b] Based on the disubstitution pattern, chiefly, there are three types of paracyclophanes, namely *pseudo-geminal*, *pseudo-ortho*, and *ortho*-derivatives that have been studied for asymmetric catalysis.[1b] The *ortho*-disubstituted paracyclophanes offer the highest level of steric crowding and a tight catalytic pocket which could be useful for asymmetric catalytic applications. However, the potential synthetic attractiveness of *ortho*-difunctionalized paracyclophane-derived ligands is limited by their challenging synthesis and non-facile structural modifications, including fine tuning of donor atom electronics.[2–4] Nevertheless, considerable effort has been devoted to this class of bidentate ligands with N,O-,[2] N,S/Se-,[3] and P,N-ligands **1**–**3** reported (Figure 1).[4] Among these, N,O-ligands have proven to be successful while other ligands showed moderate to poor levels of asymmetric induction in a range of transformations.[2–5] In 2001, Bräse introduced the first catalytic application of paracyclophane-derived ketimine N,O-ligands **1** for organozinc additions to aldehydes/imines,[5] and were highly efficient for several transformations.[6] The synthesis and application of oxazolinyl-paracyclophane N,O-ligand **3** in the diethylzinc addition to aldehydes was investigated by Bolm, but moderate enantioselectivities were obtained.[7]

Chiral oxazoline-containing ligands have been extensively applied in asymmetric catalysis,[8] whereas chiral imidazoline-based ligands, which possess an additional nitrogen atom compared to oxazoline, affords the opportunity for fine-tuning the ligand electronic and conformational properties by judicious choice of the substituent in the non-ligating nitrogen atom. This frequently accounts for significantly improved levels of reactivity and asymmetric induction relative to the comparable oxazoline-containing ligands.[9]

As a part of our interest in designing chiral imidazoline based ligands,[10] we proposed the synthesis of a series of sterically congested planar chiral [2.2]paracyclophane-derived imidazoline ligands **4**–**6** (Figure 1). In this context, the imidazoline unit acts as an in-built resolution unit, and the non-ligating nitrogen would be useful for tuning the electronic properties of the ligand. This blueprint would allow us to generate an N,O-ligand library possessing planar chirality and central chirality, along with the added advantages of convenient synthesis and resolution, modularity and electronic tunability. Here, we report the synthesis and resolution of this new class of planar chiral [2.2]paracyclophane-derived imidazoline N,O-ligands **4**–**6** and their application in the highly enantioselective Zn^{II}-catalyzed [3+2] azomethine ylide cycloadditions.

Results and Discussion

This study commenced with the ligand synthesis which was achieved in eight simple steps from commercially available [2.2]paracyclophane **7**, where the formyl group was installed by Ti-mediated formylation to furnish racemic **8** in 84 %

[*] Dr. S. V. Kumar, Prof. P. J. Guiry
Centre for Synthesis and Chemical Biology (CSCB),
School of Chemistry, University College Dublin (UCD),
Belfield, Dublin 4 (Ireland)
E-mail: p.guiry@ucd.ie

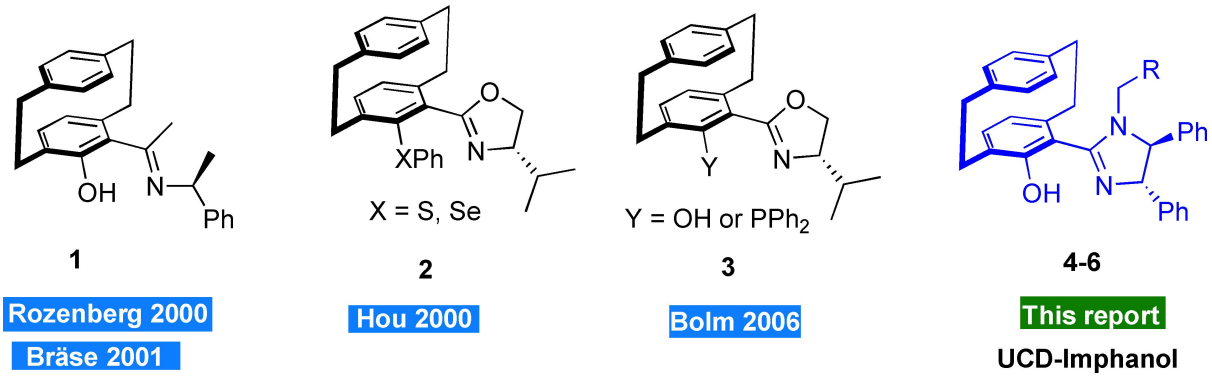
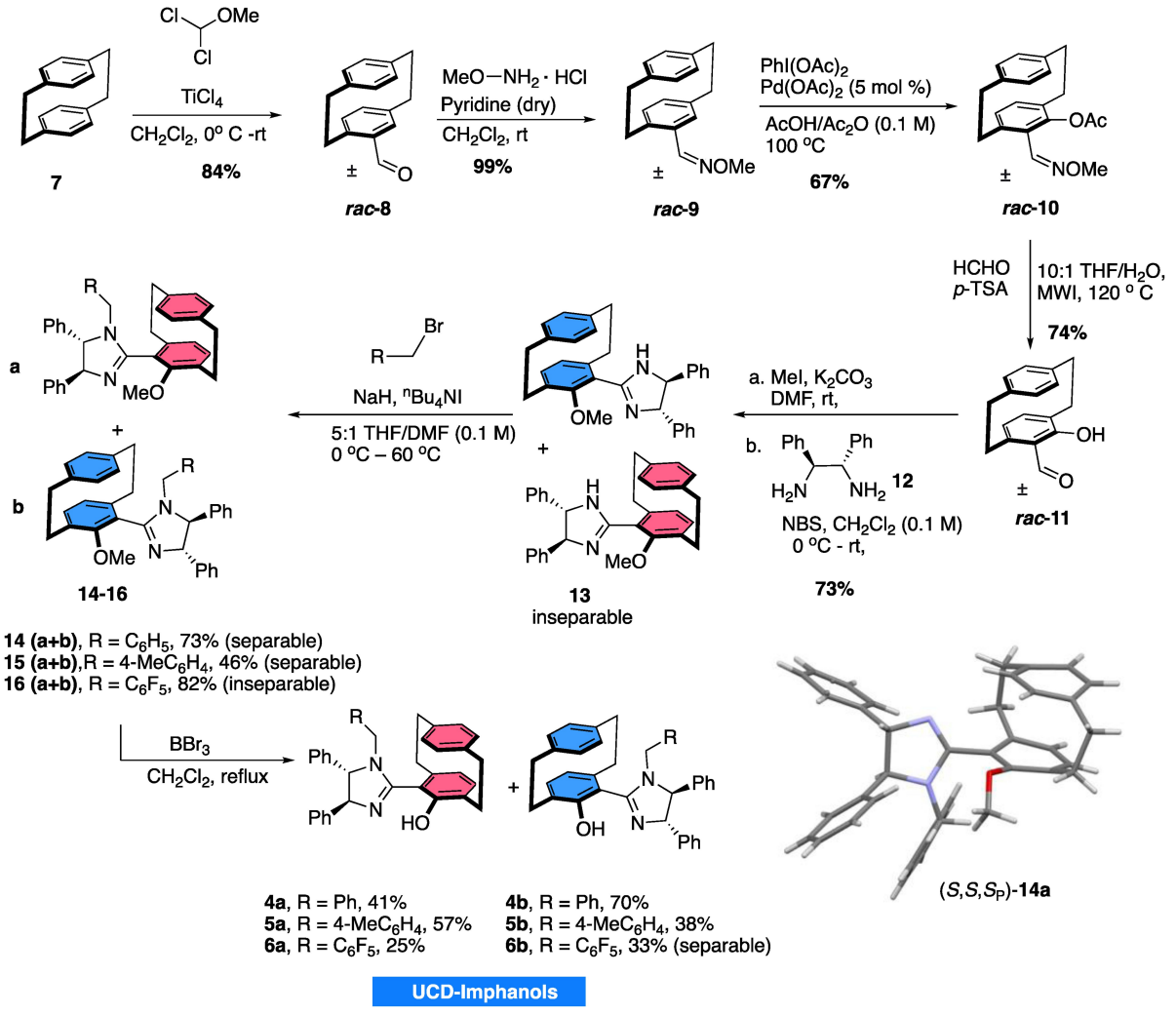


Figure 1. [2.2]Paracyclophane-derived *ortho*-disubstituted ligands.



Scheme 1. Synthesis and resolution of imidazolinyl-[2.2]paracyclophanols (UCD-Imphanols).

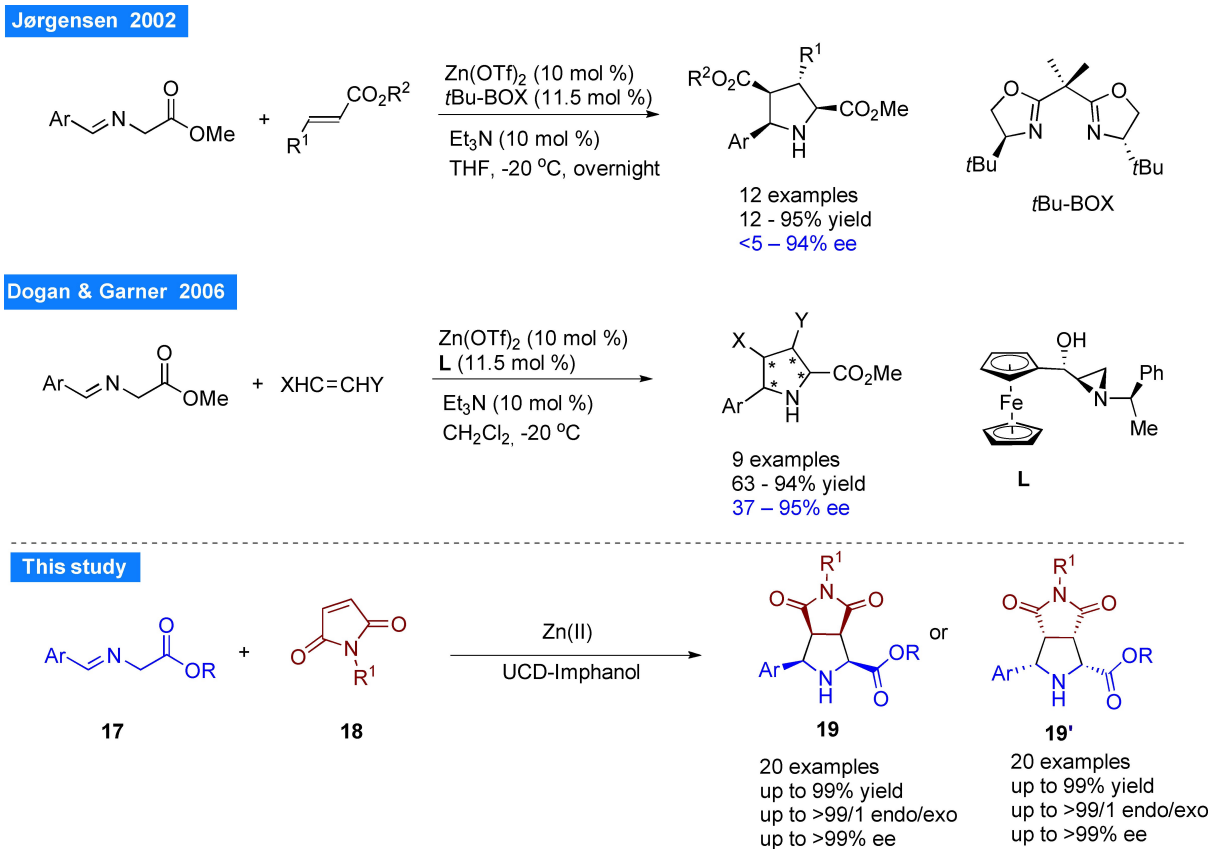
yield (Scheme 1).[11] According to Bolm's procedure,[12] the required *ortho*-acetoxylation of paracyclophane **10** was achieved by Pd-catalyzed C–H activation by a two-step process. Hydrolysis of acetyl/oxime ether **10** through the action of *p*-TsOH·H_2O/HCHO led to the aldehyde **11** in 74 % yield. Later, the hydroxy group of **11** was protected by the reaction of MeI in the presence of K_2CO_3,[13] and without further purification the intermediate was subjected to cyclization with (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine **12** mediated by NBS in CH_2Cl_2 to provide the inseparable diastereomers of the corresponding 2-substituted imidazoline **13** in 73 % yield. Imidazoline **13** was subsequently

treated with various benzyl bromide derivatives to afford the diastereomers of benzylated imidazolines **14** and **15** in 73 and 46 % (combined yields) respectively, which were readily separable. In contrast, pentafluorobenzylation afforded inseparable diastereomers **16** in 82 % yield. The absolute configuration of **14a** was unequivocally established as (S,S,S_P) by single crystal X-ray diffraction analysis.[14] Finally, methyl ether protection in **14–16** was removed by the treatment of BBr_3 leading to the smooth generation of ligands **4–6** in moderate to good yields, with diastereomers **6a** and **6b** now separable.

With a newly developed ligand library in hand, we sought to explore their reactivity in asymmetric catalysis. Asymmetric azomethine ylide cycloaddition is a widely used methodology for the construction of enantioenriched pyrrolidines,[15] useful in medicinal and biological applications.[16] Several ligand classes along with suitable metal combinations have been investigated extensively,[15b,d] and Ag^I- and Cu^I-based catalytic systems have been most prominent,[15b,d] whereas other metals such as Ca^{II},[17] Fe^{II},[18] Ni^{II}[19] and Zn^{II}[20]-based catalytic systems have been explored relatively rarely (Figure S1, Supporting Information).

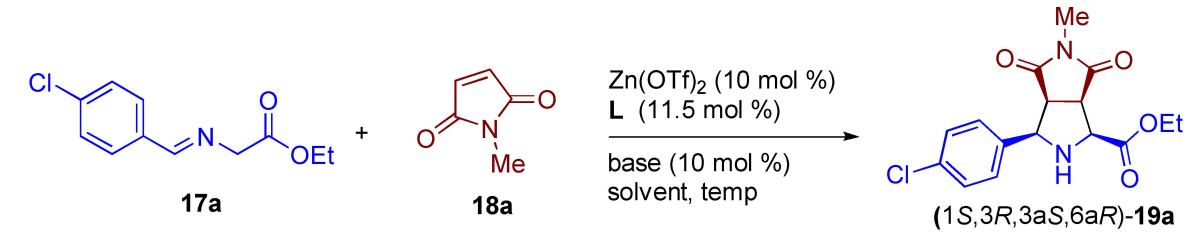
In 2002, Jørgensen established the first Zn-(*t*Bu-BOX)-catalyzed enantioselective azomethine ylide cycloaddition, which provided products in up to 94 % ee (Scheme 2).[20a] Later, Dogan and Garner reported up to 95 % ee for the synthesis of enantioenriched pyrrolidines by azomethine ylide cycloaddition using ferrocene-derived N,O-ligands/Zn^{II} (Scheme 2).[20b] Since Dogan and Garner's report, the flexibility of N,O-ligands along with a zinc platform would be more suitable to develop a general catalyst for asymmetric azomethine ylide cycloadditions. Further, the diverse coordination of Zn^{II} supported by bidentate N,O-ligands has been exploited to achieve high enantioselectivities in several asymmetric transformations.[21] Moreover, the development of Zn-based catalytic system would be desirable and valuable in terms of cost-efficiency. For these reasons, we chose to apply our novel series of planar chiral UCD-Imphanols **4–6** to this transformation.

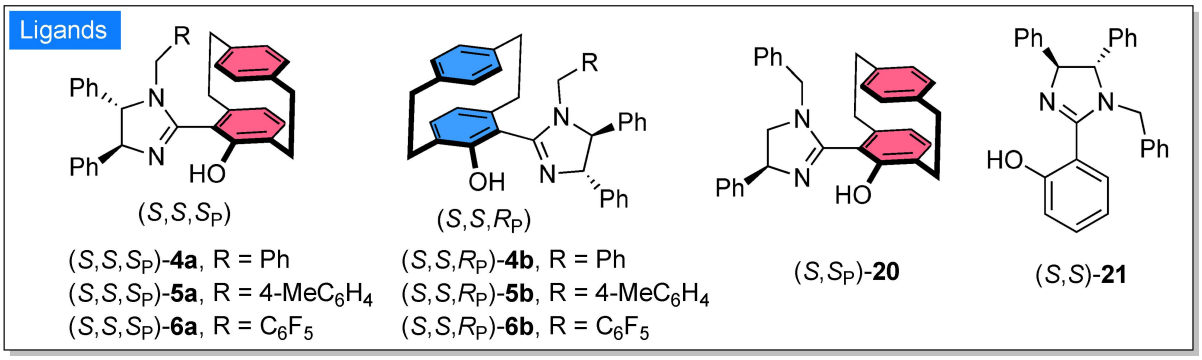
Our initial efforts on the application of ligands **4–6** in Zn-catalysis focused on the asymmetric [3+2] cycloaddition of azomethine ylide with maleimides (Table 1). The reaction proceeded smoothly at room temperature and the results clearly indicated that yield, *endo*/*exo* ratios and enantioselectivity were affected by the electronic properties of the imidazoline *N*-substituents (entries 1–6), and the planar chiral element is the dominant factor in controlling the asymmetric induction with reversal of planar chirality between ligands (S,S,S_P)-**4a–6a** and (S,S,R_P)-**4b–6b**, reversing the stereochemical outcome of the reaction. To further understand the importance of chirality at the C-5 imidazoline ring and the role of the planar chiral element in these cycloadditions, we synthesized and tested the related ligands (S,S_P)-**20** and (S,S)-**21** (see Supporting Information). Sub-



Scheme 2. Zn^{II}-catalyzed asymmetric [3+2] azomethine ylide cycloaddition.

Table 1: Optimization of reaction conditions.[a]





Entry	Ligand	Base	*T* [°C]	Yield [%][b]	*endo*/*exo*[c]	ee [%][d]
1	(S,S,S_P)-**4a**	Et_3N	rt	61	94/6	92.3
2	(S,S,S_P)-**5a**	Et_3N	rt	68	95/5	86.7
3	(S,S,S_P)-**6a**	Et_3N	rt	75	97/3	91.6
4	(S,S,R_P)-**4b**	Et_3N	rt	67	94/6	88.0[e]
5	(S,S,R_P)-**5b**	Et_3N	rt	78	95/5	85.9[e]
6	(S,S,R_P)-**6b**	Et_3N	rt	59	92/8	63.7[e]
7	(S,S_P)-**20**	Et_3N	rt	45	92/8	83.5
8	(*S*,*S*)-**21**	Et_3N	rt	34	87/13	5.6
9	(S,S,S_P)-**6a**	DABCO	0	86	99/1	99.3
10	(S,S,R_P)-**4b**	DIPEA	0	79	>99/1	95.4[e]

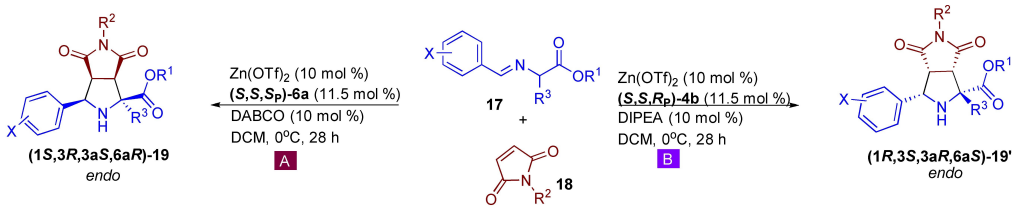
[a] Reaction conditions: **17a** (0.225 mmol) **18a** (0.15 mmol), $Zn(OTf)_2$ (10 mol%), L (11.5 mol%), base (10 mol%) in 1.0 mL of CH_2Cl_2, 8–28 h. [b] Isolated yield. [c] The *endo*/*exo* ratio was determined by ^{1}H NMR spectroscopy of crude reaction mixture. [d] The ee was determined by chiral SFC analysis. [e] Opposite enantiomer (1*R*,3*S*,3a*R*,6a*S*)-**19′a**.

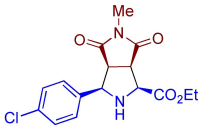
Please add color to the paracyclophane rings (as originally submitted) to Schemes 1 and 5, Table 1 and the Graphical Abstract.

Please add the X-ray crystal structure (as originally submitted) of (S,S,S_P)-**14a** to Scheme 1.

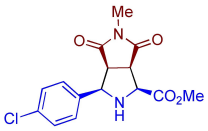
stitution at the C-5 imidazoline ring is crucial for both reactivity and selectivity (entry 7), and the non-planar chiral N,O-ligand (*S*,*S*)-**21** showed poor reactivity and enantioselectivity (entry 8), which suggests that the planar paracyclophane unit is a requirement to achieve the high reactivity, and is necessary for enhanced asymmetric induction. We selected the ligands (S,S,S_P)-**6a** and (S,S,R_P)-**4b** for further optimization studies (see Supporting Information), which found dichloromethane to be the best solvent, and 1,4-diazabicyclo[2.2.2]octane (DABCO) and *N*,*N*-diisopropylethylamine (DIPEA) the optimal base for generating the respective enantiomeric cycloadducts with the lower temperature of 0 °C providing superior ee's (entry 9 and 10).

With the optimal reaction conditions in hand, the scope of the reaction was investigated, Scheme 3, and both (S,S,S_P)-**6a** and (S,S,R_P)-**4b**, behaving as pseudo-enantiomeric ligands, performed well to furnish the respective cycloadducts in good yields and excellent levels of *endo*/*exo* ratios and enantioselectivities. A variety of imino esters **17** derived from aldehydes with different steric and electronic natures are compatible in this cycloaddition affording cycloadducts **19**/**19′** in good yields (condition A, 61–98 % yield and condition B, 62–99 % yield) with excellent levels of *endo*/*exo* (up to >99/1) and enantioselectivities (condition A, 98.0–>99.9 % ee) and condition B, 82.9–99.8 % ee). It is noteworthy that sterically hindered 2-bromo, 2-methyl and 1-naphthyl substituted imino esters **17h**–**17j** are also well tolerated to afford the products **19h**–**19j** in high yields (condition A, 91–98 % yield) and excellent *endo*/*exo* ratios and enantioselectivities (condition A, 98.4–>99.9 % ee). Ligand **4b** also displayed good reactivity (condition B, 80–98 % yield) but the levels of enantioselectivity were slightly compromised **19′h**–**19′j** (condition B, 82.9–92.4 % ee). In addition, heteroaromatic 2-thienyl derived imino ester **17k** and α-methyl substituted imino ester **19l** are also viable substrates, delivering the cycloadducts **19k**/**19k′** and **19l**/**19l′** with excellent levels of enantiocontrol. The electronic and steric nature of *N*-substitution of maleimides **18p**–**18s** has a notable influence on the reaction yields without erosion of

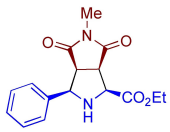




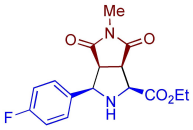
A: **19a**, 86%, *endo/exo* (99:1), 99.3% ee
B: **19'a,** 79%, *endo/exo* (>99:1), 95.4% ee



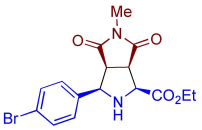
A: **19b**, 75%, *endo/exo* (96:4), 98.0% ee
B: **19'b,** 62%, *endo/exo* (99:1), 99.4% ee



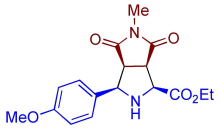
A: **19c**, 87%, *endo/exo* (98:2), 99.4% ee
B: **19'c,** 88%, *endo/exo* (99:1), 98.1% ee



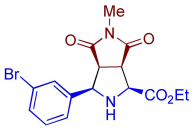
A: **19d**, 98%, *endo/exo* (99:1), 99.3% ee
B: **19'd,** 99%, *endo/exo* (99:1), 99.7% ee
B: **19'd,** 92%, *endo/exo* (>99:1), 99.7% ee[e]



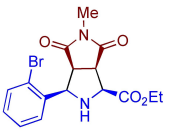
A: **19e**, 93%, *endo/exo* (98:2), 99.0% ee
B: **19'e**, 84%, *endo/exo* (99:1), 92.2% ee



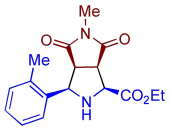
A: **19f**, 64%, *endo/exo* (98:2), >99.9% ee
B: **19'f**, 95%, *endo/exo* (99:1), 97.1% ee



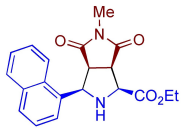
A: **19g**, 61%, *endo/exo* (98:2), 99.4% ee
B: **19'g**, 99%, *endo/exo* (>99:1), 97.5% ee



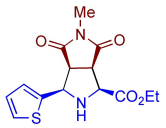
A: **19h**, 91%, *endo/exo* (99:1), 98.1% ee
B: **19'h**, 98%, *endo/exo* (99:1), 92.4% ee



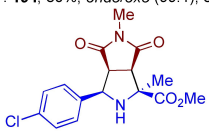
A: **19i**, 92%, *endo/exo* (97:3), >99.9% ee
A: **19i**, 85%, *endo/exo* (>99:1), 99.2% ee[e]
B: **19'i**, 80%, *endo/exo* (99:1), 88.4% ee



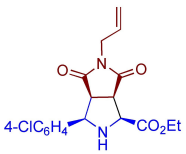
A: **19j**, 98%, *endo/exo* (97:3), 98.4% ee
B: **19'j**, 84%, *endo/exo* (99:1), 82.9% ee



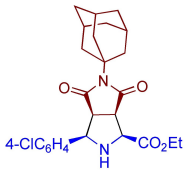
A: **19k**, 82%, *endo/exo* (99:1), 99.6% ee
B: **19'k,** 73%, *endo/exo* (99:1), 98.2% ee



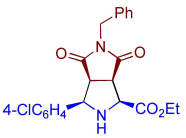
A: **19l**, 87%, *endo/exo* (99:1), 98.0% ee
B: **19'l,** 63%, *endo/exo* (>99:1), 93.0% ee



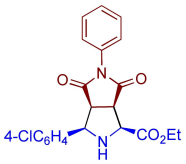
A: **19m**, 60%, *endo/exo* (99:1), 99.4% ee
B: **19'm**, 65%, *endo/exo* (99:1), 97.6% ee



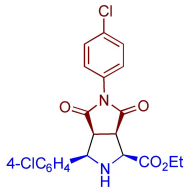
A: **19n**, 52%, *endo/exo* (99:1), 94.8% ee
B: **19'n**, 54%, *endo/exo* (99:1), 89.00% ee



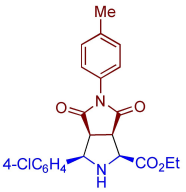
A: **19o**, 75%, *endo/exo* (99:1), 98.1% ee
B: **19'o**, 75%, *endo/exo* (99:1), 94.9% ee



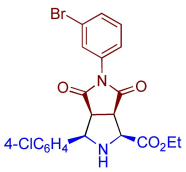
A: **19p**, 99%, *endo/exo* (>99:1), 95.2% ee
B: **19'p**, 97%, *endo/exo* (>99:1), 96.1% ee



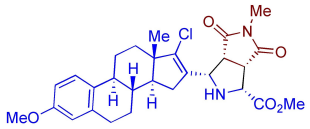
A: **19q**, 84%, *endo/exo* (>99:1), 96.9% ee
B: **19'q**, 83%, *endo/exo* (>99:1), 96.0% ee



A: **19r**, 63%, *endo/exo* (>99:1), 90.2% ee
B: **19'r**, 55%, *endo/exo* (>99:1), 93.00% ee



A: **19s**, 68%, *endo/exo* (>99:1), 94.1% ee
B: **19's,** 83%, *endo/exo* (>99:1), 96.6% ee



B: **19't**, 94%, >99% de

Scheme 3. Substrate scope.[a–d] [a] Reaction conditions: **17** (0.225 mmol) **18** (0.15 mmol), $Zn(OTf)_2$ (10 mol%), (S,S,S_P)-**6a**/(S,S,R_P)-**4b** (11.5 mol%), DABCO/DIPEA (10 mol%) in 1.0 mL of CH_2Cl_2, 28 h. [b] Isolated yield. [c] The *endo/exo* ratio was determined by ^1H NMR spectroscopy of crude reaction mixture. [d] The ee was determined by chiral SFC analysis. [e] 1 mmol scale.

endo/*exo ratio* and enantioselectivities (**19p**–**19s** and **19′p**–**19′s**).

Late-stage functionalizations of biologically active frameworks are often appealing to identify key medicinally active molecules. To demonstrate the use of our strategy in late-stage functionalization, steroid derived imino ester **17t** and *N*-methyl maleimide **18a** were subjected to the standard reaction conditions. Zinc complexes of ligands (*S*,*S*,S_P)-**6a** and (*S*,*S*,R_P)-**4b** were successful catalysts, affording the corresponding cycloadducts **19t** as a mixture of diastereomers (3:2:2:1) in 86 % yield (not shown in Scheme 3, see Supporting Information) and **19′t** exclusively as a single diastereomer (>99 % de) in 94 % yield, respectively, with the synthesis of **19′t** representing a rare example of an asymmetric approach to this class of compound. These results indicate that both catalyst and substrate control are involved in the asymmetric induction process.

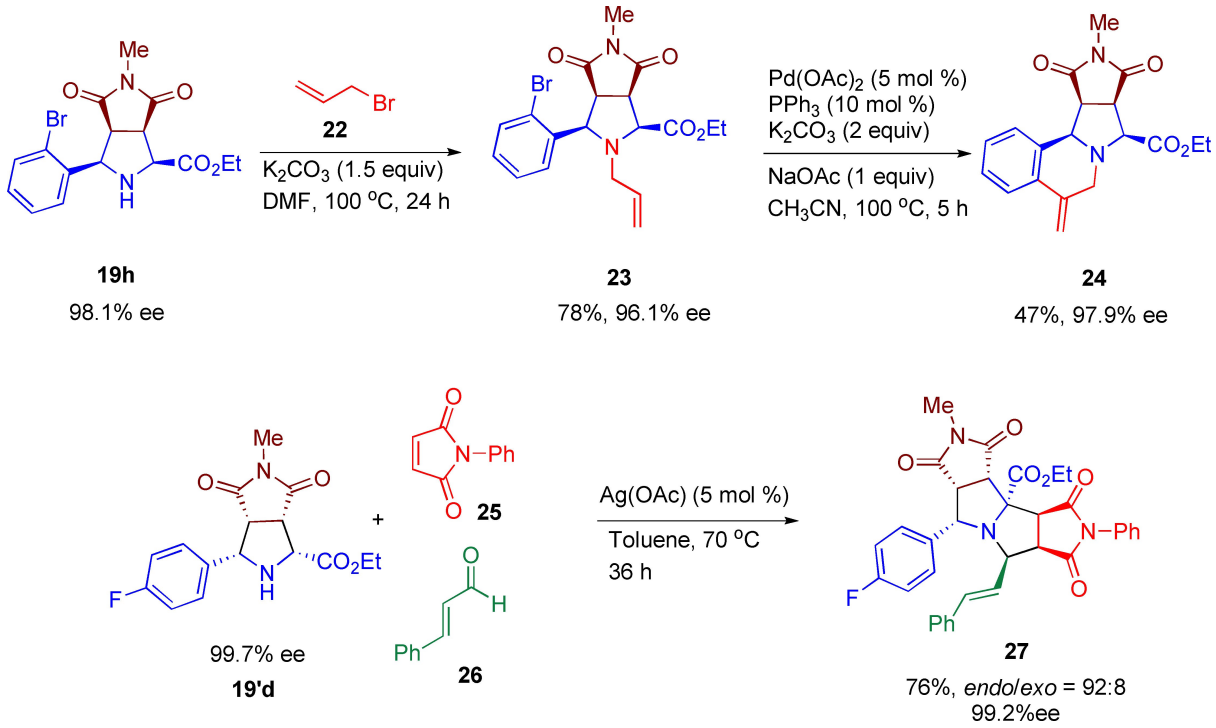
Our optimized Zn-catalyzed [3+2] cycloaddition can be easily scaled up to 1 mmol scale, furnishing **19i** in 85 % yield and excellent levels of diastereo- and enantioselectivities (*endo*/*exo* >99/1, 99.2 % ee). Similarly, the product **19′d** was isolated in 92 % yield with *endo*/*exo* >99/1 and 99.7 % ee.

Functionalities present in pyrrolidines **19** offer an opportunity for further functionalization towards synthetically useful products, without erosion of stereochemistry. As examples, product **19h** was *N*-allylated using allyl bromide **22** to generate **23** in 78 % yield, followed by a Pd-catalyzed Heck reaction of **23** to give the fused pyrroloisoquinoline **24** in 47 % yield (Scheme 4). Further, we performed the Ag-catalyzed multicomponent cycloaddition of *N*-phenylmaleimide **25**, cinnamaldehyde **26**, and product **19′d**, affording the complex fused tetracyclic pyrrolizidine **27** in 76 % yield with good diastereocontrol (*endo*/*exo* 92/8). Both pyrroloisoquinoline and pyrrolizidine cores are common in biologically active natural products.[22]

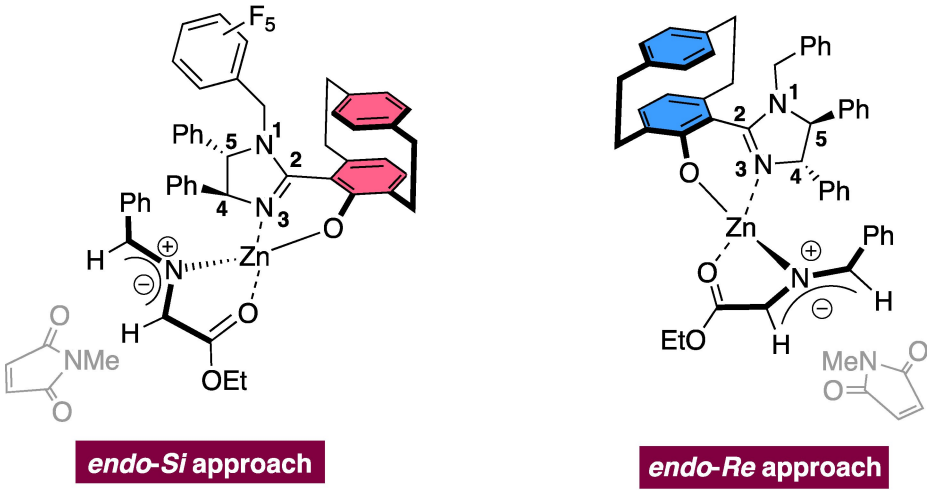
The experimentally observed high *endo* and enantioselectivities can be explained by our proposed transition-state model (Scheme 5). We suggest that the transition state contains the azomethine ylide coordinating to the Zn^{II}-imidazolinyl-paracyclophanol in a tetrahedral complex. With ligand (*S*,*S*,S_P)-**6a**, the sterically crowded paracyclophane and C-4 phenyl group effectively shield the top-face approach to the *Re*-face of the ylide, while the *Si*-face is less crowded thus allowing the dipolarophile approach in an *endo* fashion to deliver the products in exceptionally high levels of enantioselectivity. In the case of ligand (*S*,*S*,R_P)-**4b**, the sterically crowded paracyclophane and the C-5 phenyl group effectively block the *Si*-face of ylide, and the dipolarophile approaches in an *endo* fashion to the ylide *Re*-face. Even though the *Re*-face is slightly shielded by the C-4 phenyl ring, the dipolarophile approaches from the bottom-face, which leads to a slight compromise of enantioselectivity compared to ligand (*S*,*S*,S_P)-**6a**. Both observations suggest that the sterics of paracyclophane are crucial for the observed high levels of asymmetric induction.

Conclusion

In summary, we have designed and synthesized a series of new planar chiral imidazolinyl-paracyclophanol N,O-ligand (UCD-Imphanol) from commercially available [2.2]paracyclophane in eight steps. Notably, both sets of diastereomeric ligands were successfully resolved and their



Scheme 4. Synthetic transformations.



Scheme 5. Proposed transition-state model for ligands **6a** and **4b**.

configuration was assigned by XRD studies. This novel class of ligand demonstrated excellent efficiency in the enantioselective Zn^{II}-catalyzed [3+2] azomethine ylide cycloaddition, furnishing the corresponding cycloadducts in excellent diastereo- and enantioselectivities, the best reported to date.[20] Our studies also confirmed that planar chirality is the dominant role controlling asymmetric induction. The excellent level of ee's (up to >99% ee), along with easy access to both enantiomerically pure cycloadducts using less expensive Zn-catalysis, showcases our strategy as optimal compared to other Cu- or Ag-based catalytic systems. Further applications of this family of ligands in asymmetric catalysis are currently ongoing in our laboratory and will be reported in due course.

Acknowledgements

We acknowledge facilities provided by the Centre for Synthesis and Chemical Biology (CSCB), funded by the Higher Education Authority's PRTLI. We thank Dr Helge Müller-Bunz (University College Dublin) for X-ray crystal structure analysis, Dr Yannick Ortin for help with NMR spectroscopy and Dr Jimmy Muldoon for mass spectrometric analysis (supported by a Science Foundation Ireland Infrastructure Award (18/RI/5702)). S.V.K. thanks the Irish Research Council (IRC) for the award of a postdoctoral fellowship (GOIPD/2019/918). Open access funding provided by IReL.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Asymmetric Catalysis · Cycloaddition · Cyclophanes · Planar Chiral · Zinc Catalysis

[1] a) S. E. Gibson, J. D. Knight, *Org. Biomol. Chem.* **2003**, *1*, 1256–1269; b) V. Rozenberg, E. Sergeeva, H. Hopf, *Modern Cyclophane Chemistry*, Wiley-VCH, Weinheim, **2004**, pp. 435–462; c) H. Hopf, *Angew. Chem. Int. Ed.* **2008**, *47*, 9808–9812; *Angew. Chem.* **2008**, *120*, 9954–9958; d) E. Elacqua, L. R. MacGillivray, *Eur. J. Org. Chem.* **2010**, 6883–6894; e) J. Paradies, *Synthesis* **2011**, 3749–3766; f) A. Marrocchi, I. Tomasi, L. Vaccaro, *Isr. J. Chem.* **2012**, *52*, 41–52; g) G. J. Rowlands, *Isr. J. Chem.* **2012**, *52*, 60–75; h) Z. Hassan, E. Spuling, D. M. Knoll, J. Lahann, S. Bräse, *Chem. Soc. Rev.* **2018**, *47*, 6947–6963; i) Z. Hassan, E. Spuling, D. M. Knoll, S. Bräse, *Angew. Chem. Int. Ed.* **2020**, *59*, 2156–2170; *Angew. Chem.* **2020**, *132*, 2176–2190.

[2] V. Rozenberg, D. Danilova, E. Sergeeva, E. Vorontsov, Z. Starikova, K. Lysenko, Y. Belokon', *Eur. J. Org. Chem.* **2000**, 3295–3303.

[3] X.-L. Hou, X.-W. Wu, L.-X. Dai, B.-X. Cao, J. Sun, *Chem. Commun.* **2000**, 1195–1196.

[4] D. K. Whelligan, C. Bolm, *J. Org. Chem.* **2006**, *71*, 4609–4618.

[5] S. Dahmen, S. Bräse, *Org. Lett.* **2001**, *3*, 4119–4122.

[6] a) S. Dahmen, S. Bräse, *J. Am. Chem. Soc.* **2002**, *124*, 5940–5941; b) N. Hermanns, S. Dahmen, C. Bolm, S. Bräse, *Angew. Chem. Int. Ed.* **2002**, *41*, 3692–3694; *Angew. Chem.* **2002**, *114*, 3844–3846; c) S. Dahmen, S. Bräse, *Chem. Commun.* **2002**, 26–27; d) S. Bräse, S. Höfener, *Angew. Chem. Int. Ed.* **2005**, *44*, 7879–7881; *Angew. Chem.* **2005**, *117*, 8091–8093; e) S. Dahmen, *Org. Lett.* **2004**, *6*, 2113–2116; f) F. Lauterwasser, M. Nieger, H. Mansikkamäki, K. Nättinen, S. Bräse, *Chem. Eur. J.* **2005**, *11*, 4509–4525; g) S. Ay, M. Nieger, S. Bräse, *Chem. Eur. J.* **2008**, *14*, 11539–11556; h) N. V. Vorontsova, G. S. Bystrova, D. Y. Antonov, A. V. Vologzhanina, I. A. Godovikov, M. M. Il'in, *Tetrahedron: Asymmetry* **2010**, *21*, 731–738.

[7] C. Bolm, D. K. Whelligan, *Adv. Synth. Catal.* **2006**, *348*, 2093–2100.

[8] a) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151–4202; b) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561–3651; c) G. C. Hargaden, P. J. Guiry, *Chem. Rev.* **2009**, *109*, 2505–2550; d) R. Connon, B. Roche, B. V. Rokade, P. J. Guiry, *Chem. Rev.* **2021**, *121*, 6373–6521.

[9] a) J. Guo, B. Cheng, X. Shen, Z. Lu, *J. Am. Chem. Soc.* **2017**, *139*, 15316–15319; b) X. Wu, J. Qu, Y. Chen, *J. Am. Chem. Soc.* **2020**, *142*, 15654–15660; c) S. H. Lau, M. A. Borden, T. J. Steiman, L. S. Wang, M. Parasram, A. G. Doyle, *J. Am. Chem. Soc.* **2021**, *143*, 15873–15881; d) J. Li, B. Yu, Z. Lu, *Chin. J. Chem.* **2021**, *39*, 488–514.

[10] a) B. V. Rokade, P. J. Guiry, *ACS Catal.* **2017**, *7*, 2334–2338; b) B. V. Rokade, P. J. Guiry, *J. Org. Chem.* **2019**, *84*, 5763–5772.

[11] C. J. Friedmann, S. Ay, S. Bräse, *J. Org. Chem.* **2010**, *75*, 4612–4614.

[12] P. Lennartz, G. Raabe, C. Bolm, *Adv. Synth. Catal.* **2012**, *354*, 3237–3249.

[13] K. P. Jayasundera, D. N. M. Kusmus, L. Deuilhé, L. Etheridge, Z. Farrow, D. J. Lun, G. Kaur, G. J. Rowlands, *Org. Biomol. Chem.* **2016**, *14*, 10848–10860.

[14] Deposition Number 2158475 (for (S,S,S_P)-**14a**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

[15] a) M. Kissane, A. R. Maguire, *Chem. Soc. Rev.* **2010**, *39*, 845–883; b) J. Adrio, J. C. Carretero, *Chem. Commun.* **2014**, *50*, 12434–12446; c) R. Narayan, M. Potowski, Z.-J. Jia, A. P. Antonchick, H. Waldmann, *Acc. Chem. Res.* **2014**, *47*, 1296–1310; d) J. Adrio, J. C. Carretero, *Chem. Commun.* **2019**, *55*, 11979–11991; e) L. Wei, X. Chang, C.-J. Wang, *Acc. Chem. Res.* **2020**, *53*, 1084–1100.

[16] a) Q. Ding, Z. Zhang, J.-J. Liu, N. Jiang, J. Zhang, T. M. Ross, X.-J. Chu, D. Bartkovitz, F. Podlaski, C. Janson, C. Tovar, Z. M. Filipovic, B. Higgins, K. Glenn, K. Packman, L. T. Vassilev, B. Graves, *J. Med. Chem.* **2013**, *56*, 5979–5983; b) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274; c) "Privileged Scaffolds in Medicinal Chemistry: An Introduction": E. J. Barreiro, *Privileged Scaffolds in Medicinal Chemistry: Design, Synthesis, Evaluation*, Royal Society of Chemistry, London, **2015**, pp. 1–15; d) M. J. C. Scanio, X. B. Searle, B. Liu, J. R. Koenig, R. Altenbach, G. A. Gfesser, A. Bogdan, S. Greszler, G. Zhao, A. Singh, Y. Fan, A. M. Swensen, T. Vortherms, A. Manelli, C. Balut, Y. Jia, W. Gao, H. Yong, M. Schrimpf, C. Tse, P. Kym, X. Wang, *ACS Med. Chem. Lett.* **2019**, *10*, 1543–1548; e) G. L. Petri, M. V. Raimondi, V. Spanò, R. Holl, P. Barraja, A. Montalbano, *Top. Curr. Chem.* **2021**, *379*, 34.

[17] S. Saito, T. Tsubogo, S. Kobayashi, *J. Am. Chem. Soc.* **2007**, *129*, 5364–5365.

[18] H. Wu, B. Wang, H. Liu, L. Wang, *Tetrahedron* **2011**, *67*, 1210–1215.

[19] a) J. W. Shi, M.-X. Zhao, X.-Y. Lei, M. Shi, *J. Org. Chem.* **2008**, *73*, 305–308; b) T. Arai, N. Yokoyama, A. Mishiro, H. Sato, *Angew. Chem. Int. Ed.* **2010**, *49*, 7895–7898; *Angew. Chem.* **2010**, *122*, 8067–8070; c) A. Awata, T. Arai, *Chem. Eur. J.* **2012**, *18*, 8278–8282.

[20] a) A. S. Gothelf, K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2002**, *41*, 4236–4238; *Angew. Chem.* **2002**, *114*, 4410–4412; b) O. Dogan, H. Koyuncu, P. Garner, A. Bulut, W. J. Youngs, M. Panzner, *Org. Lett.* **2006**, *8*, 4687–4690.

[21] a) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824; b) T. Ahern, H. Müller-Bunz, P. J. Guiry, *J. Org. Chem.* **2006**, *71*, 7596–7602; c) H. Y. Kim, K. Oh, *Org. Lett.* **2009**, *11*, 5682–5685; d) J. Rudolph, C. Bolm, P.-O. Norrby, *J. Am. Chem. Soc.* **2005**, *127*, 1548–1552; e) M. Yamashita, K. Yamada, K. Tomioka, *Org. Lett.* **2005**, *7*, 2369–2371; f) B. M. Trost, M. Y. Ngai, G. Dong, *Org. Lett.* **2011**, *13*, 1900–1903; g) N. Chinkov, A. Warm, E. M. Carreira, *Angew. Chem. Int. Ed.* **2011**, *50*, 2957–2961; *Angew. Chem.* **2011**, *123*, 3014–3018; h) A. Tarui, H. Nishimura, T. Ikebata, A. Tahira, K. Sato, M. Omote, H. Minami, Y. Miwa, A. Ando, *Org. Lett.* **2014**, *16*, 2080–2083; i) C. Nottingham, R. Benson, H. Müller-Bunz, P. J. Guiry, *J. Org. Chem.* **2015**, *80*, 10163–10176; j) R. Liu, S. Yang, Z. Chen, X. Kong, H. Ding, X. Fang, *Org. Lett.* **2020**, *22*, 6948–6953; k) Y. Sekiguchi, N. Yoshikai, *J. Am. Chem. Soc.* **2021**, *143*, 18400–18405.

[22] a) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370; b) J. Robertson, K. Stevens, *Nat. Prod. Rep.* **2014**, *31*, 1721–1788; c) Y. Ikeda, H. Nonaka, T. Furumai, Y. Igarashi, *J. Nat. Prod.* **2005**, *68*, 572–573.

Manuscript received: April 14, 2022
Accepted manuscript online: May 23, 2022
Version of record online: June 9, 2022