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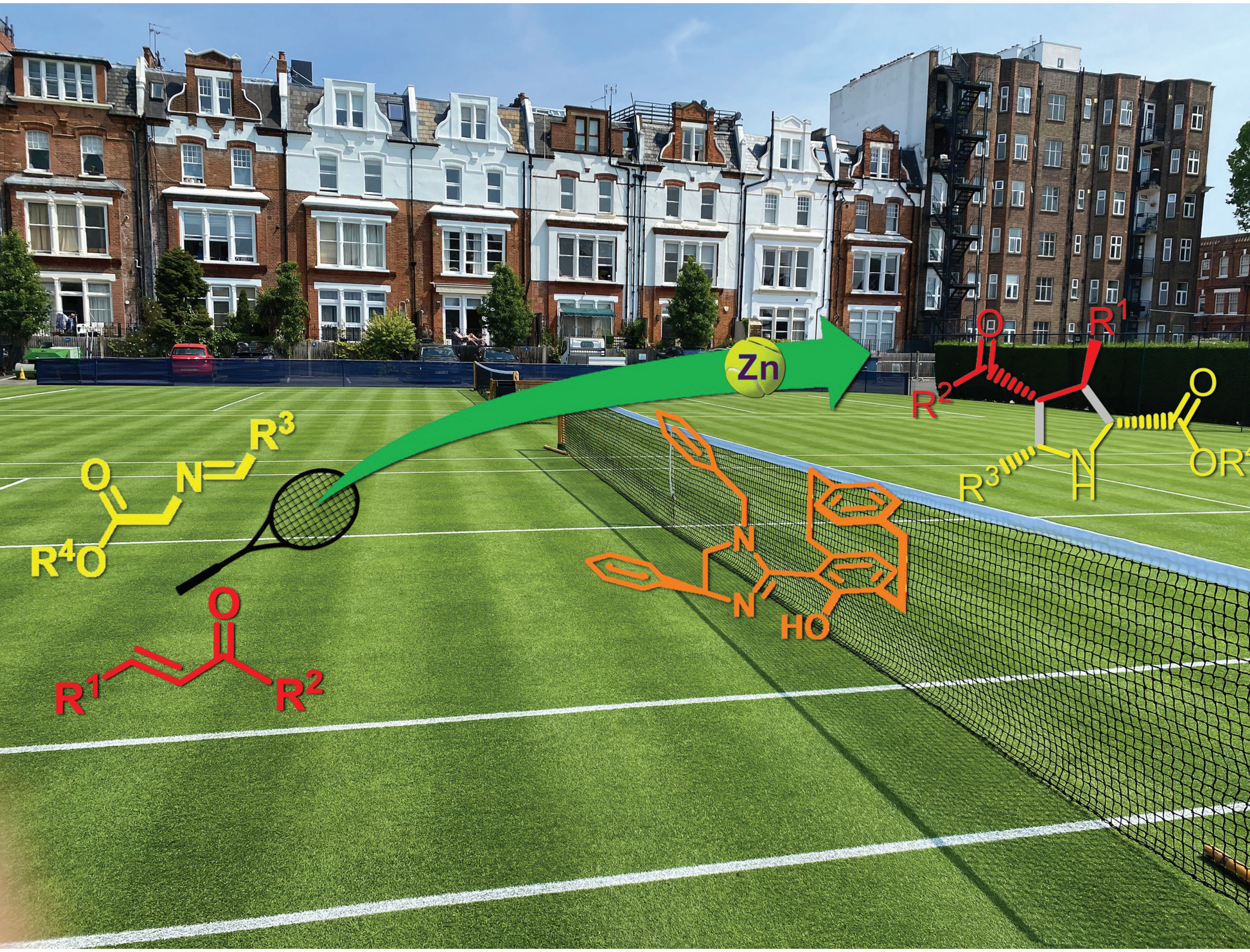

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Zn(II)-catalyzed asymmetric [3 + 2] cycloaddition of acyclic enones with azomethine ylides†

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The Zn(II)/UCD-Imphanol-catalyzed highly *endo*-selective [3 + 2] asymmetric cycloaddition of acyclic enones and azomethine ylides has been developed. Moderate to high yields (up to 94%) with excellent *endo*/*exo* selectivities (99 : 1) and enantioselectivities up to 96.5 : 3.5 er were obtained.

Introduction

The pyrrolidine ring is a pivotal core structure found in numerous natural products and bioactive compounds.[1] It is considered a privileged scaffold in pharmaceutical and medicinal chemistry, serving as a foundation for the development of novel classes of bioactive and medicinally important drugs.[2] Consequently various synthetic routes to assembling such types of frameworks have been developed.[3] Of all of the routes developed, the transition metal-catalyzed [3 + 2] asymmetric cycloaddition reaction stands out due to its convergent and atom-economical approach for the construction of pyrrolidines with more than one chiral center.[4] Various classes of dipolarophiles, such as α,β-unsaturated esters, maleimides, α,β-unsaturated nitriles, acyclic/cyclic enones, nitroalkenes, vinyl sulfones, and fullerenes, have been extensively studied. The reactivity and selectivities in these reactions are significantly influenced by the steric and electronic properties of both the dipolarophiles and dipoles, as well as the Lewis acidity of the metal–ligand complex utilized.[4] More recently, dipolarophiles such as cyclobutanone,[5] α-halonitroalkenes,[6] and electron-rich benzofulvenes[7] have also been explored. Among these, acyclic/cyclic enones have garnered significant attention due to their synthetic potential.[8–14] However, achieving high *endo*/*exo* ratios and enantioselectivities with these substrates remains challenging.

However, Carretero reported that the Cu(I)-Fesulphos complex catalyzed the [3 + 2] azomethine ylide cycloaddition of acyclic/cyclic enones, with the *endo*/*exo* selectivity being highly dependent on the *cis* or *trans* geometry of the enones.[8] In contrast, use of Cu(I)-imFerroS or Ag-imFerroS produced *endo*-cycloadducts from azomethine ylide cycloaddition of cyclic/acyclic enones, respectively.[9] Similarly, the Ag(I)-ThioClickFerrophos catalytic system afforded high levels of *endo*-selectivity in cycloadduct formation, irrespective of the *cis* or *trans* geometry of the enones.[10] The application of the Ag(I)-Xingphos catalytic system demonstrated solvent-dependent selectivities.[11]

Nájera observed metal-dependent diastereoselectivity in the application of the Cu(I)-DM-SegPhos system in the formation of an *exo*-cycloadduct with 70% ee, whereas the Ag(I)-SegPhos system yielded an *endo*-cycloadduct with 88% ee.[12] Oh reported a metal-dependent enantiodivergent [3 + 2] cycloaddition, where the Cu(I)-brucine diol system provided *endo*-selective products with good yields and enantioselectivities, compared to the Ag(I)-brucine diol system.[13] Additionally, the Au(I)-(S_a)-Binap catalytic system was reported to deliver good yields of *endo*-cycloadducts with 60–80% ee, compared to the Ag(I)-(S_a)-Binap catalytic system.[14]

Both Cu(I) and Ag(I)-based catalysts have been extensively explored, often offering complementary results in terms of *endo*/*exo* selectivity.[4] However, this trend becomes variable when acyclic enones are used as dipolarophiles.[8–14] These procedures frequently encounter one or more limitations, such as modest diastereo- or enantioselectivities and/or restricted substrate scope.

On the other hand, despite its unique advantages such as cost-effectiveness, abundance (24th most abundant element), non-toxicity, and environmental friendliness, the use of zinc catalysis in azomethine ylide cycloadditions is rather limited.[15] Recently, our group developed the UCD-Imphanol family of ligands, which proved highly efficient for Zn(II)-catalyzed [3 + 2] asymmetric cycloaddition of azomethine ylides with maleimides. These Zn(II)-UCD-Imphanol catalytic system produced *endo*-selective cycloadducts in good yields, achieving enantioselectivities of up to 99.9% ee.[15c] In continuation of our work, we present a highly *endo*-selective asymmetric [3 + 2] cycloaddition of azomethine ylides with chalcones catalyzed by Zn(II)/UCD-Imphanol (Scheme 1).

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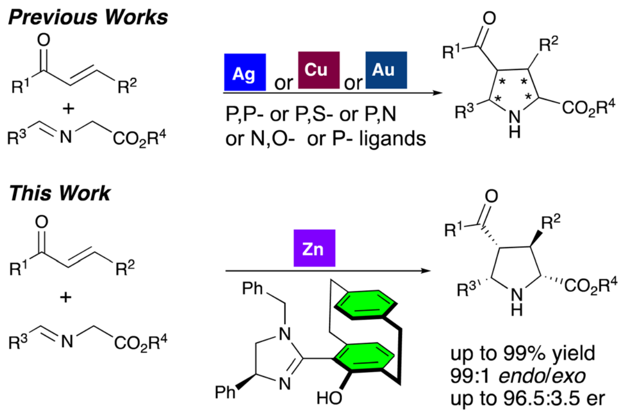


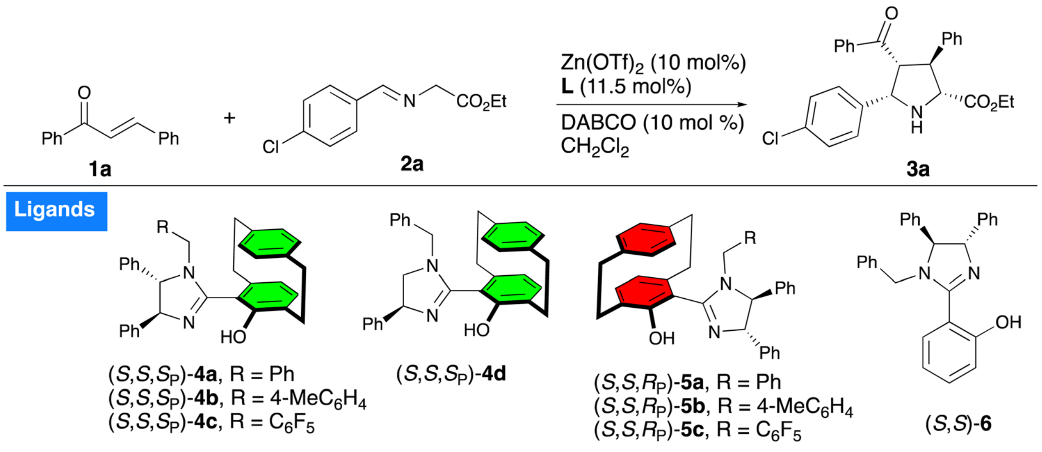
Scheme 1 Asymmetric [3 + 2] cycloaddition of azomethine ylides with acyclic enones.

Results and discussion

We began our investigation by using (*E*)-chalcone **1a**, ethyl (*E*)-2-((4-chlorobenzylidene)amino)acetate **2a** as model substrates employing DABCO as base, Zn(OTf)$_2$ as the metal catalyst to screen the series of UCD-Imphanol family of ligands including the non-planar chiral N,O-ligand **6**. The use of ligand (S,S,S_P)-**4a** gave the cycloadduct **3a** in 55% yield with a 93 : 7 *endo*/*exo* ratio and 95 : 5 er (Table 1, entry 1), whereas the use of 4-methylbenzyl- or pentafluorobenzyl-substituted ligands (S,S,S_P)-**4b** and (S,S,S_P)-**4c** led to the cycloadduct **3a** in slightly reduced yield and selectivity (Table 1, entries 2 and 3). Use of ligand **4d** afforded the cycloadduct **3a** in 79% yield with a 94 : 6 diastereoselectivity and 94.5 : 5.5 er (Table 1, entry 4). In contrast, the diastereomeric ligands (S,S,R_P)-**5a–c** showed poor levels of reactivity and selectivity (Table 1, entries 5–7). The non-planar chiral N,O-ligand **6** gave a 38% yield with moderate diastereoselectivity (78 : 12) but poor enantioselectivity (54 : 46 er) (Table 1, entry 8), which indicated that the planar chiral paracyclophane unit was necessary to achieve high levels of reactivity and selectivity. The metal salts AgOAc and Cu(OTf)$_2$ were examined; the former produced the cycloadduct **3a** in 58% yield with high diastereoselectivity and a 55 : 45 er, while the latter yielded only a trace amount of product (for full optimization studies see the ESI†). The screening of base and solvent revealed that dichloromethane and DABCO were optimal choices of solvent and base, respectively (see ESI†).

Gratifyingly, the use of an excess (2 equiv.) of **2a** led to an increase in yield to 90% without affecting selectivity (Table 1, entry 9). Further, lowering the reaction temperature to 0 °C produced the cycloadduct **3a** in 95% yield with an excellent

Table 1 Optimization of the reaction conditions[a]



Entry	L	Temp. °C	Yield[b] (%)	*Endo*/*Exo*[c]	Er[d]
1	**4a**	rt	55	93 : 7	95 : 5
2	**4b**	rt	43	90 : 10	90 : 10
3	**4c**	rt	46	92 : 8	87 : 13
4	**4d**	rt	79	94 : 6	94.5 : 5.5
5	**5a**	rt	46	85 : 15	46 : 54
6	**5b**	rt	35	81 : 19	49 : 51
7	**5c**	rt	48	83 : 12	47 : 53
8	**6**	rt	38	78 : 12	54 : 46
9[e]	**4d**	rt	90	97 : 3	94.5 : 5.5
10[e,f]	**4d**	0	95	99 : 1	96.5 : 3.5
11[g]	**4d**	0	86	99 : 1	96 : 4

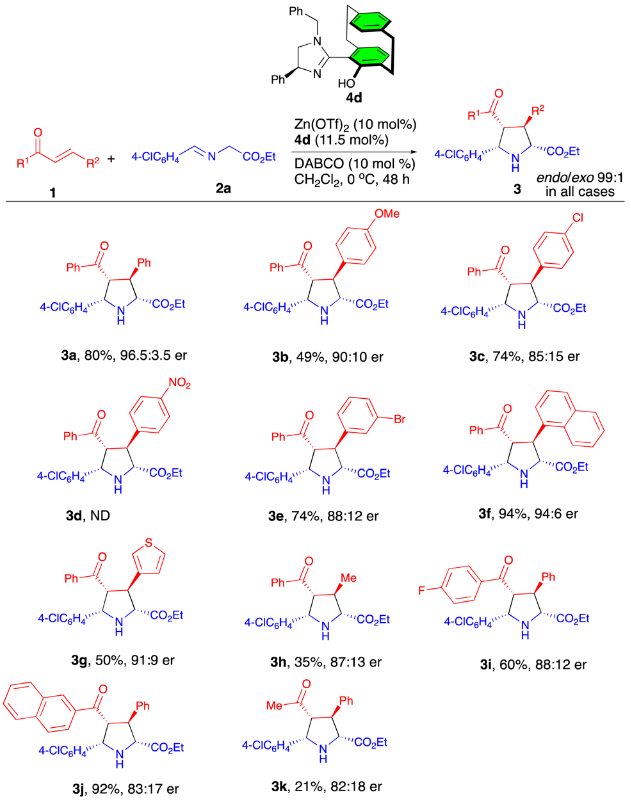
[a] All reactions were carried out with Zn(OTf)$_2$ (10 mol%), **L** (11.5 mol%), **1a** (0.15 mmol), **2a** (0.225 mmol), DABCO (10 mol%) in CH$_2$Cl$_2$ (1.5 mL) for 24 h. [b] Isolated yield after purification. [c] The *endo*/*exo* ratios were determined by analyzing the ^{1}H NMR spectra of the crude product. [d] Determined by chiral HPLC analysis. [e] 0.3 mmol of **2a** was used. [f] 48 h. [g] Zn(OTf)$_2$ (5 mol%) and **4d** (5.75 mol%) for 72 h.

endo/*exo* ratio and 96.5 : 3.5 er, our best result in this optimization study (Table 1, entry. 10). Further decreasing the catalyst loading (5 mol% of $Zn(OTf)_2$ and 5.75 mol% of **4d**) led to long reaction time with slight reduction of yield and 99 : 1 *endo*/*exo* ratio and 96 : 4 er.

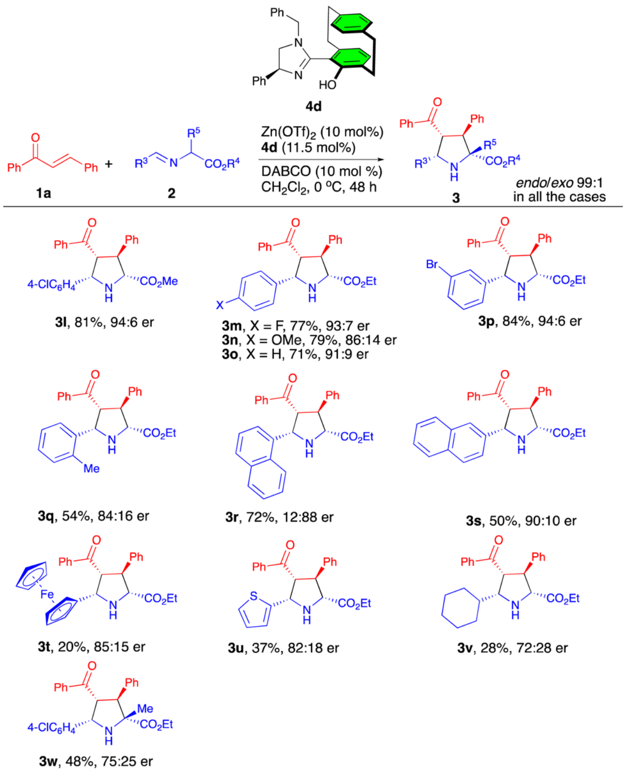
Having optimized conditions in hand, we then examined the scope of this reaction for a focused library of acyclic enones which afforded the products **3a–k** with excellent levels of diastereocontrol (99 : 1) (Scheme 2). A series of chalcones with 4-OMe, 4-Cl, and 3-Br-substituted β-aryl groups gave the corresponding products **3b–c**, **3e** in moderate to good yields with enantioselectivities of 85 : 15–90 : 10 er. In contrast, the reaction of 4-NO_2-substituted chalcone led to a complicated mixture; the expected product **3d** was not formed, which may presumably be due to the competitive coordination of the nitro group with the Zn metal. The sterically hindered 1-naphthyl and 3-thienyl derived substrates were also tolerated under these reaction conditions to yield the corresponding cycloadducts **3f** and **3g** in 94% and 50% yield with 96 : 4 and 91 : 9 er, respectively. However, the reaction with β-methyl-substituted chalcone afforded the cycloadduct **3h** in a lower yield (35%) with a lower level of enantioselectivity (87 : 13). Next, various α-benzoyl-substituted chalcones also reacted to deliver products **3i–j** in moderate to good yields with 88 : 12 and 87 : 13 er's. The use of (*E*)-benzylidene acetone gave rise to the cycloadduct **3k** in a disappointing yield of 21% with 82 : 18 er.

Next, our attention turned to exploring the scope of the α-iminoesters (Scheme 3). We were pleased to find that a wide range of α-iminoesters with varying electronics and sterics were tolerated to afford the desired products **3l–w** in 20–81% yields with 72 : 28–94 : 6 enantioselectivities and 99 : 1 *endo*/*exo* selectivities. In particular, α-iminoesters with electron-deficient and neutral substituents on the aryl ring led to the products **3m–p** in 84–71% yields with enantioselectivities of 91 : 9–94 : 6 er. The α-iminoesters with sterically hindered substituents such as *o*-tolyl, 2-naphthyl, and ferrocenyl underwent the reaction to give the products **3q**, **3s–t** in 20–54% yields with 84 : 16–90 : 10 er's. Notably, the 1-naphthyl-substituted α-iminoester provided the cycloadduct **3r** with the opposite stereochemistry (12 : 88 er) in 72% yield. Furthermore, 2-thienyl- and cyclohexyl-substituted iminoesters also showed poor reactivity (28–37% yield) for the formation of products **3u–v** with enantioselectivities in the range 72 : 28–82 : 18 er's. Moreover, the α-methyl-substituted iminoester also displayed moderate reactivity, forming the product **3w** in 48% yield with 75 : 25 er.

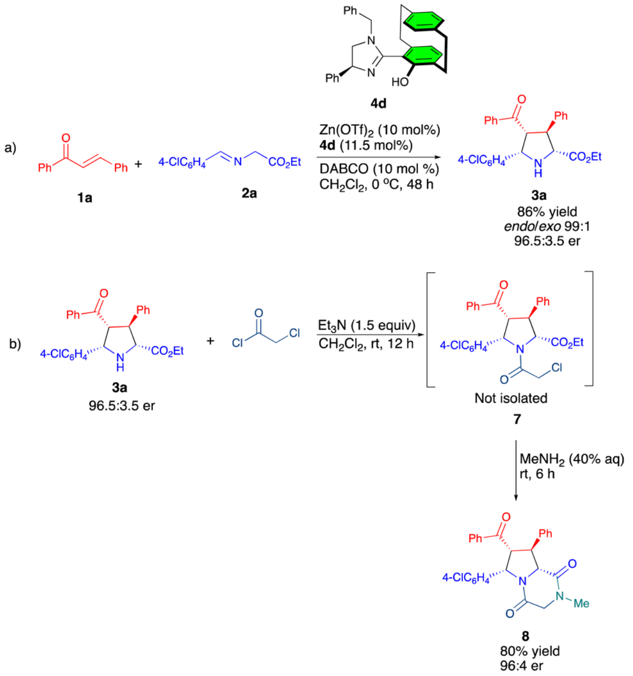
To demonstrate the synthetic potential of the present reaction, we performed the reaction on a 1 mmol scale, furnishing **3a** in 86% yield and excellent diastereo- and enantioselectivity (99 : 1 *endo*/*exo*, 96.5 : 3.5 er) (Scheme 4a). Further treatment of the product with chloroacetyl chloride led to the formation of **7**, which then reacted with 40% aq. $MeNH_2$,[17] affording the diketopiperazine derivative **8** in 80% yield with 96 : 4 er (Scheme 4b).



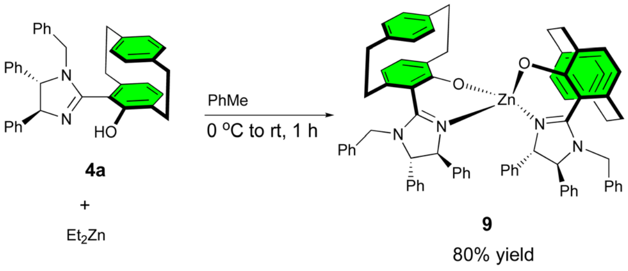
Scheme 2 Scope of the acyclic enones.



Scheme 3 Scope of the α-iminoesters.



Scheme 4 Scaled-up synthesis of **3a** and its derivatization.



Scheme 5 Preparation of complex **9**.

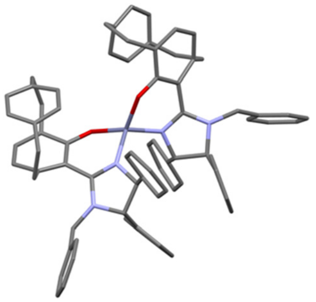


Fig. 1 Single crystal XRD analysis for **9**. All H-atoms are omitted for clarity.

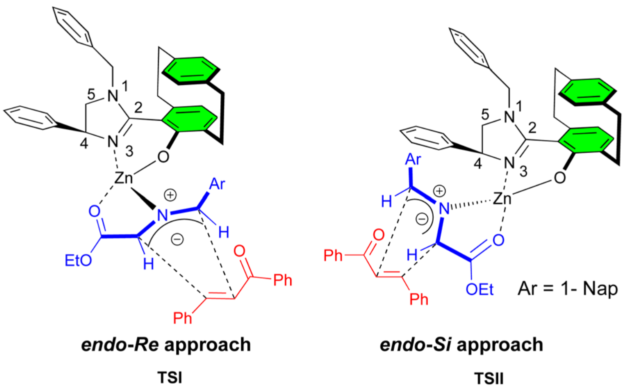


Fig. 2 Proposed stereochemical models.

A plausible transition state was tentatively proposed based on the Zn-complex **9**, which was prepared from the reaction of ligand **4a** with Et$_2$Zn, affording the homoleptic zinc(II) complex **9** (Scheme 5). The homoleptic complex was confirmed by single crystal X-ray diffraction studies (Fig. 1), and this complex would generate the heteroleptic Zn(II) complex by interaction with iminoester **2** under basic conditions that can readily react with acyclic enones.

The transition state contains the azomethine ylide coordinating with the Zn(II)-imidazolinyl-paracyclophanol in a tetrahedral complex (Fig. 2). The sterically crowded paracyclophane and C-4 phenyl group effectively shield the top-face approach to the *Si*-face of the ylide, while the *Re*-face is less crowded thus allowing the acyclic enone approach in an *endo* fashion (**TSI**) to deliver the products with good to moderate levels of enantioselectivity. Although it cannot be completely ruled out, the exceptional *endo*-selectivity that was observed may perhaps be due to the additional coordination of the α,β-unsaturated ketone carbonyl group with the metal center. Additionally, **TSII** may explain the noted opposite enantiomer in the case of 1-naphthyl iminoester since **TSI** presumably leads to a disfavored steric clash between the 1-naphthyl iminoester and the paracyclophane unit of ligand.

Conclusions

In summary, we have developed the Zn(II)-catalyzed highly *endo*-selective asymmetric [3 + 2] cycloaddition of acyclic enones with azomethine ylides by the use of the planar chiral UCD-Imphanol family of ligands, leading to chiral pyrrolidines in moderate to good yields with 99 : 1 *endo*/*exo* selectivities and enantioselectivities up to 96.5 : 3.5 er. A variety of acyclic enones and iminoester-derived azomethine ylides are compatible with the less expensive Zn-catalysis. Further detailed mechanistic studies with computational analysis are currently underway and will be reported in due course.

Experimental section

General procedure for the Zn(II)-catalyzed [3 + 2] azomethine ylide cycloaddition

Under nitrogen atmosphere, ligand (S,S,S_P)-**4d** (11.5 mol%) and Zn(OTf)$_2$ (10 mol%) was added to a flame-dried 10 mL Schlenk tube. Then dry CH$_2$Cl$_2$ (0.5 mL) was added and stirred for 60 min. After cooling to 0 °C, acyclic enone 1 (0.15 mmol, 1.0 equiv.) in CH_2Cl_2 (0.4 mL), α-iminoester 2 (0.3 mmol, 2 equiv.) in CH_2Cl_2, (0.4 mL) and DABCO (10 mol%) in CH_2Cl_2 (0.2 mL) were added sequentially. The reaction mixture was stirred at the same temperature for 48 h. After completion, the reaction mixture was directly purified by silica gel column chromatography (30% ethyl acetate in cyclohexane) to afford the desired product **3**. The *endo*/*exo* ratio was determined by ^{1}H-NMR before purification and the enantioselectivity was determined by HPLC analysis of the isolated product. The configuration of the products was assigned by comparison with the optical rotation values of prepared compounds and the reported optical rotation of the cycloadducts.[12a,16] (Note: the reaction temperature (0 °C) was maintained using a cryocooler).

Data availability

The data supporting this article have been included as part of the ESI.† CDC 2299375 contains the supplementary crystallographic data for Zinc complex **9**.†

Author contributions

PG supervised the research; S. V. K. and P. G. conceived the idea; S. V. K. and J. O. carried out all the synthetic experimental work and data acquisition. S. V. K. prepared the manuscript with contributions from J. O. and P. G. All authors approved the manuscript.

Conflicts of interest

There are no conflicts to declare.

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