Asymmetric Catalysis

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Lewis Acid Catalyzed Enantioselective Desymmetrization of Donor–Acceptor *meso*-Diaminocyclopropanes

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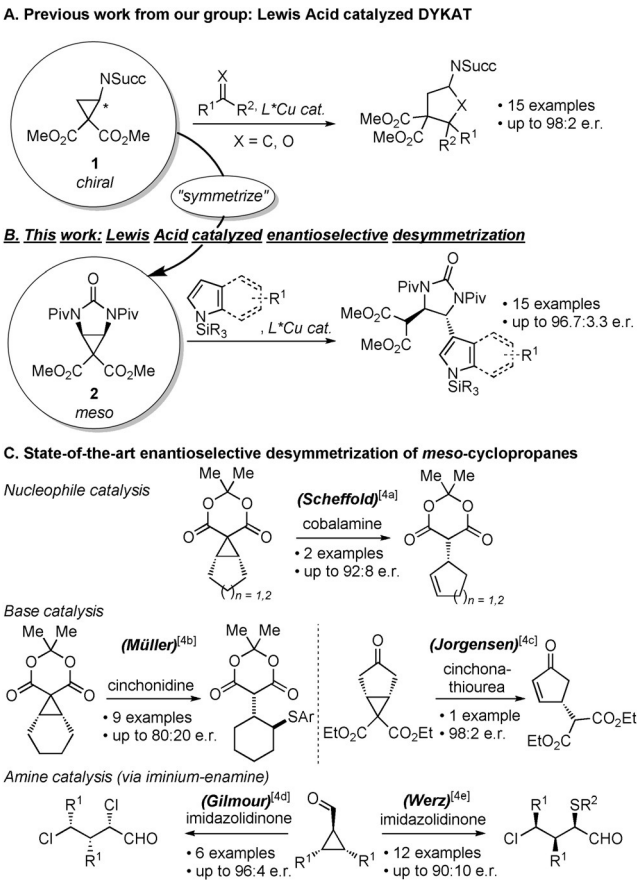
Abstract: *The first Lewis acid catalyzed enantioselective ring-opening desymmetrization of a donor–acceptor meso-diaminocyclopropane is reported. The copper(II)-catalyzed Friedel–Crafts alkylation of indoles and one pyrrole with an unprecedented meso-diaminocyclopropane delivered enantioenriched, diastereomerically pure urea products, which are structurally related to natural and synthetic bioactive compounds. The development of a new ligand through the investigation of an underexplored subclass of bis(oxazoline) ligands was essential for achieving high enantioselectivities.*

Donor–acceptor cyclopropanes are versatile building blocks in organic synthesis.[1] Enantiomerically enriched derivatives can be obtained by performing asymmetric transformations. Donor–acceptor cyclopropanes are often chiral themselves, leading to two possible scenarios: kinetic resolution or a dynamic kinetic asymmetric transformation (DYKAT).[2] Our group applied a DYKAT for the first time to donor–acceptor aminocyclopropanes (Scheme 1).[2i] However, a major drawback of DYKAT processes lies in their complex reaction mechanism, requiring both efficient facial selection and control over racemization. In contrast, the desymmetrization of achiral *meso* substrates often enables the more straightforward development of enantioselective transformations.[3] We therefore designed the novel *meso*-diaminocyclopropane **2** (Scheme 1 B). Thus far, only nucleophile, base, and amine (via iminium–enamine intermediates) catalysts have been reported for the desymmetrization of donor–acceptor *meso*-cyclopropanes (Scheme 1 C).[4]

Herein, we present the first enantioselective desymmetrization of nitrogen-substituted cyclopropanes through the Friedel–Crafts alkylation of indoles with a copper catalyst bearing an unprecedented bis(oxazoline) (BOX) ligand (Scheme 1 B). This method delivers enantioenriched urea derivatives as products, which are highly important core structures in natural products and bioactive compounds, such as tulongicin A (**3**),[5a] biotin (**4**),[5b] or (−)-agelastatin A (**5**;[5c–d] Figure 1).[5]

Investigations of the proposed transformation first required an adequate donor–acceptor *meso*-diaminocyclopropane. Based on our previous work,[2i] we chose an imido urea functional group as the donor, and a bis(ester) as the acceptor (cyclopropane **2**). The Friedel–Crafts alkylation with indoles was examined first.[2e,6] We focused our efforts on



Scheme 1. A) DYKAT of aminocyclopropanes. B) This work: enantioselective desymmetrization of donor–acceptor *meso*-diaminocyclopropanes. C) State-of-the-art enantioselective desymmetrization of cyclopropanes. Succ = succinyl, Piv = pivaloyl.

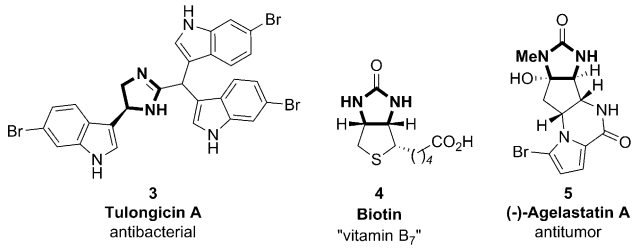


Figure 1. Natural bioactive compounds featuring urea moieties.

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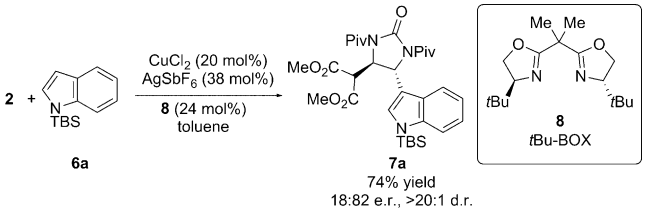
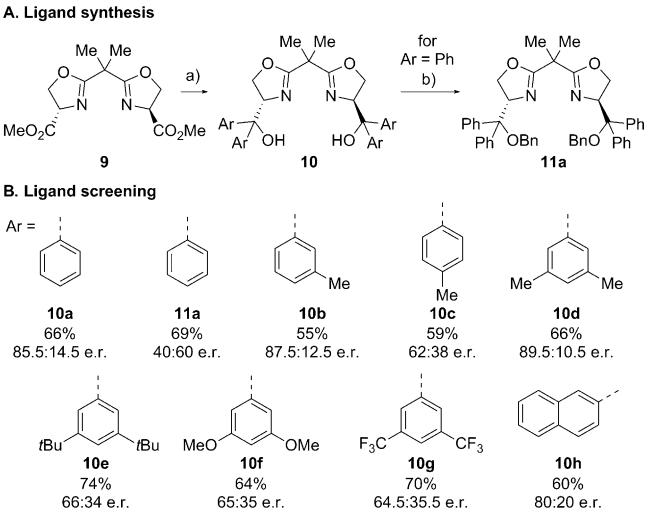
copper–BOX complexes as catalysts.[2i] Electron-withdrawing groups on both the urea N atoms and the N substituent on the indole had a strong effect on enantioselectivity (see the Supporting Information for details). The best compromise between enantiomeric ratio (e.r.) and solubility was achieved by using a pivaloyl group on urea **2** and *tert*-butyldimethylsilyl (TBS)-protected indole **6a** (Scheme 2). Copper(II) was identified as the best metal species, hexafluoroantimonate(V) as the best counterion, and BOX ligands such as **8** as a promising class of ligands. In toluene as the solvent, the desired product was obtained in 74% yield and 18:82 e.r. as a single diastereoisomer.



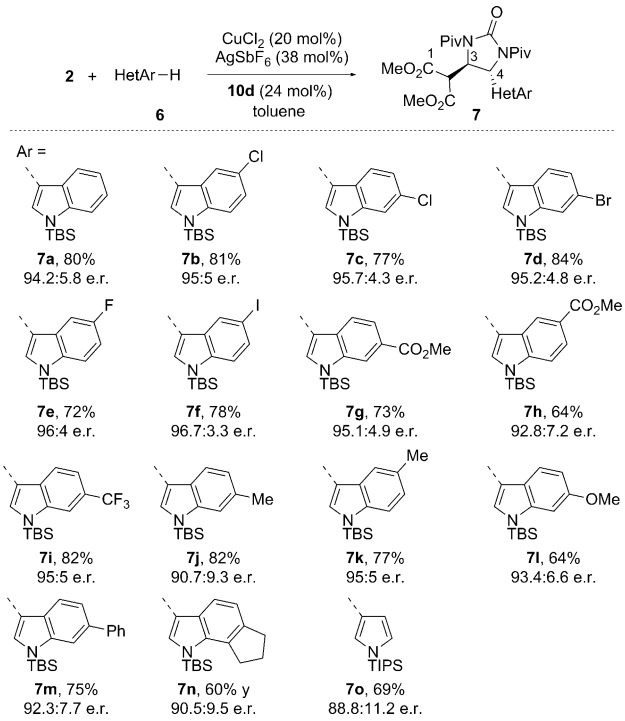
Scheme 2. Lead result for the enantioselective Friedel–Crafts alkylation of indole **6a** with cyclopropane **2**. Reaction conditions: **2** (0.05 mmol), **6a** (0.06 mmol), toluene (0.05 M), −20 °C, 48 h. TBS = *tert*-butyldimethylsilyl.

To further improve the enantioselectivity, we investigated ligand modifications at the α-position to the nitrogen atom. We were particularly interested in a subclass of BOX ligands bearing bulky diarylmethanol groups instead of the *tert*-butyl moieties of *t*Bu-BOX (Scheme 3A).[7] The aryl groups can be installed by Grignard addition to ester precursor **9**, which can be easily synthesized in two steps from serine ester.[8] Previously, only the phenyl derivative (**10a**) had been reported.[7] It was used by Reiser and co-workers for the enantioselective 1,2- and 1,4-addition of organozinc species to carbonyl compounds. The use of **10a** in our Friedel–Crafts reaction afforded a significant increase in enantiomeric ratio (Scheme 3B). When the alcohol was protected with a benzyl group (**11a**), the opposite enantiomer was obtained in lower e.r. Subsequently, the influence of the substitution pattern on the aryl groups was investigated. Substitution in the *ortho* position was not possible from a synthetic point of view but a methyl group in the *meta* position improved the enantioselectivity (ligand **10b**). Ligand **10c** with a methyl group in *para* position gave a lower e.r. The e.r. was further improved to 89.5:10.5 by adding a second methyl group in the other *meta* position (ligand **10d**). Any further changes in the *meta* positions, either by increasing the steric bulk (ligand **10e**) or by introducing electron-donating or -withdrawing substituents (ligands **10f** and **10g**) only resulted in lower enantioselectivities. Replacing the benzene by naphthalene rings was also not successful (ligand **10h**). Using 1.5 equiv of cyclopropane **2** relative to indole **6a**, lowering the temperature to −50 °C, and diluting the solution to 0.025 M finally afforded the desired product **7a** in 80% yield and 94.2:5.8 e.r. on 0.10 mmol scale (Scheme 4).

We then investigated the scope of the reaction (Scheme 4). Indoles bearing electron-withdrawing groups, such as a halide, ester, or trifluoromethyl substituent (products **7b–7i**), or electron-donating groups, such as methyl or methoxy moieties (products **7j** to **7l**), delivered the corresponding products in yields of 64–84% and 90.7:9.3 to 96.7:3.3 e.r.[9] A phenyl substituent was also well-tolerated (product **7m**), as well as a fused cyclopentyl ring (product **7n**). The



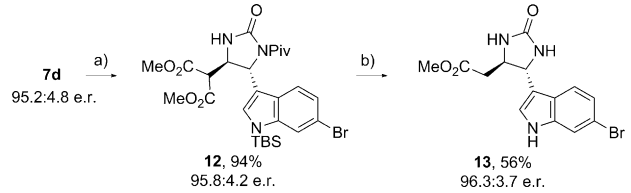
Scheme 3. A) Ligand synthesis. Reaction conditions: a) ArMgBr (6 equiv), THF (0.067 M), −78 °C to RT, 24 h; b) NaH (2.4 equiv), BnBr (2.4 equiv), DMF (0.5 M), 0 °C to RT, 16 h. B) Ligand screening for the alkylation of **6a** with **2**. Reaction conditions as in Scheme 2 but at RT for 16 h. In all cases, >20:1 d.r. The yields of isolated product and the e.r. values of **7a** are given below each ligand. Bn = benzyl.



Scheme 4. Scope of the reaction. Reaction conditions: **2** (0.15 mmol), **6** (0.10 mmol), toluene (0.025 M), −50 °C for all entries except **7g** and **7h** (−40 °C) and **7i** and **7o** (−30 °C). All compounds were obtained with >20:1 d.r. TIPS = triisopropylsilyl.

reaction could also be extended to pyrroles without reoptimization. TIPS-protected pyrrole **6o** gave product **7o** in good yield and promising e.r.[10]

A single pivaloyl group of the product could be selectively deprotected with hydrazine to deliver **12** in excellent yield without purification (Scheme 5). Basic hydrolysis then led to cleavage of the remaining pivaloyl group, the two methyl esters, as well as the silyl protecting group, releasing the free urea. Subsequent decarboxylation/methylation of the dicarboxylic acid afforded **13** in 56% yield without erosion of enantiopurity.



Scheme 5. Product derivatization. Reaction conditions: a) N_2H_4 (aq., 80 wt%, 1.5 equiv), RT; b) i) LiOH (aq., 0.5 M, 8 equiv), RT; ii) MeOH, 80 °C; iii) $TMSCHN_2$ (10 equiv), 0 °C. 56% yield over three steps.

X-ray analysis of **7d** revealed its configuration to be 3*R*,4*R* (see the Supporting Information, Figure S1).[11] The *trans* relative configuration supports an S_N2-like mechanism for the ring opening of the cyclopropane. Based on the obtained absolute configuration, a highly speculative stereochemical model can be proposed (Figure 2). We assume that

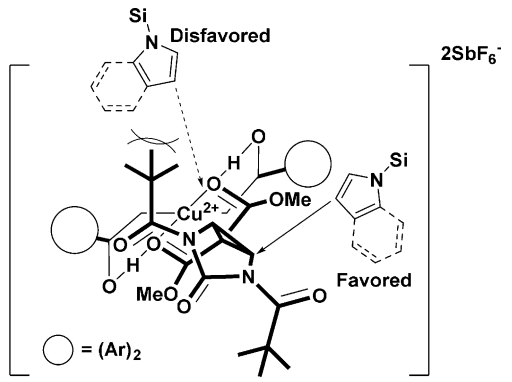


Figure 2. Speculative stereochemical model.

the copper complex adopts a distorted square-planar geometry owing to hydrogen bonds between the hydroxy groups and the esters of the cyclopropane, forcing them in the more hindered quadrants and further activating them.[12,13] Indeed, rate acceleration was observed when ligands with free hydroxy groups were employed.[14] In the resulting rigidified structure, there might be a relay of stereoinduction from the aryl groups to the pivaloyl moieties, the latter orienting their smallest substituent (carbonyl) towards the bulky aryl groups. This results in an opposite orientation of the two pivaloyl carbonyl groups compared to the urea carbonyl group, and the selective blocking of one of the electrophilic carbon atoms of the cyclopropane with a *tert*-butyl group.

In summary, we have developed the first Lewis acid catalyzed enantioselective ring-opening desymmetrization of donor–acceptor cyclopropanes. The transformation displayed high enantioselectivity and complete diastereoselectivity for a broad scope of indoles as well as one pyrrole, delivering urea derivatives that are important scaffolds in natural and synthetic bioactive compounds. The use and further modification of an underexploited class of BOX ligands readily obtained in two steps from serine ester was essential in achieving high enantioselectivities. We believe that these ligands will be useful also in other asymmetric transformations.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: BOX ligands · desymmetrization · donor–acceptor cyclopropanes · Lewis acids · ureas

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[9] Attempts to use C2-, C3-, or C4-substituted indoles gave low enantioselectivity or low reactivity.

[10] Only very low conversions were observed when either anisole or dimethylaniline was used as the nucleophile.

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[14] With ligand **8**, no reactivity was observed at −30 °C, whereas with **10d**, the reaction proceeds at −50 °C.

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