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Enantioselective Cyclopropanation of Indoles: Construction of All-Carbon Quaternary Stereocenters

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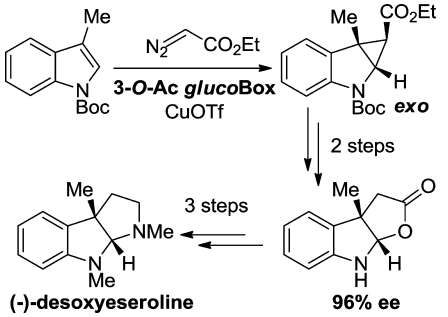
ABSTRACT



The first enantioselective copper-catalyzed cyclopropanation of *N*-acyl indoles is described. Using carbohydrate-based bis(oxazoline) ligands (*gluco*Box), the products were obtained in up to 72% ee. Cyclopropanation of *N*-Boc 3-methyl indole yielded a product with an all-carbon quaternary stereocenter, which is a valuable building block for the synthesis of indole alkaloids: Deprotection and rearrangement gave a tricyclic hemiaminal ester in 96% ee, which was subsequently employed as a key intermediate for the synthesis of (−)-desoxyeseroline.

Chiral cyclopropanes are important motifs in natural products and pharmaceuticals, and cyclopropyl units with donor and acceptor substituents[1] can be transformed into valuable synthetic intermediates via ring opening or ring expansion. Unsurprisingly considerable effort has gone into the development of stereoselective routes toward these compounds;[2] one convenient approach is the copper-catalyzed cyclopropanation of alkenes using diazo compounds. Chiral bis(oxazoline) ligands (Box),[3] such as (*S*)-**1** (Figure 1), are powerful tools for this process.[4] Carbohydrates, which are available in large amounts and diverse architectures, are interesting but comparatively rarely used starting materials for the design of chiral ligands.[5] In the course of our work we have introduced Ac *gluco*Box (**2**) based on D-glucosamine (Figure 1), which gave 82% ee in the cyclopropanation of styrene with ethyl diazoacetate.[6] To optimize the pyranosidic scaffold for this reaction, ligand family 3-*O*-R[1] *gluco*Box (**3a**–**g**) was designed.[7] The asymmetric induction of ligands **3a**–**g** was strongly dependent on the steric demand and type of the 3-*O* residues with small acyl-based groups giving the best results (up to 95% ee with **3g**).

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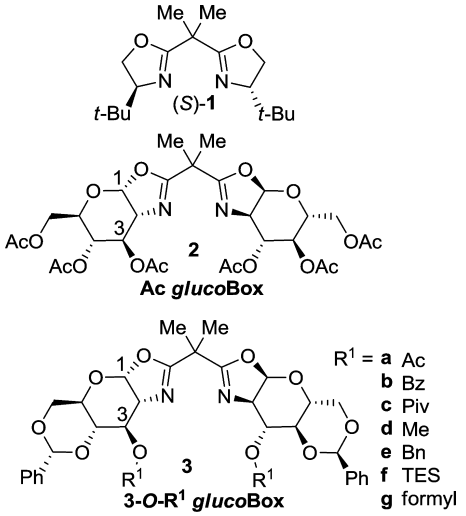
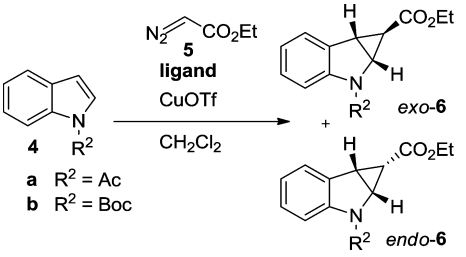


Figure 1. Conventional Box ligand (*S*)-**1**, carboydrate-based ligands Ac *gluco*Box (**2**) and 3-*O*-R[1] *gluco*Box (**3a**–**g**).

Thus optimized ligand 3-*O*-formyl *gluco*Box (**3g**) was obtained, which was suitable even for challenging aliphatic olefins: with 1-nonene, 90% ee was obtained, and the *trans*-product was used in the stereoselective synthesis of the natural product grenadamide.[8] Recently ligands **2** and **3** were employed by Reddy in copper(II)-catalyzed Henry reactions[9] and Friedel–Crafts alkylations.[10]

In contrast to other electron-rich heterocycles such as furans, benzofurans, and pyrrols, indoles have rarely been employed in cyclopropanation reactions.[11] The first examples with achiral copper catalysts were reported by Welstead,[12] Wenkert,[13] and Lehner,[14] followed by later reports by Reiser,[15] Yan,[16] and Wee.[17] Recently, cyclopropanation products of 3-substituted indoles were used as key intermediates in syntheses of complex indole alkaloids[18] containing quaternary stereocenters: Qin used intramolecular reactions of tryptamine and tryptophol derivatives for racemic syntheses of communesin[19] and minfiensine.[20] Diastereoselective examples were reported by Spino and again by Qin, who performed

Table 1. Cyclopropanation of *N*-Acyl Indoles **4a,b**[a]



entry	ligand	3-*O*-R[1]	temp [°C]	R[2]	6 yield [%]	6 *exo*/*endo*[d]	6 ee (*exo*) [%]
1	**3g**	formyl	rt	Ac	75[b]	84:16	34[e]
2	**3a**	Ac	rt	Ac	71[b]	82:18	34[e]
3	**3g**	formyl	rt	Boc	(67)[c]	nd	45[f]
4	**3a**	Ac	rt	Boc	(70)[c]	nd	**55**[f]
5	**3b**	Bz	rt	Boc	(54)[c]	nd	45[f]
6	**3c**	Piv	rt	Boc	(70)[c]	nd	38[f]
7	**2**	–	rt	Boc	(68)[c]	nd	rac.[f]
8	**3a**	Ac	10	Ac	75[b]	87:13	53[e]
9	**3a**	Ac	0	Ac	76[b]	92:8	51[e]
10	**3a**	Ac	−5	Ac	56[b]	>99:1	**61**[e]
11	**3a**	Ac	−10	Ac	9[b]	>99:1	45[e]
12	**3a**	Ac	10	Boc	(76)[c]	nd	69[f]
13	**3a**	Ac	0	Boc	(57)[c]	nd	**72**[f]
14	**3a**	Ac	−10	Boc	(62)[c]	nd	55[f]

[a] Ligand (3.3 mol %), CuOTf·0.5C_6H_6 (3 mol %), **4** (1 equiv), **5** (2.5 equiv). [b] Combined yield of **6** after chromatography. [c] Yield for of *exo*-**6b**; product contains 0.06–0.4 equiv of diethyl fumarate; yield calculated from ^{1}H NMR ratio of *exo*-**6b** to fumarate. [d] Determined after separation of the diastereomers. [e] Determined by GC. [f] Determined by HPLC.

cyclopropanations on chiral indole derivatives for the syntheses of aspidofractinine[21] and ardeemin.[22] To the best of our knowledge, no enantioselective variant of this transformation has been described so far. Now we report the first enantioselective cyclopropanation of *N*-acyl indoles using copper(I) triflate and carbohydrate ligands **2** and **3**.

At the outset, we tested the reaction of *N*-acetyl indole (**4a**) with ethyl diazoacetate (**5**) at rt in the presence of CuOTf and ligand **3g** or **3a** (Table 1, entries 1 and 2), which gave *exo*-**6a** and *endo*-**6a** (80:20) in 70–75% yield and 34% ee for *exo*-**6a**. Products **6b** from *N*-Boc indole (**4b**) were isolated together with fumarate and maleate esters, which are formed by decomposition of ethyl diazoacetate (**5**). While *exo*-**6b** and *endo*-**6b** were separable by chromatography, the byproduct could not be removed, which prevented the exact determination of yield and the *exo*/*endo* ratio for reactions with substrate **4b**. The yields given in Table 1 refer to *exo*-**6b** and were caclulated from the ^{1}H NMR ratio of *exo*-**6b** and diethyl fumarate. HPLC analysis permitted the determination of the ee for *exo*-**6b**: ligand **3g** yielded 45% ee, while **3a** with a sterically more

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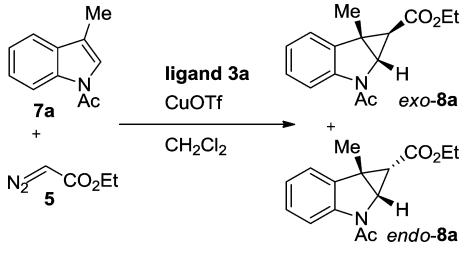
demanding 3-*O*-Ac group produced *exo*-**6b** in 55% ee. Ligands **3b,c** with larger Bz and Piv groups led to decreased ee (entries 5 and 6). Thus the steric demand of the 3-*O* substituents in ligands **3** has once again direct influence on stereoselectivity.[7c,8] Ligand **2**, lacking the 4,6-*O*-benzylidene acetal units of **3a**, led to a complete loss of stereoselectivity (entry 7). This striking difference in the asymmetric induction of ligands **3a** and **2** may be explained by the distinctly different pyranoside conformations these ligands adopt due to the presence or absence of the benzylidene acetal units.[7b,c]

To improve the ee for substrates **4a** and **4b**, reactions with ligand **3a** were performed at lower temperature. For *N*-acetyl indole (**4a**), a decrease from rt to −5 °C led to an improved *exo*/*endo* ratio and ee (entries 8−10): at −5 °C *exo*-**6a** was obtained in 61% ee and almost diastereomerically pure form. Lower temperatures resulted in a severely reduced yield and stereoselectivity (entry 11). Cyclopropanation of *N*-Boc indole (**4b**) at lower temperatures also improved the ee: while due to fumarate and maleate byproduct only a calculated yield was determined, HPLC analysis of *exo*-**6b** showed an increase of the enantioselectivity to 72% ee, when the temperature was lowered from to 0 °C (entries 12−14). However at −10 °C the stereoselectivity dropped to 55% ee.

After these promising initial results we decided to try the enantioselective cyclopropanation of *N*-acetyl 3-methyl indole (**7a**) with ligand **3a** (Table 2). This reaction is attractive as the diastereomeric products *exo*-**8a** and *endo*-**8a** contain an all-carbon quaternary stereocenter, which are challenging to construct in an asymmetric manner.[23] These cyclopropanes can be further elaborated into tricyclic hemiaminal ester **13** by cyclopropane opening

Table 2. Cyclopropanation of *N*-Acetyl 3-Methyl Indole (**7a**)[a]



		8a		
entry	temp [°C]	yield [%][b]	*exo*/*endo*[d]	ee (*exo*) [%][e]
1	rt	66	65:35	48
2	10	52	67:33	56
3	0	40[c]	71:29	52
4	−10	29[c]	>99:1	**70**
5	−20	17[c]	>99:1	71

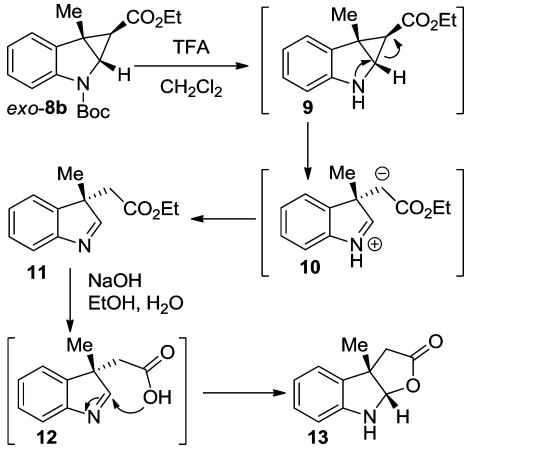
[a] Ligand (3.3 mol %), CuOTf·0.5C_6H_6 (3 mol %), **7a** (1 equiv), **5** (2.5 equiv). [b] Combined yield of **8a** after chromatography. [c] Incomplete conversion, reisolation **7a**. [d] Determined after separation of diastereomers. [e] Determined by GC.

after removal of the *N*-acetates and the ethyl esters, as was demonstrated by Wenkert for a related racemic example.[13]

At rt and 10 °C the reaction of **7a** produced *exo*-**8a** and *endo*-**8a** in modest diastereoselectivity, moderate yield, and 48% ee and 56% ee respectively (entries 1 and 2). A further decrease in temperature led to strikingly improved *exo*/*endo* ratios, albeit at the expense of the yield, while up to 70% ee was observed.

In the study from Table 1, *N*-Boc protected indole **4b** had led to a higher ee than its acetylated counterpart **4a**, so we next examined the reaction of *N*-Boc 3-methyl indole (**7b**). Unfortunately, the corresponding cyclopropanes **8b** were again obtained together with fumarate and malonate impurities that were impossible to remove. Therefore the raw cyclopropanation product *exo*-**8b** was directly transformed into hemiaminal ester **13** (Scheme 1): Acidic removal of the Boc group yielded imine **11** via ring opening of donor−acceptor cyclopropane intermediate **9**, and cleavage of the ethyl ester[24] in **11** gave acid **12**, which spontaneously cyclized to yield hemiaminal ester **13**.

Scheme 1. Transformation of *exo*-**8b** into Hemiaminal Ester **13**



Following this strategy, we studied the enantioselective synthesis of **13** (Table 3). Cyclopropanation of **7b** at rt using 3-*O*-Ac *gluco*Box (**3a**) followed by *N*-deprotection gave imine **11** in modest yield. To our delight, saponification of **11** gave (−)-**13** in 87% ee and 63% yield (entry 1). For comparison, 3-*O*-formyl ligand **3g** and conventional Box ligand (*S*)-**1** were also tested. With these **13** was obtained in 82% ee. While **3g** and **3a** gave the (−)-enantiomer of **13**, ligand (*S*)-**1** led to (+)-**13** (entries 2 and 3). The formation of (−)- and (+)-**13** with ligands **3a,g**

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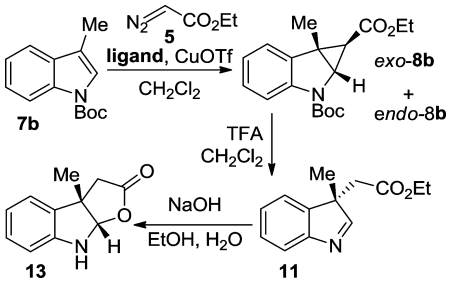
Table 3. Asymmetric Synthesis of Hemiaminal Ester **13** via Enantioselective Cyclopropanation of *N*-Boc Indole **7b**[a]

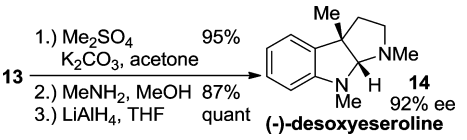


	ligand			11	13	
entry		3-*O*-R[1]	temp [°C]	yield [%][b]	yield [%]	ee [%][c]
1	**3a**	Ac	rt	17	63	87 (−)
2	**3g**	formyl	rt	14	78	82 (−)
3	(*S*)-**1**	–	rt	20	99	82 (+)
4	**3a**	Ac	10	36	75	94 (−)
5	**3a**	Ac	0	61	71	**96 (−)**
6	**3a**	Ac	−10	36	71	97 (−)
7	**3a**	Ac	−20	11	90	92 (−)

[a] Ligand (3.3 mol %), $CuOTf \cdot 0.5C_6H_6$ (3 mol %), **7b** (1 equiv), **5** (2.5 equiv). [b] Isolated yield over two steps from **7b**. [c] Determined by GC.

and (*S*)-**1** respectively was expected, as our carbohydrate ligands and (*S*)-**1** produced cyclopropanes from styrene in opposite configurations as well. Again, the ee of **13** was substantially increased, when the temperature was reduced from rt to −10 °C (entries 4−6) while lower temperatures were detrimental to yield and ee (entry 7). Cyclopropanation at 0 °C in the presence of **3a** gave **11** in 61% yield from indole **7b**, and hemiaminal ester **13** was obtained in 71% yield and excellent 96% ee after deprotection of **11** (entry 5).

Scheme 2. Synthesis of (−)-Desoxyeseroline (**14**) from **13**



The high stereoselectivity obtained for **13** makes the reaction sequence described above a highly useful approach toward indole alkaloids comprising a pyrroloindoline core, i.e. desoxyeseroline,[25] esermethole,[26] and physostigmine:[26] following a route previously described by Ikeda[27] for a racemic synthesis of esermethole, (−)-desoxyeseroline (**14**) was obtained in good overall yield from hemiaminal ester **13** via *N*-methylation[28] and aminolysis followed by hydride reduction[29] (Scheme 2). All spectroscopical data of **14** were in good agreement with the reported ones,[25] the optical purity of **14** (92% ee) was determined by ^{1}H NMR using the dirhodium method.[30]

In summary we have reported the first enantioselective copper-catalyzed cyclopropanation of indoles. *N*-Boc indole **4b** gave *exo*-**6b** in up to 72% ee, while 3-substituted *N*-Boc indole **7b** provided **13** via *exo*-**8b** in excellent 96% ee. Finally, the high utility of this process for indol alkaloid synthesis was demonstrated by the stereoselective synthesis of (−)-desoxyeseroline (**14**) from hemiaminal ester **13**. Studies on further applications are currently underway in our laboratories.

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Supporting Information Available. Experimental details, full characterization of all products, data for the determination of all enantiomeric excesses. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.