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Enantioselective dearomative [3 + 2] cycloadditions of indoles with azomethine ylides derived from alanine imino esters†

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Catalytic, enantioselective [3 + 2] cycloadditions of azomethine ylides derived from alanine imino esters with 3-nitroindoles are reported. The dearomative cycloaddition reactions occur in the presence of a catalyst generated *in situ* from Cu(OTf)₂ and (*R*)-Difluorophos to form *exo'*-pyrroloindoline cycloadducts and establish four contiguous stereogenic centers, two of which are fully substituted. The *exo'*-pyrroloindoline products are formed in moderate-to-good yields (39–85%) with high diastereoselectivities (up to 98 : 1 : 1 dr) and enantioselectivities (up to 96% ee).

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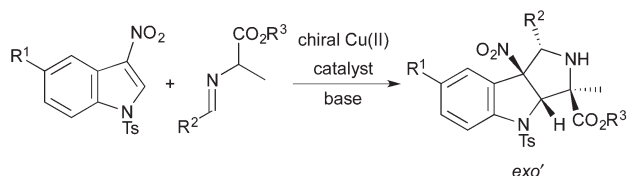
Introduction

The development of dearomatization reactions offers the potential to rapidly generate molecular complexity and new molecular frameworks.¹ In recent years, [2 + 2],² [3 + 2],³ [4 + 2],⁴ and [5 + 2]⁵ dearomative cycloadditions have emerged as promising strategies to construct polycyclic carbocycles and heterocycles from arenes and heteroarenes. Despite the steady development of new dearomative cycloadditions reactions, examples of catalytic, enantioselective dearomative cycloadditions are limited.^{2a,3e,g-i}

Among the promising classes of dearomative cycloadditions for further development are intermolecular [3 + 2] cycloadditions of nitrogen-containing 1,3-dipoles with arenes and heteroarenes. In particular, cycloadditions of azomethine ylides with arenes and heteroarenes have emerged as a viable approach to generate polycyclic nitrogen heterocycles.⁶ Gribble and co-workers initially reported cycloadditions of unstabilized azomethine ylides with 2- and 3-nitroindoles to form racemic pyrroloindolines.⁷ More recently, Chataingner, Pietre, and co-workers showed that cycloadditions of unstabilized azomethine ylides with electron-deficient arenes and heteroarenes form a wide variety of racemic, polycyclic cycloadducts in good-to-excellent yields.⁸

In 2014, Awata and Arai reported the first catalytic, enantioselective dearomative cycloadditions of stabilized azomethine ylides with 3-nitroindoles.⁹ Cycloadditions of a wide range of azomethine ylides derived from glycine imino esters occur with excellent enantioselectivity and nearly perfect *exo'*-selectivity when the reactions are run in the presence of a complex prepared from Cu(OTf)₂ and a chiral PyBidine ligand. However, catalytic, enantioselective dearomative cycloadditions of azomethine ylides derived from alanine imino esters have





Scheme 1 Enantioselective cycloadditions of 3-nitroindoles with alanine-derived azomethine ylides.

not been reported. Herein, we report the first examples of diastereo- and enantioselective dearomative cycloadditions of alanine-derived azomethine ylides with 3-nitroindoles. These reactions generate pyrroloindolines with four contiguous stereogenic centers, two of which are fully substituted (Scheme 1).

Results and discussion

To identify a diastereo- and enantioselective catalyst for dearomative cycloadditions of alanine-derived azomethine ylides, we

evaluated the model reaction of *N*-tosyl-3-nitroindole **1a** with racemic imino ester **2a** (Table 1). Initially, we found that copper(II) triflate complexes of the chiral bisphosphine ligands (*R*)-BINAP, (*R*)-Segphos, and (*R*)-Difluorophos (10 mol%) catalyzed the cycloadditions of **1a** with **2a**. These reactions formed a diastereomeric mixture of cycloadducts **3a** with *exo'*-**3a** generated as the major diastereomer (entries 1–3). The reaction of **1a** and **2a** occurred with the highest diastereoselectivity (93 : 3 : 4 *exo'*-**3a** : *exo*-**3a** : *endo*-**3a**) with the copper(II) triflate complex of (*R*)-difluorophos as catalyst (entry 3).¹⁰ The cycloadduct *exo'*-**3a** was isolated in 73% yield with 86% ee. The high enantioselectivity and diastereoselectivity observed for the model reaction led us to explore additional reaction parameters using the combination of Cu(OTf)₂ and (*R*)-difluorophos as catalyst.

By lowering the reaction temperature to 0 °C and –20 °C, we observed higher enantioselectivity for *exo'*-**3a** (92–93% ee) with lower diastereoselectivity (entries 4 and 5). For example, the reaction of **1a** with **2a** forms a 41 : 15 : 44 mixture of *exo'* : *exo* : *endo* diastereomers when the reaction is carried out at –20 °C. The *endo* selectivity of the reaction carried out at

Table 1 Identification of catalysts and reaction conditions for the cycloaddition of **1a** and **2a**^a

Entry	Ligand	Temp (°C)	Equiv. 2a	dr <i>exo'</i> : <i>exo</i> : <i>endo</i> ^b	Yield <i>exo'</i> - 3a ^c (%)	ee <i>exo'</i> - 3a ^d (%)
1	L1	rt	1.0	55 : 19 : 26	35	60
2	L2	rt	1.0	79 : 9 : 12	60	82
3	L3	rt	1.0	93 : 3 : 4	73	86
4	L3	0	1.0	73 : 9 : 18	51	92
5	L3	–20	1.0	41 : 15 : 44	34	93
6 ^e	L3	rt	1.0	71 : 11 : 18	58	76
7	L3	rt	1.2	93 : 3 : 4	75	89
8	L3	rt	1.5	92 : 3 : 5	78	88
9	L3	rt	2.0	92 : 3 : 5	72	90

^a Reaction conditions: **1a** (0.20 mmol), *rac*-**2a** (0.20–0.40 mmol), Cu(OTf)₂ (0.02 mmol, 10 mol%), ligand (0.02 mmol, 10 mol%), DBU (0.04 mmol, 20 mol%), THF (1.0 mL), 14–18 h. ^b Determined by ¹H NMR spectroscopy of the crude reaction mixture. ^c Isolated yield of *exo'*-**3a** with >95 : 5 dr. ^d Determined by chiral HPLC analysis. ^e Reaction conducted with 5 mol% of the Cu catalyst.



–20 °C led us to postulate that the model cycloaddition is *endo*-selective, but epimerization of *endo*-3a to *exo*'-3a occurs at higher temperatures through a retro-Mannich/Mannich addition pathway and leads to the observed *exo*'-selectivity.¹¹

Lowering the loading of the copper catalyst also proved detrimental to the diastereo- and enantioselectivity of the model reaction. The reaction of **1a** with **2a** in the presence of 5 mol% of the copper catalyst formed **3a** as a 71:11:18 mixture of *exo*':*exo*:*endo* diastereomers with *exo*'-3a isolated in 76% ee (entry 6). The decrease in enantioselectivity and diastereoselectivity observed at lower catalyst loading suggests: (1) the rate of uncatalyzed background reaction is likely competitive with the rate of the catalyzed process; and (2) the copper complex may catalyze the epimerization of *endo*-3a to *exo*'-3a.

Varying the concentration of imino ester **2a** has minimal impact on the yield and selectivity of the model reaction (compare entries 3 and 7–9). The diastereoselectivity remains essentially unchanged when varying the amounts of imino ester **2a** from 1.0–2.0 equivalents. However, a slight excess (1.2 equivalents, entry 7) of **2a** leads to a modest increase in enantioselectivity, but this trend does not hold when the concentration of **2a** is further increased (entries 8 and 9).

To develop a better understanding of the rates of the catalyzed reaction and the uncatalyzed background reaction and the evolution of the diastereoselectivity over time, we conducted cycloadditions of **1a** with **2a** in the presence and absence of copper catalyst and monitored the yield and diastereoselectivity over time (Table 2). The catalyzed reaction of **1a** with **2a** occurs to approximately 90% conversion after 2 h (entry 1) and is complete after 6 h (entry 3), while the uncatalyzed reaction occurs to approximately 50% and 80% conver-

sion over the same time periods (entries 2 and 4). Although the uncatalyzed background reaction is slower than the catalyzed process, this data shows that the rate of uncatalyzed cycloaddition is sufficient to negatively impact the enantioselectivity of the cycloadditions and likely explains the poor enantioselectivity observed when the catalyst loading is lowered.

The evolution of diastereoselectivity over time is greatly influenced by the presence or absence of the copper catalyst. The uncatalyzed model reaction forms a 59:6:35 ratio of *exo*':*exo*:*endo* diastereomers after 2 h, and this ratio does not change significantly over an additional 4 h (Table 2, entries 2 and 4). In contrast, the diastereoselectivity of the copper-catalyzed cycloaddition changes markedly with reaction time. The catalyzed reaction forms a 69:5:26 ratio of *exo*':*exo*:*endo* diastereomers after 2 h (entry 1); a ratio that is similar to that observed in the uncatalyzed reaction. However, the diastereomeric ratio improves to 77:9:14 (entry 3) after 6 h and to 93:3:4 (entry 5) after 16 h. The dramatic decrease in the amount of *endo*-3a and increase in the amount of *exo*'-3a indicates that the complex generated from Cu(OTf)₂ and **L3** catalyzes the epimerization of *endo*-3a to *exo*'-3a which leads to the high *exo*' selectivity of the cycloaddition reaction.

With a practical set of reaction conditions and a diastereo- and enantioselective catalyst identified, we evaluated cycloadditions of *N*-tosyl-3-nitroindole **1a** with a variety of imino esters **2b–k** derived from alanine methyl ester and an array of aromatic aldehydes. Results of these reactions are summarized in Table 3. In general, cycloadditions of **1a** with imino esters containing 4-substituted aryl groups occur to form *exo*'-3 in >70% yield with >90% ee and >90:7:3 *exo*':*exo*:*endo* diastereoselectivity (entries 1–5). The notable exceptions to these typical yields and selectivities include the reactions of imino esters **2b** (Ar = 4-F₃CC₆H₄) and **2c** (Ar = 4-ClC₆H₄). The cycloaddition of **2b** with **1a** occurs in high yield with excellent diastereoselectivity (entry 1). However, *exo*'-3b is isolated with 80% ee, possibly due to a faster rate of uncatalyzed background reaction with an azomethine ylide containing an electron-withdrawing 4-trifluoromethyl group on the arene moiety. This hypothesis is supported by a positive correlation between enantioselectivity of the reaction and increasing electron-donating ability of substituents at the 4-position on the aryl ring of the dipoles. The cycloaddition of **2c** with **1a** forms *exo*'-3b in 70% yield with 88% ee, but the reaction occurs with modest diastereoselectivity (entry 2).

Cycloadditions of imino esters **2g–k** containing 2- and 3-substituted aryl groups with **1a** generally occur with slightly lower yields and selectivities (entries 6–10) than imino esters **2b–f**. While the cycloaddition of 3-MeO-substituted imino ester **2g** occurs to form *exo*'-3g in high yield with high diastereo- and enantioselectivity (entry 6), the cycloaddition of 3-Br-substituted imino ester **2h** formed *exo*'-3h in only 40% yield with modest diastereoselectivity, likely due to a relatively slow epimerization of *endo*-3g to *exo*'-3g, and slightly lower enantioselectivity (entry 7). Cycloadditions of 2-MeO-, 2-F-, and 2-Cl-substituted imino esters **2i–k** formed *exo*'-3i–k in 39–85%


Table 2 Evolution of stereoselectivity in catalysed *versus* uncatalysed reactions of **1a** with **2a**^a

Entry	Cu(II) catalyst	Time (h)	dr <i>exo</i> ': <i>exo</i> : <i>endo</i> ^b	NMR yield ^b (%)	ee <i>exo</i> '-3a ^c (%)
1	Yes	2	69:5:26	84 (91)	87
2	No	2	59:6:35	49 (52)	—
3	Yes	6	77:9:14	99 (99)	90
4	No	6	61:10:30	78 (82)	—
5	Yes	16	93:3:4	99 (99)	89

^a Catalysed reaction conditions: **1a** (0.20 mmol), *rac*-**2a** (0.24 mmol), Cu(OTf)₂ (0.02 mmol), **L3** (0.02 mmol), DBU (0.04 mmol), THF (1.0 mL), 2–16 h. ^b Determined by ¹H NMR spectroscopy of the crude reaction mixture using dibromomethane as an internal standard. Conversion of **1a** is listed in parentheses. ^c Determined by chiral HPLC analysis after purification of *exo*'-3a by column chromatography. Isolated yields of *exo*'-3a were 65% (entry 1), 75% (entry 3), and 75% (entry 5).



Table 3 Scope of dearomative cycloadditions of indole 1a with imino esters 2b–k^a

					
Entry	rac-2 (Ar)	exo'-3	dr exo' : exo : endo ^b	Yield exo'-3 ^c (%)	ee exo'-3 ^d (%)
1	2b (4-F ₃ CC ₆ H ₄)	3b	>98 : 1 : 1	83	80
2	2c (4-ClC ₆ H ₄)	3c	78 : 5 : 17	70	88
3	2d (4-BrC ₆ H ₄)	3d	95 : 4 : 1	78	90
4	2e (4-H ₃ CC ₆ H ₄)	3e	90 : 7 : 3	76	91
5	2f (4-MeOC ₆ H ₄)	3f	95 : 4 : 1	71	96
6	2g (3-MeOC ₆ H ₄)	3g	89 : 8 : 3	72	89
7	2h (3-BrC ₆ H ₄)	3h	69 : 8 : 23	40	80
8	2i (2-MeOC ₆ H ₄)	3i	74 : 7 : 19	39	82
9	2j (2-FC ₆ H ₄)	3j	67 : 5 : 27	51	87
10	2k (2-ClC ₆ H ₄)	3k	88 : 8 : 4	85	79

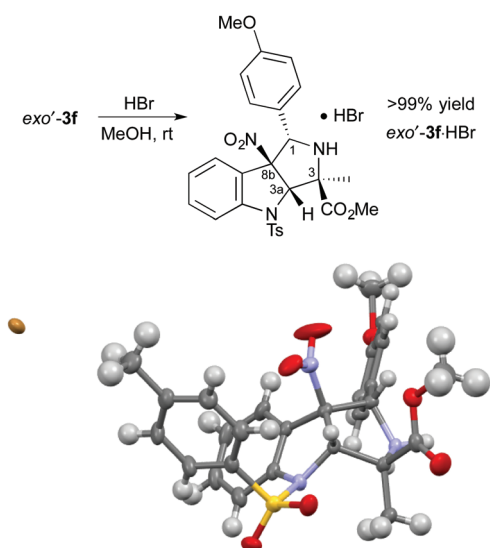
^a Reaction conditions: **1a** (0.20 mmol), **2** (0.24 mmol), Cu(OTf)₂ (0.02 mmol), **L3** (0.02 mmol), DBU (0.04 mmol), THF (1.0 mL), 14–18 h.
^b Determined by ¹H NMR spectroscopy of the crude reaction mixture. ^c Isolated yield of exo'-3a with >95 : 5 dr. ^d Determined by chiral HPLC analysis.

yield with 79–87% ee and with diastereoselectivities ranging from 67 : 5 : 27 to 88 : 8 : 4 exo' : exo : endo (entries 8–10).

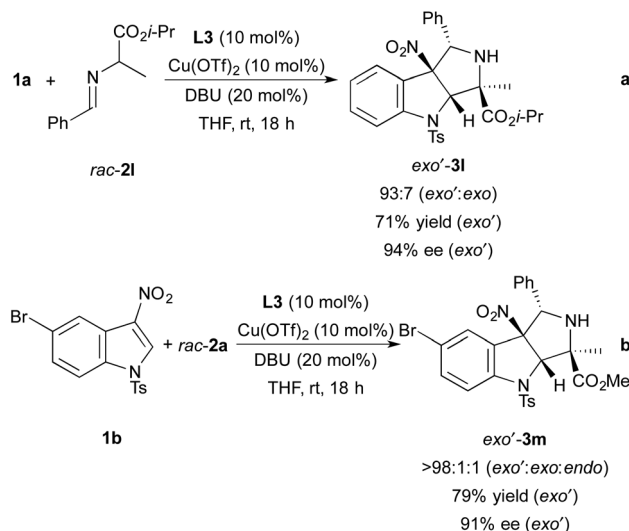
The absolute configuration of exo'-3f was determined after treatment with HBr to form exo'-3f·HBr in >99% yield (Scheme 2). The absolute configuration of exo'-3f·HBr was determined to be (1*S*,3*R*,3*aS*,8*bS*) by X-ray crystallographic analysis.

Although our studies focused on reactions of *N*-tosyl-3-nitroindole **1a** with imino esters derived from alanine methyl ester, we have also demonstrated that cycloadditions involving an imino ester derived from alanine isopropyl ester and

N-tosyl-5-bromo-3-nitroindole occur in high yields with excellent stereoselectivity (Scheme 3). For example, the reaction of *N*-tosyl-3-nitroindole **1a** with imino ester **2l** derived from alanine isopropyl ester occurs with 93 : 7 exo' : exo diastereoselectivity and forms pyrroloindoline exo'-3l in 71% yield with 94% ee (Scheme 3a). The endo diastereomer was not observed after the 18 h reaction time. The cycloaddition of imino ester **2a** with *N*-tosyl-5-bromo-3-nitroindole **1b** occurs with nearly perfect exo' selectivity (>98 : 1 : 1 exo' : exo : endo, Scheme 2b). Pyrroloindoline exo'-3m was isolated in 79% yield with 91% ee.



Scheme 2 Determination of the absolute stereochemistry of exo'-3f.

Scheme 3 Dearomative cycloadditions of indole **1a** with imino ester *rac*-2l and indole **1b** with imino ester *rac*-2a.

Conclusions

In summary, we have developed the first catalytic, enantioselective dearomative cycloadditions of alanine-derived imino esters with 3-nitroindoles. These *exo'*-selective dearomative cycloadditions form a variety of highly enantioenriched pyrroloindolines with four contiguous stereogenic centers, two of which are fully substituted, when the reactions are conducted in the presence of a catalyst generated from Cu(OTf)₂ and (*R*)-difluorophos. The high diastereoselectivities observed favoring the formation of the *exo'*-cycloadduct result from a Cu(OTf)₂/*(R)*-difluorophos-catalyzed epimerization of the *endo*-cycloadduct to the *exo'*-cycloadduct during the course of the reaction. Studies to develop new catalytic, enantioselective dearomative cycloadditions with additional classes of aromatic and heteroaromatic dipolarophiles are ongoing in our laboratory.

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