Asymmetric Catalysis

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Catalytic Asymmetric Synthesis of [2,3]-Fused Indoline Heterocycles through Inverse-Electron-Demand Aza-Diels–Alder Reaction of Indoles with Azoalkenes**

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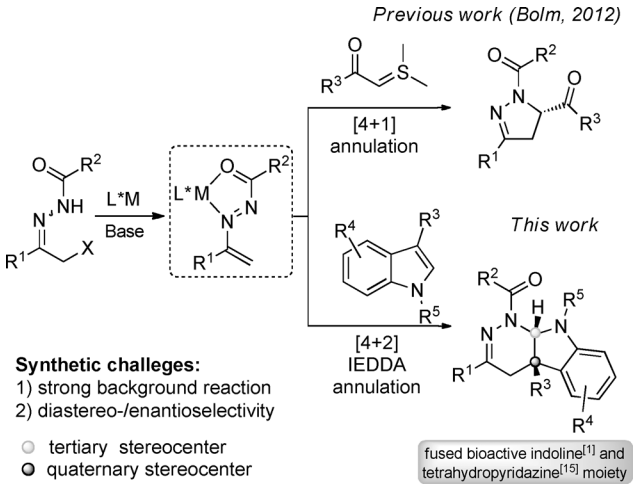
Abstract: *An unprecedented catalytic asymmetric inverse-electron-demand aza-Diels–Alder reaction of indoles with in situ formed azoalkenes is reported. A diverse set of [2,3]-fused indoline heterocycles were achieved in generally good yields (up to 97%) with high regioselectivity and diastereoselectivity (>20:1 d.r.), and with excellent enantioselectivity (up to 99% ee).*

Fused indoline heterocycles are widely found as core components in a large number of biologically active alkaloids, natural products, and pharmaceuticals.[1] As such, much attention and synthetic effort has been paid to developing efficient and straightforward methods to construct those molecules based on the cascade annulation of indoles.[2] Recently, catalytic asymmetric C2,C3-annulation of indoles,[3] which involves both the nucleophilicity on C3 (enamine-type reactivity) and electrophilicity on C2 (iminium-ion-type reactivity), has become one of the most powerful and diversity-oriented syntheses[4] for constructing enantiomerically enriched [2,3]-fused indoline derivatives. Most of the successful examples were intramolecular annulations employing indoles tethered with a built-in nucleophilic group (such as tryptamine or tryptanol derivatives) to trap the in situ formed iminium-ion intermediate.[3] Although the intermolecular C2,C3-annulation of simple and readily-available substituted indoles with potential reaction partners is highly desirable and allows for facile access to complex and diverse chiral fused-indoline heterocycles, only limited examples have been reported. In 2009, Barluenga et al. reported the first asymmetric C2,C3-annulation of indoles with tungsten Fisher carbenes bearing a chiral auxiliary group.[5] Later on, efficient transition-metal-catalyzed asymmetric C2,C3-annulation of simple indoles with vinyldiazoacetates and 2-amidoacylates were reported by the groups of Davies,[6] using $[Rh_2\{(R)\text{-Dosp}\}_4]$, and Reisman,[7] using an (*R*)-Binol/$SnCl_4$ complex. The groups of You[8] and Sun[9] recently disclosed an organo-catalyzed asymmetric C2,C3-annulation of indoles. Most recently, Tang and co-workers[10] reported a Cu^{II}/Box-catalyzed asymmetric C2,C3-cyclopentannulation of indoles with cyclopropanes.

Azoalkenes (1,2-diaza-1,3-dienes),[11] which are readily generated in situ from α-halogeno hydrazone, have been commonly employed as key intermediates for the synthesis of various five- or six-membered achiral nitrogen-containing heterocycles.[12] Very surprisingly, azoalkenes have seldom been employed as synthons in catalytic asymmetric cycloaddition reactions. To date, only one example has been documented,[13] in which Bolm and co-workers pioneered the catalytic asymmetric formal [4+1]-cycloaddition of azoalkenes with sulfur ylides to access five-membered dihydropyrazole derivatives. Distinct from their finds, we envisioned that azoalkenes could be utilized as electron-deficient heterodienes in the inverse-electron-demand aza-Diels–Alder reaction (IEDDA)[14] with indoles through C2,C3-annulation for the direct construction of biologically attractive and enantiopure [2,3]-fused indoline heterocycles. Herein, we report an unprecedented Cu^{I}-catalyzed asymmetric C2,C3-annulation of simple indoles with in situ formed azoalkenes to afford highly functionalized [2,3]-fused indolines bearing contiguous quaternary and tertiary stereogenic centers with excellent diastereoselectivity and enantioselectivity (Scheme 1). Another key feature of this annulation process is that a tetrahydropyridazine moiety was constructed simultaneously, which also constitutes the core structure of numerous pharmaceuticals.[15]



Scheme 1. [4+1] Annulation of azoalkene with sulfur ylide (previous work) and [4+2] inverse electron-demand aza-Diels–Alder (IEDDA) reaction of azoalkene with indole (this work).

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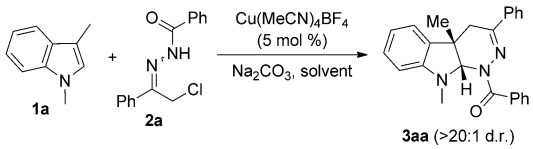
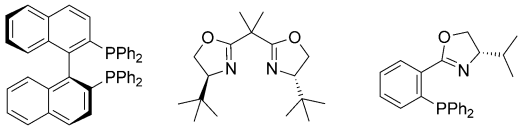
We started our investigation with readily available α-chloro *N*-benzoyl hydrazone **2a** as the 1,2-diazo-1,3-diene precursor, to probe the feasibility of the aza-Diels Alder reaction between 1,3-dimethly indole **1a** and the in situ formed azoalkene. With Na_2CO_3 as the base, the uncatalyzed inverse-electron-demand aza-Diels–Alder reaction proceeded smoothly, affording the [2,3]-fused indoline/tetrahydropyridazine cycloadduct **3aa** in 75% yield, with exclusive regioselectivity and excellent diastereoselectivity (Table 1, entry 1). Thus, an efficient catalyst for this challenging transformation needs to 1) control the annulation process between heterodienes and dienophiles in stereoselective manner, and 2) exhibit higher reactivity than the uncatalyzed background reaction.

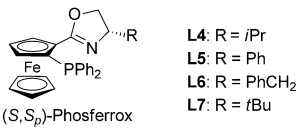
Table 1: Optimization of the reaction conditions.[a]



Entry	Ligand	Solvent	*T* [°C]	Time [h]	Yield [%][c]	*ee* [%][d]
1[b]	–	CH_2Cl_2	0	24	75	–
2	**L1**	CH_2Cl_2	0	12	91	55
3	**L2**	CH_2Cl_2	0	12	30	0
4	**L3**	CH_2Cl_2	0	12	83	3
5	**L4**	CH_2Cl_2	0	12	92	79
6	**L5**	CH_2Cl_2	0	12	71	52
7	**L6**	CH_2Cl_2	0	8	91	87
8	**L7**	CH_2Cl_2	0	8	94	95
9[e]	**L7**	CH_2Cl_2	0	24	35	66
10	**L7**	toluene	0	8	29	5
11	**L7**	CH_3CN	0	8	79	92
12	**L7**	THF	0	8	13	7
13	**L7**	CH_2Cl_2	RT	8	95	92
14	**L7**	CH_2Cl_2	−20	18	95	97

[a] All reactions were carried out with **1a** (0.3 mmol) and **2a** (0.5 mmol) in solvent (4.0 mL). [b] Without catalyst. [c] Yield of isolated product. [d] *ee* value was determined by HPLC analysis; >20:1 d.r. was established by ^{1}H NMR analysis of the crude product. [e] N-unsubstituted 3-methylindole was used.

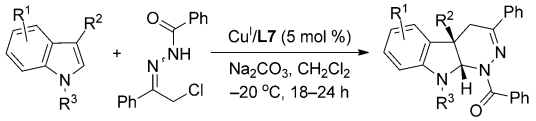




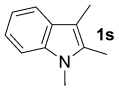
We envisioned that the reactivity of the in situ formed azoalkene could be enhanced by coordination with a chiral transition-metal complex, and therefore realize this annulation with stereoselective control. Hence, different transition-metal sources and some readily available chiral ligands were examined, and the representative results are shown in Table 1. When Cu^I/Binap was employed as the catalyst, the reaction was finished in less than 12 h affording the desired adduct **3aa** in 91% yield with high diastereoselectivity and 55% *ee* (Table 1, entry 2). However, further screening of several Binap-type axially bisphosphine ligands failed to improve the enantioselectivity (see the Supporting Information for details). A chiral Cu^I/Box (**L2**) complex was also tested, and only racemic product was obtained with low conversion (entry 3). The chiral Cu^I complex generated from the (*S*)-Phox ligand promoted the annulation process smoothly, leading to the desired adduct in good yield, albeit with very low enantioselectivity (entry 4). To our delight, by switching the backbone of the chiral P,N-ligand ligand from benzene to ferrocene, both the conversion and the enantioselectivity of this cycloaddition were improved significantly (entry 5). Remarkably, (S,S_p)-*t*Bu-Phosferrox[16] (**L7**) bearing bulky *tert*-butyl group on the oxazoline ring delivered the best results in terms of the yields and stereoselectivity (entry 8). When *N*-unsubstituted 3-methyl indole was employed, much lower conversion and moderate enantioselectivity were observed, probably owing to reduced nucleophilicity at C3 and reduced electrophilicity at C2 of 3-methyl indole (entry 9). A study of this cycloaddition with Cu^I/(*S*)-**L7** in various solvents identified MeCN as a suitable alternative to CH_2Cl_2, whereas toluene and THF had a detrimental effect on this transformation (entries 8 and 10–12). Reducing the reaction temperature proved beneficial to the control of enantioselectivity, and 97% *ee* with full conversion were achieved at −20°C (entry 14).

Under the optimized reaction conditions, we tested various substituted indoles to examine the generality of this annulation, and the results are shown in Table 2. In general, a broad range of differently substituted indoles, bearing electron-neutral (Table 1, entry 1) or electron-deficient (entries 2–4) on the indole framework, reacted with *N*-benzoyl hydrazone **1a** smoothly to form a series of [2,3]-fused indoline molecules in high yields (85–95%) with high diastereoselectivities (>20:1 d.r.) and excellent enantioselectivities (93–98% *ee*). Remarkably, this method was also compatible with the sterically hindered 4-bromo- (**1b**), 4-methyl- (**1e**), and 7-methyl-substituted (**1h**) indoles in terms of enantioselectivity and reactivity (entries 2, 5, and 8). Various C3-substituted indoles have also been employed as the reaction partners. It was found that both simple alkyl groups and functionalized alkyl groups containing ether, amide, and ester moieties were tolerated at the C3-position of the indoles, affording the desired cycloadducts in good yields with high stereoselectivities (entries 10–16). Notably, indoles bearing a sterically hindered C3-substituted group, such as *iso*-propyl and phenyl, also worked well in this transformation (entries 11 and 13). No annulation occurred when indoles without C3-substitution were employed under the optimized reaction conditions. Subsequent studies revealed that *N*-allyl- and *N*-benzyl-substituted indoles **1q** and **1r** are also viable substrates in this catalytic system, affording the corresponding heterocycles in good yields and with excellent enantioselectivity (entries 17 and 18). Further exploration revealed that 1,2,3-trimethyl indole **1s** was also a suitable substrate, providing the cycloadduct **3sa**, which bears two contiguous

Table 2: Substrate scope of the Cu^{I}-catalyzed aza-Diels–Alder reaction of various indoles **1** with hydrazone **2a**.[a]



1 **2a** **3** (>20:1 d.r.)

Entry	R^1	R^2	R^3	**1**	**3**	Yield [%][b]	*ee* [%][c]
1	H	Me	Me	**1a**	**3aa**	95	97
2	4-Br	Me	Me	**1b**	**3ba**	85	97
3	5-Br	Me	Bn	**1c**	**3ca**	87	95
4	6-Cl	Me	Me	**1d**	**3da**	90	98
5	4-Me	Me	Me	**1e**	**3ea**	88	96
6	5-Me	Me	Me	**1f**	**3fa**	89	97
7	6-Me	Me	Me	**1g**	**3ga**	92	98
8	7-Me	Me	Me	**1h**	**3ha**	89	93
9	7-MeO	Me	Me	**1i**	**3ia**	91	96
10	H	Et	Me	**1j**	**3ja**	88	97
11	H	*i*Pr	Me	**1k**	**3ka**	90	97
12	H	Bn	Me	**1l**	**3la**	89	97
13	H	Ph	Me	**1m**	**3ma**	91	97
14	H	$(CH_2)_2OTBS$	Me	**1n**	**3na**	93	97
15	H	$(CH_2)_2NBoc$	Me	**1o**	**3on**	88	96
16	H	$(CH_2)_2CO_2Me$	Me	**1p**	**3pa**	91	97
17	H	Me	allyl	**1q**	**3qa**	89	97
18	H	Me	Bn	**1r**	**3ra**	87	94
19				**1s**	**3sa**	97	92

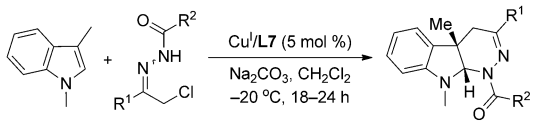
[a] All reactions were carried out with **1** (0.3 mmol) and **2a** (0.5 mmol) in CH_2Cl_2 (4.0 mL). [b] Yield of isolated product. [c] *ee* value was determined by HPLC analysis; >20:1 d.r. was established by ^{1}H NMR analysis of the crude product. Bn = benzyl, Boc = *tert*-butyloxycarbonyl, TBS = *tert*-butyldimethylsilyl.

quaternary stereogenic centers, in good yield with excellent diastereoselectivity and 92% *ee* (entry 19).

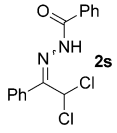
Encouraged by the excellent results with various substituted indoles as the dieneophiles, we then investigated the aza-Diels Alder cycloaddition with respect to the heterodienes. As shown in Table 3, a variety of α-chloro- or α-bromo *N*-benzoyl hydrazones have proven to be excellent azoalkene precursors in this cycloaddition reaction, affording the expected heterocycles (**3aa**–**3ai**) in high yields and with high diastereoselectivities and excellent enantioselectivities. Both electronic properties (e.g., electron-neutral, -deficient, or -rich) and substitution pattern (e.g., *para*-, *meta*-, or *ortho*-) of the substituted groups on the aromatic ring in *N*-benzoyl hydrazones had little effect on the reactivity and stereoselectivity (Table 3, entries 1–8). In addition, the challenging heteroaromatic 3-pyridyl-substituted *N*-benzoyl hydrazone **2i** also proceeded well with indole **1a**, affording adduct **3ai** in 87% yield and 78% *ee* (entry 9). Alkenyl- and alkyl-substituted hydrazone **2j** and **2k** also worked well, leading to good yields of adducts with 93% *ee* (entries 10 and 11). The generality of hydrazones with different *N*-acyl groups was further investigated under the optimized reaction conditions. Consistently high diastereoselectivity and excellent enantioselectivity were obtained with various substituted *N*-benzoyl groups (entries 12–15). The substrate *N*-thiophene-2-carbonyl hydrazone **2p** also worked well in this transformation, leading to 88% yield and 97% *ee* (entry 16). Noticeably, 96% *ee* and 94% *ee* were achieved even for the challenging *N*-acetyl (**2q**) and *N*-Boc (**2r**) hydrazones (entries 17 and 18); these hydrazones had been shown to be relatively challenging substrates in a previous report.[13] Remarkably, the branched α,α-dichloro hydrazone **2s** was also well tolerated, affording the heterocycle **3as**, which bears three contiguous stereogenic centers, in good yield with exclusive diastereoselectivities and excellent enantioselectivity (entry 19). The absolute configuration of the cycloadducts **3ab** and **3as** was unequivocally determined to be (4a*S*,9a*S*) and (4*S*,4a*S*,9a*S*), based on X-ray diffraction analysis (Figure 1).[17]

To further probe the scalability of this aza-Diels–Alder reaction, we carried out the reaction of 1,3-dimethyl indole **1a** with α-chloro hydrazone **2a** and α,α-dichloro hydrazone **2s** on a gram scale, and the fused indolines **3aa** and **3as** were isolated in good yields with excellent enantioselectivity (Scheme 2). The optically active fused indoline heterocycle **3aa** can be readily elaborated, as shown in Scheme 2. Under

Table 3: Substrate scope of the Cu^{I}-catalyzed aza-Diels–Alder reaction of indole **1a** with various hydrazones **2**.[a]



1a **2** **3** (> 20:1 d.r.)

Entry	R^1	R^2	**2**	**3**	Yield [%][b]	*ee* [%][c]
1	Ph	Ph	**2a**	**3aa**	95	97
2	*p*-BrC_6H_4	Ph	**2b**	**3ab**	86	98
3	*o*-ClC_6H_4	Ph	**2c**	**3ac**	84	99
4[d]	*p*-$CF_3C_6H_4$	Ph	**2d**	**3ad**	82	93
5[d]	*m*-MeC_6H_4	Ph	**2e**	**3ae**	81	94
6	*p*-MeC_6H_4	Ph	**2f**	**3af**	89	98
7	*p*-$MeOC_6H_4$	Ph	**2g**	**3ag**	86	97
8[d]	2-naphthyl	Ph	**2h**	**3ah**	84	93
9[d]	3-pyridyl	Ph	**2i**	**3ai**	87	78
10	PhCH=CH	Ph	**2j**	**3aj**	88	93
11[d]	Me	*o*-$MeOC_6H_4$	**2k**	**3ak**	85	93
12	Ph	*p*-$MeOC_6H_4$	**2l**	**3al**	87	96
13	Ph	*o*-$MeOC_6H_4$	**2m**	**3am**	88	97
14	Ph	*m*-MeC_6H_4	**2n**	**3an**	85	98
15	Ph	*p*-$CF_3C_6H_4$	**2o**	**3ao**	82	95
16	Ph	2-thienyl	**2p**	**3ap**	88	97
17	Ph	Me	**2q**	**3aq**	85	96
18	Ph	O*t*Bu	**2r**	**3ar**	84	94
19			**2s**	**3as**	95	99

[a] All reactions were carried out with **1a** (0.3 mmol) and **2a** (0.5 mmol) in CH_2Cl_2 (4.0 mL). [b] Yield of isolated product. [c] *ee* value was determined by HPLC analysis; >20:1 d.r. was established by ^{1}H NMR analysis of the crude product. [d] α-bromo-*N*-benzoylhydrazone was used.

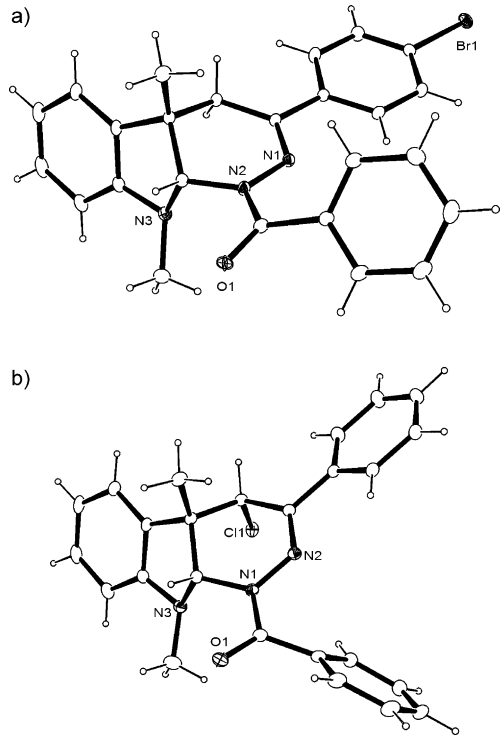
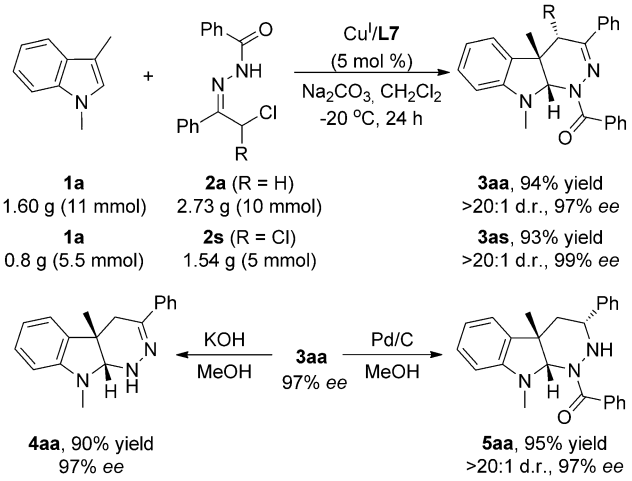


Figure 1. ORTEP representations of (4a*S*,9a*S*)-**3ab** (a) and (4*S*,4a*S*,9a*S*)-**3as** (b).



Scheme 2. Scale-up of catalytic asymmetric azo-Diels–Alder reaction and synthetic transformations of the cycloadduct **3aa**.

basic conditions, the *N*-benzoyl group of **3aa** could be easily removed by hydrolysis to afford **4aa** without loss of diastereo- or enantioselectivity. Direct hydrogenation of **3aa** in the presence of a catalytic amount of Pd/C led to the reduction of the C=N bond, providing compound **5aa** as single isomer in good yield.

In conclusion, we have successfully developed the first catalytic asymmetric inverse-electron-demand aza-Diels–Alder reaction of indoles with in situ formed azoalkenes catalyzed by a Cu^I/*t*Bu-Phosferrox complex. The current method provides facile access to a diverse set of biologically important [2,3]-fused indoline tetrahydropyridazine heterocycles in good yields (up to 97%) with high regioselectivity and diastereoselectivity (>20:1 d.r.), and excellent enantioselectivity (up to 99% *ee*). Mechanistic studies aimed at understanding the origin of the excellent stereoselective control, and further investigation of the substrate scope and synthetic application of this method are ongoing in our laboratory.

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[17] CCDC 971351 (**3ab**) and 979241 (**3as**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

