Aza-Diels–Alder Reactions

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Regio- and Enantioselective Aza-Diels–Alder Reactions of 3-Vinylindoles: A Concise Synthesis of the Antimalarial Spiroindolone NITD609

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Abstract: *An asymmetric aza-Diels–Alder reaction of 3-vinylindoles with isatin-derived ketimines has been developed. A series of spiroindolone derivatives were thus obtained in good to excellent yields with excellent enantioselectivity (up to 96% yield and 99% ee). Furthermore, the antimalarial compound NITD609 could be obtained in three steps with an overall yield of 40.6%. Control experiments and operando IR experiments imply a concerted reaction pathway. The regioselectivity and exo selectivity result from π–π interactions between the two indoline rings of the two reactants.*

Multicyclic 3-spirooxindole alkaloids represent a privileged structural motif that is found in a number of natural products with important biological activities.[1] Spirooxindole-tetrahydro-β-carbolines have been discovered to be potent novel antimalarial leads in an in vivo activity screening.[2] In particular, 1*R*,3*S*-configured spiroindolone NITD609 (Figure 1) stood out from approximately 200 derivatives, and it ideally meets the criteria of a new antimalarial drug.[3] This compound can be synthesized in eight steps; however, the active enantiomer is obtained by expensive separation on a chiral column.[2,3] Asymmetric catalysis is an ideal method for synthesizing these optically active spirocyclic oxindoles, but diastereo- and enantioselective constructions of spirocyclic fused cores and a tertiary carbon center remain a synthetic challenge. Franz and co-workers reported an enantioselective Pictet–Spengler reaction between isatins and 5-methoxytryptamine catalyzed by chiral phosphoric acids.[4] Chiral spirooxindole-tetrahydro-β-carbolines were obtained in high yields, but the substrate scope was limited, and the drug target could not be synthesized by this method. Therefore, more efficient and straightforward asymmetric catalytic strategies are required for the development of an enantioselective synthesis of spiroindolone NITD609.

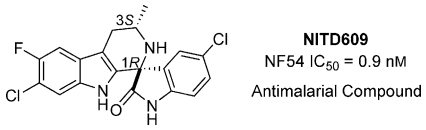
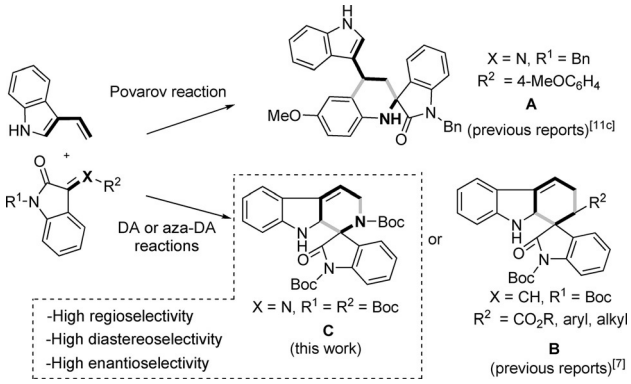


Figure 1. Structure and in vitro activity of spiroindolone NITD609.

3-Vinylindole has been used as a versatile building block for the asymmetric synthesis of heterocycles that bear an indole moiety. It has acted as an electron-rich diene in Diels–Alder reactions with benzoquinones,[5] maleimides,[6] methyleneindolinones,[7] and α,β-unsaturated aldehydes,[8] giving access to carbazole derivatives, and in an intramolecular imino Diels–Alder reaction that afforded (±)-eburnamonine.[9] As a dienophile, it can undergo inverse-electron-demand Diels–Alder reactions with chromone heterodienes.[10] Interestingly, a Povarov reaction or a [2+2+2] domino reaction occurred when *N*-aryl imines were used (Scheme 1 A).[11] In these cases, the vinylindole dienes are more electron-rich at the terminal carbon atom of their exocyclic double bond; therefore, the terminal methylene group of 3-vinylindole acts as a nucleophile and adds to the electron-poor carbon atom of the dienophile. As part of our ongoing efforts to expand the applicability of chiral *N*,*N*′-dioxide metal complexes as catalysts for the synthesis of biologically important molecules, we recently reported an enantioselective nickel(II)-mediated Diels–Alder reaction for the synthesis of carbazolespirooxindoles (Scheme 1 B).[7b] We then pursued the asymmetric synthesis of spirooxindole-tetrahydro-β-carbolines by the cycloaddition of 3-vinylindole and *N*-Boc-protected isatin-derived ketimines[12] (Scheme 1 C), with the notion that the catalyst could activate this



Scheme 1. Povarov and [4+2] cycloaddition reactions of 3-vinylindole. Boc = *tert*-butyloxycarbonyl.

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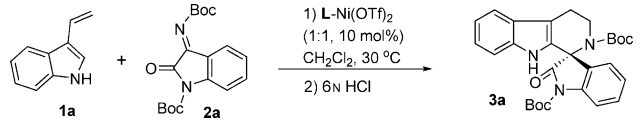
kind of aza dienophile through selectively binding the two carbonyl groups in a bidentate fashion, similar to *N*-Boc-protected methyleneindolinone.[7b] We subsequently found that the installation of two Boc groups on this imine successfully enabled an asymmetric aza-Diels–Alder reaction. Remarkably, 3-vinylindole underwent a cycloaddition in which bonds were formed between the C2 carbon atom of the indole framework and the electron-poor carbon atom of the C=N bond and between the exocyclic terminal carbon atom and the nitrogen atom (Scheme 1C), leading to the formation of the parent structure of spiroindolone NITD609. Herein, we report regio-, diastereo-, and enantioselective aza-Diels–Alder reactions of 3-vinylindoles and their application in the concise synthesis of the antimalarial drug candidate NITD609.

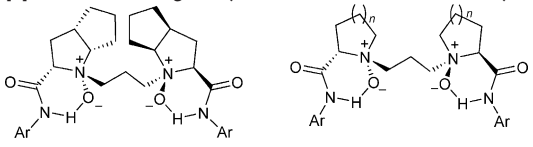
In our preliminary screen, *N*-Boc-protected ketimine **2a**, which is derived from isatin, and 3-vinylindole (**1a**) were selected as the model substrates to evaluate the title reaction (Table 1). When the chiral *N*,*N*′-dioxide ligand L-RaMe$_2$ was

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



Entry	L	*T* [°C]	Yield [%][b]	e.r.[c]
1	L-RaMe$_2$	30	13	68:32
2	L-RaPr$_2$	30	60	89:11
3	L-PrPr$_2$	30	16	80:20
4	L-PiPr$_2$	30	24	78:22
5	L-RaPr$_3$	30	70	92:8
6[d]	L-RaPr$_3$	−10	78	97.5:2.5

[a] Unless otherwise noted, the reactions were performed with **L**/Ni(OTf)$_2$ (10 mol%), **2a** (0.1 mmol), and **1a** (0.15 mmol) in CH_2Cl_2 (1.2 mL) at 30°C for 2 days; then, aq. HCl (6N, 0.2 mL) was added, and the reaction mixture was stirred for 4–6 hours. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phases. [d] At −10°C for eight days. Tf = trifluoromethanesulfonyl.



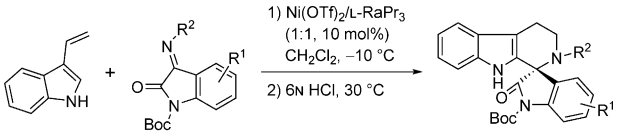
L-RaMe$_2$: Ar = 2,6-Me$_2$C$_6$H$_3$
L-RaPr$_2$: Ar = 2,6-*i*Pr$_2$C$_6$H$_3$
L-RaPr$_3$: Ar = 2,4,6-*i*Pr$_3$C$_6$H$_2$

L-PrPr$_2$: *n* = 1, Ar = 2,6-*i*Pr$_2$C$_6$H$_3$
L-PiPr$_2$: *n* = 2, Ar = 2,6-*i*Pr$_2$C$_6$H$_3$

used in combination with Ni(OTf)$_2$, adduct **C** was formed (Scheme 1). The desired spiroindolone **3a** was obtained through a double-bond shift by treating the reaction mixture with aqueous HCl. However, the reaction proceeded with low reactivity and enantioselectivity; after 48 hours, adduct **3a** was obtained in only 13% yield and 68:32 e.r. (entry 1). Pleasingly, a subsequent evaluation of various chiral ligands led to improvements in terms of both the yield and the enantioselectivity (entries 2–5). The ligand L-RaPr$_3$, which entails *i*Pr substituents at the aniline moiety and an L-ramipril backbone, provided a marked increase to 70% yield and 92:8 e.r. (entry 5). Decreasing the reaction temperature from 30 to −10°C led to the formation of the desired product in 78% yield and 97.5:2.5 e.r. when the reaction time was prolonged (entry 6). Further experiments did not provide any improved results (for details, see the Supporting Information). The exclusion of air and moisture is unnecessary for this process.

With the optimized conditions in hand, we next examined the scope of this transformation with respect to the isatin-derived ketimines **2** (Table 2). Protection of the imine moiety

Table 2: Variation of the isatin-derived ketimine.[a]



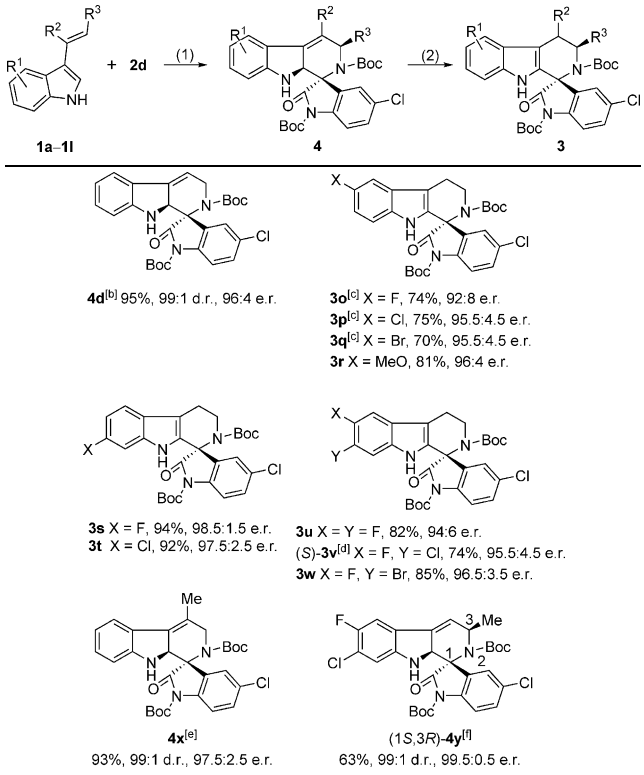
Entry	R^1; R^2	2	Yield [%][b]	e.r.[c]
1[d,e]	H; CO_2Et	**2b**	75 (**3b**)	97:3
2	5-F; Boc	**2c**	94 (**3c**)	95.5:4.5
3	5-Cl; Boc	**2d**	95 (**3d**)	96:4
4	5-Br; Boc	**2e**	95 (**3e**)	95:5
5	5-I; Boc	**2f**	95 (**3f**)	94.5:5.5
6[d]	5-Me; Boc	**2g**	85 (**3g**)	97:3
7[d]	5-MeO; Boc	**2h**	81 (**3h**)	97:3
8	5-CF_3O; Boc	**2i**	90 (**3i**)	95:5
9	5-NO_2; Boc	**2j**	81 (**3j**)	81:19
10	6-Cl; Boc	**2k**	92 (**3k**)	96:4
11	6-Br; Boc	**2l**	96 (**3l**)	96:4
12	4-Br; Boc	**2m**	88 (**3m**)	94.5:5.5
13	7-Br; Boc	**2n**	88 (**3n**)	94.5:5.5

[a] Unless otherwise noted, the reactions were performed with L-RaPr$_3$/Ni(OTf)$_2$ (10 mol%), **2** (0.1 mmol), and **1a** (0.15 mmol) in CH_2Cl_2 (1.2 mL) at −10°C for 4 days; then, aq. HCl (6N, 0.2 mL) was added, and the reaction mixture was stirred for 4–6 hours at 30°C. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] At −10°C for 8 days. [e] The deprotected (R^2) product was obtained (for details, see the Supporting Information).

with a CO_2Et group was tolerated, and the corresponding product was isolated in 75% yield and 97:3 e.r. (entry 1). Ketimines **2c**–**2f**, which bear halide substituents at the C5 position, underwent the aza-Diels–Alder reaction in higher yields than **2g** and **2h**, which entail electron-donating substituents at the same position (entries 2–5 vs. entries 6 and 7), while the enantioselectivities were only slightly affected (94.5:3.5 to 97:3 e.r.). Notably, 5-trifluoromethoxy-substituted ketimine **2i** was also a suitable substrate under the optimized reaction conditions (90% yield and 95:5 e.r.; entry 8). 5-Nitro-substituted substrate **2j** smoothly gave the desired product in 81% yield and 81:19 e.r. (entry 9). Furthermore, halide substituents at the C4, C6, and C7 positions on the isatin backbone were also tolerated, and the corresponding products **3k**–**3n** were afforded in 88–96% yield and 94.5:5.5–96:4 e.r. (entries 10–13).

Next, considering that chloro-substituted spiroindolones are of higher biological activity, we selected 5-chloro-substituted ketimine **2d** as a dienophile for cycloaddition reactions with various 3-vinylindoles (Table 3). 5-Methoxy-3-vinylindole smoothly underwent the aza-Diels–Alder reaction, giving **3r** in 81% yield and 96:4 e.r. 5-Halo-3-vinylindoles displayed high reactivities, and good enantioselectiv-

Table 3: Variation of the 3-vinylindole.[a]



[a] Reaction conditions: 1) L-RaPr$_3$/Ni(OTf)$_2$ (10 mol%), **2d** (0.10 mmol, 1.0 equiv), **1** (1.5 equiv), CH_2Cl_2, −10°C, 4 days; 2) 6N HCl at 30°C for 4–6 h. [b] Results based on analysis of product **3d**. [c] 1) At −30°C for 8 days, 0.10 mmol scale; 2) 6N HCl at 30°C for 4–6 h. [d] 2.0 mmol scale. [e] Without aq. HCl treatment. [f] **1l** (*Z*/*E* = 1:2, 2.5 equiv) at −20°C for 4 days without aq. HCl treatment.

ities were achieved by decreasing the reaction temperature from −10 to −30°C. Notably, 6-halo-3-vinylindoles were also highly efficient in the cycloaddition reactions, and the corresponding products **3s** and **3t** were generated in up to 94% yield and 98.5:1.5 e.r. 5,6-Dihalo-substituted 3-vinylindoles were suitable diene coupling partners for the synthesis of spiroindolones **3u**–**3w**, which were obtained in 74–85% yield and 94:6–96.5:3.5 e.r. The absolute configuration of the product **3v** was confirmed to be *S* by X-ray crystallography.[13] Moreover, 3-propen-2-yl-indole was also a viable substrate, the direct aza-Diels–Alder product **4x** was isolated in 93% yield, 99:1 d.r., and 97.5:2.5 e.r. To our delight, the reaction between 3-propen-1-yl-indole (as an *Z*,*E* mixture) and ketimine **2d** provided *N*-Boc-protected spiroindolone intermediate **4y** in 63% yield, 99:1 d.r., and 99% *ee*. Only *E*-configured 3-propen-1-yl-indole participated under the optimized conditions, giving the adduct **4y** in high diastereoselectivity.

To illustrate the utility of this process for the synthesis of NITD609, a reaction was performed on gram scale. The target 1*R*,3*S* isomer of *ent*-**3y** could be obtained when enantiomeric *ent*-L-RaPr$_3$ was used as the chiral ligand. A high level of selectivity was maintained, and the adduct *ent*-**4y** was obtained in 62% yield, 99:1 d.r., and 99% *ee*. After an acid-promoted 1,3-proton shift and deprotection, optically pure NITD609 could be obtained in an overall yield of 40.6% in three steps (Scheme 2).

To gain information on the reaction mechanism, operando IR experiments were performed to determine the process of the reaction between 3-vinylindole (**1a**) and isatin-derived ketimine **2d** (Figure 2). As the peaks at 1326, 1149, and 1119 cm^{-1}, which are related to the substrates, gradually decreased in intensity, the peak of the cycloaddition intermediate **4d** at 1372 cm^{-1} increased. No additional peaks related to Mannich addition intermediates were detected, indicating that this aza-Diels–Alder reaction proceeded by a concerted pathway. Furthermore, only a trace amount of the adduct of 3-methylindole and ketimine **2a** was detected under the standard reaction conditions (for details, see the Supporting information), excluding a stepwise pathway initiated by a Friedel–Crafts reaction.

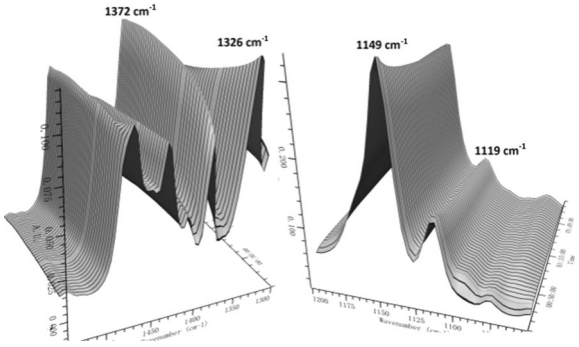
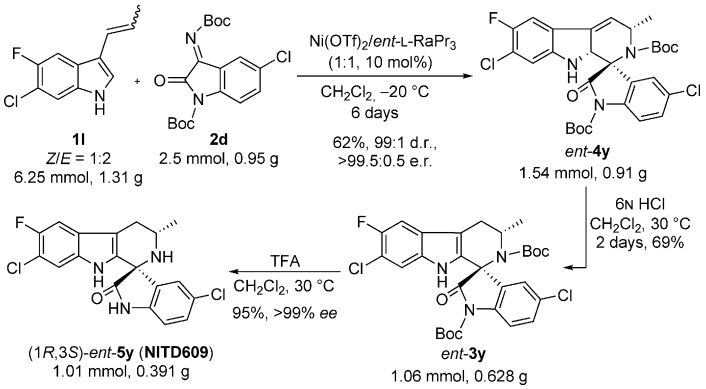


Figure 2. Operando IR experiments.

The regioselectivity and *exo* selectivity with which the aza-Diels–Alder products **4** and **3** were obtained suggest that there are additional interactions between the isatin-derived ketimine and 3-vinylindole. On the basis of the results of the control experiments, operando IR experiments, our previous work,[14] and the absolute configuration of the product **3v**,[13] a possible transition state was proposed. As shown in Figure 3, the L-RaPr$_3$/Ni^{II} complex selectively binds the two carbonyl groups of the *N*-Boc-substituted isatin backbone of **2d**, decreasing the LUMO energy. The π–π interactions



Scheme 2. Concise synthesis of NITD609.

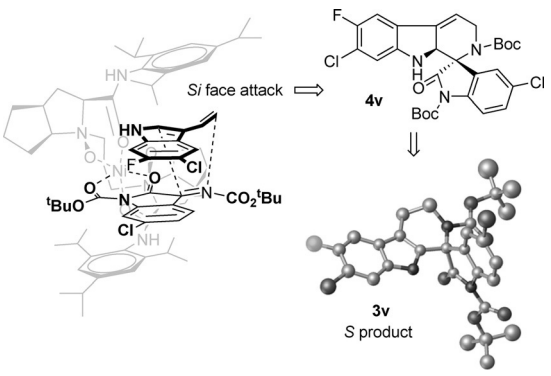


Figure 3. Proposed transition state.

between the two indoline rings of the two substrates and the nucleophilicity of the C2 position of the indole[15] enable the addition of the less-electron-rich C2 carbon atom, rather than the more electron-rich terminal double bond, to the carbon atom of the C=N bond. The 2,4,6-triisopropylaniline group underneath the ligand shields the *Re* face of the ketimine. Therefore, predominant *Si* face attack of 3-vinylindole **1i** results in the formation of product **4v** exclusively in an *exo* fashion. The *S*-configured product **3v** is then obtained by a 1,3-proton shift.

In summary, we have developed a regio-, diastereo-, and enantioselective aza-Diels–Alder reaction of 3-vinylindoles with isatin-derived ketimines. The reaction occurs by formation of a bond between the C2 atom of 3-vinylindole and the carbon atom of the C=N bond, and affords various spirooxindole-tetrahydro-β-carbolines. Excellent enantioselectivities and good yields were obtained by the use of a privileged chiral *N*,*N*′-dioxide $Ni(OTf)_2$ complex as the catalyst. In particular, a direct and highly efficient method for the construction of the antimalarial drug NITD609 has thus been developed. Operando IR experiments and various control experiments imply a concerted reaction pathway, and the regioselectivity and *exo* selectivity are due to π–π interactions between the two indoline rings of the two reactants. Further studies regarding the application of this method for the preparation of biologically relevant molecules are ongoing in our laboratory.

Experimental Section

General procedure for the aza-Diels–Alder reaction of 3-vinylindoles with isatin-derived ketimines: L-$RaPr_3$ (0.01 mmol), $Ni(OTf)_2$ (0.01 mmol), and an isatin-derived ketimine **2** (0.1 mmol) in CH_2Cl_2 (1.0 mL) were stirred at 30 °C for 30 min. The mixture was cooled to −10 °C, then a 3-vinylindole **1** (0.15 mmol, 1.5 equiv) dissolved in CH_2Cl_2 (0.2 mL) was added in one portion. The mixture was stirred at −10 °C for 4 days. Then, 6.0 N HCl (0.2 mL) was added, and the reaction mixture was warmed to 30 °C for 4–6 h. After completion, the desired product **3** was isolated by flash column chromatography (petroleum ether/EtOAc = 10:1).

Acknowledgements

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Keywords: asymmetric catalysis · aza-Diels–Alder reactions · indoles · ketimines · nickel catalysis

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[13] CCDC 1035848 (**3v**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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