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Catalytic Asymmetric Synthesis of Pyrroloindolines via a Rhodium(II)-Catalyzed Annulation of Indoles

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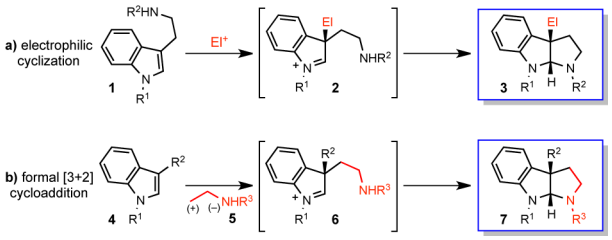
Supporting Information

ABSTRACT: Herein we report the synthesis of pyrroloindolines via a catalytic enantioselective formal [3+2] cycloaddition of C(3)-substituted indoles. This methodology utilizes 4-aryl-1-sulfonyl-1,2,3-triazoles as carbenoid precursors and the rhodium(II)-tetracarboxylate catalyst Rh_2(*S*-PTAD)$_4$. A variety of aryl-substituted pyrroloindolines were prepared in good yields and with high levels of enantioinduction.

Pyrroloindoline alkaloids comprise an important subclass of alkaloid natural products[1] and have exhibited promising activity as potential anti-cancer,[2a,b] anti-nociceptive,[2c] antibiotic,[2d] and anti-inflammatory agents.[2e] Consequently, an array of methods have been developed for the formation of pyrroloindolines.[3] As shown in Scheme 1, the majority of these

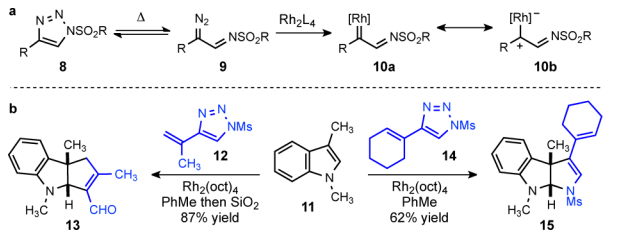
Scheme 1. Synthesis of Pyrroloindolines from Indoles



syntheses utilize indole precursors and can be classified into two distinct reaction pathways. The more ubiquitous of these techniques entails the reaction of a tryptamine precursor (**1**) with a carbon- or heteroatom-based electrophile to induce an intramolecular cyclization of the pendant amine.[4] This process can be rendered asymmetric with a variety of chiral organocatalysts and metal complexes.[5,6] Alternatively, the pyrroloindoline core can be accessed via a formal [3+2] cycloaddition of an indole (**4**) with an intermediate that exhibits dipole-like reactivity (**5**).[7] This complementary approach can provide access to pyrroloindoline products (**7**) with substitution patterns that are inaccessible from tryptamines. While both of these reaction classes enable diversification at the bridgehead position of the pyrroloindoline core, substitution of the pendant pyrrolidine ring cannot be readily achieved.

In 2010 our group reported a method for a Rh(II)-catalyzed annulation of indoles to provide indoline derivatives via a formal [3+2] cycloaddition with carbenoids derived from vinyl diazoacetates.[8] In our recent attempts to extrapolate this chemistry to Rh(II)-bound carbenoids derived from 4-vinyl-1-sulfonyl-1,2,3-triazoles we found that the reaction of triazole **12** with 1,3-dimethyl indole (**11**) provides the expected indoline product **13** (Scheme 2) after hydrolysis of the resultant *N*-

Scheme 2. Reaction of 1,3-Dimethylindole with 4-Vinyl-1-sulfonyl-1,2,3-triazoles



sulfonylimine.[9] However, we were surprised to find the corresponding reaction of triazole **14** provides pyrroloindoline **15**, wherein the imine of the Rh(II)-bound carbenoid has participated in a cycloaddition with the indole core.[10]

We recognized that this serendipitous discovery could offer a new and complementary approach for the synthesis of pyrroloindoline products via a formal [3+2] cycloaddition of indoles and the formal dipole **10b**. The novelty of this transformation, in conjunction with the potential for synthesizing uniquely substituted pyrroloindoline architectures, prompted us to develop this reaction into a convergent method for the enantioselective synthesis of pyrroloindoline products from 4-aryl-1-sulfonyl-1,2,3-triazoles and C(3)-substituted indoles.

Our preliminary reaction development was conducted with 4-phenyl-1-(methanesulfonyl)-1,2,3-triazole **16a** and an excess of 1,3-dimethyl indole (**11**, 5.0 equiv) in the presence of 1.0 mol % Rh_2(*S*-PTAD)$_4$[11a] (**18**, Table 1). Polar solvents such as chloroform and 1,2-dichloroethane, which are the optimal solvents for most of the reactions of carbenoids derived from 1-sulfonyl-1,2,3-triazoles,[9] proved ineffective for this transformation (entries 1−4). However, the use of nonpolar hydrocarbon solvents provides substantially improved yields of pyrroloindoline **17a** with uniformly high levels of enantioinduction (entries 5−7). When cyclohexane was employed as the reaction solvent, pyrroloindoline **17a** was obtained in 81% isolated yield and 94% ee (entry 7). An examination of other chiral Rh(II)-tetracarboxylate catalysts demonstrated that Rh_2(*S*-PTAD)$_4$ is the optimal catalyst for this transformation.

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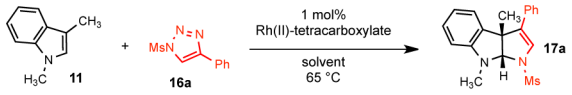
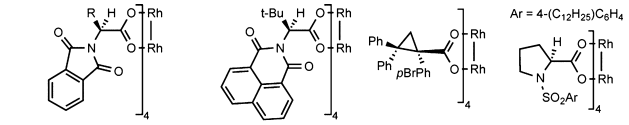
Table 1. Optimization of Pyrroloindoline Formation[a,b]



entry	catalyst	solvent	yield (%)[c]	ee (%)[d]
1	Rh_2(*S*-PTAD)$_4$	$CHCl_3$	0	n.a.
2	Rh_2(*S*-PTAD)$_4$	EtOAc	0	n.a.
3	Rh_2(*S*-PTAD)$_4$	$PhCF_3$	0	n.a.
4	Rh_2(*S*-PTAD)$_4$	1,2-DCE	12	82
5	Rh_2(*S*-PTAD)$_4$	toluene	41	92
6	Rh_2(*S*-PTAD)$_4$	heptane	54	94
7	*Rh_2(S-PTAD)$_4$*	*cyclohexane*	*81*	*94*
8[e]	Rh_2(*S*-PTAD)$_4$	cyclohexane	36	92
9[f]	Rh_2(*S*-PTAD)$_4$	cyclohexane	0	n.a.
10	Rh_2(*S*-PTTL)$_4$	cyclohexane	63	94
11	Rh_2(*S*-NTTL)$_4$	cyclohexane	0	n.a.
12	Rh_2(*S*-DOSP)$_4$	cyclohexane	61	-8
13	Rh_2(*S*-BTPCP)$_4$	cyclohexane	18	-13

[a]Reactions run with 5.0 equiv of indole **11** unless otherwise indicated. [b]Products formed in >20:1 dr as determined by ^{1}H NMR of crude reaction mixture. [c]Isolated yields. [d]Determined by HPLC analysis. [e]2.5 equiv of indole **11**. [f]1.0 equiv of indole **11**.

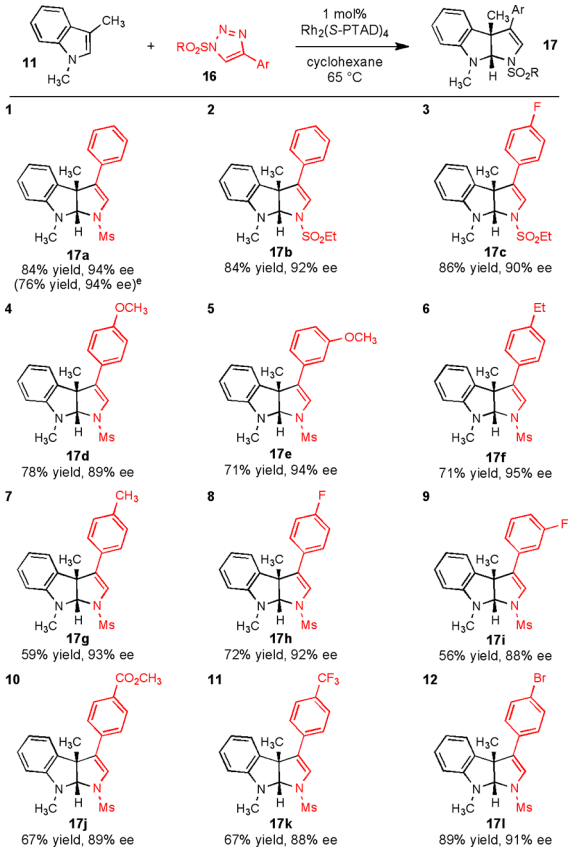


Rh_2(*S*-PTTL)$_4$[11b] provided a similar level of enantioinduction but a significantly lower yield of **17a** (entry 10), while the bulkier Rh_2(*S*-NTTL)$_4$[11c] and Rh_2(*S*-BTPCP)$_4$[11d] catalysts were ineffective (entries 11 and 13). Rh_2(*S*-DOSP)$_4$[11e] (entry 12) gave a moderate yield of **17a** with a low level of enantioinduction.

Having developed optimized reaction conditions for the synthesis of pyrroloindoline **17a**, we subsequently explored the scope of this transformation with respect to the triazole coupling partner. As shown in Table 2, a broad range of triazoles (**16**) react to provide the corresponding pyrroloindoline products in good yield and with high levels of enantioinduction. Electron-donating and -withdrawing substituents in the *para* (entries 3, 4, 6–8, 10–12, 59–89% yield, 88–95% ee) or *meta* (entries 5 and 9, 56–71% yield, 88–94% ee) position of the aryl ring are compatible with this transformation. The use of 1-(ethanesulfonyl)-1,2,3-triazole derivatives also provides the corresponding pyrroloindoline products in good yield and with high levels of enantioselectivity (entries 2 and 3, 84–86% yield, 90–92% ee). However, the reaction was found to be sensitive to steric effects and the use of bulkier 1-sulfonyl-1,2,3-triazoles (e.g., 1-Ts) fails to provide any of the desired product. This reaction also proceeds well on a large scale (5.0 mmol triazole **16**, entry 1, 76% yield, 94% ee). The absolute stereochemistry of compound **17b** was established by X-ray crystallography and extended to the other pyrroloindoline products by analogy.[12]

As illustrated in Table 3, this enantioselective pyrroloindoline formation is applicable to a range of C(3)-alkyl indoles (**23**). An evaluation of substituents on the indolic nitrogen revealed that N–H and *N*-allyl indoles are both compatible with this transformation, although the products were formed with a much lower level of enantioselectivity (entries 2 and 3, 62–64% yield, 37–80% ee) than the corresponding *N*-methyl product (entry 1, 100% yield, 92% ee). However, bulkier (TBS, Bn) or electron-withdrawing (e.g., Ts, CO_2Me, Boc) groups on the indolic nitrogen are not tolerated. An array of electron-rich

Table 2. Scope of Triazole Component[a–d]



[a]Reactions run with 5.0 equiv of indole **11**. [b]Products formed in >20:1 dr as determined by ^{1}H NMR of crude reaction mixture. [c]Isolated yields. [d]ee determined by HPLC analysis after purification. [e]Reaction conducted on 5.0 mmol scale.

(entries 5–8, 73–97% yield, 86–94% ee) and electron-deficient indoles (entries 1 and 4, 96–100% yield, 92–93% ee) substituted at C(5)–C(7) of the indolic core also provide the corresponding pyrroloindoline products in excellent yields and with high levels of enantiomeric excess. In contrast to the parent 1,3-dimethyl indole (**11**), indole substrates that are substituted on the aryl ring can be used in an equimolar ratio with respect to the triazole coupling partner with only a slight depreciation in yield. For example, with 1.0 equiv of the indole coupling partner, pyrroloindoline **24a** was isolated in 86% yield and 92% ee (e.g., Table 3, entries 1, 4–7; compare to Table 1, entries 8 and 9). We attribute this improved chemoselectivity to a steric deactivation of the aniline motif in the product pyrroloindolines toward reaction with an electrophilic Rh(II)-bound carbenoid.[13]

Indoles with bulkier C(3)-substituents are also competent substrates in this transformation (entries 9–12). C(3)-ethyl and C(3)-butyl indoles react to provide the corresponding pyrroloindoline products in good yield and with high levels of enantioinduction (entries 9 and 10, 75–81% yield, 91–92% ee). While 3-phenyl-1-methylindole provides **24k** in modest yield (entry 11, 49%, 89% ee), substitution of the aryl ring substantially augments the yield of the desired product **24l** (entry 12, 72%, 89% ee). With these more hindered substrates the use of 1-(methanesulfonyl)-1,2,3-triazoles is critical; the use of bulkier 1-(ethanesulfonyl)-1,2,3-triazoles leads to both low

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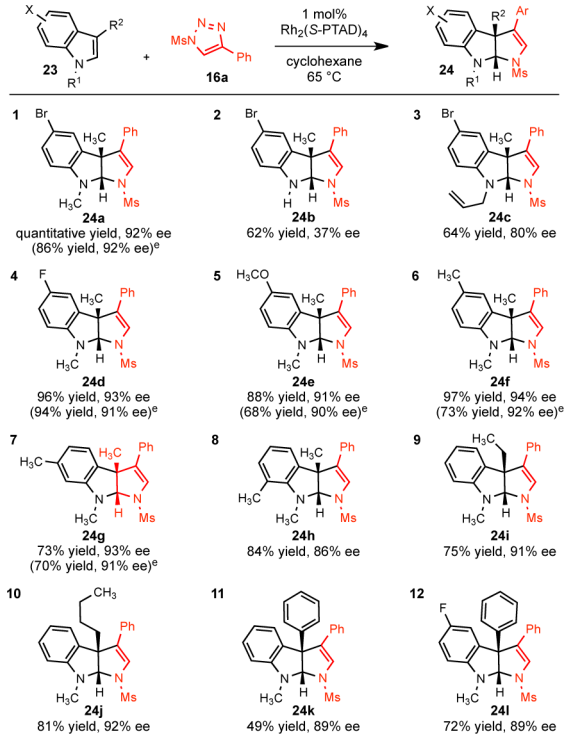
Table 3. Scope of Indole Substrate[a−d]

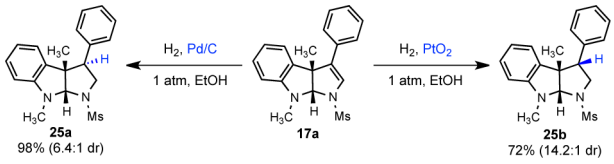


[a]Reactions run with 5.0 equiv of indole **23** unless otherwise indicated. [b]Products formed in >20:1 dr as determined by ^{1}H NMR of crude reaction mixture. [c]Isolated yields. [d]ee determined by HPLC analysis after purification. [e]1.0 equiv of indole **23**.

yields (<15%) and poor levels of enantioselectivity for the desired products.

Stereodivergent transformation of the pyrroloindoline products to the corresponding saturated compounds can be achieved via transition metal-catalyzed hydrogenation. As shown in Scheme 3, hydrogenation of pyrroloindoline **17a**

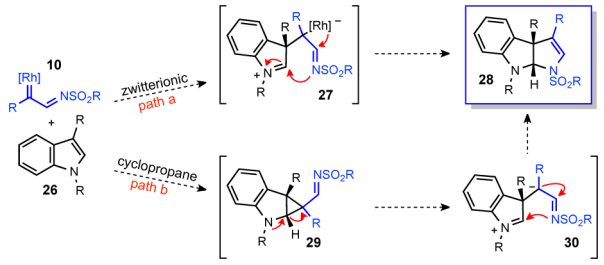
Scheme 3. Stereodivergent Hydrogenation



with Pd/C proceeds selectively from the concave face to provide **25a** (98% yield, 6.4:1 dr). However, the use of Pt_2O provides the diastereomeric product, **25b** (72% yield, 14.2:1 dr), wherein the hydrogenation reaction has occurred selectively from the convex face of **17a**.[14]

Electron-rich *N*-alkyl indoles are generally proposed to react with electrophilic Rh(II)-bound carbenoids via a zwitterionic-type pathway due to substantial polarization of the C(2)−C(3) olefin (Scheme 4, path a). In these reactions, the regioselectivity of the indole toward a Friedel−Crafts-type substitution is generally dictated by the steric bulk of the Rh(II)-bound carbenoid, which can overcome the standard electronic bias of the heterocycle. As such, C(3)-unsubstituted indoles generally undergo reaction at C(3), while C(3)-substituted indoles will react at C(2) with Rh(II)-bound carbenoids.[15] We observed this effect in our 2010 report of a

Scheme 4. Proposed Mechanistic Pathways



Rh(II)-catalyzed cyclization of indoles to indolines via a formal [3+2] cycloaddition reaction, wherein the regioselectivity of the annulation was controlled by C(2)- or C(3)-substitution of the indole core.[8] While indoles that bear an electron-withdrawing group on the indolic nitrogen (e.g., Boc, CO_2Me, Ts) have been reported to undergo a concerted cyclopropanation of the C(2)−C(3) alkene with Rh(II)-bound carbenoids to provide isolable cyclopropylindolines, their intermediacy in reactions with electron-rich indoles is less established.[4o−r,7e] However, the abnormal regioselectivity and the strong solvent effect observed in this transformation have led us to speculate that this reaction occurs via an initial cyclopropanation of the C(2)−C(3) bond of the indole (**29**, Scheme 4, path b). Subsequent ring opening of the strained cyclopropylindoline intermediate and recombination would provide the observed pyrroloindoline (**28**).[16]

In conclusion, we have developed a method for the catalytic enantioselective synthesis of pyrroloindoline architectures via the union of C(3)-substituted indoles and the Rh(II)-bound carbenoids derived from 4-aryl-1-sulfonyl-1,2,3-triazoles. The pyrroloindoline products synthesized in this manner are uniquely substituted and can be stereodivergently hydrogenated. As such, we envision that this methodology will enable the synthesis of a novel class of pyrroloindoline alkaloids for biological studies. Additional experiments and computational studies to further elucidate the mechanism of this transformation are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Procedures, characterization, and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(14) The relative stereochemistry of **25a** and **25b** was assigned by NOE studies (Supporting Information) and X-ray crystallography of **25a**. This crystal structure has been deposited in the Cambridge Database (CCD927318).
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(16) We suspect that a concerted [3+2] cycloaddition would be disfavored due to steric repulsion. A related mechanism was proposed by Fox and co-workers. DeAngelis, A.; Shurtleff, V. W.; Dmitrenko, O.; Fox, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 1650−1653.