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Rh_2 (*S*-biTISP)$_2$-Catalyzed Asymmetric Functionalization of Indoles and Pyrroles with Vinylcarbenoids

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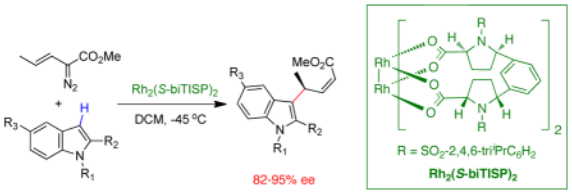
Abstract



Asymmetric functionalization of *N*-heterocycles by vinylcarbenoids in the presence of catalytic amounts of Rh_2 (*S*-biTISP)$_2$ has been successfully developed. This bridged dirhodium catalyst not only selectively enforces the reaction to occur at the vinylogous position of the carbenoid, but also, affords high levels of asymmetric induction.

Asymmetric methods for the selective functionalization of indoles or pyrroles are in great demand[1] because these electron-rich heterocycles are constituents of many natural products and pharmaceutical agents.[2] The most widely used approach has been the conjugate addition of heterocycles to α,β-unsaturated carbonyl compounds using chiral transition-metal catalysts[3] or organocatalysts.[4] An alternative approach has been to use carbenoid intermediates.[5] We have demonstrated that chiral 4-substituted indoles can be generated in a cascade sequence involving a combined C—H functionalization/Cope rearrangement.[5a] Fox[5b] and Hashimoto[5g] have shown that the electrophilic substitution reactions of methyl 2-diazoalkanoate generate chiral 3-substituted indoles with high levels of asymmetric induction. In this paper we describe an alternative carbenoid approach for the asymmetric synthesis of 3-substituted indoles by exploiting the vinylogous electrophilic character of vinylcarbenoids (Scheme 1). This transformation occurs with substrates that are too sterically crowded to react with the carbenoid site of the vinylcarbenoid

We have recently described the functionalization of electron rich heterocycles using 2-diazo-3-pentenoates as the carbenoid source.[6] These reactions proceed by attack of the heterocycles at the vinylogous position of the vinylcarbenoid.[6,7] Vinylogous reactivity of the carbenoid is more pronounced in *Z*-vinylcarbenoids than *E*-vinylcarbenoids.[6] For example, the reaction of *Z*-2-diazopentenoate **1a** with 1,2,5-trimethylpyrrole (**2**) gave the vinylogous alkylation product **3** in 78% yield exclusively (Scheme 2), whereas the major product from the reaction with the *E*-2-diazopentenoate **1b** with **2** was **4**, derived from electrophilic attack at the carbenoid center.[6] The objective of the current study was to identify suitable chiral catalysts that enable the application of this unusual vinylogous reactivity to the asymmetric functionalization of electron rich heterocycles.

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Supporting Information Available. Full experimental data, X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

We initiated this study by exploring the enantioinduction by some of the standard chiral dirhodium catalysts that have been developed for the reactions of vinyldiazoacetates (Figure 1).[8] The alkylation of indole **5** with *Z*-vinyldiazoacetate **1a** was used as the standard screening reaction and the results are summarized in Table 1. All the catalysts in our study produced the alkylation product **6** in excellent yields (up to 93%). The two most versatile chiral catalysts for the asymmetric transformations of donor/acceptor carbenoids, Rh_2(*S*-PTAD)$_4$ (**7**) and Rh_2(*S*-DOSP)$_4$ (**8**), failed to give high levels of asymmetric induction in the test reaction. The more bulky catalysts Rh_2(*S*-TISP)$_4$ (**9**) gave slightly higher enantioselectvity than Rh_2(*S*-DOSP)$_4$ (26% ee vs 10% ee) but the bulky and conformationally constrained catalyst Rh_2(*S*-biTISP)$_2$ (**10**)[9] gave 0% ee.

Having failed to achieve high levels of asymmetric induction with the *Z*-vinyldiazoacetate **1a**, we decided to re-explore the possibility of using *E*-vinyldiazoacetate **1b** as an effective reagent for vinylogous reactivity. Recently, we calculated that the *s-cis* configuration (conformer **B**) of *Z*-vinyldiazoacetates is sterically unfavorable.[10] In contrast *E*-vinyldiazoacetates exist as equilibrating mixture of *s-trans* and *s-cis* conformers (conformers **C** and **D**) (Figure 2). On the basis of the reactivity patterns we have observed to date,[6,10] we propose that carbenoids in s-*trans* configurations (conformers **A** and **C**) are more likely to display vinylogous reactivity than carbenoids in s-*cis* configurations (conformers **B** and **D**). The double bond geometry of the products derived from vinylogous reactivity is indicative of the reacting conformation of the carbenoid.[6] Thus, the reaction of Z-vinyldiazoacetate with indole **5** proceeds through the s-*trans* conformer, leading to the formation of Z-**6**. Donor/acceptor carbenoids are known to be sensitive to steric effects, and if the nucleophile is sterically demanding, reactions at the vinylogous position of the carbenoid are enhanced.[7c] We, therefore, hypothesized that it would be possible to enhance the vinylogous reactivity of *E*-vinyldiazoacetates by re-enforcing the s-*trans* conformation of the carbenoid through the use of highly bulky catalysts.

In order to explore this hypothesis, three standard achiral catalysts and four chiral catalysts were screened in the rhodium(II)-catalyzed decomposition of the (*E*)-vinyldiazoacetate **1b** with 1,2-dimethylindole **5** (Table 2). These reactions afforded variable mixtures of three products (**6, 11** and **12**). Products **6** and **11** arise from the vinylogous reactivity of the *s-trans* and *s-cis* conformers of the vinylcarbenoid, respectively. Product **12** is derived from attack of the heterocycle at the carbenoid center and could, in principle, be derived from reaction with either conformer of the vinylcarbenoid. The product ratio is dependent on the catalyst structure. While the sterically less crowded catalysts Rh_2(OAc)$_4$ and Rh_2(OAc)$_4$ give considerable amounts of **11** and **12** (entries 1,2), the bulkier catalysts Rh_2(esp)$_4$, Rh_2(*S*-PTAD)$_4$, Rh_2(*S*-TISP)$_4$ and Rh_2(*S*-biTISP)$_2$ show a strong preference for the formation of **6** (entries 3,4,6,7). Most notable is the comparison between Rh_2(*S*-DOSP)$_4$, which gives near equimolar amounts of the three compounds (entry 5), and Rh_2(*S*-TISP)$_4$, which gives about a 8:1 preference for **6** over the two other products (entry 6). Furthermore, in the Rh_2(*S*-biTISP)$_2$ catalyzed reaction, **6** is isolated in 66% yield (after purification) and in 89% ee (entry 7).

The Rh_2(*S*-biTISP)$_2$-catalyzed asymmetric vinylogous alkylation is applicable to a range of substituted indoles as illustrated in Figure 3. The desired transformation was observed for all substrates tested and the (*Z*)-pent-2-enoates **13–24** were produced in 48–86% yields with good levels of enantioselectivity (82–95% ee). Protected and unprotected 2-methylindoles are both effective in producing the vinylogous alkylation products, although increasing the size of the protecting group enhanced the asymmetric induction slightly (compare **13**, **6**, **14–16**). This transformation was also successful with 2-methylindoles bearing different functionalities on the 5-position. However, 3-substituted indoles did not results in an efficient transformation. Good yields and excellent enantioselectivities were achieved with

indoles containing bulky groups at the 2-position, such as TMS and pinacol boronate ester (**23** and **24**). The generation of **23** and **24** may offer the opportunity for further functionalization. The absolute configuration of **17** was unambiguously assigned by X-ray crystallography[11] and the other products were assigned by analogy.

This reaction can be extended to pyrrole derivatives as shown in Figure 4. Due to the decreased reactivity of pyrroles, the reaction was conducted at −20 °C instead of −45 °C.[12] Even so, the alkylation products **25–27** were obtained in good yield with high levels of enantioselectivity (87–91% ee). The absolute configuration of these products was assigned by analogy to the absolute configuration of **17**.

In conclusion, the Rh_2(*S*-biTISP)$_2$-catalyzed asymmetric vinylogous alkylation between *N*-heterocycles and methyl *E*-2-diazo-3pentenoate is an effective method for C-3 functionalization of indoles and pyrroles. This work illustrates the subtle controlling elements of dirhodium catalysts on the chemistry of donor/acceptor carbenoids.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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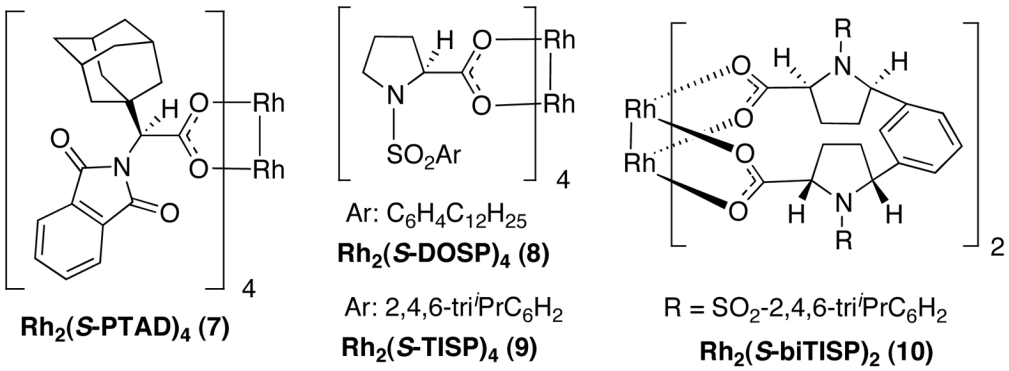


Figure 1.
Chiral dirhodium catalysts

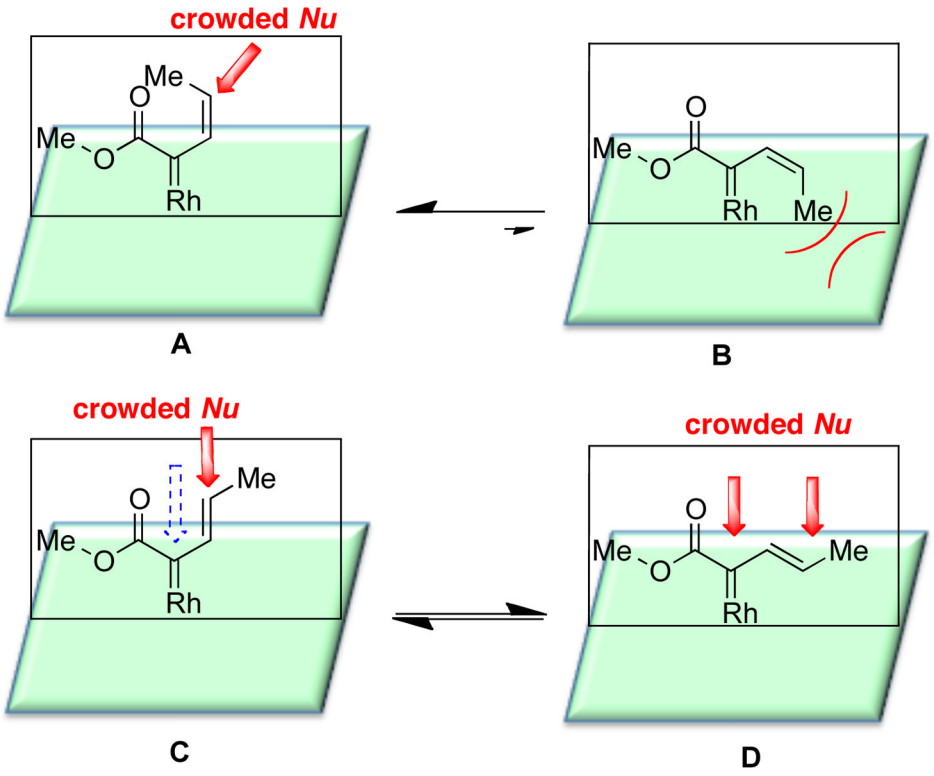


Figure 2.
Steric influence on the conformation and reactivity of vinylcarbenoids

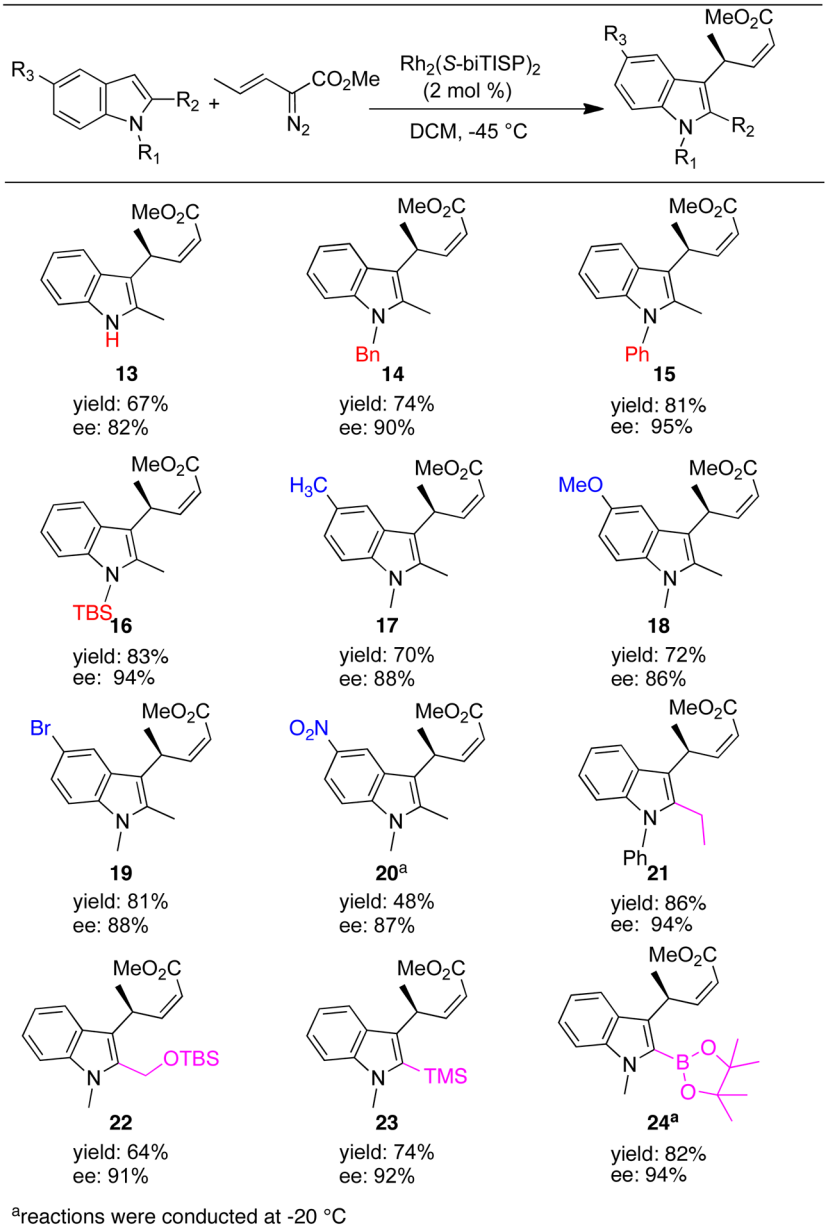


Figure 3.
Substrate scope of asymmetric vinylogous reactivity
[a]reactions were conducted at −20 °C

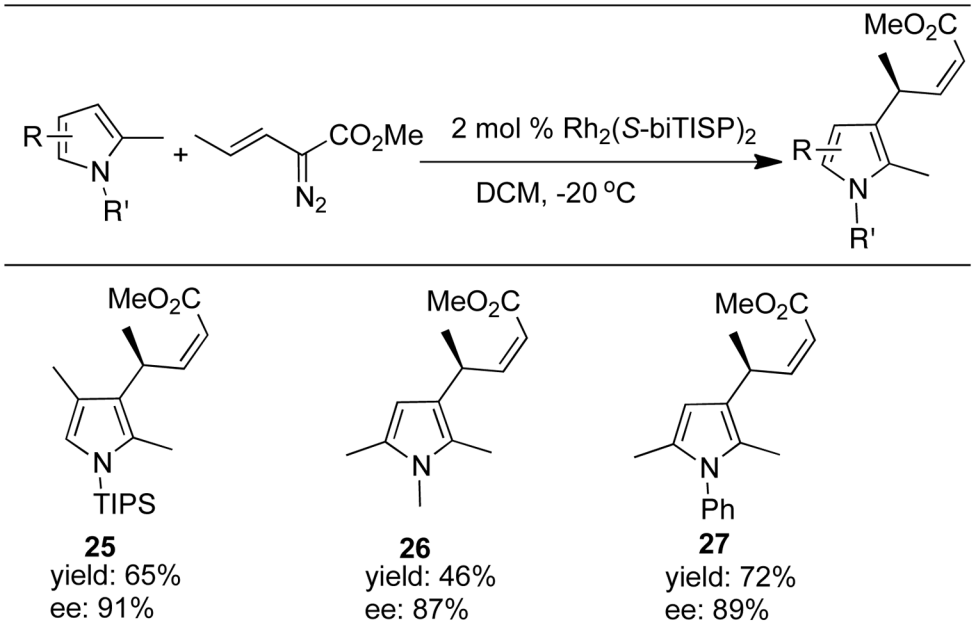
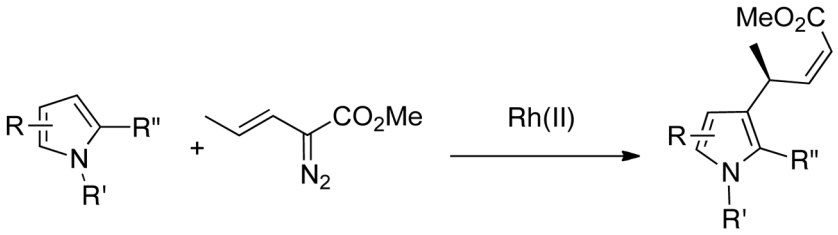
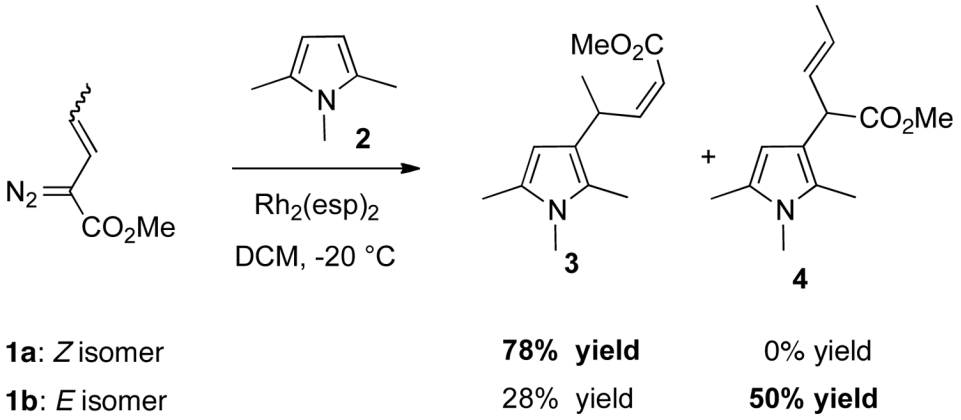


Figure 4.
Scope of asymmetric vinylogous reactivity with pyrroles



Scheme 1.



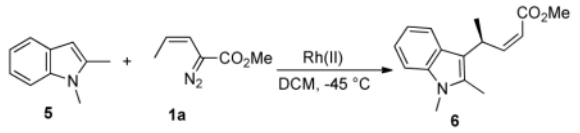
1a: *Z* isomer **78% yield** 0% yield

1b: *E* isomer 28% yield **50% yield**

Scheme 2.

Table 1

Asymmetric alkylation of indole **5** by *Z*-vinyldiazoacetate **1a**

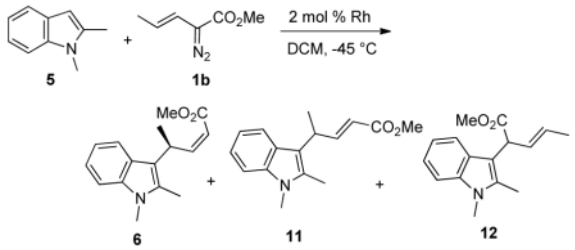


entry	catalyst	yield (%)	ee (%)[a]
1	Rh_2(*S*-PTAD)$_4$	88	48
2	Rh_2(*S*-DOSP)$_4$	93	−10
3	Rh_2(*S*-TISP)$_4$	84	−26
4	Rh2(*S*-biTISP)$_2$	90	0

[a]Negative value indicates opposite asymmetric induction.

Table 2

Asymmetric alkylation of indole 5 with *E*-vinyldiazoacetate **1b**



entry	catalyst	ratio[a] of 6/11/12	yield[b] of 6 (%)	ee of 6 (%)
1	$Rh_2(OAc)_4$	62/33/5	57	---
2	$Rh_2(TFA)_4$	49/44/7	43	---
3	$Rh_2(esp)_2$	74/26/0	52	---
4	Rh_2(*S*-PTAD)$_4$	76/16/8	55	−8
5	Rh_2(*S*-DOSP)$_4$	26/38/36	22	17
6	Rh_2(*S*-TISP)$_4$	**89**/6/5	66	39
7	Rh_2(*S*-biTISP)$_2$	**88**/9/3	66	89

[a] ratio was the average of two runs and determined from the ^{1}H NMR of the crude reaction mixture.

[b] isolated yield