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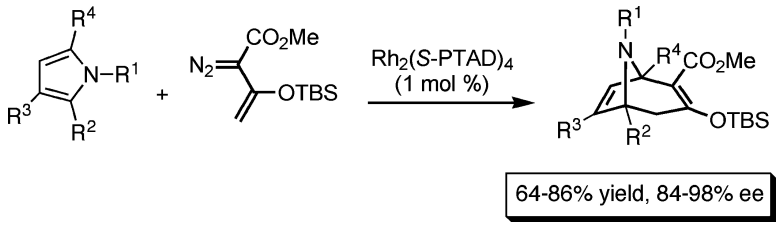

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Asymmetric Synthesis of Tropanes by Rhodium-Catalyzed [4 + 3] Cycloaddition

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The 8-azabicyclo[3.2.1]octane framework (tropane) is common in a wide range of natural products[1] and pharmaceutical agents.[2] Synthetic methods to tropanes have a long history[3] and is still a very active field.[4] [4 + 3] Cycloadditions between pyrroles and 3-carbon electrophiles offer direct entries to tropanes, and considerable efforts have been expended to render these reactions enantioselective.[5,6] The most broadly explored approach has been the reaction of allyl cations with pyrroles,[5] while we have developed the tandem cyclopropanation/Cope rearrangement (TCCR) between vinylcarbenoids and pyrroles.[6]

Early studies on the use of chiral catalysts for an enantioselective entry to tropanes using the TCCR sequence were not very promising.[6] Even though the dirhodium tetraprolinates, Rh_2(*S*-TBSP)$_4$ and Rh_2(*S*-DOSP)$_4$ (Figure 1), are exceptional in a range of vinylcarbenoid reactions,[7] their application to tropane synthesis with the vinyldiazoacetate **2** has been disappointing.[6] Due to their highly electrophilic nature, side products derived from zwitterionic intermediates, such as **5** and **6**, dominated the reaction (Scheme 1).[6] Introduction of a 2-siloxy substituent onto the vinylcarbenoid eliminated the formation of the side products,[6] but the dirhodium tetraprolinates gave low levels of enantioselectivity with this type of vinylcarbenoid.[8] An effective TCCR sequence to form tropanes was eventually achieved using chiral auxiliaries,[6] but this is not as desirable as a successful outcome using a chiral catalyst.

The impetus for this study came from Müller's observation that Rh_2(*S*-NTTL)$_4$ is capable of highly enantioselective intermolecular cyclopropanations with a 2-(siloxyvinyl)diazoacetate.[9] We have shown that dirhodium catalysts containing an adamantyl group rather than a *tert*-butyl group give higher levels of enantioselectivity in certain carbenoid reactions.[10] In this paper, we describe that the adamantyl glycine-derived catalyst Rh_2(*S*-PTAD)$_4$ is very effective for the enantioselective synthesis of tropanes.

The Rh_2(*S*-PTAD)$_4$-catalyzed reaction of vinyldiazoacetate **2** with *N*-Boc-pyrrole (**7**) eliminated the formation of zwitterionic side products, but carbenoid trimerization[11] to form **9** became a major side reaction. The optimum conditions with 10 equiv of *N*-Boc-pyrrole gave the tropane **8** in 58% yield and 65% ee (Scheme 2).The reaction of *N*-Boc-pyrrole (**7**) with the 2-(siloxy)vinyldiazoacetate **10** gave much better results (Table 1). As expected, Rh_2(*S*-DOSP)$_4$ gave low enantioselectivity (31% ee), but much higher levels were obtained with Hashimoto's catalyst, Rh_2(*S*-PTTL)$_4$[12] (88% ee) and Rh_2(*S*-NTTL)$_4$[9] (85% ee). The enantioselectivity was further improved to 91% ee when Rh_2(*S*-PTAD)$_4$[10] was used as catalyst. Rh_2(*S*-DOSP)$_4$ gave the same sense of asymmetric induction as the other catalysts, which is opposite to that observed in previous studies.[10] The room temperature reactions were relatively low yielding due to low conversions, but when the reaction was conducted at 50 °C, the yield of **11** was 86%. The reaction can be conducted with the pyrrole **7** as the limiting agent, which offers the opportunity to extend the reaction to elaborate pyrroles. 2,2-Dimethylbutane was used as solvent, but as the pyrrole is a reactive trapping agent, hexanes can also be used.

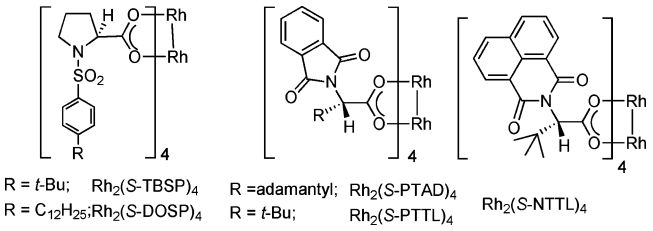
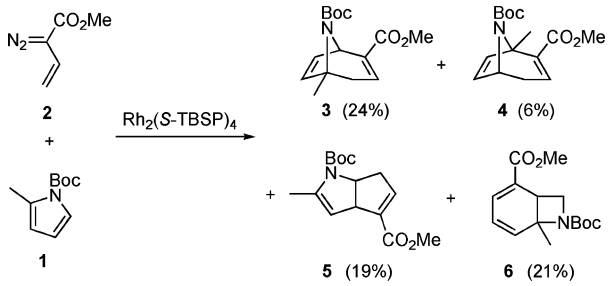
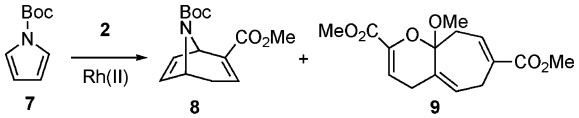


Figure 1. Chiral dirhodium catalysts.

Scheme 1



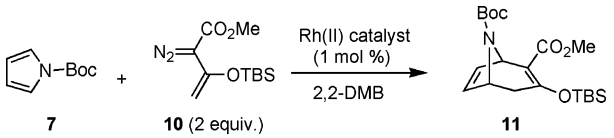
Scheme 2



catalyst	**7:2** ratio	**8:9** ratio	**8** yield (%)	**8** ee (%)
Rh_2(*S*-PTAD)$_4$	1:2	1:2	19	64
Rh_2(*R*-PTAD)$_4$	10:1	4:1	58	65 (-)

The Rh_2(*S*-PTAD)$_4$-catalyzed reaction with **10** is applicable to a range of substituted pyrroles. Under the standard reaction conditions

Table 1. Catalyst Evaluation Studies



catalyst	temp (°C)	yield (%)	ee (%)
Rh_2(*R*-DOSP)$_4$	23	31	(−) 29
Rh_2(*S*-NTTL)$_4$	23	25	85
Rh_2(*S*-PTTL)$_4$	23	34	88
Rh_2(*S*-PTAD)$_4$	23	38	91
Rh_2(*S*-PTAD)$_4$	50	86	92
Rh_2(*S*-PTAD)$_4$	69[a]	81	85

[a] Reaction was performed in hexane. 2,2-DMB = 2,2-dimethylbutane.

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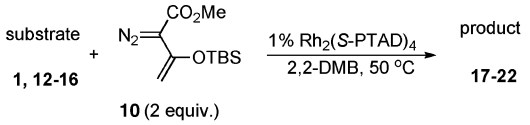
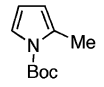
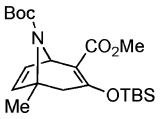
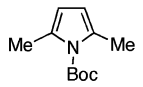
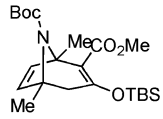
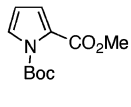
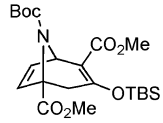
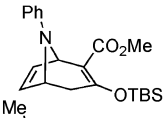
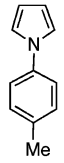
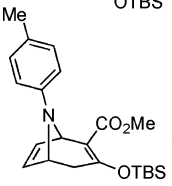
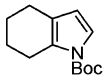
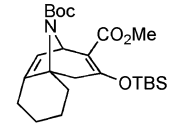
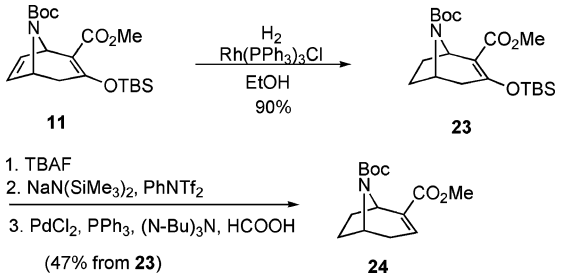
Table 2. Enantioselective Synthesis of Tropanes



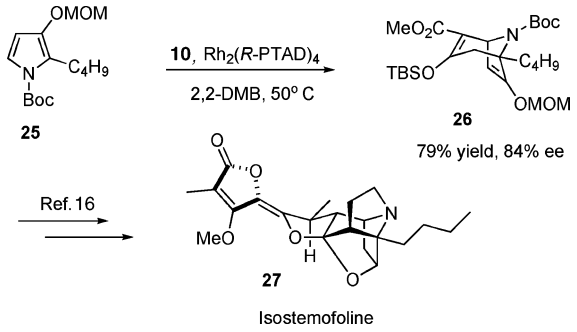
substrate		product		yield (%)	ee (%)
	**1**		**17**	69	96
	**12**		**18**	72	98
	**13**		**19**	71	89
	**14**		**20**	64	97
	**15**		**21**	68	94
	**16**		**22**	76	91

Scheme 3



(1 mol % of catalyst, 2,2-dimethylbutane (DMB) as solvent, 50 °C), *N*-Boc and *N*-phenyl-substituted pyrroles are compatible with this chemistry. 2-Substituted, 2,3- and 2,5-disubstituted pyrroles also resulted in good yields of tropane products with excellent levels of enantioselectivity (Table 2). The value of this chemistry is illustrated by the ready conversion of **11** to the tropane **24** (Scheme 3), an important intermediate used in the synthesis of biologically active tropanes.[2,6,13] Comparison of the optical rotation of **24** confirmed that the absolute configuration of **24** is (1*R*,5*S*).[6,14] The absolute configuration of the other tropanes is assigned by assuming an analogous chiral influence by the catalyst in each case and with the expectation that the non-synchronous cyclopropanation initiates at the C-3 position of the pyrrole.[6,15]An enantioselective version of a key step used by Kende and Smalley in the synthesis of (±)-isostemofoline[16] further illustrates the potential of this chemistry. Rh_2(*R*-PTAD)$_4$-catalyzed TCCR of the pyrrole **25** with the 2-(siloxy)vinyldiazoacetate **10** generated the highly functionalized tropane **26** in 79% yield and 84% ee (Scheme 4). In conclusion, we have reported a novel methodology for the asymmetric synthesis of tropanes from the Rh_2(*S*-PTAD)$_4$-catalyzed decomposition of a 2-(siloxy)vinyldiazoacetate in the presence of pyrroles. The reaction proceeds via a tandem cyclopropanation/Cope rearrangement mechanism, resulting in good yields of the tropanes with high asymmetric induction. The further application of this chemistry to the synthesis of novel pharmaceutical targets is currently in progress.

Scheme 4



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Supporting Information Available: Full experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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