Enantioselective Synthesis of D-*threo*-Methylphenidate

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Methylphenidate (Ritalin) is the most commonly prescribed psychotropic medication for children in the United States.[1] It is currently marketed as a racemate, although the D-*threo* isomer is ca. 13 times more active than its mirror image.[2] Various strategies for the preparation of the more active isomer of methylphenidate have been examined, including resolution[3] and synthesis from scalemic precursors.[4] We report herein that the rhodium-mediated C−H insertion reaction of methyl phenyldiazoacetate **1** with N-Boc-piperidine **2** (R = N-Boc) leads to a remarkably efficient and highly stereoselective process for the formation of the bioactive isomer of methylphenidate **3** (Scheme 1).[5,6]

The pioneering work of Doyle has established that scalemic ligands on rhodium can lead to high levels of enantioselectivity in the C−H insertion reaction.[5,7] While the intramolecular C−H insertion pathway in our recently disclosed diastereoselective synthesis of methylphenidate[8] was not sensitive to metal catalysis,[9] we are delighted to report that the *intermolecular* C−H insertion reaction proceeds in the presence of the Doyle catalyst Rh_2(5R-MEPY)$_4$[10] with exceedingly high levels of stereochemical control.[11] Reaction of methyl phenyldiazoacetate **1**[12] with N-Boc-piperidine **2**[13] (R = N−Boc) in the presence of 1 mol % of Rh_2(5R-MEPY)$_4$ leads to the selective formation of D-*threo*-methylphenidate in 94% de and 69% ee.[14] Two recrystallizations of the crude product from ethanol/diethyl ether gave D-*threo*-methylphenidate in 95% de and >95% ee.

Scheme 1

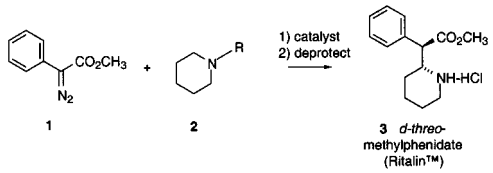
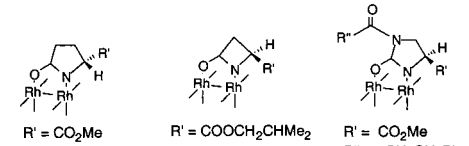
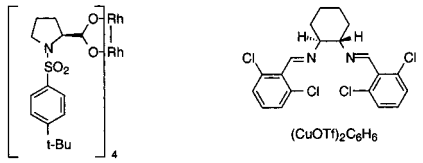


Table 1

Catalyst	Temp (0 °C)		de	ee
4, Rh_2(5R-MEPY)$_4$	50	R=Boc	94	69 (95[a])
5, Rh_2(4S-IBAZ)$_4$	50	R=Boc	85	26
6, Rh_2(4S-MPPIM)$_4$	90	R=Boc	10	16
7	50	R=Boc	5	30
8	-40	R=Boc	39	18
4	80	R=Cbz	63	45
4	60	R=Alloc	64	53



4 Rh_2(5R-MEPY)$_4$ **5** Rh_2(4S-IBAZ)$_4$ **6** Rh_2(4S-MPPIM)$_4$



7 **8**

[a] The initially observed 69% ee was increased to >95% by two recrystallizations from 1:1 v/v diethyl ether/ethanol.

The effect of varying both the catalyst employed and the protecting group on the piperidine nitrogen on the stereochemical outcome of the C−H insertion reaction was next examined, and our results are summarized in Table 1. Both the Rh_2(IBAZ)$_4$ **5**[15] and the Rh_2(MPPIM)$_4$ **6**[16] catalysts led to attenuated diastereo- and enantioselectivities. Similarly, the McKervey proline sulfonamide catalyst **7**[17] gave only modest diastereoselectivity and enantioselectivity. Finally, the Jacobsen catalyst **8**, which has recently been reported to effect highly enantioselective Si−H insertion,[18] led to only modest stereoselection in this reaction.

The stereoselective formation of the D-*threo* stereoisomer of methylphenidate **3** with Rh_2(5R-MEPY)$_4$ **4** can be rationalized as shown in Figure 1. The carbene can coordinate to the rhodium

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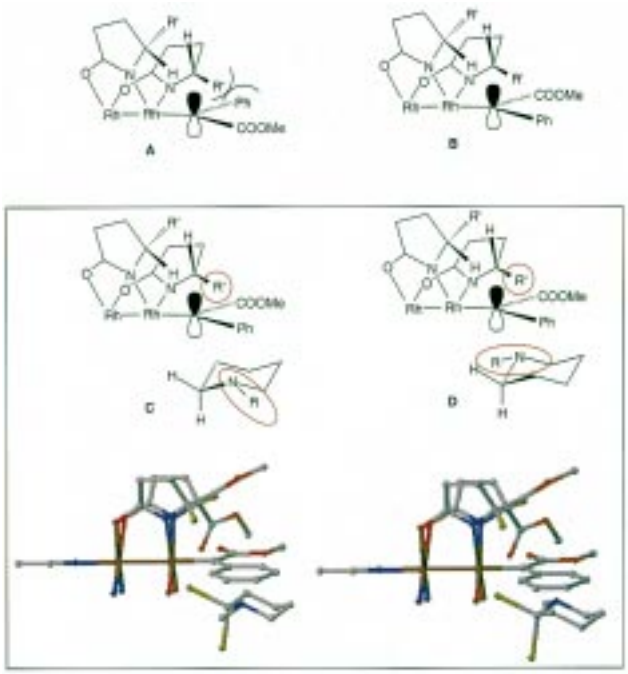

Figure 1.

as indicated in either A or B, and the orientation shown in B minimizes the interaction between the phenyl ring and the indicated ester moiety (R′) on the pyrrolidine ring.[19] Approach of the equatorial C−H bond of the N-Boc piperidine[20] to the carbene can occur as shown in either C or D, in which the protected piperidine nitrogen is oriented away from or toward the carbomethoxy group on the indicated pyrrolidinone ring as shown in C and D, respectively. Support for this model for the reaction of **1** and **2** is obtained by decreasing the size of R, the nitrogen protecting group (see Table 1, R = Cbz or Alloc), which leads to an attenuation of the stereoselectivity of the insertion reaction. It is interesting to note that reaction of N-Boc-diethylamine with methyl phenyldiazoacetate **1** in the presence of Rh_2(5R-MEPY)$_4$ **4** occurs in a stereorandom manner, indicating that the more highly ordered six-membered ring substrate is critical to the stereoselectivity of the reaction.

These results establish a highly stereoselective and efficient pathway for the synthesis of methylphenidate in scalemic form. Further studies on the generality of both the enantioselectivities and diastereoselectivities that have distinguished this work are currently in progress, and our results will be reported in due course.

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Supporting Information Available: Synthetic procedures and spectroscopic data for the preparation of D-*threo*-methylphenidate (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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