Highly Regio-, Diastereo-, and Enantioselective C−H Insertions of Methyl Aryldiazoacetates into Cyclic N-Boc-Protected Amines. Asymmetric Synthesis of Novel C_2-Symmetric Amines and *threo*-Methylphenidate

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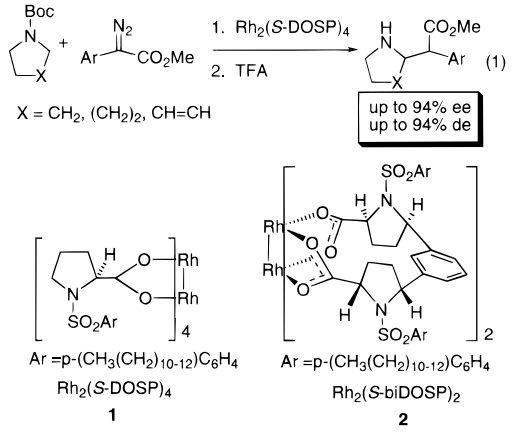
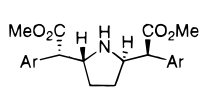
The development of selective methods for asymmetric C−H activation is a challenging goal in organic synthesis.[1] Metal-stabilized carbenoid intermediates have been impressively used for intramolecular asymmetric C−H activation,[2] but the intermolecular version of this reaction is not generally considered to be synthetically useful.[2,3] We have previously communicated that Rh_2(*S*-DOSP)$_4$ (**1**)[4]-catalyzed decomposition of aryldiazoacetates results in asymmetric C−H insertion into cyclohexane and tetrahydrofuran.[5] This was the first report of enantioselective intermolecular C−H insertion using metal carbenoid intermediates. In this paper we describe that highly regio-, diastereo-, and enantioselective C−H insertions of aryldiazoacetates into cyclic N-BOC-protected amines can be achieved (eq 1).[6] The catalyst that was used in most of this study was Rh_2(*S*-DOSP)$_4$ (**1**), but in one case, the novel Rh_2(*S*-biDOSP)$_2$ (**2**) catalyst[7] was used.



The potential of this chemistry is illustrated by means of a two-step asymmetric synthesis of a novel class of C_2-symmetric amines (**3**)[8] and of *threo*-methylphenidate (Ritalin) (**4**).[9] C_2-Symmetric amines are especially useful in organic synthesis,[8] and the direct approach to highly elaborate C_2-symmetric amines described here is likely to be of great interest. *threo*-Methylphenidate is an important pharmaceutical agent that is used in racemic form for the treatment of attention deficit disorders.[9] Considering that, within the last year, two fairly lengthy asymmetric syntheses (eight and nine steps) of *threo*-methylphenidate have been reported,[10,11] the two-step asymmetric synthesis reported herein should be of considerable value.



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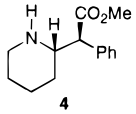

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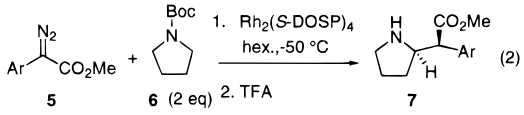
In the original study on asymmetric C−H insertion into cycloalkanes and tetrahydrofuran, high levels of enantioselectivity were achieved.[5] In the current study with N-BOC-protected cyclic amines, we discovered that high diastereoselectivity is also feasible in intermolecular C−H insertions, although the issues that control the diastereoselectivity in these reactions are subtle. Rh_2(*S*-DOSP)$_4$-catalyzed (1% of catalyst) decomposition of **5a** in the presence of N-BOC-pyrrolidine (**6**, 2 equiv) in hexane at −50 °C results in the formation of the C−H insertion product **7a** in 94% ee and 92% de (eq 2). The C−H insertion into N-BOC-pyrrolidine is a general process that can be extended to a range of aryldiazoacetates. In all cases, the diastereoselectivity and the enantioselectivity in these reactions are greater than 90% de and 90% ee, respectively.[12]



5 **6** (2 eq) **7**

	Ar	yield, %	ee, %	de,%
a	Ph	72	94	92
b	p-Cl-Ph	70	94	94
c	p-Me-Ph	67	93	94
d	2-Naphthyl	49	93	92

The next issue that was examined was whether a second C−H insertion was a feasible process. These reactions were carried out

(1) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154.

(2) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp 112−162.

(3) For representative examples of intermolecular C−H insertions, see: (a) Scott, L. T.; DeCicco, G. J. *J. Am. Chem. Soc.* **1974**, *96*, 322. (b) Ambramovitch, R. A.; Roy, J. *J. Chem. Soc., Chem. Commun.* **1965**, 542. (c) Adams, J.; Poupart, M.-A.; Greainer, L.; Schaller, C.; Quimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749. (d) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688. (e) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *Bull. Soc. Chim. Belg.* **1984**, *93*, 945. (f) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Mol. Catal.* **1988**, *49*, L13. (g) Callott, H. J.; Metz, F. *Tetrahedron Lett.* **1982**, *23*, 4321. (h) Callott, H. J.; Metz, F. *Nouv. J. Chim.* **1985**, *9*, 167.

(4) Davies, H, M. L. *Aldrichim. Acta* **1997**, *30*, 107.

(5) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075.

(6) The majority of this Communication was presented previously: Davies, H. M. L.; Hodges, L. M.; Hansen, T. Asymmetric synthesis of heterocycles using rhodium-stabilized carbenoids. *Abstracts of Papers*, 216th National Meeting of the Americal Chemical Society, Boston, MA, August 23−27, 1998; ACS: Washington, DC, 1998; ORGN 254.

(7) Davies, H. M. L.; Panaro, S. A. *Tetrahedron Lett.*, submitted.

(8) (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161. (b) Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581. (c) Takahata, H.; Kouno, S.; Momose, T. *Tetrahedron: Asymmetry* **1995**, *6*, 1085.

(9) For racemic syntheses of **4**, see: (a) Pannizon, L. *Helv. Chim. Acta* **1944**, *27*, 1748. (b) Deutsch, H.; Shi, Q.; Gruaszecka-Kowalik, E.; Schweri, M. *J. Med. Chem.* **1996**, *39*, 1201. (c) Axten, J. M.; Krim, L.; Kung, H. F.; Winkler, J. D. *J. Org. Chem.* **1998**, *63*, 9628.

(10) Thai, D. L.; Sapko, M. T.; Reiter, C. T.; Bierer, D. E.; Perel, J. M. *J. Med. Chem.* **1998**, *41*, 591.

(11) Prashad, M.; Kim, H.-Y.; Lu, Y.; Liu, Y.; Har, D.; Repic, O.; Blacklock, T. J.; Giannousis, P. *J. Org. Chem.* **1999**, *64*, 1750.

(12) The diastereoselectivity for the formation of **7** was determined from the ^{1}H NMR of the crude amine after extraction and removal of solvent. The yields for **7a,c**−**e** represents the amount of crystalline hydrochloride salt that was obtained after treatment of the crude amine with ethereal HCl. The yield of **7b** represented the pure amine after purification by column chromatography. The enantioselectivity was determined by conversion of the crude amine to its trifluoroacetamide derivative, followed by chiral HPLC or GC analysis. The relative stereochemistry of **7c** was readily determined by conversion of **7c** to a fused β-lactam, in which the cis arrangement of the two protons in the β-lactam ring was assigned on the basis on a distinctive coupling (J = 5.1 Hz) and NOE experiments (Coulton, S.; Gilchrist, T. L.; Graham, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1193). The absolute stereochemistry of **7a** was determined to be (2*S*,2′*R*) using the Mosher amide method developed by Hoye (Hoye, T. R.; Renner, M. K. *J. Org. Chem.* **1996**, *61*, 8489).

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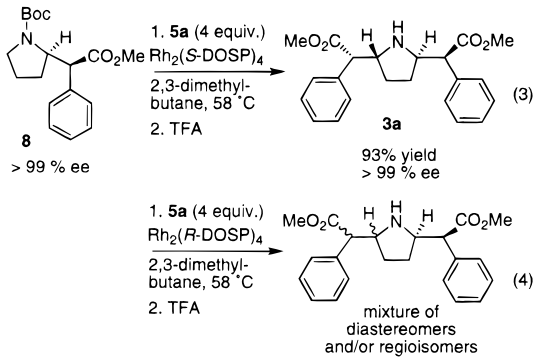
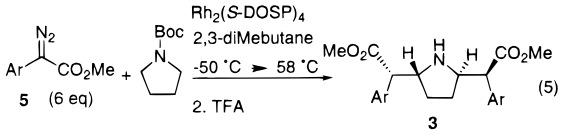
on enantiomerically pure **8**, which was obtained from **7a** that was first recrystallized as its hydrochloride salt to obtain enantiomerically pure material and then treated with $(BOC)_2O$. Reaction of **8** with the phenyldiazoacetate **5a** (4 equiv) using $Rh_2(S\text{-DOSP})_4$ as catalyst in 2,3-dimethylbutane as solvent resulted in the formation of **3a** in 93% yield (eq 3). The compound was shown to be C_2-symmetric because in the ^{13}C NMR only nine signals were apparent, yet the compound was chiral, which rules out the meso diastereomer. In contrast, reaction of **8** with excess **5a** using $Rh_2(R\text{-DOSP})_4$ as catalyst resulted in the formation of a mixture of diastereomers and/or regioisomers that were not resolvable (eq 4).



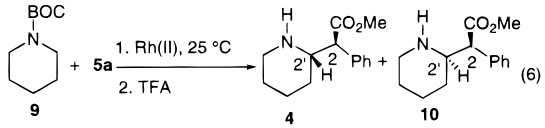
Further experimentation demonstrated that the C_2-symmetric amines could be formed in a single step. $Rh_2(S\text{-DOSP})_4$-catalyzed decomposition of **5a** (1.5 equiv) at −50 °C in the presence of N-BOC-pyrrolidine, followed by heating of the mixture under reflux and addition of a further 4.5 equiv of **5a**, generated the C_2-symmetric amine **3a** in 78% yield and 97% ee (eq 5). Similar bis C−H insertion reactions were possible with aryldiazoacetates **5b**−**e**, leading to the formation of the amines **3b**−**e**. These amines are appropriately functionalized for further conversion by ester reduction or Grignard addition to highly functionalized and potentially useful C_2-symmetric bases. Further studies to evaluate the synthetic utility of such C_2-symmetric bases are in progress.

If a similar reaction would be feasible with N-BOC-piperidine,



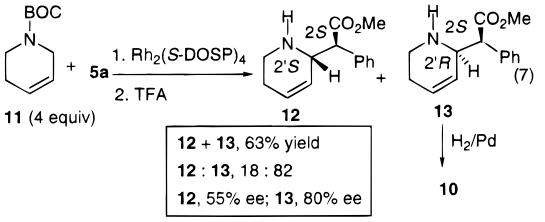
	Ar	yield, %	ee, %
a	Ph	78	97
b	p-Cl-Ph	50	96
c	p-Me-Ph	51	96
d	2-Naphthyl	62	88
e	p-MeO-Ph	40	97

a very direct asymmetric synthesis of *threo*-methylphenidate would be achieved. $Rh_2(S\text{-DOSP})_4$ (**1**)-catalyzed decomposition of methyl phenyldiazoacetate (**5a**) in the presence of N-BOC-piperidine (**9**, 4 equiv) in 2,3-dimethylbutane at room temperature, followed by treatment with trifluoroacetic acid, resulted in the formation of a mixture of *threo*- and *erythro*-methylphenidate, **4** and **10**, in 49% yield.[13,14] However, the threo isomer **4** was the minor diastereomer and was formed in only 34% ee. The combined yield of **4** and **10** could be improved to 86% by using N-BOC-piperidine as the limiting agent. This result is very different from what was observed with N-BOC-pyrrolidine, which gave bis C−H insertion when an excess of phenyldiazoacetate was used. A major improvement in enantioselectivity and diastereoselectivity was possible by carrying out the reaction with the $Rh_2(S\text{-biDOSP})_2$ (**2**) catalyst.[7] The ratio of **4**:**10** (73% yield) was improved to 2.5:1, and (2*R*, 2′*R*)-threo isomer **4** was formed in 86% ee and 52% isolated yield. It is well established that $Rh_2(S\text{-biDOSP})_2$ (**2**) results in opposite asymmetric induction to $Rh_2(S\text{-DOSP})_4$,[7] and in the reaction of **5a** and **9** catalyzed by **2**, the biologically active enantiomer of *threo*-methylphenidate is formed.



Rh(II)	equiv. of **9**	**4**+**10** yield, %	**4**:**10** ratio	**4** ee, %	**10** ee,%
1	4.0	49	43:57	34 (2*S*)	81 (2*S*)
1	0.25	86	50:50	25 (2*S*)	79 (2*S*)
2	0.25	73	71:29	86 (2*R*)	65 (2*R*)

Access to the erythro diastereomer of methylphenidate was achieved by carrying out the reaction with tetrahydropyridine **11** as illustrated in eq 7. $Rh_2(S\text{-DOSP})_4$-catalyzed decomposition of **5a** in the presence of **11** (4 equiv) in 2,3-dimethylbutane at room temperature, followed by treatment with TFA, resulted in a 63% yield of C−H insertion products **12** and **13**. Remarkably, the erythro diastereomer **13** was the major diastereomer (62% de) and was isolated in 53% yield and 80% ee. Determination of the relative and absolute stereochemistry of **13** as (2*S*, 2′*R*) was readily achieved by conversion of **13** to *erythro*-methylphenidate **10**[10] by catalytic hydrogenation.



In summary, the reaction of cyclic N-BOC-protected amines with aryldiazoacetate catalyzed by $Rh_2(S\text{-DOSP})_4$ or $Rh_2(S\text{-biDOSP})_2$ is an attractive method for the asymmetric synthesis of elaborate chiral amines. The synthetic utility of this method was demonstrated by means of a two-step asymmetric synthesis of a novel class of C_2-symmetric amines and of *threo*-methylphenidate. These studies demonstrate that the intermolecular C−H insertions with aryldiazoacetates can be achieved with high diastereoselectivity in addition to high enantioselectivity. These studies also demonstrate that these carbenoids are especially selective toward C−H insertions into methylene groups adjacent to amide nitrogen functionality.[15] The combination of regioselectivity and stereoselectivity exhibited in these reactions would indicate that aryldiazoacetate C−H insertions offer tremendous opportunities in organic synthesis. Further studies to explore the full scope of this chemistry and to determine the factors that control the diastereoselectivity in these reactions are underway.

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Supporting Information Available: Full experimental data for compounds **3**, **4**, **7**, **10**, and **13** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Winkler and co-workers have described at the 217th ACS Meeting in Anaheim, CA, March 21−25, 1999 (Organic Division Paper No. 142) that decomposition of **5a** in the presence of N-BOC-piperidine using Doyle's $Rh_2(MEPY)_4$ catalyst generates *threo*-methylphenidate in 45% yield and 69% ee.

(14) The absolute stereochemistry of **4** and **10** was determined by comparison of the optical rotation with the literature values (ref 10).

(15) For examples of intramolecular C−H insertions of aryldiazoacetates into pyrrolines, see: Lim H. J.; Sulikowski, G. A. *J. Org. Chem.* **1995**, *60*, 2326.