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Kinetic Resolution and Double Stereodifferentiation in Catalytic Asymmetric C–H Activation of 2-Substituted Pyrrolidines

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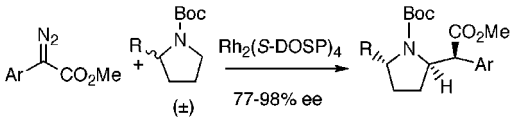
ABSTRACT

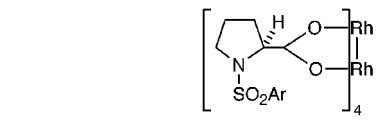


Dirhodium tetrakis(*S*-(*N*-dodecylbenzenesulfonyl)prolinate) (Rh_2(*S*-DOSP)$_4$) catalyzed decomposition of methyl aryldiazoacetates in the presence of 2-substituted pyrrolidines results in highly diastereoselective and enantioselective C–H insertions. These reactions can proceed with impressive levels of double stereodifferentiation and kinetic resolution, which allows for three stereocenters to be controlled during the C–H insertion step.

In recent years there has been considerable interest in the development of new methods for catalytic C−H activation.[1] One particularly attractive method is the C−H insertion by metal carbenoid intermediates.[2] The intramolecular version of this reaction is well established and has been elegantly used in a number of total syntheses.[2] Recently, the rhodium carbenoids derived from aryldiazoacetates have been demonstrated to be exceptional at intermolecular C−H insertion.[3,4] A notable example is the Rh_2(*S*-DOSP)$_4$ catalyzed reaction of *N*-BOC pyrrolidine which leads to a highly regio- and stereoselective C−H activation (Scheme 1).[3d] This reaction can be considered as a surrogate for an asymmetric Mannich reaction.[5]

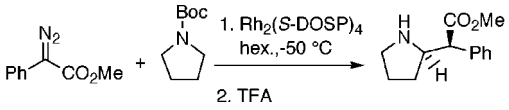
In this Letter we describe that impressive double stereodifferentiation and kinetic resolution can occur during the catalytic asymmetric C−H insertion step (Scheme 2).[6] This allows for three or even four stereocenters to be controlled during the C−H insertion. These studies highlight the remarkable stereoselectivity that is possible in the reactions of aryldiazoacetates and offer considerable promise for their utilization in organic synthesis.

Scheme 1



Ar = *p*-($C_{12}H_{25}$)C_6H_4

Rh_2(*S*-DOSP)$_4$



72% yield, 94% ee, 92% de

(1) (a) Shilov, A. E.; Shul′pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Arndtsen, B. A.; Bergman, R. G.; Mobley, T. A.; Peterson, T. H. *Acc. Chem. Res.* **1995**, *28*, 154. (c) Waltz, K. M.; Hartwig, J. F. *Science* **1997**, *277*, 211.

(2) (a) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp 133−162. (b) Lim, H.-J.; Sulikowski, G. A. *J. Org. Chem.* **1995**, *60*, 2326.

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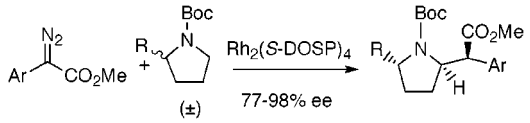
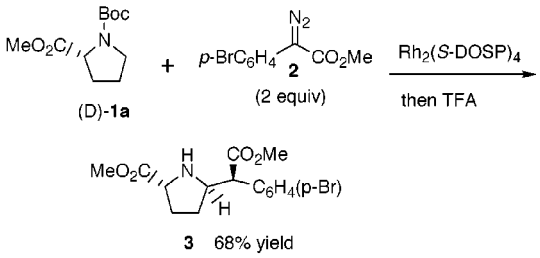
Scheme 2



To evaluate the effect of double stereodifferentiation on the C−H activation, the reaction of both D and L proline methyl ester (**1**) with methyl *p*-bromophenyldiazoacetate (**2**) was examined. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of **2** (2 equiv) in the presence of D-**1a** in 2,2-dimethylbutane as solvent at 50 °C resulted in a very clean transformation (Scheme 3). After removal of the BOC group with TFA,

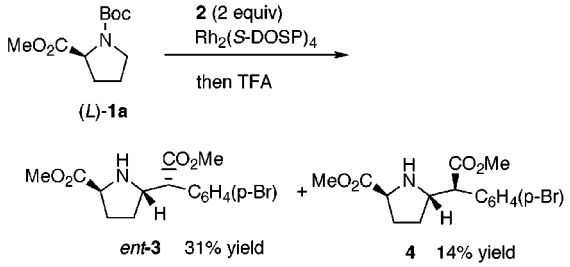
Scheme 3



the C−H insertion product **3** was formed as a single diastereomer in 68% yield. The relative configuration of **3** was determined from NOE studies and distinctive chemical shifts for the C-4 methylene proton,[7] and this was confirmed by X-ray crystallography.

In contrast to the above result, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of **2** with L-**1a** generated a mixture of C−H insertion products (Scheme 4). A mixture of *ent*-**3** (31% yield) and the second diastereomer **4** (14% yield) is formed. The structure of **4** was determined on the basis of distinctive ^{1}H NMR chemical shifts and NOE studies. It is well-established

Scheme 4



that the Rh_2(*S*-DOSP)$_4$-catalyzed C−H insertions on *N*-BOC-pyrrolidine generate the (*S*) configuration at the stereogenic center formed at the original carbenoid site.[3d] Thus, the reaction with D-**1a** is the matched reaction, while the reaction with L-**1a** is the mismatched reaction.

A predictive model has been developed to determine the expected relative and absolute stereochemistry of these C−H insertions (Figure 1). The C−H insertion is considered to

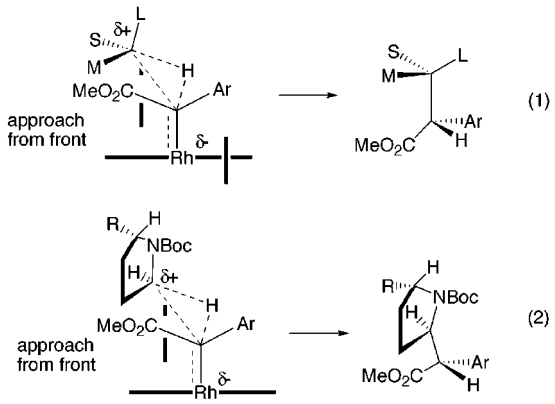


Figure 1. Predictive stereochemical models.

be a concerted and nonsynchronous process, occurring over the position of the ester group.[3,4] Although the actual orientation of the substrates is not known, the arrangement shown here, in which the alkane approaches from the front with the large group (L) pointing up and away from the catalyst, the medium group (M) pointing forward of the catalyst, and the small group (S) points backward toward the catalyst, has been successful in predicting the relative stereochemistry of these reactions (eq 1). The extension of this model to the matched reaction of 2-substituted pyrrolidines is shown in eq 2. The reaction with the D-pyrrolidine derivatives is correctly predicted to be the matched reaction and leads to the observed stereochemistry. In the mismatched case, the pyrrolidine substituent would interfere with the site of C−H insertion. This leads to low-yielding reactions and unexpected stereochemistry as was seen with L-**1a**, which generated ***ent*-3**.

The matched reaction with a series of 2-substituted pyrrolidines was then examined as summarized in Table 1.

(3) (a) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075. (b) Davies, H. M. L.; Stafford, D. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 233. (c) Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 383. (d) Davies, H. M. L.; Hansen, T.; Hopper, D.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509. (e) Axten, J. M.; Ivy, R.; Krim, L.; Winkler, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6511. (f) Davies, H. M. L.; Stafford, D. G.; Hansen, T.; Churchill, M. R.; Keil, K. M. *Tetrahedron Lett.* **2000**, *41*, 2035. (g) Muller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725. (h) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (i) Davies, H. M. L.; Antoulinakis, E. G. *Org. Lett.* **2000**, *2*, 4153. (j) Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2071.

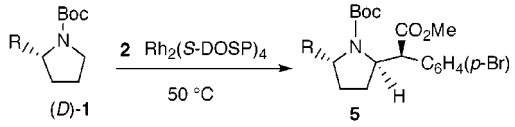
(4) For a general review, see: Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*−*618*, 45.

(5) For a general review, see: Denmark, S. E.; Nicaise, O. J.-C. In *Comprhensive Asymmetric Catalysis*, Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; pp 954−958.

(6) Enantiomer differentitaion and double stereodifferentiation by use of chiral catalysts have been reported for intramolecular cyclopropanation and C−H insertion. (a) Doyle, M. P.; Dyatkin, A. B.; Kalinin, A. V.; Ruppar, D. A.; Martin, S. F.; Spaller, M. R.; Liras, S. *J. Am. Chem. Soc.* **1995**, *117*, 11021. (b) Martin, S. F.; Spaller, M. R.; Liras, S.; Hartmann, B. *J. Am. Chem. Soc.* **1994**, *116*, 4493. (c) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837.

(7) Davies, H. M. L.; Ren, P. *Tetrahedron Lett.*, in press.

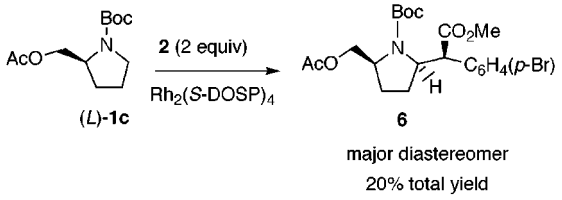
Table 1. Matched C−H Insertions of 2-Substituted Pyrrolidines



substrate	R	yield, %	de, %
a	CO_2Me	83	>94
b	$CO_2{}^tBu$	85	>94
c	CH_2OAc	85	>94
d	$CH_2OTBDPS$	85	>94

In each case a highly diastereoselective C−H insertion was obtained in yields ranging from 83 to 85%. In contrast, the mismatched reactions proceeded in poor yield. In the case of the silyl ether L-**1d**, no C−H insertion product was obtained, while with the *tert*-butyl proline L-**1b**, a mixture of diastereomers was obtained in 22% overall yield. The reaction with the acetyl derivative L-**1c** was most interesting because in this case the major diastereomer was the cis-substituted pyrrolidine **6** (Scheme 5).

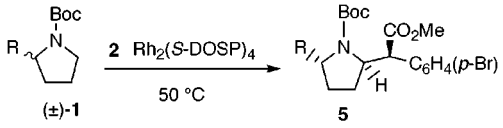
Scheme 5



Having determined that the reaction with the 2-substituted pyrrolidines displayed considerable double stereodifferentiation, we then explored the possibility of kinetic resolution in these reactions (Table 2). As the most useful aspect of this work would be the asymmetric synthesis of the products with three stereogenic centers rather than isolation of enriched starting material, these reactions were carried out with the (±)-2-substituted pyrrolidines in excess (2−4 equiv). In all instances, the C−H insertion products were produced with moderate to high enantioselectivity (77−98% ee). The high enantioselectivity in the formation of the C−H insertion products **5** is due to a combination of the inherent kinetic resolution and the enantiomer product differentiation by the catalyst. Reaction of **2** with the silyl derivative **1d** is most impressive as the C−H insertion product **5d** is formed in 85% yield, 98% ee, and >94% de.

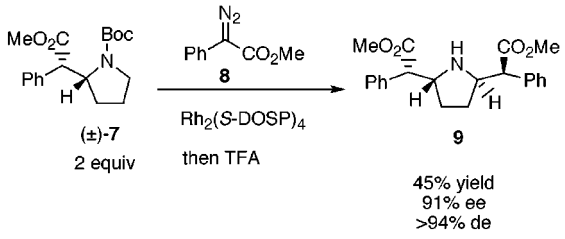
A final example of the kinetic resolution that is possible is seen in the reaction with (±)-**7** (Scheme 6). Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of methyl phenyldiazoacetate (**8**) in the presence of (±)-**7** resulted in the formation of the C−H insertion product **9**[3d] in 91% ee.

Table 2. Kinetic Resolutions in C−H Insertions of 2-Substituted Pyrrolidines



	R	equiv of (±)-**1**	yield, %	ee, %	de, %
a	CO_2Me	2	64	77	86
		4	66	79	86
b	$CO_2{}^tBu$	2	58	83	>94
		4	60	87	>94
c	CH_2OAc	2	58	88	76
		4	62	94	78
d	$CH_2OTBDPS$	2	85	98	>94

Scheme 6



In summary, these results show that impressive levels of kinetic resolution and double stereodifferentiation can occur in Rh_2(*S*-DOSP)$_4$-catalyzed intermolecular C−H insertions. In the matched case, highly diastereoselective reactions were obtained by generating highly functionalized products containing up to four stereogenic centers. These studies further underscore the highly chemoselective nature of rhodium carbenoids derived from aryldiazoacetates.

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Supporting Information Available: Full experimental data of all new compounds and X-ray crystallographic data for **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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