ORGANIC LETTERS

2001
Vol. 3, No. 10
1475−1477

Asymmetric Intramolecular C–H Insertions of Aryldiazoacetates

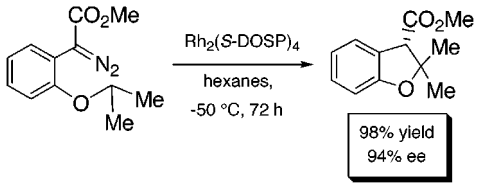
Huw M. L. Davies,* Mônica V. A. Grazini,‡ and Emmanuel Aouad

Department of Chemistry, University at Buffalo, The State University of New York, Bufalo, New York 14260-3000

hdavies@acsu.buffalo.edu

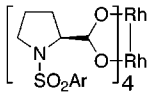
Received March 2, 2001

ABSTRACT

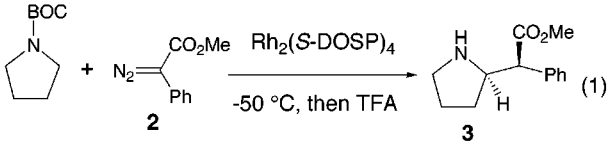


The enantioselectivity of Rh_2(*S*-DOSP)$_4$ catalyzed C–H insertion of aryldiazoacetates is very dependent on the site of the C–H insertion. The highest enantioselectivity is obtained for insertion into methine C–H bonds.

Recently, it has been shown that the intermolecular C−H insertion of aryldiazoacetates is a very effective method for asymmetric C−H activation.[1,2] For example, the reaction of methyl phenyldiazoacetate (**2**) with N-BOC pyrrolidine, catalyzed by Rh_2(*S*-DOSP)$_4$ (**1a**), generates the C−H insertion product **3** in 92% de and 94% ee (eq 1).[1d] Excellent regio-, diastereo-, and enantiocontrol are possible in this chemistry.



1a: Ar = *p*-$C_{12}H_{25}C_6H_4$ Rh_2(*S*-DOSP)$_4$
1b: Ar = *p*-^{t}BuC_6H_4 Rh_2(*S*-TBSP)$_4$



72% yield, 92% de, 94% ee

Considering the efficiency of rhodium prolinate catalyzed intermolecular C−H insertions of aryldiazoacetates, we were intrigued with the very low enantioselectivity that Sulikowski reported[3] for Rh_2(*S*-TBSP)$_4$ (**1b**) catalyzed intramolecular C−H insertion of aryldiazoacetate **4** to form the C−H insertion products **5a**−**d** that were ultimately converted to the fused indole **6** (Scheme 1). Rh_2(*S*-TBSP)$_4$ (**1b**) usually performs very well as a chiral catalyst when aryldiazoacetates are used as substrates,[4] but the results in Scheme 1 are far inferior to the intermolecular example shown in eq 1. Prompted by the apparent dichotomy between the inter- and intramolecular C−H insertions of aryl diazoacetates,[5] we decided to carry out a systematic study on intramolecular

‡ Visiting professor from Centro de Ciências Exatas e de Tecnologia da Universidade de Mogi das Cruzes, Mogi das Cruzes, SP, Brazil 0870-911.

10.1021/ol0157858 CCC: $20.00
Published on Web 04/21/2001

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

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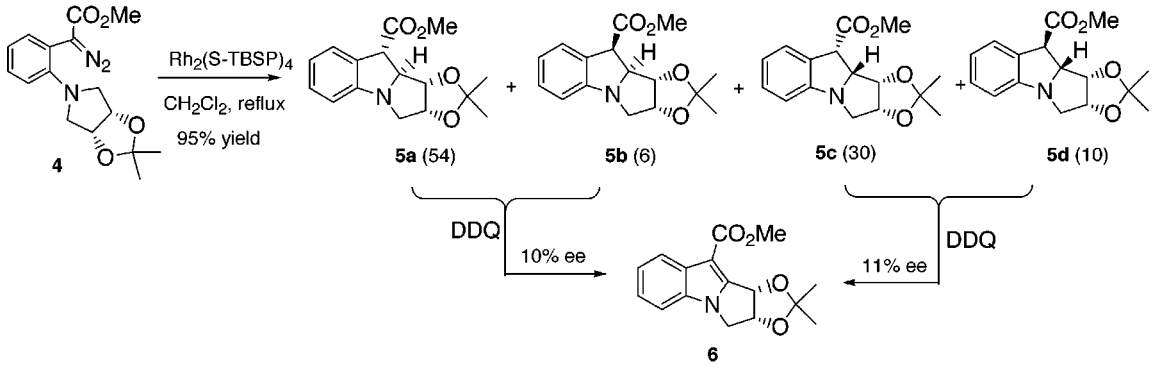
(4) (a) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459. (b) Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 105.

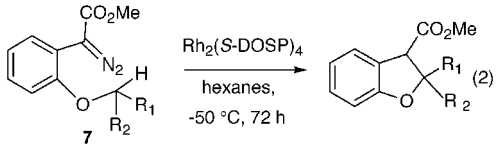
(5) Dirhodium tertaprolinates have been successfully used for intermolecular C−H insertions of other classes of diazoacetates; see: (a) Ye, T.; García, C. F.; McKervey, M. A. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1373. (b) García, C. F.; McKervey, M. A.; Ye, T. *Chem. Commun.* **1996**, 1465.

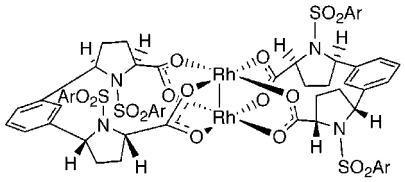
Scheme 1

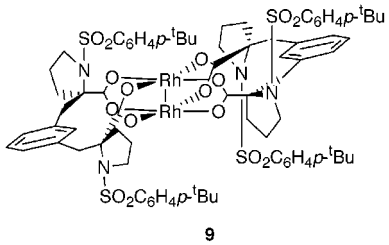


C−H insertions in order to reconcile the differences between the two modes of reaction.

A complicating feature associated with Sulikowski's system is that four diastereomeric products, **5a**−**d**, are formed in the C−H insertion step. These compounds were not individually analyzed. Instead, pairs of diastereomers were oxidized to the indole **6**. Thus, the overall enantioselectivity that was reported is not directly related to the carbenoid face selectivity during the reaction. Furthermore, the reaction conditions that were used (CH_2Cl_2, reflux) are far from the ideal conditions established for asymmetric catalysis by rhodium prolinates (hydrocarbon solvent, temperatures as low as −78 °C).[6] Consequently, we decided to study the intramolecular C−H insertions of aryldiazoacetates by using a simpler system, **7** (eq 2). This system

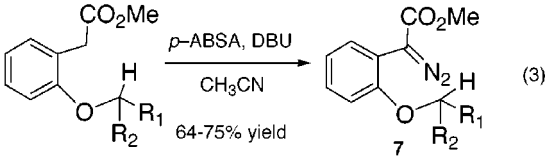






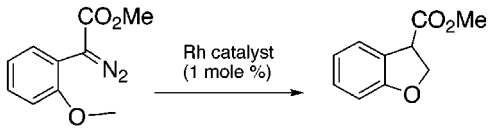
would enable the differences in asymmetric induction between inter- and intramolecular C−H insertions of aryldiazoacetates to be determined. The results of these studies using Rh_2(*S*-DOSP)$_4$ (**1a**) and the second generation bridged prolinate catalysts Rh_2(*S*-biTISP)$_2$ (**8**)[7] and **9**[8] are described in this paper.

Our intermolecular studies have established that the carbenoid from aryldiazoacetates displays subtle chemoselectivity for insertion at secondary or tertiary sites. Electronically, attack at a tertiary site is preferred, but this is balanced by steric factors that favor attack at a secondary site. On the basis of this reactivity pattern, the intramolecular substrates **7** that were used were chosen to explore the effect of substitution at the C−H insertion site on the outcome of the reaction. The aryldiazoacetates were readily prepared by a diazotransfer reaction using *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU as base (eq 3).[9]



The first system that was examined, **7a**, would only be able to undergo a C−H insertion into a methyl group (Scheme 2). So far, no effective C−H insertion into a methyl

Scheme 2



catalyst	solvent/temp	yield, %	ee, %
1a	hexanes, rt	98	<5
8	CH_2Cl_2, -50 °C	70	43 (−)
9	CH_2Cl_2, -50 °C	70	68 (−)

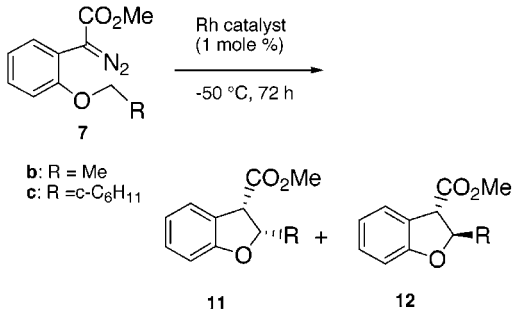
group has been reported for the intermolecular reactions. Rh_2(*S*-DOSP)$_4$ catalyzed decomposition of **7a** at −50 °C failed

(6) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897.

to generate any C−H insertion product. Carbene dimer was the major product. In contrast, repeating the reaction at room temperature resulted in a 98% yield of C−H insertion product **10a**. The enantioselectivity, however, for the formation of **10a** was very low (<5% ee). As a result of the rigid nature of the bridged catalysts **8** and **9**, CH_2Cl_2 can be used as solvent with these catalysts without a detrimental effect on asymmetric induction.[7,8] Decomposition of **7a** at −50 °C with either **8** or **9** generated **10a** in 43% and 68% ee, respectively.

The next substrates that were examined, **7b** and **7c**, would be expected to undergo C−H insertion into a methylene group. Rh_2(*S*-DOSP)$_4$ (**1a**) catalyzed decomposition of **7b** at −50 °C resulted in the formation of the dihydrobenzofurans **11b** and **12b** in 85% yield as a 4:1 mixture of cis and trans isomers (Scheme 3).[10] Furthermore, the major cis isomer was formed in 60% ee. An even more highly diastereoselective reaction occurred with **7c**, in which the size of the methylene substituent was increased from methyl to cyclohexyl. The *cis*-dihydrobenzofuran **11c** was formed in 95% de and 63% ee. The reaction of **7b** with the bridged prolinate catalysts **8** and **9** occurred with enantioselectivity similar but opposite to that of the reaction catalyzed by Rh_2(*S*-DOSP)$_4$. Opposite asymmetric induction between Rh_2(*S*-DOSP)$_4$ and the bridged prolinate catalysts has been observed previously in cyclopropanation reactions.[7,8] The reaction of **7c** catalyzed by either **8** and **9** was considerably less diastereoselective and enantioselective than the reaction catalyzed by Rh_2(*S*-DOSP)$_4$.

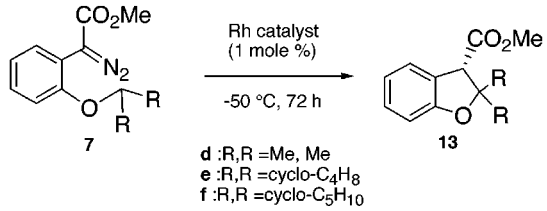
Scheme 3



compound	catalyst/solvent	11 +12 yield, %	11 de, %	11 ee, %
b	**1a**/hexanes	85	60	60 (−)
b	**8**/CH_2Cl_2	50	70	53 (+)
b	**9**/CH_2Cl_2	70	75	45 (+)
c	**1a**/hexanes	72	95	63 (−)
c	**8**/CH_2Cl_2	22	60	22
c	**9**/CH_2Cl_2	35	75	35

The final substrates, **7d**−**f**, would be expected to undergo insertion into a methine position. Rh_2(*S*-DOSP)$_4$ (**1a**) catalyzed decomposition of the isopropyl derivative **7d** at −50 °C resulted in a very efficient transformation (Scheme 4).

Scheme 4



compound	catalyst/solvent	yield, %	ee, %
d	**1a**/hexanes	98	94 (+)
d	**8**/CH_2Cl_2	48	60 (−)
d	**9**/CH_2Cl_2	57	65 (−)
e	**1a**/hexanes	93	90 (+)
f	**1a**/hexanes	12	80 (+)

The C−H insertion product **13d** was formed in 98% yield and 94% ee. The reaction of **7d** catalyzed by either **8** and **9** was considerably less enantioselective than the reaction catalyzed by Rh_2(*S*-DOSP)$_4$. The Rh_2(*S*-DOSP)$_4$ catalyzed reaction with the cyclopentyl derivative **7e** generated the C−H insertion product **13e** in 93% yield and 90% ee. Reaction of the cyclohexyl derivative **13f**, however, resulted in a very low yield of the C−H insertion product. Carbene dimer formation predominates in this case. This may be an indication that an axial C−H bond in cyclohexane does not react well in these C−H insertions of carebenoids derived from aryldiazoacetates.

These studies demonstrate that effective asymmetric intramolecular C−H insertion is possible with aryldiazoacetate derivatives but the extent of asymmetric induction is very dependent on the site of C−H insertion and the catalyst. With the bridged prolinate catalysts, **8** and **9**, the highest enantioselectivity is obtained for insertion into a methyl group. The highest enantioselectivity using Rh_2(*S*-DOSP)$_4$ is obtained for insertion into methine C−H bonds. This trend is different from that observed in the intermolecular C−H insertions, where reasonably high enantioselectivity generally occurs for insertion into methylene C−H bonds.[2]

Acknowledgment. Financial support of this work by the National Science Foundation (CHE-0092490) is gratefully acknowledged. We also thank the State of São Paulo Research Foundation for a postdoctoral fellowship to M.V.A.G. We thank Dr. Tadamichi Nagashima and Stephen A. Panaro for the preparation of catalysts **8** and **9**.

Supporting Information Available: Experimental conditions and spectral data for **7** and **10**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0157858

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(8) Davies, H. M. L.; Kong, N. *Tetrahedron Lett.* **1997**, *40*, 4203.
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(10) The absolute stereochemistry for the C−H insertions products has not been unamabiguously determined, but the configuration that is drawn is that expected from the predictive model for Rh_2(*S*-DOSP)$_4$ catalyzed C−H insertions (see ref 2).