Asymmetric Intermolecular Carbenoid C−H Insertions Catalyzed by Rhodium(II) (*S*)-*N*-(*p*-Dodecylphenyl)sulfonylprolinate

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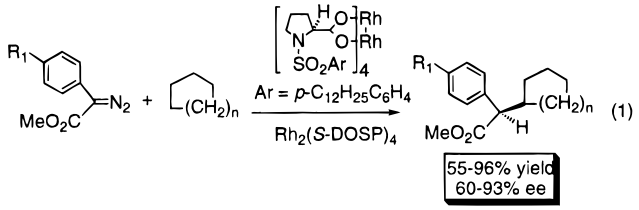
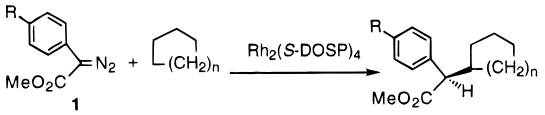
Selective activation of unfunctionalized C−H bonds represents a major challenge in organic synthesis.[1] One notable method is the intramolecular carbenoid C−H insertion, which is particularly useful for the synthesis of five-membered rings with excellent control of relative and absolute stereochemistry.[2,3] In contrast, the *intermolecular* carbenoid C−H insertion has not been greatly utilized and has been generally regarded as a rather inefficient and unselective process.[3,4] The most significant papers in the field are by Noels[5] and Callott,[6] which reported that reasonable yields of intermolecular C−H insertion products could be obtained from rhodium-catalyzed decomposition of ethyl diazoacetate in the presence of alkanes. In recent years, we have found that vinyldiazoacetates[7] and phenyldiazoacetates[8] are capable of highly stereoselective cyclopropanations on rhodium(II) (*S*)-*N*-(*p*-alkylphenyl)sulfonylprolinate Rh_2(*S*-DOSP)$_4$-catalyzed decomposition in the presence of alkenes. In this paper we describe that the decomposition of aryldiazoacetates by Rh_2(*S*-DOSP)$_4$ results in intermolecular C−H insertions in excellent yields and high levels of asymmetric induction (eq 1).



(1)

The initial determination of the feasibility of the intermolecular C−H insertion reaction was carried out with a series of aryldiazoacetates (**1a**−**c**) in the presence of cycloalkanes as solvent (Table 1). The yields of the C−H insertion products were found to be much higher when the reactions were conducted under refluxing conditions instead of at room temperature. Under these conditions the C−H insertion products were obtained in yields ranging from 55 to 96%. Even though fairly forcing reactions conditions were used, moderate to high levels of asymmetric induction were obtained (60−89% ee (enantiomeric excess)). The effect of temperature is clearly seen in the formation of **3c**; under refluxing conditions, **3c** is formed in 91% yield and 86% ee, while under ambient conditions, **3c** is formed in 53% yield and 93% ee. For the phenyl, chlorophenyl, and methoxyphenyl derivatives (**1a**−**c**), a steady increase in both yield and enantioselectivity was seen on going from the electron-donating to the electron-withdrawing aromatic substituent. The apparent trend toward enhanced enantioselectivity could not be extended to the *p*-nitro derivative of **1** because of the insolubility of the diazo compound in the hydrocarbon solvent. The absolute stereochemistry of **2b** was determined to be *R* by comparison of the optical rotation of the acid derived from **2b** with the literature value.[9,10] The absolute stereochemistry of the other C−H insertion products is tentatively assumed to be *R* in analogy to **2b**.

Table 1. Asymmetric C−H Insertions into Cycloalkanes



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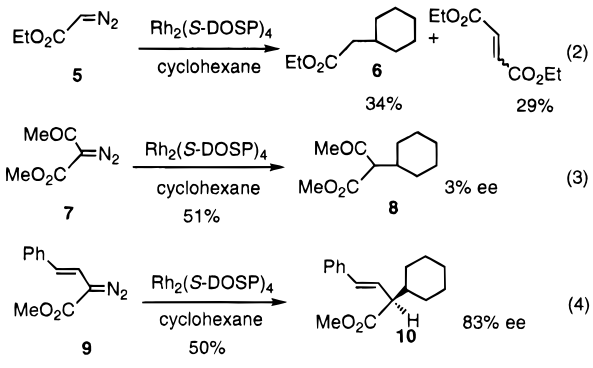
entry	product	R	*n*	temp	yield (%)	ee, (%)[a]
1	**2a**	OMe	1	50	55	83
2	**2b**	H	1	50	84	87
3	**2c**	Cl	1	50	78	89
4	**3a**	OMe	2	81	85	67
5	**3b**	H	2	81	83	81
6	**3b**	H	2	50	69	88
7	**3c**	Cl	2	81	91	86
8	**3c**	Cl	2	25	53	93
9	**4a**	MeO	3	118	78	60
10	**4b**	H	3	118	84	70
11	**4c**	Cl	3	118	96	81

[a] Enantiomeric excesses (ee values) were determined either by ^{1}H NMR using tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato]europium(III) as a chiral shift reagent or by HPLC using a Daicel OD analytical column.

The efficiency of the aryldiazoacetate system for asymmetric C−H insertion is in sharp contrast to the results that were obtained with the more traditional carbenoid precursors. Even though the reaction with ethyl diazoacetate (**5**) does not generate a stereogenic center, the reaction is instructive because in addition to the C−H insertion product **6** a significant amount of butenedioate products are formed (eq 2).[5] No dimeric



5 **6** **7** **8** **9** **10**

carbene products were seen in the reaction of the aryldiazoacetates described in Table 1. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of methyl diazoacetoacetate (**7**) in the presence of cyclohexane resulted in the C−H insertion product **8** in only

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

(2) For recent examples, see: (a) Doyle, M. P.; Kalinin, A. V.; Ene, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 8837. (b) Taber, D. F.; You, K. K.; Rheingold, A. L. *J. Am. Chem. Soc.* **1996**, *118*, 547.

(3) For a general review, see: Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091.

(4) (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.

(5) (a) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688. (b) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *Bull. Soc. Chim. Belg.* **1984**, *93*, 945. (c) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Mol. Catal*. **1988**, *49*, L13.

(6) (a) Callott, H. J.; Metz, F. *Tetrahedron Lett.* **1982**, *23*, 4321. (b) Callott, H. J.; Metz, F. *Nouv. J. Chim.* **1985**, *9*, 167.

(7) (a) Davies, H. M. L.; Hutcheson, D. K. *Tetrahedron Lett.* **1993**, *34*, 7243. (b) Davies, H. M. L.; Peng, Z. Q.; Houser, J. H. *Tetrahedron Lett.* **1994**, *35*, 8939. (c) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. (d) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373.

(8) (a) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133. (b) Doyle, M. P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M. A.; McKervey, M. A.; Garcia, C. F. *Tetrahedron Lett.* **1996**, *37*, 4129.

(9) Camps, P.; Gimenez, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1227.

(10) Lit. value: $[\alpha]^{25}_D = -38.8°$ (c = 20.0, $CHCl_3$) (Barlow, R. B.; Franks, F. M.; Pearson, J. D. *J. Med. Chem.* **1973**, *16*, 493). Found: $[\alpha]^{24}_D = -28.3°$ (c = 0.48, $CHCl_3$).

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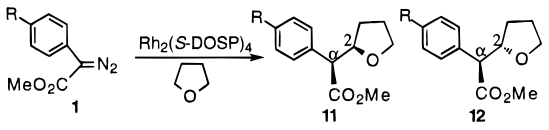
Table 2. Asymmetric C−H Insertion into Tetrahydrofuran



entry	substrate	R	temp	yield (%)	**11**:**12**[a]	ee[b] **11** (%)	ee[b] **12** (%)
1	**1a**	MeO	65	63	2.5	68	66
2	**1b**	H	65	82	2.3	60	61
3	**1c**	Cl	65	48	1.7	52	51
4	**1c**	Cl	25	57	1.9	76	71
5	**1d**	NO_2	65	50	1.8	69	58

[a] **11**:**12** ratios determined from ^{1}H NMR of crude reaction mixtures. [b] Enantiomeric excesses (ee values) were determined either by ^{1}H NMR using tris[3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato]europium(III) as a chiral shift reagent or by HPLC using a Daicel OD analytical column.

3% ee (eq 3). However, the reaction with the vinylcarbenoid precursor **9** was very effective resulting in the C−H insertion product **10** in 83% ee (eq 4). These observations parallel the trends that were seen in the asymmetric cyclopropanation by Rh_2(*S*-DOSP)$_4$ in which high asymmetric induction occurred only with donor−acceptor metal carbenes from vinyl- or aryldiazoacetates.[8a]

Extension of the reaction to tetrahydrofuran as the carbenoid trap illustrates that the C−H insertion of aryldiazoacetates also holds promise for good regioselectivity (Table 2).[4c,11] Rh_2(*S*-DOSP)$_4$ catalyzed decomposition of **1b** in the presence of tetrahydrofuran, heated under reflux, resulted in the formation of a diastereomeric mixture of products **11b** and **12b**. These products are formed by C−H insertion into the methylene group adjacent to the ether. The major diastereomer **11b** was assigned to be the (2*R**,α*S**) isomer on the basis of its NMR spectral data, which is similar to that published for the carboxylic acid of **11b**.[12] The enantioselectivity in the process was lower than for the cycloalkanes, resulting in 60% ee of **11b** and 61% ee of **12b**. Similar results were seen with the other aryldiazoacetates **1b**−**d**. Once again improved enantioselectivity was possible

(11) Stork, G.; Nakatani, K. *Tetrahedron Lett.* **1988**, *29*, 2283.

(12) Mead, K. T.; Yang, H.-L. *J. Org. Chem.* **1990**, *55*, 2991. The relative configuration of the acid of **11b** is not drawn in this paper, but due to its mechanism of formation, it can be assigned as (2*R**,α*S**).

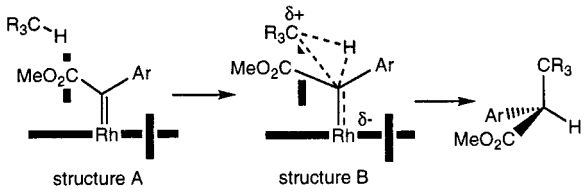


Figure 1.

on carrying out the reaction at ambient temperature as seen for **1c** (76% ee for **11c**, 71% ee for **12c)**. The absolute stereochemistry of **11** and **12** has not been determined, but if the asymmetric induction runs parallel to the cycloalkane insertions, the products would be expected to be (2*R*,α*S*) and (2*S*,α*S*), respectviely.

The asymmetric induction observed in the formation of **2b** can be rationalized by a similar model to the one that we have proposed for the asymmetric cyclopropanation by Rh_2(*S*-DOSP)$_4$ (Figure 1).[7c] In this model the catalyst is considered to behave as if it has D_2 symmetry and the rhodium−carbenoid complex can be represented as structure A.[7c] Positive charge build up occurs in the transition state. The approach of the cycloalkane is considered to occur over the side of the ester group of the carbenoid, in an analogous manner to the asymmetric cyclopropanation.[7c] Completion of the reaction by rotation of the cycloalkane away from the catalyst would lead to the observed *R* configuration in the product.

In summary, the Rh_2(*S*-DOSP)$_4$-catalyzed intermolecular C−H insertion reaction of aryldiazoacetates shows considerable promise for the asymmetric synthesis of arylacetic acid derivatives. These studies reconfirm that the Rh_2(*S*-DOSP)$_4$/donor−acceptor-substituted carbenoid is an excellent combination for enantioselective carbenoid transformations. Further evaluation of the scope of the intermolecular C−H insertions is in progress.

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Supporting Information Available: Experimental details (5 pages). See any current masthead page for ordering and Internet access instructions.

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