JOC Article

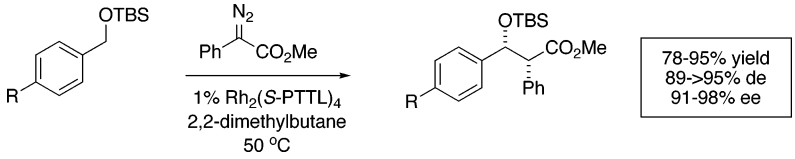
Asymmetric Intermolecular C−H Functionalization of Benzyl Silyl Ethers Mediated by Chiral Auxiliary-Based Aryldiazoacetates and Chiral Dirhodium Catalysts

Huw M. L. Davies,* Simon J. Hedley, and Brooks R. Bohall

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

hdavies@acsu.buffalo.edu

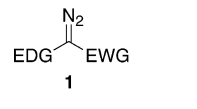
Received August 18, 2005



C−H functionalization of benzyl silyl ethers by means of rhodium-catalyzed insertions of aryldiazoacetates can be achieved in a highly diastereoselective and enantioselective manner by judicious choice of chiral catalyst or auxiliary. The dirhodium tetraprolinates such as Rh_2((*S*)-DOSP)$_4$ have been widely successful as chiral catalysts in the C−H functionalization chemistry of aryldiazoacetates, but give poor enantioselectivity in the reactions of aryldiazoacetates with benzyl silyl ether derivatives. The use of (*S*)-lactate as a chiral auxiliary resulted in C−H functionalization with moderately high diastereoselectivity (79−88% de) and enantioselectivity (68−85% ee). The best results (91−95% de, 95−98% ee), however, were achieved using Hashimoto's Rh_2((*S*)-PTTL)$_4$ catalyst.

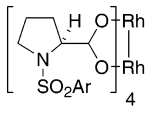
Introduction

Intermolecular C−H functionalization by means of a rhodium carbenoid-induced C−H insertion is an attractive strategic reaction for organic synthesis.[1] A key requirement for a successful C−H functionalization methodology has been the use of carbenoids flanked by an acceptor and a donor group (**1**).[2] Moreover, when the C−H functionalization is catalyzed by dirhodium prolinates such as Rh_2((*S*)-DOSP)$_4$ **2**[3] or bridged catalyst Rh_2((*S*)-biTISP)$_2$ **3**,[4] high asymmetric induction can be achieved with a wide range of substrates.[1,2] The reaction has been developed as a new disconnection strategy, equivalent to some of the classic reactions of organic synthesis such as the aldol reaction,[5] the Mannich reaction,[6] the Michael reaction,[7] and the Claisen rearrangement.[8] During studies on the C−H functionalization of benzyl silyl ether derivatives, we found that the generally reliable Rh_2(DOSP)$_4$ catalyst failed to achieve high levels of asymmetric induction. In this paper, we describe two alternative strategies for obtaining high asymmetric induction in this intermolecular C−H functionalization: the first approach relies on the use of (*S*)-lactate as a chiral auxiliary **4**, whereas the second involves the employment of Hashimoto's *N*-phthaloyl-based Rh_2((*S*)-PTTL)$_4$ catalyst **5**.



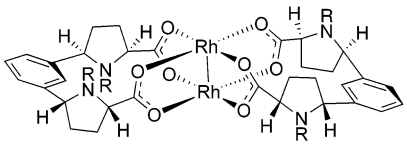
1

EDG = Aryl, vinyl, alkynyl
EWG = CO_2Me

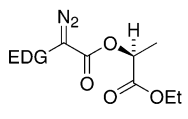


4

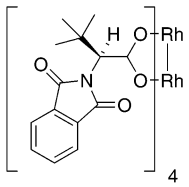
Ar = 4-C_6H_4-$C_{12}H_{25}$
Rh_2(*S*-DOSP)$_4$ **2**



R=SO_2-2,4,6-tri-^{i}PrC_6H_2
Rh_2(*S*-biTISP)$_2$ **3**



4

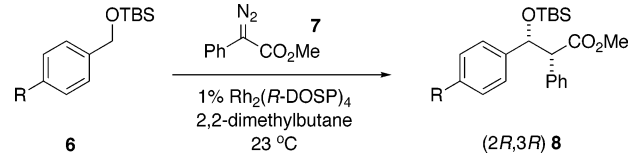


Rh_2(*S*-PTTL)$_4$ **5**

(1) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861.
(2) (a) Davies, H. M. L.; Antoulinakis, E. *J. Organomet. Chem.* **2001**, *617*, 47. (b) Davies, H. M. L. *J. Mol. Catal. A: Chem.* **2002**, *189*, 125.
(3) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6896.
(4) Davies, H. M. L.; Panaro, S. A. *Tetrahedron Lett.* **1999**, *40*, 5287.
(5) (a) Davies, H. M. L.; Beckwith, R. E. J.; Antoulinakis, E. G.; Jin, Q. *J. Org. Chem.* **2003**, *68*, 6126. (b) Davies, H. M. L.; Antoulinakis, E. G. *Org. Lett.* **2000**, *2*, 4153. (c) Davies, H. M. L.; Antoulinakis, E. G.; Hansen, T. *Org. Lett.* **1999**, *1*, 383.

10.1021/jo051747g CCC: $30.25
Published on Web 11/17/2005

TABLE 1. Rh_2((*R*)-DOSP)$_4$-Catalyzed C−H Functionalization of Benzyl *tert*-Butyldimethylsilyl Ethers 6a−e



entry	compound	R	yield (%)	de (%)	ee (%)
1	**a**	OMe	85	88	35
2	**b**	Me	84	91	30
3	**c**	H	83	91	17
4	**d**	Cl	88	94	10
5	**e**	CF_3	74	93	30

Results and Discussion

Dirhodium Prolinate-Catalyzed Reactions. We have previously shown that benzylic C−H functionalization at methylene and methyl sites is a very effective process, resulting in high asymmetric induction when the reaction is catalyzed by Rh_2((*S*)-DOSP)$_4$.[9] To employ this chemistry in the synthesis of podophyllotoxin analogues,[10] we needed to achieve an effective C−H functionalization of benzyl silyl ethers. Consequently, we undertook model studies of the Rh_2((*R*)-DOSP)$_4$-catalyzed decomposition of methyl phenyldiazoacetate **7** with a range of benzyl silyl ethers **6**. We found it was a very effective transformation, resulting in the desired product **8** in high yield (74−88%) and diastereoselectivity favoring the syn isomer (88−94% de). However, the enantiomeric excess of the major isomer arising from this reaction was consistently low (10−35% ee).[11]

The results in Table 1 were unexpected because Rh_2((*R*)-DOSP)$_4$ has generally been shown to be an effective catalyst for intermolecular C−H functionalization with methyl phenyldiazoacetate **7** for virtually all substrates previously examined; ordinarily, the reaction products are isolated with high enantioselectivity, whereas the diastereoselectivity is variable and strongly substrate specific.[1,2] To understand why **8** was formed with such low enantioselectivity, we conducted a study to determine the effect of modifying the silyl substituent, the ester group on the diazoacetate, and the reaction conditions (Table 2). Analogous studies have shown that conducting Rh_2((*R*)-DOSP)$_4$-catalyzed reactions at lower temperature tends to improve the enantioselectivity,[3,4,7,12] but in this case, no improvement in enantioselectivity was obtained when the reaction was conducted at 0 °C (entry 2). At even lower temperatures (entry 3), the yield of the C−H functionalization product **8a** drops precipitously. 2,2-Dimethylbutane has been demonstrated to be an excellent solvent for C−H functionalization reactions,[12] usually providing high asymmetric induction in Rh_2(DOSP)$_4$-catalyzed reactions, and the same trends are seen here (entries 1 and 4−6). The use of a TMS group instead of a TBS group does not have much impact on the enantioselectivity (entry 7), whereas the larger silicon protecting group TIPS results in a much lower yield and enantioselectivity of C−H functionalization. A very interesting effect was observed with the use of *tert*-butyl ester **9** instead of methyl ester **7** because much higher enantioselectivity was obtained, and furthermore, the product **10c** was obtained with the 2*S*,3*S* configuration (entry 9). This trend is opposite to what has been previously seen, which is that a bulky ester group results in lower enantioselectivity in Rh_2(DOSP)$_4$-catalyzed reactions.[3,12]

Chiral Auxiliary-Mediated C−H Functionalization Reactions. The above studies demonstrate that the dirhodium tetraprolinate-catalyzed C−H functionalization of benzyl silyl ethers comprises a very unusual system, displaying very different trends in enantioselectivity compared to all the other substrates previously studied.[1−9] As the enantioselectivity was unsatisfactory with chiral catalysis, the use of methyl (*S*)-lactate as a chiral auxiliary was examined. α-Hydroxyesters such as (*S*)-lactate were discovered to be excellent chiral auxiliaries for rhodium carbenoid cyclopropanations,[13] and since then, they have been applied to various rhodium carbenoid-mediated reactions,[14] including a recent example of intramolecular C−H insertion as a key step in the total synthesis of (−)-ephedradine A.[14l−n] However, to the best of our knowledge, these chiral auxiliaries have not been utilized in an intermolecular C−H insertion reaction, and hence this procedure could be very beneficial as a fall-back strategy when chiral catalysis is ineffective. The feasibility of such an approach was determined by the reaction of diazoacetate **11** with **6a** (Scheme 1). The chiral auxiliary did not interfere with the efficiency of the C−H functionalization, as **12a** was formed in 83% yield and as a 12.9:1 ratio of syn and anti diastereomers. The asymmetric induction for the syn diastereomer was determined to be 79% ee, by reduction

(6) (a) Davies, H. M. L.; Venkataramani, C.; Hansen, T.; Hopper, D. W. *J. Am. Chem. Soc.* **2003**, *125*, 6462. (b) Davies, H. M. L.; Hansen, T.; Hopper, D.; Panaro, S. A. *J. Am. Chem. Soc.* **1999**, *121*, 6509. (c) Davies, H. M. L.; Venkataramani, C. *Org. Lett.* **2001**, *3*, 1773. (d) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197.

(7) Davies, H. M. L.; Ren, P. *J. Am. Chem. Soc.* **2001**, *123*, 2071.

(8) Davies, H. M. L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, *3*, 3587.

(9) (a) Davies, H. M. L.; Ren, P.; Jin, Q.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165. (b) Davies, H. M. L.; Jin, Q. *Tetrahedron: Asymmetry* **2003**, *14*, 941.

(10) Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75.

(11) Relative stereochemistry was assigned on the basis of the distinctive proton NMR chemical-shift differences: Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2001**, *42*, 3149. Absolute stereochemistry was determined later by X-ray crystallographic analysis of compound **23** (see ref 23 and the Supporting Information), and the configuration of the other reaction products was assigned by analogy from these data.

(12) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063.

(13) Davies, H. M. L.; Huby, N. J. S.; Cantrell, W. R., Jr.; Olive, J. L. *J. Am. Chem. Soc.* **1993**, *115*, 9468.

(14) (a) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774. (b) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095. (c) Davies, H. M. L.; Ahmed, G.; Calvo, R. L.; Churchill, M. R.; Churchill, D. G. *J. Org. Chem.* **1998**, *63*, 2641. (d) He, M.; Tanimori, S.; Ohira, S.; Nakayama, M. *Tetrahedron* **1997**, *53*, 13307. (e) Moore, J. D.; Hanson, P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 873. (f) Moore, J. D.; Sprott, K. T.; Wrobleski, A. D.; Hanson, P. R. *Org. Lett.* **2002**, *4*, 2357. (g) Ye, T.; McKervey, M. A.; Bandes, B.; Doyle, M. P. *Tetrahedron Lett.* **1994**, *35*, 7269. (h) Landais, Y.; Planchenault, D.; Weber, V. *Tetrahedron Lett.* **1994**, *35*, 9549. (i) Landais, Y.; Planchenault, D. *Tetrahedron* **1997**, *53*, 2855. (j) Bulugahapitiya, P.; Landais, Y.; Parra-Rapado, L.; Planchenault, D.; Weber, V. *J. Org. Chem.* **1997**, *62*, 1630. (k) Doyle, M. P.; Yan, M. *Tetrahedron Lett.* **2002**, *43*, 5929. (l) Kurosawa, W.; Kan, T.; Fukuyama, T. *Synlett* **2003**, 1028. (m) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112. (n) Kurosawa, W.; Kobayashi, H.; Kan, T.; Fukuyama, T. *Tetrahedron* **2004**, *60*, 9615.

(15) Davies, H. M. L.; Kong, N. *Tetrahedron Lett.* **1997**, *38*, 4203.

TABLE 2. C−H Functionalization of *p*-Methoxybenzyl *tert*-Butyldimethylsilyl Ether 6a: Optimization of Reaction Conditions

entry	product	SiR_3	R	conditions	yield (%)	de (%)	ee (%)
1	**8a**	TBS	Me	2,2-DMB,[a] 23 °C	85	88	35 (2*R*,3*R*)
2	**8a**	TBS	Me	2,2-DMB, 0 °C	81	91	31 (2*R*,3*R*)
3	**8a**	TBS	Me	2,2-DMB, −40 °C	34	90	34 (2*R*,3*R*)
4	**8a**	TBS	Me	CH_2Cl_2, 23 °C	69	62	<1
5	**8a**	TBS	Me	toluene, 23 °C	67	83	24 (2*R*,3*R*)
6	**8a**	TBS	Me	$PhCF_3$, 23 °C	51	63	35 (2*R*,3*R*)
7	**10a**	TMS	Me	2,2-DMB, 23 °C	71	83	38 (2*R*,3*R*)
8	**10b**	TIPS	Me	2,2-DMB, 23 °C	46	>95	15 (2*R*,3*R*)
9	**10c**	TBS	*t*-Bu	2,2-DMB[a] 23 °C	73	78	72 (2*S*,3*S*)[b]

[a] 2,2-DMB = 2,2-dimethylbutane. [b] % ee determined by chiral HPLC of the corresponding alcohol **13a**.

SCHEME 1

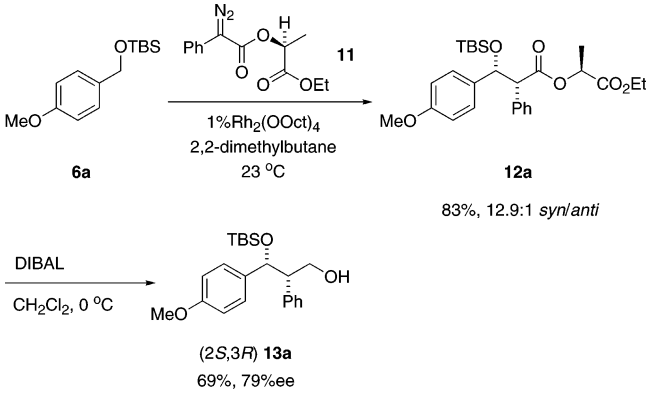
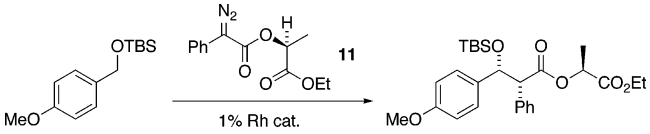


TABLE 3. C−H Functionalization of *para*-Methoxybenzyl *tert*-Butyldimethylsilyl Ether 6a with Ethyl (*S*)-Lactate-Based Aryldiazoacetate 11



entry	conditions	yield (%)	syn/anti	ee (%)[a]
1	Rh_2(OOct)$_4$, 2,2-DMB, 23 °C	83	12.9:1	79
2	Rh_2(OOct)$_4$, 2,2-DMB, 0 °C	64	14.4:1	83
3	Rh_2(OOct)$_4$, 2,2-DMB, −78 °C	35	6.3:1	81
4	Rh_2(OOct)$_4$, CH_2Cl_2, 23 °C	43	1.9:1	33
5	Rh_2((*S*)-DOSP)$_4$, 2,2-DMB, 23 °C	69	5.4:1	61
6	Rh_2((*R*)-DOSP)$_4$, 2,2-DMB, 23 °C	67	8.0:1	10

[a] % ee determined by chiral HPLC of the corresponding alcohol **13a**.

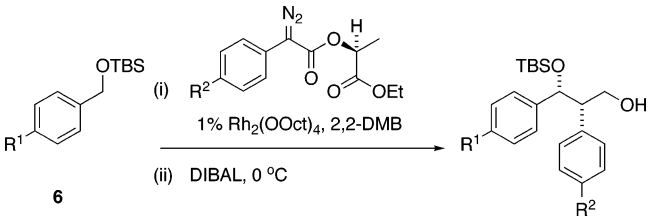
of ester **12a** to the alcohol **13a** followed by chiral HPLC analysis of compound **13a**.

Further studies to elucidate the optimum conditions (Table 3) revealed that a decrease in temperature to 0 °C furnished **12a** with a moderate improvement in enantioselectivity, albeit in lower yield. A further decrease in temperature to −78 °C resulted in an even lower product yield, and no improvement in enantioselectivity. As previously shown in Table 2, 2,2-dimethylbutane was a far superior solvent than dichloromethane for this reaction, and even though double stereodifferentiation was observed with chiral catalysts, the enantioselectivity for even the matched reaction with Rh_2((*S*)-DOSP)$_4$ (entry 5) was not as high as the outcome with Rh_2(OOct)$_4$. Similar behavior was observed in our earlier studies in the asymmetric cyclopropanation, in which catalysts with increasingly bulky ligands reduced the enantioselectivity when chiral auxiliaries were employed.[13]

With an effective method for the C−H functionalization reaction of benzyl silyl ether derivatives with high asymmetric induction in hand, we decided to investigate the scope of this transformation. Additionally, it was felt that a direct one-pot reaction comprising C−H functionalization followed by reduction would provide a more attractive route to synthetically useful building blocks. We were delighted to find that in all cases, the products **13**−**17** were isolated with much higher enantioselectivity than could be achieved using chiral catalysis with Rh_2((*R*)-DOSP)$_4$ (see Table 4). Although the enantioselectivity of the C−H functionalization reaction was shown to be optimal at 0 °C for a benzyl silyl ether with a strongly electron-donating substituent **6a**, when the less activated substrate **6b** was subjected to these conditions, a low yield (35%) of **13b** was obtained, and hence the majority of these reactions were carried out at room temperature. Aryldiazoacetates containing an electron-rich aromatic ring required elevated temperatures in order to induce an efficient reaction toward products **14** and **15**.

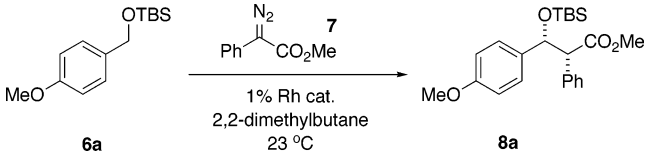
Rh_2((*S*)-PTTL)$_4$-Catalyzed C−H Functionalization Reactions. Although the development of the chiral auxiliary approach constituted a more-than-suitable alternative protocol, modern synthetic chemistry demands that a truly efficient process utilizes a chiral catalyst. With this in mind, a series of dirhodium catalysts was investigated for comparison to the already-studied Rh_2((*R*)-DOSP)$_4$ (Table 5). The Rh_2((*S*)-biTISP)$_2$ (**3**)-catalyzed reaction resulted in considerably higher enantioselectivity than the Rh_2((*R*)-DOSP)$_4$-catalyzed reaction, but the diastereoselectivity was inferior (entry

TABLE 4. One-Pot Combined Chiral Auxiliary-Mediated C−H Functionalization Reaction and Reduction



R^1	R^2	product	temp (°C)	yield (%)	de (%)	ee (%)
OMe	H	**13a**	23	70	83	79
OMe	H	**13a**	0	62	87	83
Me	H	**13b**	23	86	79	80
Me	H	**13b**	0	35	80	86
H	H	**13c**	23	69	88	84
Cl	H	**13d**	23	91	88	82
CF_3	H	**13e**	23	89	82	85
OMe	Me	**14**	50	65	84	68
OMe	OMe	**15**	50	66	85	82
OMe	Br	**16**	23	63	82	82
OMe	CF_3	**17**	23	65	80	76

TABLE 5. Investigation of Dirhodium Catalysts in C−H Functionalization of *p*-Methoxybenzyl *tert*-Butyldimethylsilyl Ether 6a

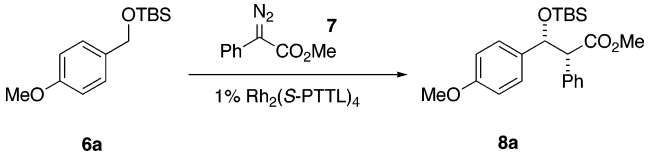


entry	Rh cat	yield (%)	de (%)	ee (%)	abs. conf.
1	Rh_2((*S*)-biTISP)$_2$ **3**	82	38	69	2*S*,3*S*
2	**18**	61	14	40	2*R*,3*R*
3	Rh_2((*S*)-PTTL)$_4$ **5**	64	91	97	2*R*,3*R*
4	Rh_2((*S*)-NTTL)$_4$ **19**	8	65	57	2*R*,3*R*
5	Rh_2((*S*)-BNP)$_4$ **20**	2	43	nd[a]	nd

[a] Not determined.

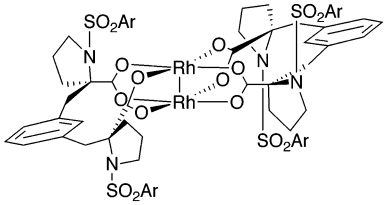
4). A very surprising result obtained in this study was the formation of **8a** with opposite asymmetric induction, because all previous studies have shown that Rh_2((*S*)-biTISP)$_2$- and Rh_2((*R*)-DOSP)$_4$-catalyzed reactions provide the same enantiomer of the product.[4,11] Prior to the development of the Rh_2((*S*)-biTISP)$_2$ catalyst, we had reported a bridged catalyst **18**.[15] In comparison with the Rh_2((*S*)-biTISP)$_2$ result, the product was isolated with low diastereoselectivity, but unlike the former result, high enantioselectivity was not observed with catalyst **18**. Hashimoto's Rh_2((*S*)-PTTL)$_4$ catalyst **5** has shown excellent utility in intramolecular carbenoid cyclization reactions,[16] including examples involving C−H insertion at a benzylic ether site,[17] but has not been reported to be particularly effective at general intermolecular C−H insertion reactions.[18] In this study, the Rh_2((*S*)-PTTL)$_4$ catalyst **5** provided the C−H functionalization product

TABLE 6. Optimization of Rh_2((*S*)-PTTL)$_4$-Catalyzed C−H Functionalization of *para*-Methoxybenzyl *tert*-Butyldimethylsilyl Ether 6a

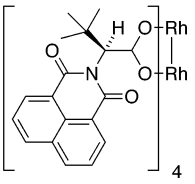


entry	solvent	temp (°C)	yield (%)	de (%)	ee (%)
1	2,2-DMB	50	78	89	91
2	CH_2Cl_2	23	28	50	4
3	$PhCF_3$	23	51	81	76

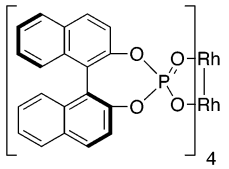
8a in exceptionally high levels of diastereoselectivity and enantioselectivity, which was even higher than for any other process, including the Rh_2((*S*)-biTISP)$_2$-catalyzed and the (*S*)-lactate-mediated approach. Inspired by this result, we also examined Müller's Rh_2((*S*)-NTTL)$_4$ catalyst **19**, which has been shown to outperform Rh_2((*S*)-PTTL)$_4$ in some reactions,[19] and Pirrung's Rh_2((*S*)-BNP)$_4$ **20**.[20] However, Rh_2((*S*)-NTTL)$_4$ gave a very poor yield of product **8a**, and Pirrung's phosphonate based catalyst Rh_2((*S*)-BNP)$_4$ was even less satisfactory.



18



Rh_2(*S*-NTTL)$_4$ **19**



Rh_2(*S*-BNP)$_4$ **20**

From these results, it was determined that Rh_2((*S*)-PTTL)$_4$ was the superior catalyst for this system, and accordingly, optimization of the reaction conditions using this catalyst was the next logical step (Table 6). Similar to earlier results (Tables 2 and 3), 2,2-dimethylbutane was the best solvent for this reaction, and conducting the reaction under reflux allowed isolation of the product **8a**

(16) (a) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 5173. (b) Takahashi, T.; Tsutsui, H.; Tamura, M.; Kitagaki, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2001**, 1604. (c) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79. (d) Anada, M.; Watanabe, N.; Hashimoto, S. *Chem. Commun.* **1998**, 1517. (e) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Synlett* **1994**, 353.

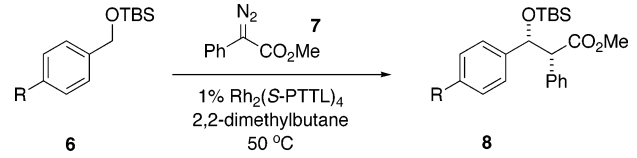
(17) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887.

(18) To the best of our knowledge, Rh_2((*S*)-PTTL)$_4$ has not been reported in the literature as a catalyst for an intermolecular cyclopropanation or intermolecular C−H insertion reaction. However, for an example of the use of the related *N*-phthaloyl-based catalyst Rh_2((*S*)-PTPA)$_4$ in intermolecular cyclopropanation and C−H insertion reactions see: Müller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725. It reported that the Rh_2((*S*)-PTPA)$_4$-mediated decomposition of **7** in the presence of cyclohexene provided a 1:1 ratio of C−H insertion product (6% de, 45% ee for the *S* enantiomer) to cyclopropane product in a combined yield of 45%. The corresponding Rh_2((*S*)-DOSP)$_4$-catalyzed reaction was demonstrated to proceed in 73% yield, with a 79:21 ratio of C−H insertion product to cyclopropane product, with the former isolated with poor diastereoselectivity but excellent enantioselectivity (93% ee, *R* enantiomer: ref 8).

(19) Müller, P.; Bernardinelli, G.; Allenbach, Y. F.; Ferri, M.; Flack, H. D. *Org. Lett.* **2004**, *6*, 1725.

(20) Pirrung, M. C.; Zhang, J. *Tetrahedron Lett.* **1992**, *33*, 5987.

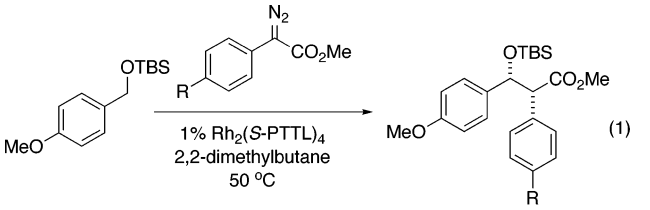
TABLE 7. Scope of the Rh_2((*S*)-PTTL)$_4$-Catalyzed C−H Functionalization of Benzyl Silyl Ether Derivatives 6



entry	compound	R	yield (%)	de (%)	ee (%)
1	**a**	OMe	78	89	91
2	**b**	Me	84	94	98
3	**c**	H	95	>95	98
4	**d**	Cl	84	>95	97
5	**e**	CF_3	90	>95	95

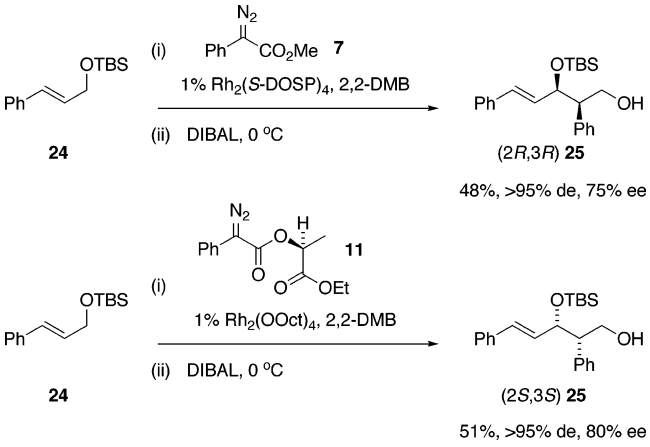
in higher yield while still maintaining the excellent selectivity (Table 6, entry 1). As observed with the Rh_2-((*R*)-DOSP)$_4$-catalyzed and chiral auxiliary-mediated reactions, dichloromethane was a poor solvent for the reaction (entry 2), generating the product **8a** in very low yield as an almost racemic mixture.

With the optimum conditions determined, we examined the scope of the Rh_2((*S*)-PTTL)$_4$-catalyzed reaction (Table 7). As for the Rh_2((*R*)-DOSP)$_4$-catalyzed and (*S*)-lactate-mediated reactions, the conditions are compatible with electron-rich, neutral, and electron-deficient aromatic rings, generating the desired product in high yield along with exceptional levels of asymmetric induction with much higher enantioselectivity than any method previously employed. Additionally, the reaction works well with electron-rich and electron-deficient aryldiazoacetates (eq 1).

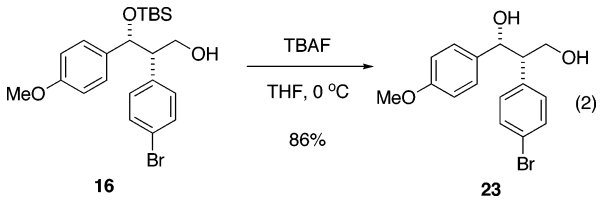


Determination of Absolute Stereochemistry. Rh_2-((*S*)-DOSP)$_4$ catalyst has been shown to furnish products with the same sense of asymmetric induction as the (*S*)-lactate chiral auxiliary in several different examples of cyclopropanation reactions of vinyldiazoacetates[3,13] and Si−H insertions.[14h−j,21] From our previous studies on enantioselective C−H functionalization with aryldiazoacetates, the Rh_2((*S*)-DOSP)$_4$ catalyst predictably directs attack to the *re* face of the carbenoid,[1] generally with high asymmetric induction. The current study is very anomalous because the enantioselectivity of the reactions conducted with Rh_2((*S*)-DOSP)$_4$ is low, and the (*S*)-chiral catalyst and (*S*)-chiral auxiliary approaches lead to opposite asymmetric inductions. Therefore, it was deemed necessary to unambiguously determine the absolute configuration of the reaction products. This was achieved by treatment of **16** (derived from reduction of Rh_2((*S*)-PTTL)$_4$-catalyzed C−H functionalization product **21**) with

SCHEME 2



TBAF in order to furnish diol **23** (eq 2). Recrystallization of diol **23** generated suitable crystals for X-ray crystallographic analysis, which confirmed the absolute stereochemistry as 1*R*,2*S*.[22] This result means that the chiral auxiliary model,[14] which has been an excellent predictor for enantioselective cyclopropanation reactions, gave the wrong result in this C−H functionalization.



To further establish whether the chiral auxiliary behaves differently in C−H functionalization chemistry compared to cyclopropanation chemistry, a second substrate was examined that had already been shown to give excellent enantiocontrol in a Rh_2((*S*)-DOSP)$_4$-catalyzed C−H functionalization. Rh_2((*S*)-DOSP)$_4$-catalyzed decomposition of **7** in the presence of the cinnamyl silyl ether **25** followed by reduction furnished the alcohol **25** in >95% de and 75% ee, and the absolute configuration was determined to be 2*R*,3*R*[5] (Scheme 2). In comparison, the reaction of the (*S*)-lactate derivative **11** with the silyl ether **24** was examined, and this reaction again proceeded in high diastereoselectivity and enantioselectivity; however, the absolute configuration of product **25** was opposite to that of the Rh_2((*S*)-DOSP)$_4$-catalyzed reaction. This result clearly indicates that the influence of the chiral auxiliary in cyclopropanation reactions[13] is very different from that which occurs in the C−H functionalization reactions.

Conclusions

In conclusion, these results demonstrate that although the established dirhodium tetraprolinates such as Rh_2-((*S*)-DOSP)$_4$ and Rh_2((*R*)-DOSP)$_4$ are generally excellent catalysts for intermolecular C−H functionalization reactions, in the case of benzyl silyl ethers, the observed

(21) Davies, H. M. L.; Hansen, T.; Rutberg, J.; Bruzinski, P. R. *Tetrahedron Lett.* **1997**, *38*, 1741.

(22) The crystal structure has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 277546 has been allocated (Gerlits, O. O.; Coppens, P. Personal communication).

enantioselectivity was uniformly rather poor. Furthermore, these substrates display anomalous behavior when compared to previously studied systems. This paper described two approaches that solved the problem of low enantioselectivity. Initially, we developed the readily available α-hydroxyester chiral auxiliary-based aryldiazoacetates, which allow for efficient C−H functionalization to furnish the products in high enantioselectivity. After this work, we also found that Hashimoto's Rh_2((*S*)-PTTL)$_4$ catalyst served as an excellent catalyst for this reaction, providing the desired product in high yield, diastereoselectivity, and enantioselectivity. These two approaches can be considered as useful general alternative strategies when Rh_2((*S*)-DOSP)$_4$ does not work well in an intermolecular C−H insertion.

Experimental Section

General considerations, experimental procedures, and spectral data for all new compounds, including X-ray data for diol **23**, are included in the Supporting Information.

Synthesis of (2*R*,3*R*)-3-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-phenylpropionic Acid Methyl Ester (8a). Procedure A. A solution of methyl phenyldiazoacetate **7** (352 mg, 2.00 mmol, 2.00 equiv) in degassed 2,2-dimethylbutane (8 mL) was added via syringe pump over 2 h to a solution of Rh_2((*R*)-DOSP)$_4$ (19 mg, 0.01 mmol, 0.01 equiv) and compound **6a** (252 mg, 1.00 mmol, 1.00 equiv) in degassed 2,2-dimethylbutane (1 mL). After the addition was complete, the reaction mixture was stirred for 1 h and then concentrated in vacuo. Diastereoselectivity (88% de) was determined by ^{1}H NMR of the crude reaction mixture, and the products were purified by flash chromatography on silica gel using 18:1 hexane/Et_2O as eluant to provide the anti isomer as a white solid (15 mg), a mixture of anti and syn isomers as a white solid (41 mg), and pure syn isomer as a white solid (283 mg), with a total yield of 85%. **Procedure B.** A solution of methyl phenyldiazoacetate **7** (176 mg, 1.00 mmol, 2.00 equiv) in degassed 2,2-dimethylbutane (6 mL) was added to a solution of Rh_2((*S*)-PTTL)$_4$ (6 mg, 0.005 mmol, 0.01 equiv), compound **6a** (126 mg, 0.50 mmol, 1.00 equiv), and degassed 2,2-dimethylbutane (3 mL) under reflux via syringe pump at a rate of 2 mL/h. After the addition was complete, the reaction mixture was stirred at 50 °C for 30 min, allowed to cool to room temperature, and concentrated in vacuo. Diastereoselectivity (89% de) was determined by ^{1}H NMR of the crude reaction mixture, and the products were purified by flash chromatography on silica gel using 18:1 hexane/Et_2O as eluant to provide a mixture of anti and syn isomers as a white solid (9 mg), and pure syn isomer as a white solid (147 mg), with a total yield of 78%). Syn isomer: mp 62−64 °C; $[\alpha]_D$ +75.9 (ee 91%) (*c* 1.16, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, 2H, J = 7.5 Hz), 7.34−7.21 (m, 5H), 6.81 (d, 2H, J = 9.0 Hz), 5.06 (d, 1H, J = 9.0 Hz), 3.79 (s, 3H), 3.78 (d, 1H, J = 9.0 Hz), 3.43 (s, 3H), 0.61 (s, 9H), −0.37 (s, 3H), −0.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 158.9, 136.6, 135.0, 129.3, 128.1 (2C), 127.3, 113.2, 76.7, 61.7, 55.1, 51.6, 25.4, 17.8, −5.0, −5.8; IR ($CHCl_3$) 2953, 2929, 2856, 1736, 1612, 1512 cm^{-1}; *m/z* (ESI) 423 (MNa^+, 65%), 270 (14%), 269 (100%). Anal. Calcd for $C_{23}H_{32}O_4Si$: C, 68.96; H, 8.05. Found: C, 68.94; H, 8.08. HPLC analysis: 91% ee (Chiralcel OD-H, 1% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 4.8 min, minor; t_R = 5.7 min, major).

Synthesis of (2S,3*R*)-3-(*tert*-Butyldimethylsilanyloxy)-3-(4-methoxyphenyl)-2-phenylpropan-1-ol (13a). A solution of $Rh_2(OOct)_4$ (3.9 mg, 0.005 mmol, 0.01 equiv) and compound **6a** (126 mg, 0.50 mmol, 1.00 equiv) in degassed 2,2-dimethylbutane (5 mL) was heated under reflux for 45 min, and then allowed to cool to room temperature. A solution of compound **11** (262 mg, 1.00 mmol, 2.00 equiv) in degassed 2,2-dimethylbutane (9 mL) was added via syringe pump over 3 h. After addition was complete, the reaction mixture was stirred for 1 h, and then cooled to 0 °C. Diisobutylaluminum hydride (1.0 M in toluene, 3.0 mL, 3.00 mmol, 6.00 equiv) was added, and the reaction mixture was stirred for 2 h at 0 °C and then for 10 h at room temperature. The reaction mixture was then poured into a 1:1 mixture (50 mL) of Et_2O and saturated sodium potassium tartrate solution. The biphasic mixture was stirred for 45 min. The layers were separated, and the aqueous layer was further extracted with Et_2O (2×). The combined organic fractions were dried (Na_2SO_4), and concentrated in vacuo. Diastereoselectivity (83% de) was determined by ^{1}H NMR of the crude reaction mixture, and the product was purified by flash chromatography on silica gel using 10:1 hexane/Et_2O as eluant to isolate a mixture of the anti and syn isomers as a colorless oil (53 mg), and the pure syn isomer as a colorless oil (78 mg). Total mass: 131 mg (70%). Syn isomer: $[\alpha]_D$ +38.2 (ee 79%) (*c* 1.22, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26−7.21 (m, 3H), 7.08−7.05 (m, 2H), 6.99 (d, 2H, J = 8.5 Hz), 6.77 (d, 2H, J = 8.5 Hz), 4.91 (d, 1H, J = 6.0 Hz), 3.88 (dd, 1H, J = 11.0, 7.5 Hz), 3.80 (s, 3H), 3.77 (dd, 1H, J = 11.0, 7.0 Hz), 3.15 (dd, 1H, J = 13.0, 7.0 Hz), 1.21 (br s, 1H), 0.79 (s, 9H), −0.10 (s, 3H), −0.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 139.1, 134.4, 129.3, 128.0, 127.9, 126.8, 113.1, 77.0, 63.7, 56.4, 55.1, 25.7, 18.0, −4.8, −5.5; IR ($CHCl_3$) 3456, 2958, 1512, 1248, 1083 cm^{-1}; *m/z* (EI) 373 (M^+, 1%), 357 (36%), 251 (100%). Anal. Calcd for $C_{22}H_{32}O_3Si$: C, 70.92; H, 8.66. Found: C, 70.81; H, 8.62. HPLC analysis: 79% ee (*R*,*R*-Whelk-O1, 3% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 10.1 min, minor; t_R = 11.9 min, major).

Acknowledgment. Financial support from the National Science Foundation (CHE-0350536) is gratefully acknowledged. We thank Ms. Oksana O. Gerlits for the X-ray crystallographic studies, which allowed for the determination of the absolute stereochemistry of diol **23**. We thank Dr. Evan Antoulinakis for technical assistance with the early studies in this project.

Supporting Information Available: Experimental procedures and spectral data for all novel compounds and X-ray data for diol **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO051747G