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Catalytic Asymmetric Synthesis of Diarylacetates and 4,4-Diarylbutanoates. A Formal Asymmetric Synthesis of (+)-Sertraline

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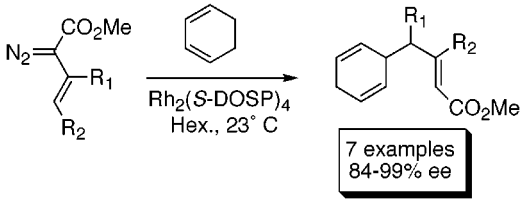
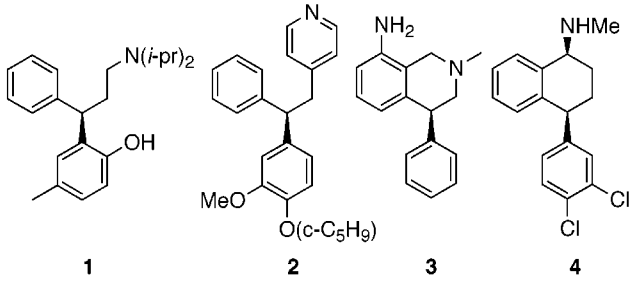
ABSTRACT



The intermolecular C–H insertion chemistry of phenyldiazoacetates catalyzed by dirhodium tetrakis((*S*)-*N*-(dodecylbenzenesulfonyl)prolinate) (Rh_2(S-DOSP)$_4$) can be effectively carried out on cyclohexadienes, leading to the asymmetric synthesis of diarylacetates. The reaction of vinyldiazoacetates with cyclohexadienes results in an unprecedented carbenoid reaction that is formally a combined C–H insertion/Cope rearrangement. The synthetic utility of this novel transformation was demonstrated by its utilization in a formal asymmetric synthesis of (+)-sertraline.

The *gem*-diarylalkyl group is present in a number of important pharmaceuticals,[1] such as tolterodine (**1**),[1a,b] CDP-840 (**2**),[1c] and nomifensine (**3**).[1d] Consequently, a number of reports have recently appeared describing methods for the asymmetric synthesis of *gem*-diarylalkyl derivatives.[2] Particularly effective have been the asymmetric conjugate addition of organometallic reagents to cinnamates[2a−e] and the aryl cuprate addition to enantiomerically pure dimethyl 2-phenylcyclopropane-1,1-dicarboxylate.[2f] In this paper we



1 **2** **3** **4**

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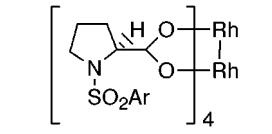
describe a novel method for the synthesis of diarylacetates and 4,4-diarylbutanoates that is based on asymmetric carbenoid transformations.[3] The practical utility of this methodology is demonstrated by a short formal synthesis of the antidepressant (+)-sertraline (**4**).[4]

The two general methods used to prepare *gem*-diarylalkyl compounds were discovered during exploratory studies into the synthetic potential of intermolecular asymmetric C−H insertions of Rh_2(*S*-DOSP)$_4$ (**5**) catalyzed[5] decomposition of



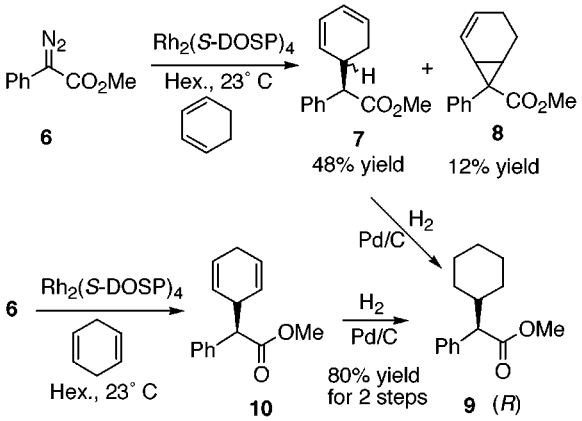
Ar =p-($CH_3(CH_2)_{10\text{-}12}$)$C_6H_4$

Rh_2(*S*-DOSP)$_4$

5

aryldiazoacetates.[6] Previously, we had shown that the decomposition of aryldiazoacetates in the presence of cycloalkanes or tetrahydrofuran resulted in C−H insertion with high asymmetric induction.[5] On evaluation of the possibility that this reaction may be favored at allylic C−H bonds, it was discovered that the reaction of **6** with 1,3-cyclohexadiene resulted in the preferential formation of the C−H insertion product **7** rather than the cyclopropanated product **8** (Scheme 1). The C−H insertion product **7** was formed as an

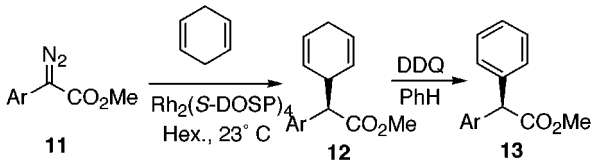
Scheme 1



inseparable 4:1 mixture of diastereomers, and so in order to determine the extent of the asymmetric induction, **7** was reduced to the known cyclohexane **9**, which was formed in 92% ee (*R* configuration).[7] An even more effective C−H insertion was achieved on reaction of **6** with 1,4-cyclohexadiene, as this resulted in the formation of the C−H insertion product **10** with very little occurrence of the cyclopropanation reaction. The absolute stereochemistry of **10** was determined to be *R* by reduction of **10** to the cyclohexane **9** (80% overall yield from **6** with a 91% ee).

The reaction with 1,4-cyclohexadiene could be carried out with a range of aryldiazoacetates **11,** as illustrated in Scheme 2. In each case the C−H insertion product **12** was produced

Scheme 2

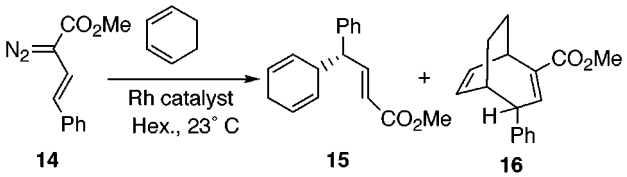


	Ar	yield **12** (%)	ee **12** (%)	yield **13** (%)	ee **13** (%)
a	4-ClC_6H_4	84	95	86	95
b	4-MeC_6H_4	84	94	89	94
c	4-MeOC_6H_4	69	93	87	93
d	2-naphthyl	64	92	88	92

in >90% ee. Furthermore, **12** could be readily oxidized by DDQ to the diarylacetate **13** without racemization. The absolute stereochemistry for **12** and **13** is tentatively assigned on the assumption that the asymmetric induction would parallel that observed in the formation of **10**.

The new strategy to 4,4-diarylbutanoates was discovered on attempting the C−H insertion reaction with the phenylvinyldiazoacetate **14**. Reaction of **14** with 1,3-cyclohexadiene did not result in the formation of the expected C−H insertion product. Instead, the 1,4-cyclohexadiene **15** was formed in 63% yield and 98% ee (Scheme 3). A side product in this reaction is the cyclopropanation/Cope rearrangement product **16**. The catalyst has a major effect on the product distribution in this reaction.[8] When rhodium(II) octanoate is used as

Scheme 3



(98% ee for Rh_2(*S*-DOSP)$_4$)

Rh catalyst	**15** : **16**
Rh_2(*S*-DOSP) $_4$	84 : 16
Rh_2(OOct) $_4$	26 : 74
Rh_2(OPiv) $_4$	19 : 81
Rh_2(TFA) $_4$	46 : 54
Rh_2(TPA) $_4$	30 : 70

(4) (a) Coe, B. K.; Weissman, A.; Welch, W. M.; Broune, R. G. *J. Pharmacol. Exp. Ther.* **1983**, *226*, 686. (b) Welch, W. M.; Kraska, A. R.; Sarges, R.; Coe, K. B. *J. Med. Chem.* **1984**, *27*, 1508. (c) Quallich, G. J.; Woodall, T. M. *Tetrahedron* **1992**, *48*, 10239.

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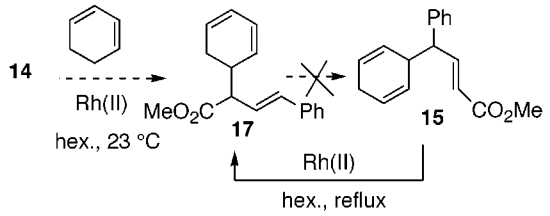
(7) Camps, P.; Gimenez, S. *Tetrahedron: Asymmetry* **1996**, *7*, 1227.

catalyst, cyclopropanation becomes the preferred reaction, and from the range of catalysts that were studied, it is apparent that the catalyst exhibits a subtle combination of steric and electronic effects. So far, Rh_2(*S*-DOSP)$_4$ is the best catalyst for limiting the cyclopropanation reaction, resulting in a 84:16 ratio of **15** to **16**.

The most obvious mechanism for the formation of cyclohexadiene **15** would be an allylic C−H insertion between **14** and 1,3-cyclohexadiene to form **17**, followed by a Cope rearrangement to **15** (Scheme 4). There is no obvious driving

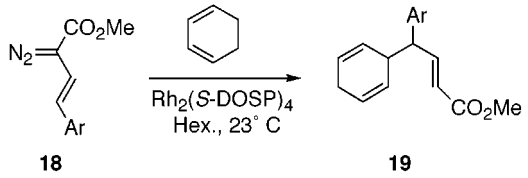
Scheme 4



force, however, for the Cope rearrangement of **17** to **15**. Indeed, it was confirmed that the driving force for the Cope rearrangement is in the reverse direction by heating **15** in refluxing hexane, because under these conditions, **15** slowly rearranged to **17**. Consequently, alternative mechanistic possibilities need to be considered. It is conceivable that **15** is derived by an intercepted C−H insertion process or by means of an ene reaction where the vinylcarbenoid reacts as a 2π system. Further studies will be needed to determine the actual mechanism of this most unusual carbenoid transformation.

The reaction can be extended to a range of arylvinyldiazoacetates **18**, as illustrated in Scheme 5.[9] The reactions with *m*- or *p*-substituted benzenes **18a** and **18b** or 2-naphthyl (**18c**) result in the formation of **19a**−**c** with exceptionally high levels of asymmetric induction (99% ee). In contrast,

Scheme 5



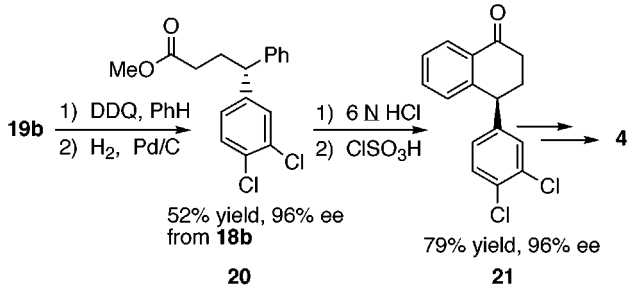
18 **19**

	Ar′	yield **19** (%)	ee **19** (%)
a	4-MeOC$_6$H$_4$	58	99
b	3,4-diClC$_6$H$_3$	59	99
c	2-naphthyl	50	99
d	2-MeOC$_6$H$_4$	17	86
e	1-naphthyl	22	84

the reactions with *o*-substituted benzene **18d** or 1-naphthyl (**18e**) result in the formation of **19d** or **19e** with lower enantioselectivity (84−86% ee). Also the yields of **19d** and **19e** were greatly decreased compared to those of **19a**−**c**, because the major product in these last two reactions was the cyclopropanation/Cope rearrangement product, analogous to **16**.

The cyclohexadiene **19b** is an excellent precursor for the formal synthesis of (+)-sertraline, as illustrated in Scheme 6. Oxidation of **19b** with DDQ followed by catalytic

Scheme 6



20 **21**

hydrogenation formed the 4,4-diarylbutanoate **20** (52% yield for 3 steps from **18b**) with minimal racemization (96% ee). Ester hydrolysis of **20** followed by an intramolecular Friedel−Crafts acylation generated the tetralone **21** (79% yield for two steps), which has been previously converted to (+)-sertraline.[2f,10]

The general chemistry is applicable to other vinylcarbenoid systems, as illustrated in Scheme 7. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of the cyclic vinyldiazoacetate **22** in the

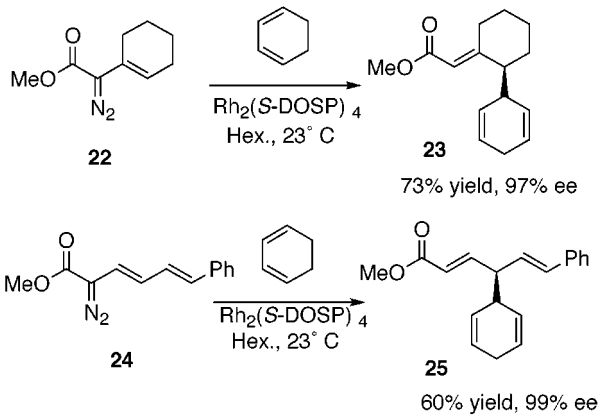
(8) For other examples of ligand effects on carbenoid reactivity, see: (a) Padwa, A.; Ustin, D. J.; Price, A. T.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N.; Winchester, W. R.; Tran, A. *J. Am. Chem. Soc.* **1993**, *115*, 8669. (b) Padwa, A.; Austin, D. J.; Hornbuckle, S. F.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc.* **1992**, *114*, 1874. (c) Davies, H. M. L.; Saikali, E.; Clark, T. J.; Chee, E. H. *Tetrahedron Lett.* **1990**, *31*, 6299.

(9) **General Procedure for Rh_2(*S*-DOSP)$_4$ Catalyzed Decomposition of Vinyldiazomethanes in the Presence of Cyclohexadienes**. A solution of vinyldiazoacetate **18b** (207 mg, 0.764 mmol) in dry hexanes (20 mL) was added dropwise over 15 min to a flame-dried flask containing a stirred solution of Rh_2(*S*-DOSP)$_4$ (12 mg, 6.4×10^{-3} mmol) and the diene (0.4 mL, 4 mmol) in dry hexane (30 mL) at room temperature. After 16 h the solvent was removed under reduced pressure. Purification by flash silica gel column chromatography (9:1 petroleum ether/Et_2O, R_f = 0.24) gave **19b** in 59% yield as a clear oil: 99% ee (determined by HPLC: Daicel-OD, 0.8% *i*-Pr-OH in hexanes, 0.8 mL/min; T_r = 12.06 min (minor), 23.73 min (major)); $[\alpha]^{25}_D = +4°$ (*c* 2.08, $CHCl_3$); IR (neat) 3029, 2954, 2863, 2817, 1726, 1651 cm^{-1}; ^{1}H NMR (300 MHz) δ 7.36 (d, 1 H, *J* = 8.0 Hz), 7.27 (d, 1 H, *J* = 2.5 Hz), 7.10 (dd, 1 H, *J* = 15.5, 8.5 Hz), 7.02 (dd, 1 H, *J* = 8.0, 2.5 Hz), 5.81 (d, 1 H, *J* = 15.5 Hz), 5.75 (br d, 2 H, *J* = 12.0 Hz), 5.57 (br d, 1 H, *J* = 10.0 Hz), 5.43 (br d, 1 H, *J* = 10.0 Hz), 3.71 (s, 3 H), 3.38 (dd, 1 H, *J* = 8.5, 8.0 Hz), 3.17−3.15 (m, 1 H), 2.62−2.48 (m, 2 H); ^{13}C NMR (125 MHz) δ 166.5, 148.1, 140.7, 132.4, 130.8, 130.4, 130.2, 127.6, 126.83, 126.79, 125.7, 125.3, 122.9, 53.6, 51.6, 40.1, 26.3; HRMS calcd for $C_{17}H_{16}O_2Cl_2$ 322.0527, found 322.0504.

(10) The absolute configuration of compound **21** is *S*: found $[\alpha]^{26}_D$ = +66° (*c* = 2.04, PhH); lit.[2f] value $[\alpha]^{23}_D$ = +71.3° (*c* = 1.1, PhH), *S*-isomer.

(11) The absolute configuration of compound **23** was determined by DDQ oxidation and ozonolysis to afford partially racemized 2-phenylcyclohexanone in 56% yield: found $[\alpha]^{26}_D$ = −17 (*c* = 1.66, PhH); lit. value $[\alpha]^{24}_D$ = −113.5 (*c* = 0.60, PhH), *S*-isomer (Berti, G.; Macchia, B.; Macchia, F.; Monti, L. *J. Chem. Soc.* **1971**, 3371).

Scheme 7



presence of 1,3-cyclohexadiene resulted in the formation of the 1,4-cyclohexadiene **23** in 73% yield and 97% ee.[11] Similarly, decomposition of the dienyldiazoacetate **24** in the presence of 1,3-cyclohexadiene resulted in the formation of **25** (60% yield and 99% ee), in which both diene components have moved out of conjugation.

In summary, the intermolecular C−H insertion chemistry of phenyldiazoacetates can be effectively carried out on cyclohexadienes, leading to the asymmetric synthesis of diarylacetates. The reactions of vinyldiazoacetates with cyclohexadienes result in an unprecedented carbenoid reaction that is formally a combined C−H insertion/Cope rearrangement. The synthetic utility of this novel transformation was demonstrated by its utilization in a formal asymmetric synthesis of (+)-sertraline.

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Supporting Information Available: Full experimental data for compounds **13**, **15**−**21**, **23**, and **25**. This material is available free of charge via the Internet at http://pubs.acs.org.

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