JOC Article

Investigation into Factors Influencing Stereoselectivity in the Reactions of Heterocycles with Donor−Acceptor-Substituted Rhodium Carbenoids

Simon J. Hedley, Dominic L. Ventura, Paulina M. Dominiak, Cara L. Nygren, and Huw M. L. Davies*

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

hdavies@buffalo.edu

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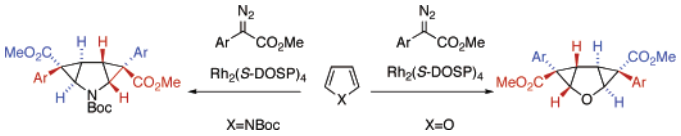

Rhodium-catalyzed decomposition of aryldiazoacetates in the presence of pyrroles or furans results in mono- or biscyclopropanation of the heterocycle, but with opposite enantioinduction. In the absence of sterically encumbering groups, the cyclopropanation of furan occurs with initial bond formation at the 2-position. If this pathway is sterically blocked, cyclopropanation can occur with initial bond formation at the 3-position of the furan ring; in this case, the cyclopropanation reaction takes place on the opposite face of the heterocycle, and the opposite enantioinduction is observed. Upon extension of this methodology to benzofurans, a highly enantioselective monocyclopropanation reaction occurs to furnish a product derived from initial bond formation at the 2-position of the benzofuran. When this reaction pathway is inhibited by sterically encumbering substituents on the benzofuran, no cyclopropanation of the furan ring is observed, and instead, double cyclopropanation of the benzene ring occurs. Double cyclopropanation of the benzene ring was also observed in reactions with indoles.

Introduction

Metal carbenoids, which are readily generated by metal-catalyzed decomposition of diazoacetates, occupy an established position as versatile synthetic intermediates in organic chemistry.[1] In comparison to free carbenes, metal carbenoids have increased stability and are capable of highly selective reactions.[2] The reactivity profile of these transient metal-stabilized carbenoids is very dependent on the structure of the carbenoid and the metal.[3] In recent years, dirhodium complexes have been extensively used as catalysts.[1,4] The most widely used classes of rhodium carbenoids contain one or two electron-withdrawing groups on the carbenoid, defined in Chart 1 as acceptor- and acceptor−acceptor-substituted carbenoids. The presence of an electron-withdrawing substituent causes the carbenoid to be highly electrophilic and amenable to participate in a variety of reactions.[5] More recently, donor−acceptor carbenoids, which are flanked by an electron-withdrawing group and an electron-donating group, have come to prominence.[3] These metal carbenoids are considerably more stable than the traditional rhodium carbenoids as a result of the presence of this electron-donating moiety. Thus, this class of carbenoid is capable of highly chemoselective reactions[3] and, furthermore, is less prone to dimer formation than carbenoids derived from alkyl diazoacetates.[6]

The cyclopropanation reactions of alkenes with donor−acceptor carbenoids are highly diastereoselective,[7] and in the reaction of dienes with vinyldiazoacetates, the resultant *cis*-divinylcyclopropanes undergo ring expansion via a Cope rearrangement to generate seven-membered rings with full control of the relative configuration at up to three stereogenic

(1) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, 1997.
(2) Paulissenen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, Ph. *Tetrahedron Lett.* **1973**, *14*, 2233.
(3) (a) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (b) Davies, H. M. L. *Curr. Org. Chem.* **1998**, *2*, 463.
(4) Maas, G. *Top. Curr. Chem.* **1987**, *137*, 76.
(5) Dorwald, F. Z. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: Weinhem, Germany, 1999.
(6) Davies, H. M. L.; Hodges, L. M.; Matasi, J. J.; Hansen, T.; Stafford, D. G. *Tetrahedron Lett.* **1998**, *39*, 4417.
(7) Davies, H. M. L.; Clark, T. J.; Church, L. A. *Tetrahedron Lett.* **1989**, *30*, 5057.

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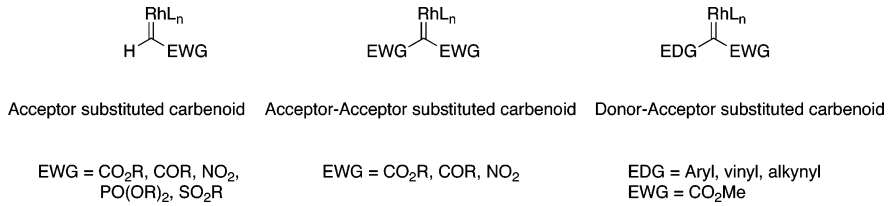
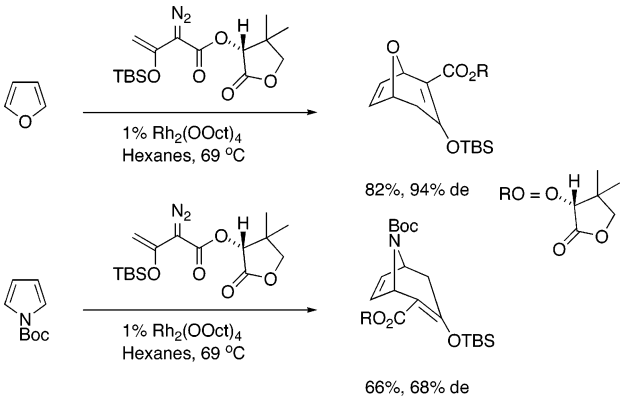
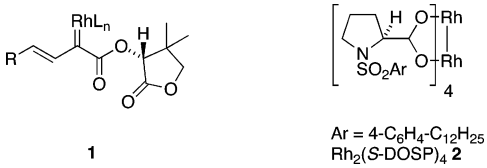
CHART 1. Classification of Rhodium Carbenoids



SCHEME 1

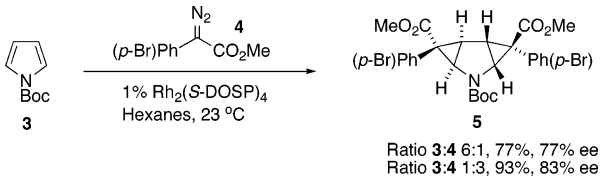


centers.[8] Furthermore, highly enantioselective cyclopropanations can be achieved by utilizing α-hydroxy esters as chiral auxiliaries on the carbenoid (**1**),[9] or the chiral dirhodium tetraprolinate, Rh_2(*S*-DOSP)$_4$ (**2**).[10]



The tandem cyclopropanation/Cope rearrangement between vinylcarbenoids and furans or pyrroles has been developed into a very attractive approach for the asymmetric synthesis of oxa- and azabicyclic systems comprising a formal [4+3] cycloaddition reaction.[11] Chiral auxiliaries have been demonstrated to be more effective than chiral catalysts in this chemistry, because the reaction of these electron-rich heterocycles catalyzed by dirhodium tetraprolinates leads to side products derived from zwitterionic intermediates.[11] A most intriguing feature of this chemistry is the observation that the reaction of vinyldiazoacetates with furan and *N*-Boc pyrrole led to opposite asymmetric induction, even though the same chiral auxiliary was used in both cases (Scheme 1).[11] This paper describes a systematic study to explore further how the structure of the heterocycle influences the enantioinduction in the rhodium-catalyzed reaction with donor−acceptor carbenoids.

SCHEME 2



Reactions With *N*-Boc-pyrrole. The rhodium-catalyzed reaction between vinylcarbenoids and *N*-Boc-pyrrole generally leads to tropane derivatives via the tandem cyclopropanation/Cope rearrangement.[11b] A single example exists, however, where the Cope rearrangement of the cyclopropane was comparatively sluggish, and the reaction instead furnished a product where a second cyclopropanation took place at the remaining enamine.[12] This contrasts with the chemistry of acceptor-substituted metal carbenoids, in which a monocyclopropanation product tends to predominate.[13,14] For example, copper(I) bromide-catalyzed decomposition of ethyl diazoacetate with *N*-acylated pyrrole substrates has been shown to be a rather poor reaction, leading mainly to monocyclopropanation products in poor yield (17%), with only a small amount of product (5%) arising from a double cyclopropanation reaction.[13] These cyclopropane products tend to decompose on attempted distillation to give formal substitution products and a regenerated aromatic ring. A more recent procedure,[14] which utilizes catalytic copper(II) triflate activated by phenylhydrazine, also gives monocyclopropanation product in higher yield (39%), again with only a small amount (3%) of the double cyclopropanation product.

In the current study, aryldiazoacetates were used as the precursors to the donor−acceptor carbenoids. These substrates would limit further rearrangement of the products and the formation of side products derived from zwitterionic intermediates, which tends to occur in the dirhodium tetraprolinate-catalyzed reactions of vinyldiazoacetates.[11b] Even though a variety of aryldiazoacetates are compatible with the carbenoid chemistry,[3] methyl *para*-bromophenyldiazoacetate **4** was used as the source of carbenoid to simplify the determination of the absolute configuration of the products. Decomposition of **4** in the presence of *N*-Boc pyrrole **3** (Scheme 2) allowed clean isolation of the biscyclopropane **5** as a single diastereomer in high yield and good enantioselectivity. Biscyclopropane **5** was preferentially formed even when 6 equiv of *N*-Boc-pyrrole **3** was used, which indicates that the monocyclopropane intermediate **6** is much more efficiently cyclopropanated by **4** than is *N*-Boc pyrrole **3**. The absolute configuration of **5** was assigned

(8) (a) Davies, H. M. L. *Tetrahedron* **1993**, *49*, 5203. (b) Davies, H. M. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press, Inc.: Greenwich, CT, 1999; Vol. 5, pp 119−164.

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

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

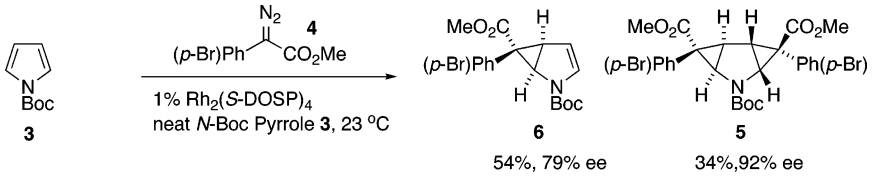
(11) (a) Davies, H. M. L.; Ahmed, G.; Churchill, M. R. *J. Am. Chem. Soc.* **1996**, *118*, 10774. (b) Davies, H. M. L.; Matasi, J. J.; Hodges, L. M.; Huby, N. J. S.; Thornley, C.; Kong, N.; Houser, J. H. *J. Org. Chem.* **1997**, *62*, 1095.

(12) Davies, H. M. L.; Young, W. B.; Smith, H. D. *Tetrahedron Lett.* **1989**, *30*, 4653.

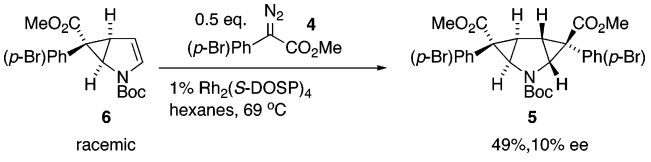
(13) (a) Tanny, S. R.; Grossman, J.; Fowler, F. W. *J. Am. Chem. Soc.* **1972**, *94*, 6495. (b) Biellmann, J. F.; Goeldner, M. P. *Tetrahedron* **1971**, *27*, 2957.

(14) Beumer, R.; Bubert, C.; Cabrele, C.; Vielhauer, O.; Pietzsch, M.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 8960.

SCHEME 3



SCHEME 4



by X-ray crystallographic analysis of material recrystallized to high enantiomeric purity.[15]

The monocyclopropane **6** can be isolated when *N*-Boc pyrrole **3** is used in vast excess as the reaction solvent (Scheme 3). The initial cyclopropanation was shown to proceed to furnish product **6** in 79% ee, while subjection of racemic **6** to a subsequent Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation reaction shows the biscyclopropane **5** is formed with only 10% ee (Scheme 4). As a result of the lack of solubility of (±)-**6** at room temperaure, these reactions had to be conducted in refluxing hexanes. Even so, these results show that the most significant step for asymmetric induction in the formation of the biscyclopropane **5** is the first cyclopropanation event.

Reactions with Furans. The reaction of carbenoids with furans usually leads to the unraveling of the heterocycle, resulting in the formation of differentially functionalized dienes in good yield.[16] Additionally, the furanocyclopropane derived from the $Rh_2(OAc)_4$-catalyzed reaction with ethyl diazoacetate and furan is unstable and rearranges on standing to the (*Z*,*E*)-diene.[16] Reiser has reported some success in the enantioselective cyclopropanation of furans using a copper(I)-bis(oxazoline)-catalyzed procedure, although high enantioselectivity was only observed when the furan was substituted at the 2-position with an ethyl ester.[17]

Unlike the above reactions with *N*-Boc-pyrrole **3** (Scheme 2), the reaction with furan (**7**) provided a range of products, with the distribution highly dependent on the reaction conditions. When **4** was used as the limiting reagent, the major product **8** was found to arise from a single cyclopropanation reaction, along with double cyclopropanation to provide **9** as a minor product (Scheme 5, eq 1). Formation of **9** could be suppressed by conducting the reaction with **7** as solvent (Scheme 5, eq 2). Conversely, **9** could be generated in high yield by using a relative excess of **4** (Scheme 5, eq 3). Additionally, relatively minor amounts of diene products **10** and **11** were observed in these reactions. This study indicates that donor−acceptor carbenoids display a different reactivity profile to the carbenoids derived from ethyl diazoacetate,[16] which generated dienes similar to **10** as the major reaction products. The absolute stereochemistry of the biscyclopropane **9** was determined by X-ray crystallography[18] and is opposite to the biscyclopropane **5** derived from *N*-Boc pyrrole **3**, despite the fact that the same enantiomer of the catalyst (Rh_2(*S*-DOSP)$_4$) was used in these reactions.[17]

The absolute stereochemistry of the monocyclopropane **8** could not be determined directly by X-ray crystallography, as suitable enantioenriched crystals of **8** could not be obtained. However, this could be determined later, as hydrogenation of **8** provided **12** (Scheme 6), where the absolute configuration was shown to be the opposite enantiomer to **ent-12** (see Scheme 7), which itself was determined by X-ray crystallography.[19]

Upon resubjection of racemic **8** to the rhodium carbenoid reaction, double cyclopropanation product **9** was isolated with low (9% ee) enantioselectivity (Scheme 8). This again indicates that the second cyclopropanation is not greatly influenced by the chiral catalysts.

To probe further the change of enantioinduction for *N*-Boc-pyrrole **3** and furan **7**, the reaction of 2,3-dihydrofuran (**13**) was examined. A very efficient cyclopropanation occurred to generate a single diastereomer of **ent-12** in 81% yield and 77% ee (Scheme 7). The absolute stereochemistry of **ent-12** from this reaction was determined by X-ray crystallography of an enriched sample,[19] and also shown by chiral HPLC to be the opposite enantiomer to **12** derived from hydrogenation of **8** (see Scheme 6).

We reasoned that studying more substituted furan derivatives would allow further insight into the stereoselectivity of this reaction. Accordingly, 2,5-dimethylfuran **14** was subjected to the reaction conditions (Scheme 9). This resulted in a clean reaction to form a single diastereomer of the biscyclopropane **15** in 76% yield and 84% ee. X-ray crystallography of an enriched sample of **15** showed that the sense of asymmetric induction of **15** was the same as it was for the biscyclopropane **5**,[20] derived from the reaction of *N*-Boc pyrrole **3**, and it was opposite from that of the biscyclopropane **9**, derived from furan **7**. Notably, no diene products arising from the unraveling of the heterocyclic ring were observed in this reaction.

Previous studies have shown that the reactions of vinyldiazoacetates with furans substituted at C-2 with electron-donating groups strongly favor the unraveling of the heterocycle by means of a zwitterionic reaction pathway.[21] The same reactivity was observed in the reaction of the aryldiazoacetate **4** with 2-meth-

(15) The crystal structure of **5** has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 604170 has been allocated [Dominiak, P. A.; Coppens, P. Private communication].

(16) (a) Nvak, J.; Sorm, F. *Collect. Czech. Chem. Commun.* **1958**, *23*, 1126. (b) Schenck, G. O.; Steinmetz, R. *Liebigs Ann.* **1963**, *668*, 19. (c) Wenkert, E.; Bakuzis, M. L. F.; Buckwalter, B. L.; Woodgate, P. D. *Synth. Commun.* **1981**, *11*, 533. (d) Nevedov, O. M.; Shostakovsky, V. M.; Samoilova, M. Y.; Kravchenko, M. I. *Izv. Akad. Nauk, Ser. Khim.* **1972**, 2342. (e) Nevedov, O. M.; Saltykova, L. E.; Vasilvitskii, L. E.; Shostakovsky, A. E. *Izv. Akad. Nauk, Ser. Khim.* **1986**, 2625.

(17) Schinnerl, M.; Böhm, C.; Seitz, M.; Reiser, O. *Tetrahedron: Asymmetry* **2003**, *14*, 765.

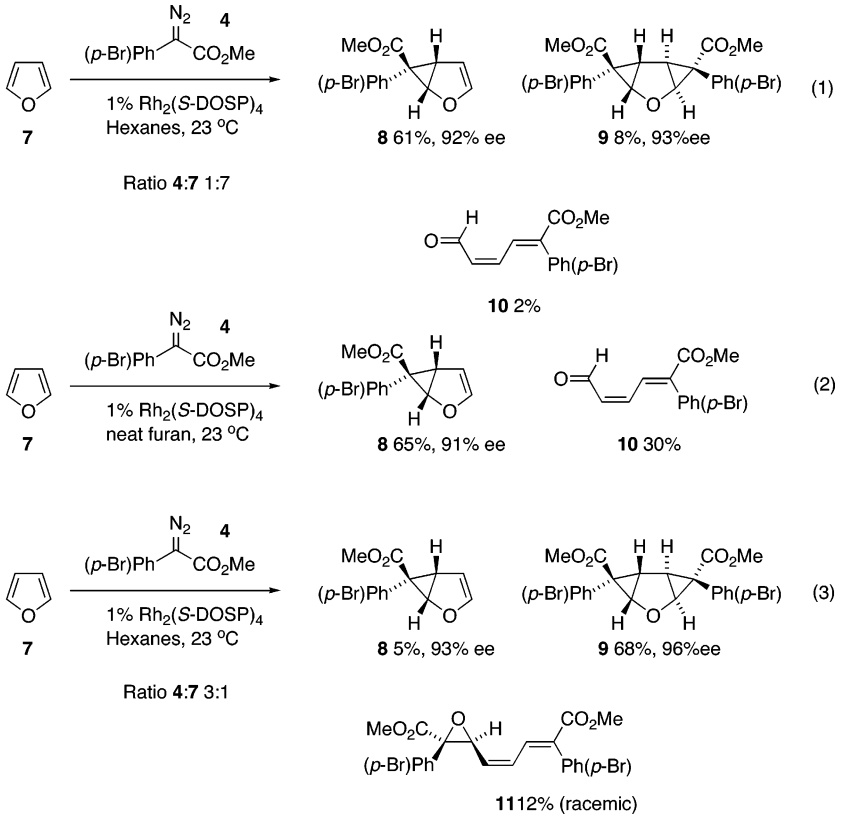
(18) The crystal structure of **9** has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 603126 has been allocated [Dominiak, P. A.; Coppens, P. Private communication].

(19) The crystal structure of **ent-12** has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 603045 has been allocated [Nygren, C. L.; Coppens, P. Private communication].

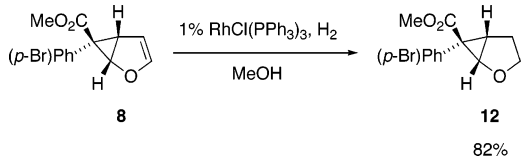
(20) The crystal structure of **15** has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 603125 has been allocated [Dominiak, P. L.; Coppens, P. Private communication].

(21) Davies, H. M. L.; Clark, D. M.; Alligood, D. B.; Eiband, G. R. *Tetrahedron* **1987**, *43*, 4265.

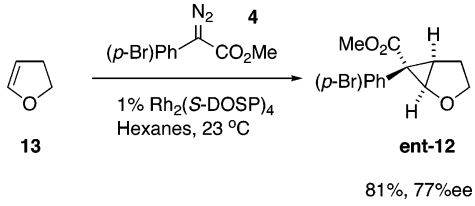
SCHEME 5



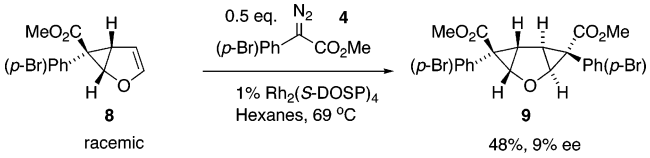
SCHEME 6



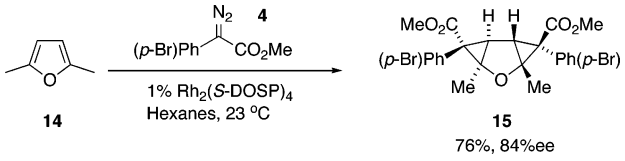
SCHEME 7



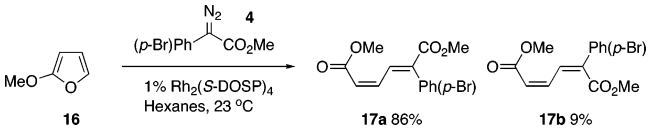
SCHEME 8



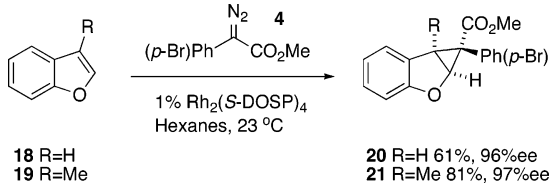
SCHEME 9



SCHEME 10



SCHEME 11



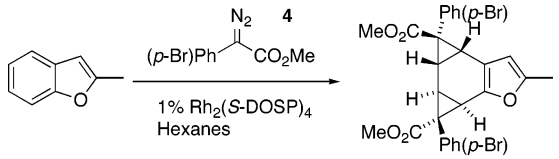
oxyfuran (**16**), as no cyclopropanation products were observed, and dienes **17a**,**b** were the only reaction products (Scheme 10). The assigned diene geometry was determined by NOE experiments.

Reaction with Benzofurans. Copper-catalyzed decomposition of ethyl diazoacetate in benzofuran has been reported to proceed with cyclopropanation of the enol ether double bond as a 7:1 mix of diastereoisomers.[22] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of benzofuran **18** with **4** provided a single diastereomer of the cyclopropane **20** in 61% yield with very high enantioselectivity (96% ee; Scheme 11). An exceptionally efficient reaction was also observed with 3-methylbenzofuran **19**, generating a single diastereomer of the cyclopropane **21** in 81% yield and 97% ee. The absolute configuration of **20** was determined by X-ray crystallography.[23] Suitable crystals of **21**

(22) Wenkert, E.; Alonso, M. E.; Gottlieb, H. E.; Sanchez, E. L.; Pellicciari, R.; Cogolli, P. *J. Org. Chem.* **1977**, *42*, 3945.

(23) The crystal structure of **20** has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 270718 has been allocated [Dominiak, P. A.; Coppens, P. Private communication].

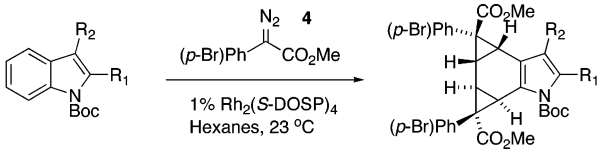
SCHEME 12



22 **23**

23 °C 47%, 51% ee
69 °C 49%, 32% ee

SCHEME 13



24 R_1=H, R_2=Me
25 R_1=Me, R_2=H

26 R_1=H, R_2=Me 85%, 79% ee
27 R_1=Me, R_2=H 61%, 87% ee

for X-ray crystallographic determination could not be formed and, therefore, the absolute configuration of **21** was tentatively assigned by circular dichroism (CD) comparison with both enantiomers of **20**.[24]

The substitution on the benzofuran has a major effect on the outcome of the reaction with the donor−acceptor carbenoid. This was clearly seen in the reaction of the aryldiazoacetate **4** with 2-methylbenzofuran (**22**). In this case, no cyclopropanation of the furan ring was observed. Instead, the major product, formed in 47% yield was a single diastereomer of **23** arising from double cyclopropanation of the benzenoid ring (Scheme 12). The enantioinduction in this case was relatively low (51% ee) and, because of this, the absolute configuration of the major enantiomer was not determined.

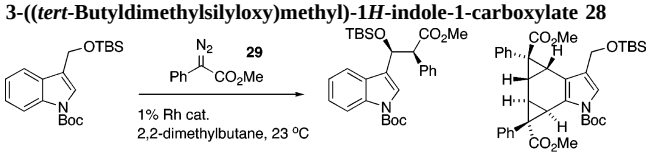
Reaction with Indoles. The copper-catalyzed reaction of ethyl diazoacetate with *N*-Boc-indole has been reported, resulting in cyclopropanation of the heterocyclic ring.[22,25] The Rh_2(*S*-DOSP)$_4$-catalyzed reaction of aryldiazoacetate **4** with unsubstituted *N*-Boc-indole resulted in recovery of starting material and the products of carbene dimerization. In contrast, effective reactions were possible with the 2- and 3-methyl indoles **24** and **25**, but the reaction resulted in the double cyclopropanation of the benzenoid ring to provide **26** and **27** (Scheme 13) as observed above (Scheme 12).

An understanding of the reactivity patterns of the heterocycles can be used to develop strategies for selective transformations in the presence of heterocycles. An example of this is shown in the attempted intermolecular C−H insertion of the 3-substituted indole **28**. As demonstrated in Scheme 13, the "pyrrole" portion of the indole will be unreactive, and so, the competing reactions are limited to C−H insertion to form **30** and the double cyclopropanation of the "benzene" portion of the indole to form **31**. The competition between the two processes is very dependent on which catalyst is used. The Rh_2(*S*-DOSP)$_4$-catalyzed

(24) The CD spectra of both enantiomers of **20** (derived from using Rh_2(*S*-DOSP)$_4$ or Rh_2(*R*-DOSP)$_4$ as catalyst), where the absolute stereochemistry has been verified by X-ray crystallography, were compared to the CD spectra of both enantiomers of **21**. This spectra suggests that the compounds have the absolute configuration assigned above in Scheme 11 and Figure 3 (see Supporting Information).

(25) Gnad, F.; Poleschak, M.; Reiser, O. *Tetrahedron Lett.* **2004**, *45*, 4277.

TABLE 1. Rh(II)-Catalyzed Decomposition of Methyl Phenyldiazoaceate 29 in the Presence of *tert*-Butyl 3-((*tert*-Butyldimethylsilyloxy)methyl)-1*H*-indole-1-carboxylate 28

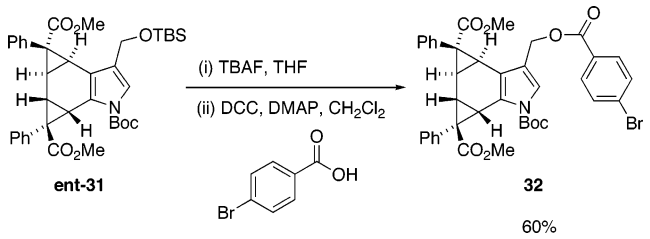


28 **30** **31**

entry	Rh cat.	yield, % **30**	de, % **30**	ee, % **30**	yield, % **31**	ee, % **31**
1	Rh_2(*S*-DOSP)$_4$	25	91	36	66	64
2	Rh_2(OOct)$_4$	70	87	n/a	0	n/a
3	Rh_2(*S*-PTTL)$_4$[a]	0	n/a	n/a	91	94[b]

[a] Reaction conducted at 50 °C. [b] Absolute stereochemistry of the product **ent-31** from Rh_2(*S*-PTTL)$_4$ (entry 3) is opposite to product **31** from the Rh_2(*S*-DOSP)$_4$-catalyzed reaction (entry 1) and confirmed by X-ray crystallography of derivative **32** (Scheme 14).

SCHEME 14



ent-31 **32**

60%

reaction gave a 1:2.5 mixture of **30** and **31**, while the Rh_2(OOct)$_4$-catalyzed reaction gave exclusively the C−H insertion product **30**. In contrast, the reaction catalyzed by Rh_2(*S*-PTTL)$_4$, the optimum catalyst for highly enantioselective C−H insertion of benzyl silyl ethers,[26] gave only the double cyclopropanation product **31**.

The absolute stereochemistry of product **ent-31**, derived from Rh_2(*S*-PTTL)$_4$ (Table 1, entry 3), was determined by the removal of the silyl group and esterification to provide **32**, which was subjected to X-ray analysis to confirm the absolute stereochemistry (Scheme 14).[27]

Strategies are available to alter the reactivity profile of the carbenoid to ensure that the C−H insertion becomes the dominant process. One approach is to use (*S*)-lactate as a chiral auxiliary. The effectiveness of this auxiliary in carbenoid chemistry is proposed to arise from the coordination of the ester carbonyl to the carbenoid, which leads to effective asymmetric induction and modulation of the carbenoid reactivity.[9] The Rh_2(OOct)$_4$-catalyzed reaction of the lactate **33** with the 3-substituted indole **28** generated the C−H insertion product **34** in 42% yield as a 6.4:1 mixture of syn/anti diastereomers (Scheme 15). Reduction of **34** with DIBAL generated the syn alcohol **35** in 50% yield and 72% ee. The absolute configuration of **35** has not been assigned unequivocally, but when similar enantioinduction to the benzyl silyl ethers is assumed,[26] the (*S*)-lactate-mediated reaction has been shown to give the opposite enantiomer to Rh_2(*S*-DOSP)$_4$ in C−H insertion reactions.

A benzene ring can be sterically protected from the double cyclopropanation as long as it is at least 1,4-disubstituted.[28] Thus, an even better method to suppress the double cyclopro-

(26) Davies, H. M. L.; Hedley, S. J.; Bohall, B. R. *J. Org. Chem.* **2005**, *70*, 10737.

(27) The crystal structure of **32** has been deposited at the Cambridge Crystallographic Data Centre, and the deposition number CCDC 603044 has been allocated [Nygren, C. L.; Coppens, P. Private communication].

SCHEME 15

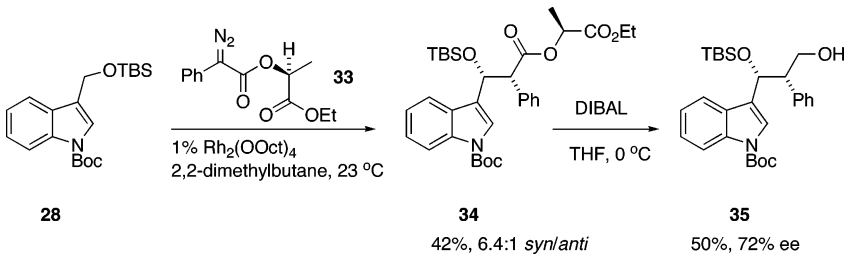
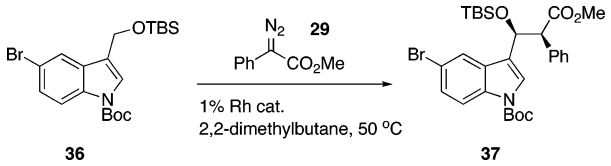


TABLE 2. Rh(II)-Catalyzed C−H Activation Reaction of *tert*-Butyl 5-Bromo-3-((*tert*-butyldimethylsilyloxy)methyl)-1*H*-indole-1-carboxylate 36 with Methyl Phenyldiazoacetate 29



entry	Rh cat.	yield, %	de, %	ee, %
1	Rh_2(*S*-DOSP)$_4$	74	69	51
2	Rh_2(OOct)$_4$	60	77	n/a
3	Rh_2(*S*-PTTL)$_4$	68	61	94[a]

[a] Absolute stereochemistry of **37** when Rh_2(*S*-PTTL)$_4$ is used (entry 3) is opposite to that shown.

panation is to use the brominated indole **36**. With this substrate, all three catalysts give only the C−H insertion product **37** (Table 2). No trace of any cyclopropanation products was observed. In accordance with previously reported results using benzyl silyl ether derivatives,[26] Rh_2(*S*-PTTL)$_4$ was the most effective chiral catalyst resulting in the formation of *syn*-**37** in 94% ee and 61% de. The absolute configuration of **37** has not been assigned unequivocally, but when similar enantioinduction to the benzyl silyl ethers is assumed,[26] the predicted configuration would be (2*S*,3*S*)-**37** for the Rh_2(*S*-DOSP)$_4$-catalyzed reaction and (2*R*,3*R*)-**37** for the Rh_2(*S*-PTTL)$_4$-catalyzed reaction.[29]

Discussion

Donor−acceptor rhodium carbenoids display a very different reactivity profile to the more traditional types of rhodium carbenoids.[3] The presence of the donor group greatly stabilizes the carbenoid, and this results in greatly increased selectivity in the resulting reactions of the carbenoid. For example, cyclopropanation reactions are routinely highly diastereoselective,[7] and selective intermolecular C−H insertions[3] are readily achieved. Hammett studies have shown that positive charge build-up at the carbene occurs during both the cyclopropanation[30] and C−H insertion,[28a] and electronic factors are much more pronounced in the donor−acceptor carbenoids compared to those of the carbenoids lacking an acceptor group. Furthermore, these carbenoids appear to be sterically quite demanding, and if the intended site of reaction is too crowded, it will be totally inert to the carbenoid, even though it may be electronically very activated.[3]

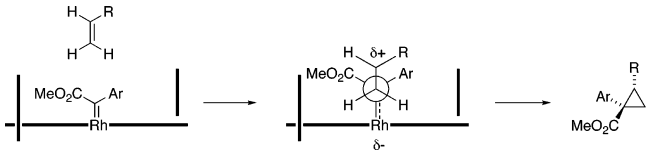


FIGURE 1. Predictive model for the Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation reaction of simple alkenes.

Dirhodium tetracarboxylate catalysts such as Rh_2(*S*-DOSP)$_4$ have been shown to be especially well-suited for the asymmetric transformations of the donor−acceptor carbenoids.[3] A very effective predictive model has been developed for both the diastereo- and the enantioselectivity, and this is summarized in Figure 1.[10] The catalyst is considered to behave as if it is D_2 symmetric, which means that the catalyst can be viewed simply as one surface with blocking groups in the front and back. Computational studies have indicated that the alkene would approach end-on with substituents facing the side of the donor group, and this is fully consistent with the observed selectivity in the cyclopropanation of simple alkenes.[31]

A most interesting phenomenon in these studies is that the sense of asymmetric induction can vary depending on which heterocycle is used. The enantioinduction in the reaction with furan **7** is opposite to the enantioinduction in the reactions with dihydrofuran **13**, 2,5-dimethylfuran **14**, and *N*-Boc-pyrrole **3**, even though the same chiral catalyst (Rh_2(*S*-DOSP)$_4$) is used in all cases. This apparent anomaly has been observed previously in the [4+3] cycloaddition reactions of vinyldiazoacetates with furans and *N*-acyl pyrroles.[11] When the current model for cyclopropanation reactions is applied where the substrate alkene approaches the rhodium carbenoid core in an end-on trajectory (Figure 2),[30] there are two possible approach vectors for the five-membered ring heterocycles. Furan (**7**) proceeds through the cyclopropanation pathway with initial bond formation at the 2-position, following the expected regiochemistry for aromatic electrophilic substitution of electron-rich five-membered heterocycles.[32] This model would explain the observed relative and absolute stereochemistry of the reaction with furan to form **8**. The more surprising result is the reaction with *N*-Boc pyrrole **3** because in order to obtain the opposite enantioinduction the reaction would need to proceed through an alternative pathway with initial bond formation at the 3-position to form **6**. Presumably, the steric influence of the *N*-Boc group overrides the usual electronic bias of *N*-Boc-pyrrole.[33] An intriguing

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

(29) For a discussion of the predictive models used in Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTTL)$_4$-catalyzed C−H insertion reactions, see ref 3a. Rh_2(*S*-DOSP)$_4$ and Rh_2(*S*-PTTL)$_4$ have been shown to give the opposite enantiomer in intermolecular C−H insertion reactions: see ref 26 and Müller, P.; Tohill, S. *Tetrahedron* **2000**, *56*, 1725.

(30) Davies, H. M. L.; Panaro, S. A. *Tetrahedron* **2000**, *56*, 4871.

(31) Nowlan, D. T., III; Gregg, T. M.; Davies, H. M. L.; Singleton, D. A. *J. Am. Chem. Soc.* **2003**, *125*, 15902.

(32) Gilchrist, T. L. *Heterocyclic Chemistry*; Pitman Publishing, Ltd.: London, 1985.

(33) Bray, B. L.; Mathies, P. H.; Naef, R.; Solas, D. R.; Tidwell, T. T.; Artis, D. R.; Muchowski, J. M. *J. Org. Chem.* **1990**, *55*, 6317.

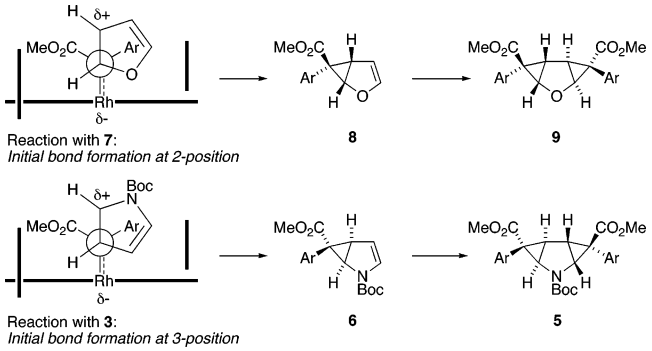


FIGURE 2. Predictive model for the Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation reaction: the consequenes of the different facial selectivities of furan **7** and *N*-Boc pyrrole **3** (Ar = *para*-bromophenyl).

feature of this analysis is the conclusion that the diastereoselectivity is independent of whether bond formation is initiated at the 2- or 3-positions, but the enantioselection is totally switched. This model can also readily explain the change in enantioinduction upon moving from furan to 2,3-dihydrofuran **13** or 2,5-dimethylfuran **14**. As an enol ether, electronically dihydrofuran would greatly favor initial bond formation at the C-3 position,[34] while this position would also be favored by 2,5-dimethylfurans as a result of the steric influence of the methyl groups.

The main contribution to the enantioselectivity appears to be governed by the initial step. The products **6** and **8**, derived from a single cyclopropanation of *N*-Boc pyrrole **3** (Scheme 3) and furan **7** (Scheme 5, eq 2), respectively, are isolated in high enantioselectivity. In contrast, the subjection of racemic cyclopropanes **6** or **8** to a second cyclopropanation reaction allows the isolation of products **5** and **9** only in low enantioselectivity (9−10% ee). These results indicate that the effect of the chiral catalyst is relatively minor in the second cyclopropanation reaction, and, hence, the initial cyclopropanation is the most important for enantioselectivity.

It is well-known that, unlike indoles, benzofurans react with electrophiles at the 2-position.[35] The same trend is observed in the cyclopropanation of **18**, as from the X-ray crystal data, and it is apparent that the product **20** arises from initial bond formation at the 2-position. A reasonable explanation for the lack of product arising from initial bond formation at the 3-position may be due to steric clash between the rhodium catalyst core and the benzenoid ring, especially the hydrogen atoms at the 4- and 5-positions. This is further supported by the fact that 3-methylbenzofuran (**19**) does not have an adverse effect on the efficiency or selectivity of the reaction. In fact, a higher yield of product was obtained with **19** compared to **18** (Scheme 11), and this may be due to increased stabilization of the developing positive charge at the 3-position of the intermediate through hyperconjugation (Figure 3). Furthermore, when 2-methylbenzofuran **22** is subjected to the reaction conditions, no cyclopropanation of the furan ring occurs (Scheme 12). It is particularly noteworthy that the steric demands of this reaction lead to the disruption of a more stable benzenoid ring over a more electron-rich heterocycle. According

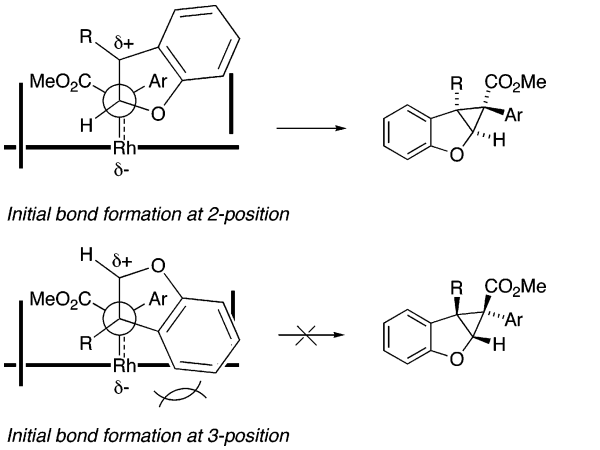


FIGURE 3. Predictive model for the Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation reactions of benzofuran derivatives **18** (R=H) and **19** (R=Me; Ar = *para*-bromophenyl).

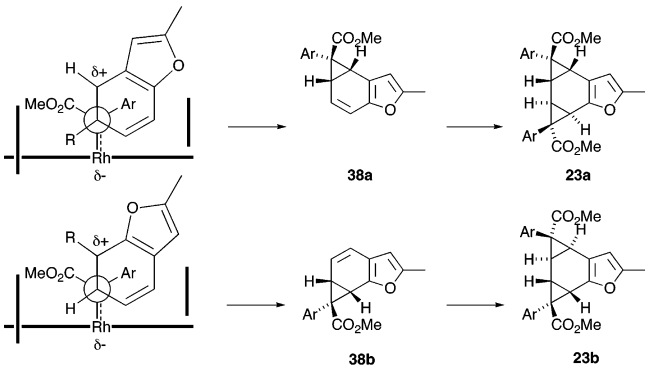


FIGURE 4. Rh_2(*S*-DOSP)$_4$−catalyzed double cyclopropanation reaction of 2-methylbenzofuran **22** and consequences for the enantioselectivity of product **23** (Ar = *para*-bromophenyl).

to the model proposed in Figure 3, 2-methylbenzofuran **22** would not be expected to favor initial bond formation at C-2 because the methyl group would interfere sterically. The inability of benzofurans **18**, **19**, or **22** to undergo the cyclopropanation reaction with initial bond formation at the 3-position is reflected in the high enantioselectivity (96−97% ee) of **20** and **21** in these reactions, and verified by the formation of double cyclopropanation product **23**.

The enantioselectivity of the double cyclopropanation product **23** derived from **22** is significantly lower than the double cyclopropanation products derived from furans and pyrroles. This could possibly be attributed to the fact that in the case of **22**, there is not much differentiation between the two alkenes of the benzenoid ring. Following the initial cyclopropanation reaction to generate **38a** and **38b**, the second reaction with the rhodium carbenoid must then take place on the opposite face (Figure 4). Both transition states are reasonable on steric grounds.

The inability of indoles to undergo cyclopropanation of the pyrrole ring with donor−acceptor compounds is not surprising given the trends that have been observed with other heterocycles in this study. The *N*-Boc group on pyrrole **3** effectively blocks cyclopropanation with initial bond formation at the 2-position (Scheme 2), while the studies with benzofurans show that these substrates do not undergo cyclopropanation with initial bond formation at the 3-position (Schemes 11 and 12). Therefore, in

(34) Davies, H. M. L.; Kong, N.; Churchill, M. R. *J. Org. Chem.* **1998**, *63*, 6586.

(35) Sargent, M. V.; Dean, F. M. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, pp 599−656.

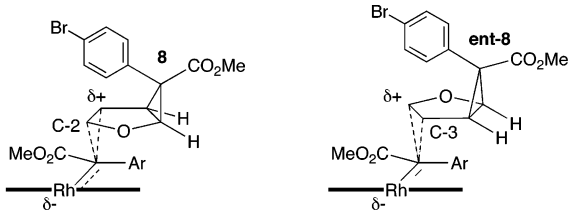


FIGURE 5. Steric and electronic considerations in the cyclopropanation reaction of **8**, catalyzed by Rh_2(*S*-DOSP)$_4$, with initial bond formation at C-2 or C-3.

the case of indoles **24** and **25**, the cyclopropanation of the pyrrole ring is effectively blocked at both positions and, hence, reactivity takes place on the benzenoid ring in a manner similar to **22**.

One of the most intriguing features of the chemistry of the donor−acceptor carbenoid with heterocycles is the tendency to form the double cyclopropanation products, essentially as single diastereomers, even though six new stereogenic centers are formed. This reactivity is different from the reactions of ethyl diazoacetate with *N*-Boc-pyrrole or furan, where the monocyclopropane is typically formed.[13,14,16,17] This behavior presumably demonstrates the greater selectivity of the donor−acceptor carbenoids because they are able to selectively react with the monocyclopropane even in the presence of an excess of aromatic starting material. The reaction with *N*-Boc-pyrrole **3** is a clear example of this trend because no monocyclopropane product **6** is observed even when 6 equiv of the *N*-Boc-pyrrole **3** is used (Scheme 2), and even when **3** is used as solvent, a significant amount (34%) of **5** is isolated (Scheme 3). The double cyclopropanation of furan **7** is more complex, especially when the enantioinduction of the process is considered. As already explained in Figure 2, the Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation would be expected to generate the monocyclopropane **8**. As **8** is a dihydrofuran derivative, the second cyclopropanation would be expected to initiate at C-3, but this is only possible for **ent-8** (Figure 5). A reasonable model for the Rh_2(*S*-DOSP)$_4$-catalyzed cyclopropanation of **8** is only possible if the reaction initiates at the C-2 position. On electronic grounds, this would appear to be a mismatched reaction, but the control experiments with racemic monocyclopropane **6** or **8** show that the chiral influence of the catalyst is not very pronounced in the second cyclopropanation (Schemes 3 and 8).

Conclusion

These studies demonstrate that donor−acceptor carbenoids have a markedly different reactivity profile in comparison to that of traditional carbenoids in regard to their reactivity with a variety of standard heterocycles. Efficient reactions can be achieved, and the products are often inaccessible by other means. An interesting effect in these reactions is that the enantioinduction is markedly influenced by the structure of the heterocyclic substrate. The cyclopropanation is considered to proceed in a concerted nonsynchronous manner, and depending on which bond of the heterocycle initially interacts with the carbenoid, either face of the heterocycle can be attacked under the influence of the same chiral catalyst. Control is governed by a delicate interplay of steric and electronic influences.

Experimental Section

Representative Experimental Procedure: Preparation of Compound 5. A solution of methyl *para*-bromophenyldiazoacetate (**4**; 457 mg, 1.79 mmol, 3.00 equiv) in hexanes (10 mL) was added by syringe pump over 1 h to a solution of *N*-Boc-pyrrole **3** (0.10 mL, 0.61 mmol, 1.00 equiv) and Rh_2(*S*-DOSP)$_4$ (34 mg, 0.018 mmol, 0.01 equiv) in hexanes (5 mL). The reaction mixture was stirred for an additional 1 h and then concentrated in vacuo. Purification by flash chromatography on silica gel using 9:1 to 5:1 hexane/Et_2O as eluent gave **5** as a white solid (354 mg, 93%). Mp 196−199 °C. $[\alpha]_D$ 234.4 (83% ee; *c* 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55−7.48 (m, 4H), 7.16 (d, 2H, J = 8.5 Hz), 7.11 (d, 2H, J = 8.0 Hz), 3.56 (s, 3H), 3.52 (s, 3H), 3.07 (d, 1H, J = 6.5 Hz), 2.98 (d, 1H, J = 6.5 Hz), 2.59 (d, 1H, J = 6.5 Hz), 2.56 (d, 1H, J = 6.5 Hz), 1.51 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.9, 154.3, 133.4, 133.0, 132.0, 131.8, 130.9, 130.7, 122.2, 122.1, 81.5, 52.7, 52.6, 47.7, 47.1, 37.0, 36.8, 32.9, 31.7, 28.4. IR ($CHCl_3$): 2973, 1714, 1699, 1409, 1346, 1324, 1237, 1128, 965, 868, 739, 703 cm^{-1}. EI (*m*/*z*): 623 ($M^{81}Br_2Na^+$, 33%), 621 ($M^{81}Br^{79}BrNa^+$, 65%), 619 ($M^{79}Br_2Na^+$, 32%), 591 (55%), 589 (100%), 587 (48%). Anal Calcd for $C_{27}H_{27}Br_2NO_6$: C, 52.19; H, 4.38; N, 2.25. Found: C, 51.87; H, 4.14; N, 2.25. HPLC analysis: 83% ee (Chiralcel AD-H, 1.0% *i*-PrOH in hexane, 0.8 mL/min, λ = 254 nm, t_R = 32.1 min, minor; t_R = 47.5 min, major).

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Supporting Information Available: Experimental procedures and spectral data for all novel compounds; X-ray data for compounds **5**, **9**, **ent-12**, **15**, **20**, and **32**; and CD spectra for compounds **20** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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