Catalytic Asymmetric Benzylic C−H Activation by Means of Carbenoid-Induced C−H Insertions

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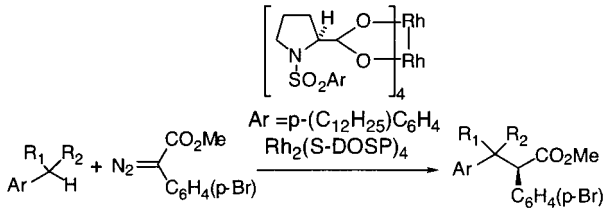
Tetrakis[*N*-[4-dodecylphenyl)sulfonyl]-(*S*)-prolinate]dirhodium [Rh_2(*S*-DOSP)$_4$]-catalyzed decomposition of methyl aryldiazoacetates in the presence of substituted ethylbenzenes results in benzylic C−H activation by means of a rhodium−carbenoid-induced C−H insertion. A Hammet study showed that positive charge buildup occurred on the benzylic carbon in the transition state of the C−H activation step. C−H activation of toluene and isopropylbenzene is possible, but a competing double cyclopropanation occurs with these substrates. The C−H activation is highly regioselective and enantioselective, and in certain cases, moderate diastereoselectivity is also possible.

Introduction

Rhodium carbenoid induced C−H insertions represent a powerful approach for catalytic asymmetric C−H activation.[1,2] The dirhodium tetraprolinate catalyst Rh_2(*S*-DOSP)$_4$ has been shown to be highly effective for these reactions.[3] The requirement for a successful outcome in this chemistry is the use of carbenoid systems containing both donor and acceptor groups.[4] The most widely used carbenoid precursors have been aryl diazoacetates, and with this system, highly effective intermolecular C−H activation of a variety of systems has been achieved. These include alkanes,[3e] such as cyclohexane, 2-methylbutane, and adamantane, but even more efficient reactions can be achieved at activated positions such as allylic,[3g,i] or α to nitrogen[3d,h] or oxygen.[3c,f] In this paper, we describe our studies of C−H activation at benzylic positions (Scheme 1). These studies demonstrate the remarkable chemoselectivity that is possible in these reactions.

One of the most interesting aspects of these C−H activation reactions is that they display excellent regiocontrol.[3c] C−H insertion into a methyl group is rarely observed while there is a subtle balance between insertion into methylene and methine C−H bonds. Methine C−H are favored on either electronic grounds or simply due to relative bond strengths, but this is counterbalanced by the steric demands of the rhodium−carbenoid complex. In general, selective C−H activation at methylene sites has been the most widely observed transformation.[3e]

Scheme 1



Results and Discussion

To explore the efficiency of insertions into benzylic positions, the studies were initiated by comparing the reactions of a standard aryldiazoactetate (**1**) with various ethylbenzene derivatives catalyzed by Rh_2(*S*-DOSP)$_4$. The results are summarized in Table 1. The most efficient conditions for carrying out these reactions were addition of a degassed solution of the diazo compound **1** in 2,2-dimethylbutane into a degassed solution of 6 equiv of the ethylbenzene **2** and 1 mol % of Rh_2(*S*-DOSP)$_4$ under refluxing conditions. The reactions resulted in the formation of a 2−5:1 diastereomeric mixture[5] of the C−H insertion products **3** and **4**, in which the major diastereomer was formed in 83−89% ee. The reaction with 4-ethylanisole **2a** is one of the most remarkable reactions because this is a very electron-rich aromatic ring but still a very efficient C−H insertion was observed.

As a series of ethyl-substituted aromatic compounds are capable of undergoing these C−H insertions, an opportunity existed to explore the electronic effect of the aromatic substituent on the C−H activation. Competition experiments were carried out as illustrated in Table 2.

† The X-ray crystallograpic data were obtained by Dr. Andrey Yu Kovalevsky.

(1) Doyle, M. P.; McKervey, M. A.; Ye, T. In *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998; pp 133−162.

(2) For recent reviews on other methods for C−H activation, see: (a) Shilov, A. E.; Shul′pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *28*, 1698. (c) Arndsten, B. A.; Bergman, R. G. *Science* **1995**, *270*, 1970.

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

(5) Relative stereochemistry is readily determined on the basis of distinctive chemical shifts in the proton NMR. For details, see: Davies, H. M. L.; Ren, P. *Tetrahedron Lett.* **2001**, *42*, 3149.

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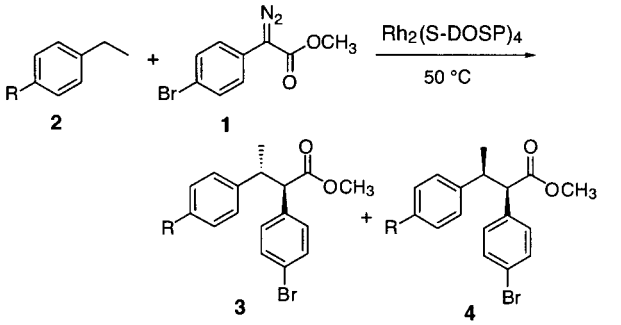
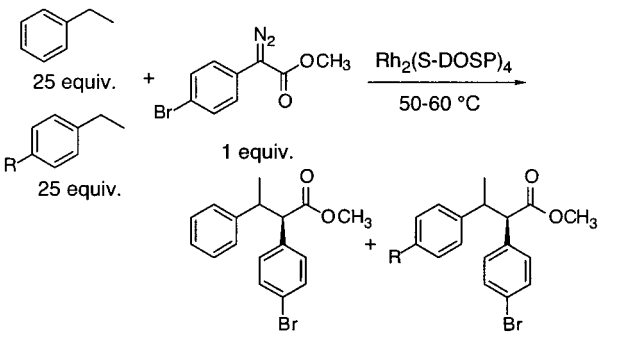
Table 1. Reaction of 1 with Substituted Ethylbenzenes



compd	R	yield (%) **3** + **4**	ratio[a] **3**/**4**	ee of **3** (%)	ee of **4** (%)
a	MeO	86	68:32	89[b]	76[b]
b	Et	71	75:25	89[c]	70[c]
c	Me	64	82:18	89[b]	74[b]
d	H	49	84:16	86[c]	
e	Br	38	73:27	88[c]	58[c]
f	OAc	77	78:22	86[c]	53[c]
g	$MeCO_2$	56	80:20	83[c]	58[c]

[a] Ratio determined by proton NMR of the crude reaction mixture. [b] Ee determined by chiral HPLC of the corresponding alcohol. [c] Ee determined by chiral HPLC of the esters.

Table 2. Competition Reactions of 1 with Substituted Ethylbenzenes



compd	R	σ	σ^+	ratio (**3d** + **4d**)/(**3** + **4**)
2a	MeO	−0.12	−0.78	1:11.1
2c	Me	−0.14	−0.31	1:3.1
2e	Br	0.26	0.15	1.23:1
2f	OAc	0.31	0.18	1.97:1
2g	$MeCO_2$	0.44	0.44	2.75:1

The ethylbenzenes substituted with an electron-donating substituent are much more effective substrates. The Hammet analysis,[6] summarized in Figure 1, shows that the charge stabilization in the transition state is due to resonance effects because the correlation to σ^+ ($R = 0.99$) is much better than to σ ($R = 0.87$). The ρ value of −1.27 indicates positive charge buildup in the transition state of the C−H insertion step. This is consistent with the concerted nonsynchronous three-membered transition-state model that we have proposed for the intermolecular C−H insertions[3e] and that others have proposed for the intramolecular C−H insertions. A similar ρ value (−1.26) was obtained in intramolecular C−H insertions of carbenoids derived from diazoacetoacetates, catalyzed by dirhodium tetraacetate.[7]

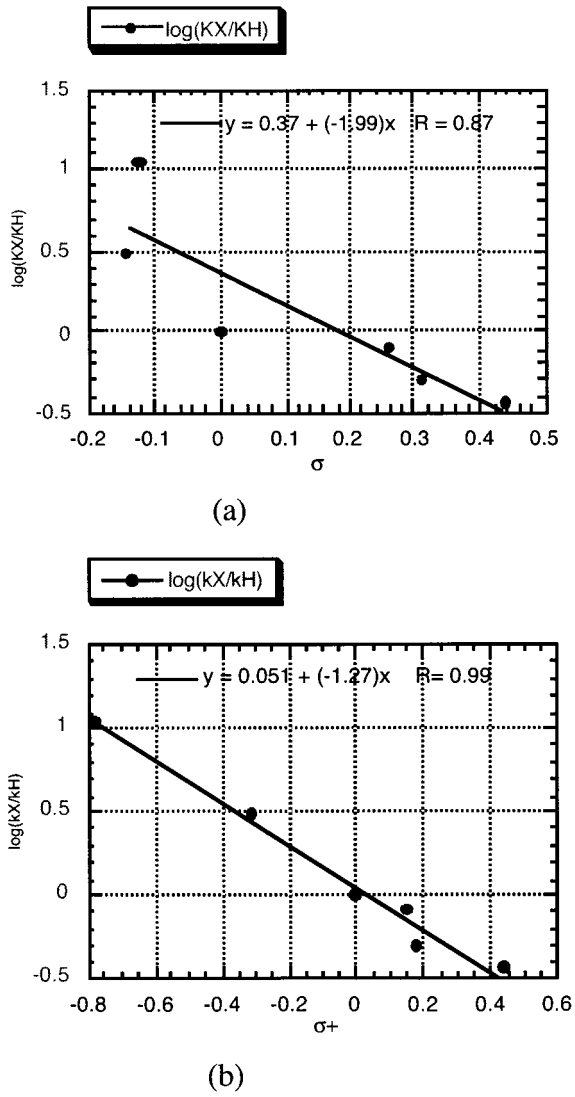
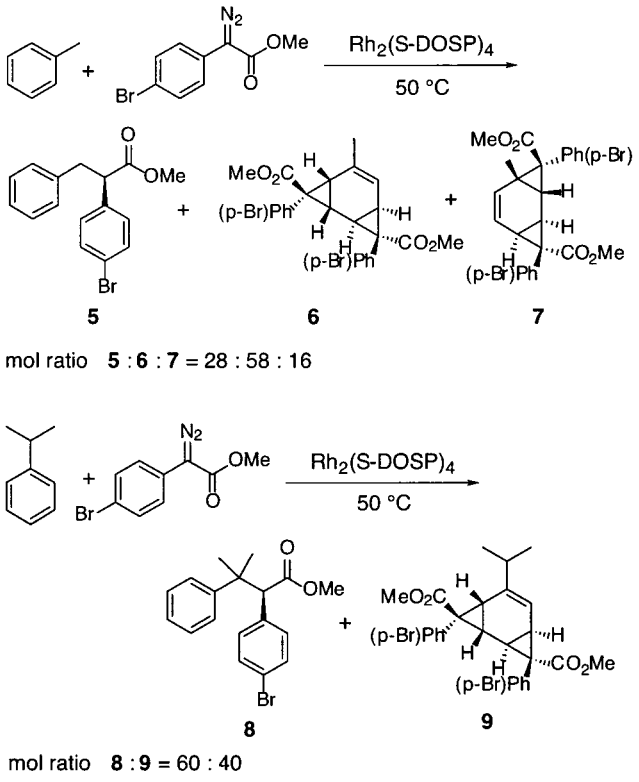


Figure 1. Hammet studies for reaction of **1** with substituted ethylbenzenes: (a) plot vs σ; (b) plot vs σ^+.

To explore fully the effect of steric demands on the C−H insertion, a comparison of ethylbenzene with toluene and isopropylbenzene was performed. These reactions were carried out using the optimized procedure with 2,2-dimethylbutane as solvent. A reasonable amount of carbenoid trapping products was obtained in each case, but the product distribution was very different as illustrated in Scheme 2. The reaction with toluene gave a mixture of three products **5**−**7** in a combined yield of 50%. The C−H insertion product **5** was a minor product, and the major product was a mixture of **6** and **7**, two regioisomeric double cyclopropanation products. The standard reaction of ethyl diazoacetate with benzene generates a cyclohepatatriene because the initial cyclopropanation product, a norcaradiene, undergoes an electrocyclic ring opening.[8] If the norcaradiene electrocyclic ring opening is not thermodynamically favorable, a second cyclopropanation can occur, and this has been observed in the reaction of benzene with dimethyl diazomalonate.[9] Very effective double cyclopropanation of pyrrole has also been previously observed.[10] The reaction

(6) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry: Part A, Structure and Mechanisms*; Plenum: New York, 1990.
(7) Wang, J.; Chen, B.; Bao, J. *J. Org. Chem.* **1998**, *63*, 1853.
(8) Anciaux, A. J.; Demonceau, A.; Noels, A. F.; Hubert, A. J.; Warin, R.; Teyssie, P. *J. Org. Chem.* **1981**, *46*, 873.
(9) Yang, M.; Webb, T. R.; Livant, P. *J. Org. Chem.* **2001**, *66*, 4945

Scheme 2



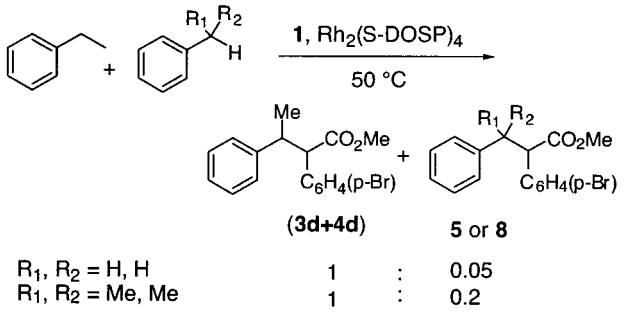
with isopropylbenzene gave a mixture of C−H insertion product **8** and a single regioisomer of the double-cyclopropanation product **9** in a combined yield of 61%. Even though the methine C−H bond in isopropylbenzene would be expected to be highly activated, it is presumably too sterically crowded for an effective C−H insertion. The observation that steric hindrance slows what might be otherwise a favorable C−H insertion has been previously observed in intramolecular C−H insertions.[11] The clean formation of a single regioisomer **9** of the biscyclopropanation product is also due to the steric influence of the isopropyl group. A further interesting feature of the reaction with isopropylbenzene is that the enantioselectivity for the formation of the C−H insertion product (50% ee) is considerable lower than observed for ethylbenzene.

Having recognized that biscyclopropanation was a viable possibility for alkylbenzene derivatives, the reactions of the ethylbenzene derivatives were reexamined. In the case of ethylbenzene, traces (<10%) of the bis cyclopropanation products were observed, but in the para-substituted ethylbenzene derivatives, none were observed. Competition studies between toluene, ethylbenzene, and isopropylbenzene confirmed that ethylbenzene had enhanced relative reactivity (Scheme 3). The C−H insertion into ethylbenzene was 20 times more favorable than C−H insertion into toluene and five times more favorable than C−H insertion into isopropylbenzene.

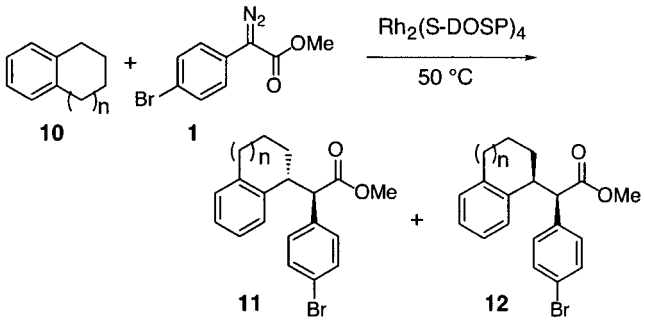
The final series of reactions examined the reactivity of indan and tetrahydronaphthalene. With both substrates, effective C−H insertion occurred but the diastereoselectivity was different. The reaction with indan gave a 4:1 mixture of diastereomers while the reaction with tetrahydronaphthalene gave a slight preference for the opposite diastereomer. Ring size appears to have a significant effect because a similar change in diastereoselectivity has been previously seen in the reactions of *N*-BOC-pyrrolidine and *N*-BOC-piperidine (Scheme 4).[3d]

The reaction with 6-methoxy-1,2,3,4-tetrahydronaphthalene **13** further demonstrated the directing effect of a *p*-methoxy substituent because ~98% of the C−H insertion occurred at the most activated benzylic position to form a diastereomeric mixture of **14** and **15**. The enantioselectivity of this C−H activation was excellent as the major diastereomer **15** was formed in 94% ee (Scheme 5).[5]

Scheme 3



Scheme 4



	yield %	11 : 12	ee of 11, %	ee of 12, %
n=0	62	80 : 20	89[a]	85[b]
n=1	43	43 : 57	67[b]	89[b]

[a] ee determined by chiral HPLC of the corresponding alcohol. [b] ee determined by chiral HPLC of the ester.

Conclusion

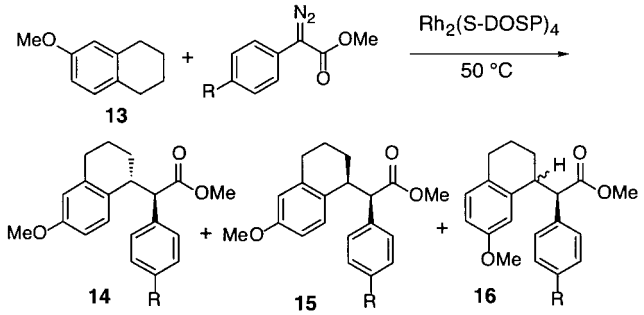
In summary, these results demonstrate that the rhodium carbenoids derived from aryldiazoacetates are effective at C−H activation of benzylic positions. A methylene site is the most favorable for C−H activation, demonstrating the subtle interplay of steric and electronic effects that is involved in this chemistry.

Experiment Section

General Information. ^{1}H NMR spectra were run at either 400 or 500 MHz and ^{13}C NMR at 125 MHz with the sample solvent being $CDCl_3$ unless otherwise noted. Mass spectral determinations were carried out at 70 eV or performed by

(10) Davies, H. M. L.; Young, W. B.; Smith, H. D. *Tetrahedron Lett.* **1989**, *30*, 4653.
(11) Taber, D. F.; Ruckle, R. E., Jr. *J. Am. Chem. Soc.* **1986**, *108*, 7686.

Scheme 5



	yield %	14 : 15 : 16	ee of [a] 14, %	ee of [a] 15, %
R=Br	72	20 : 79 : 1	ND	94
R=H	78	19 : 79 : 2	74	94

[a] ee determined by chiral HPLC of the ester.

Nebraska Center for Mass Spectrometry, University of Nebraska, Lincon. Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. Column chromatography was carried out on silica gel 60 (230−400) mesh. Enantiomeric excess was determined by either ^{1}H NMR using chiral shift reagent or HPLC using chiral analytical columns. Degassing was carried out by bubbling Ar gas through the solution for 5−10 min.

General Procedure for C−H Activation Reactions. To a refluxing and degassed solution of substituted benzene (3.0 mmol) and Rh_2(*S*-DOSP)$_4$ (9.5 mg, 0.005 mmol) in 2,2-dimethylbutane (3 mL) was added a degassed solution of methyl *p*-bromophenyldiazoacetate (127.5 mg, 0.5 mmol) in 2,2-dimethylbutane (6−10 mL) by syringe pump over 1 h. The reaction mixture was stirred for another 0.5 h after the addition was complete. Solvent was removed in vacuo, and the crude product was purified by flash chromatography on silica gel. The diastereomeric ratio was determined from the ^{1}H NMR of the crude reaction mixture.

Decomposition of Methyl *p*-Bromophenyldiazoacetate in the Presence of *p*-Ethylanisole. (α*R*,β*R*)-(*p*-Methoxybenzene)propanoic Acid, α-(*p*-Bromophenyl)-β-methyl-, Methyl Ester (3a) and (α*R*,β*S*)-(*p*-Methoxybenzene)propanoic Acid, α-(*p*-Bromophenyl)-β-methyl-, Methyl Ester (4a). Purified by flash chromatography on silica gel (10:1 pentane/ether eluent) to provide 105.1 mg (58% yield) of the major product (**3a**) as colorless oil and 50.4 mg (28% yield) of the minor product (**4a**) as colorless oil (total 86% yield). Major: R_f 0.22 (10:1 pentane/ether); FTIR (film) 2955, 1733, 1612, 1512, 1488, 1428, 1160 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 3.70 (s, 3H), 3.69 (s, 3H), 3.62 (d, J = 11.0 Hz, 1H), 3.37 (dq, J = 11.0, 6.6 Hz, 1H), 1.34 (d, J = 6.6 Hz, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.7, 157.9, 136.6, 135.2, 131.2, 130.2, 128.3, 121.0, 113.6, 58.8, 55.0, 52.0, 43.0, 21.1; HRMS (EI) m/z calcd for $[C_{18}H_{19}BrO_3]^+$ 362.0518, found 362.0520. Minor: R_f 0.15 (10:1 pentane/ether); FTIR (film) 2955, 1733, 1612, 1512, 1488, 1428, 1160 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.19 (d, J = 8.6 Hz, 2H), 6.85 (d, J = 8.6 Hz, 2H), 3.79 (s, 3H), 3.62 (d, J = 11.3 Hz, 1H), 3.38 (s, 3H), 3.35 (dq, J = 11.3, 7.0 Hz, 1H), 1.00 (d, J = 7.0 Hz, 3H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.1, 158.2, 136.7, 136.3, 131.7, 130.3, 128.2, 121.5, 113.8, 59.2, 55.2, 51.7, 42.6, 19.9; HRMS (EI) m/z calcd for $[C_{18}H_{19}BrO_3]^+$ 362.0518, found 362.0508.

Ee Determination of 3a and 4a by Reduction of the Ester to the Alcohol. Reduction of 77 mg of the *major* product (**3a**) to the corresponding alcohol was achieved by using 4 equiv of Dibal-H in toluene. The crude product was purified by flash chromatography on silica gel (1:1 pentane/ether eluent) to provide 68.5 mg (96% yield) of the alcohol as a colorless oil: R_f 0.29 (1:1 pentane/ether); $[\alpha]^{25}_D$ −21.2 (*c* 2.70, $CHCl_3$); FTIR (film) 3405, 2961, 2931, 1611, 1511, 1488, 1247 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 6.69 (d, J = 8.5 Hz, 2H), 3.92 (dd, J = 11.0, 5.2 Hz, 1H), 3.83 (dd, J = 11.0, 7.9 Hz, 1H), 3.73 (s, 3H), 3.09 (dq, J = 7.6, 7.0 Hz, 1H), 2.94 (ddd, J = 7.9, 7.9, 5.2 Hz, 1H), 1.29 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 139.6, 136.1, 131.1, 130.7, 128.7, 120.3, 113.3, 64.5, 55.1, 54.3, 40.6, 20.0; HRMS (EI) m/z calcd for $[C_{17}H_{19}BrO_2]^+$ 334.0568, found 334.0588; HPLC analysis 89% ee (*R*,*R*-Whelk-O1, 5% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 15.4 min, major; t_R = 19.0 min, minor). Reduction of 17 mg of the *minor* product (**4a**) to the corresponding alcohol was achieved by using 4 equiv of Dibal-H in toluene. The crude product was purified by flash chromatography on silica gel (1:1 pentane/ether eluent) to provide 14.4 mg (92% yield) of product as a colorless oil: R_f 0.19 (2:1 pentane/ether); $[\alpha]^{25}_D$ −8.2 (*c* 0.49, $CHCl_3$); FTIR (film) 3406, 2959, 2926, 1610, 1511, 1487, 1246 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.2 Hz, 2H), 7.16 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 3.81 (s, 3H), 3.55−3.51 (m, 2H), 2.95−2.88 (m, 1H), 2.86−2.82 (m, 1H), 1.00 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 140.8, 137.1, 131.7, 130.3, 128.1, 120.6, 114.0, 65.7, 55.3 (2C), 41.5, 20.9; HRMS (EI) m/z calcd for $[C_{17}H_{19}BrO_2]^+$ 334.0568, found 334.0545; HPLC analysis 76% ee (*R*,*R*-Whelk-O1, 5% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 15.2 min, major; t_R = 23.9 min, minor).

Decomposition of Methyl *p*-Bromophenyldiazoacetate in the Presence of *p*-Ethylphenyl Acetate. (α*R*,β*R*)-(*p*-Acetoxybenzene)propanoic Acid, α-(*p*-Bromophenyl)-β-methyl-, Methyl Ester (3f) and (α*R*,β*S*)-(*p*-Acetoxybenzene)propanoic Acid, α-(*p*-Bromophenyl)-β-methyl-, Methyl Ester (4f). Purified by flash chromatography on silica gel (4:1 pentane/ether eluent) to provide 103.9 mg (53% yield) of the major product (**3f**) as a white solid, 20.5 mg (10% yield) of the minor product (**4f**) as a white solid, and 26.5 mg of a mixture (total 77% yield). Major: R_f 0.57 (2:1 pentane/ether); $[\alpha]^{25}_D$ −132.4 (*c* 2.10, $CHCl_3$); FTIR ($CHCl_3$) 2965, 1763, 1734, 1508, 1489, 1205, 1165, 1011, 912, 823 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, J = 8.5 Hz, 2H), 7.00 (d, J = 8.5 Hz, 2H), 6.95 (d, J = 8.5 Hz, 2H), 6.86 (d, J = 8.5 Hz, 2H), 3.70 (s, 3H), 3.63 (d, J = 11.0 Hz, 1H), 3.41 (dq, J = 11.0, 7.0 Hz, 1H), 2.23 (s, 3H), 1.36 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4, 169.3, 148.9, 140.6, 136.3, 131.3, 130.1, 128.3, 121.2, 121.1, 58.6, 52.1, 43.2, 21.1, 20.8; MS (EI) m/z 121.1, 163.1, 390.0 (M^+); HPLC analysis 86% ee (*R*,*R*-Whelk-O1, 10% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 14.6 min, major; t_R = 19.2 min, minor). Anal. Calcd for $C_{19}H_{19}BrO_4$: C, 58.33; H, 4.99. Found: C, 58.42; H, 4.89. Minor: R_f 0.54 (2:1 pentane/ether); FTIR (CH_2Cl_2) 1763, 1735, 1508, 1488, 1202, 1160, 1011 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 8.2 Hz, 2H), 7.32 (d, J = 8.2 Hz, 2H), 7.28 (d, J = 8.2 Hz, 2H), 7.03 (d, J = 8.2 Hz, 2H), 3.63 (d, J = 11.3 Hz, 1H), 3.45−3.38 (m, 1H), 3.38 (s, 3H), 2.29 (s, 3H), 1.01 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.9, 169.5, 149.3, 141.8, 136.4, 131.8, 130.2, 128.3, 121.6, 121.5, 59.0, 51.8, 42.8, 21.1, 19.7; MS (FAB) m/z 154.1, 391.3 (M^+ + 1); HPLC analysis 53% ee (*R*,*R*-Whelk-O1, 5% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 20.9 min, major; t_R = 23.4 min, minor). Anal. Calcd for $C_{19}H_{19}BrO_4$: C, 58.33; H, 4.89. Found: C, 58.42; H, 4.94.

Decomposition of Methyl *p*-Bromophenyldiazoacetate in the Presence of Toluene. (*R*)-Benzenepropanoic Acid, α-(*p*-Bromophenyl)-, Methyl Ester (5). Purified by flash chromatography on silica gel (20:1 pentane/ether eluent) to provide a colorless oil (9.7 mg, 6% yield): R_f 0.48 (10:1 pentane/ether); $[\alpha]^{25}_D$ −108.0 (*c* 0.25, $CHCl_3$); FTIR (film) 3028, 2951, 1736, 1488, 1435, 1161, 1074, 1011, 749, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, J = 8.2 Hz, 2H), 7.28−7.21 (m, 2H), 7.21−7.14 (m, 3H), 7.08 (d, J = 7.6 Hz, 2H), 3.81 9dd, J = 8.5, 7.3 Hz, 1H), 3.61 (s, 3H), 3.38 (dd, J = 13.7, 8.5 Hz, 1H), 2.99 (dd, J = 13.7, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.4 (C), 138.5 (C), 137.5 (C), 131.7 (CH), 129.7 (CH), 128.9 (CH), 128.4 (CH), 126.5 (CH), 121.4 (C), 53.0 (CH), 52.1

(CH_3), 39.6 (CH_2); HRMS (EI) *m/z* calcd for $[C_{16}H_{15}BrO_2]^+$ 318.0255, found 318.0256.

Compound 6. Purified by flash chromatography on silica gel (2:1 pentane/ether eluent) to provide a pale yellow oil (46.7 mg, 34% yield): R_f 0.42 (2:1 pentane/ether); FTIR (film) 2951, 2926, 1716, 1488, 1434, 1240, 1073, 1011, 910, 733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, J = 8.4 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 5.12 (br, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 2.46 (d, J = 9.0 Hz, 1H), 2.44 (d, J = 9.0 Hz, 1H), 1.60 (d, J = 9.0 Hz, 1H), 1.58 (s, 3H), 1.41 (d, J = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.05, 173.03, 134.6, 134.5, 132.7, 132.5, 131.3, 131.2, 130.9, 121.4, 121.2, 118.3, 52.7, 52.6, 39.1, 38.8, 31.0, 27.8, 27.6, 26.1, 23.2; HRMS (EI) *m/z* calcd for $[C_{25}H_{22}Br_2O_4]^+$ 543.9885, found 543.9820.

Compound 7. Purified by flash chromatography on silica gel (5:1 pentane/ether eluent) to provide a pale yellow oil (13.8 mg, 10% yield): R_f 0.23 (5:1 pentane/ether); $[\alpha]^{25}_D$ +118.0 (*c* 0.2, $CHCl_3$); FTIR (film) 3030, 2951, 2926, 1717, 1488, 1434, 1232, 1073, 1011, 911, 732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, J = 8.5 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.05 (d, J = 8.5 Hz, 2H), 7.08−7.00 (m, 2H), 5.38 (dd, J = 9.8, 4.9 Hz, 1H), 5.17 (d, J = 9.8 Hz, 1H), 3.58 (s, 3H), 3.55 (s, 3H), 2.58 (d, J = 9.2 Hz, 1H), 2.57 (s, 1H), 1.66 (dd, J = 9.2, 4.9 Hz, 1H), 0.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.8, 171.0, 134.8, 134.5, 134.2, 132.3, 130.93, 130.88, 129.4, 122.7, 121.28, 121.23, 52.7, 52.5, 44.4, 39.8, 29.1, 29.0, 28.4, 26.4, 18.3; HRMS (EI) *m/z* calcd for $[C_{25}H_{22}Br_2O_4]^+$ 543.9885, found 543.9873.

Decomposition of Methyl *p*-Bromophenyldiazoacetate in the Presence of Cumene. (α*R*)-Benzenepropanoic Acid, α-(*p*-Bromophenyl)-*β*-dimethyl-, Methyl Ester (8). Purified by flash chromatography on silica gel (25:1 pentane/ether eluent) to provide a colorless oil (39.9 mg, 23% yield): R_f 0.53 (20:1 pentane/ether); $[\alpha]^{25}_D$ −44.0 (*c* 1.2, $CHCl_3$); FTIR (film) 1734, 1489, 1267, 1160, 1101, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, J = 8.5 Hz, 2H), 7.29−7.24 (m, 3H), 7.22−7.17 (m, 1H), 7.05 (d, J = 8.5 Hz, 2H), 3.84 (s, 1H), 3.46 (s, 3H), 1.48 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 146.6, 134.4, 131.6, 130.7, 127.9, 126.4, 126.2, 121.4, 61.7, 51.4, 41.2, 25.7, 25.1; MS (FAB) *m/z* 154.0, 333.0 (M^+ + 1); 50% ee (determined by ^1H NMR using $Eu(hfc)_3$ as chiral shift reagent). Anal. Calcd for $C_{18}H_{19}BrO_2$: C, 62.26; H, 5.52. Found: C, 62.47; H, 5.65.

Compound 9. Purified by flash chromatography on silica gel (3:1 pentane/ether eluent) to provide a colorless oil (55.3 mg, 38% yield): R_f 0.42 (2:1 pentane/ether); FTIR (film) 2958, 1716, 1489, 1434, 1240, 1011, 910, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 7.00 (d, J = 8.4 Hz, 2H), 5.07 (d, J = 4.8 Hz, 1H), 3.57 (s, 3H), 3.56 (s, 3H), 2.53 (d, J = 9.5 Hz, 1H), 2.47 (d, J = 9.2 Hz, 1H), 2.04 (7, J = 6.8 Hz, 1H), 1.63−1.56 (m, 2H), 0.88 (d, J = 6.8 Hz, 3H), 0.60 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 173.0, 140.9, 134.8, 133.8, 132.7, 132.6, 131.1, 131.0, 121.3, 121.1, 115.0, 52.8, 52.6, 39.0, 38.9, 34.2, 30.0, 27.7, 27.6, 21.3, 20.2; HRMS (EI) *m/z* calcd for $C_{27}H_{26}Br_2O_4$ 572.0198, found 572.0175.

Decompostion of Methyl *p*-Bromophenyldiazoacetate in the Presence of 6-Methoxy-1,2,3,4-tetrahydronaphthalene (14, 15, R = H). Purified by flash chromatography on silica gel (10:1 pentane/ether eluent) to provide 20.6 mg (13% yield) of the *minor* (**14**, R = H) product as a white solid and 99.9 mg (64% yield) of the *major* (**15**, R = H) product as a white solid (total 78% yield). Major: R_f 0.35 (10:1 pentane/ether); $[\alpha]^{25}_D$ +60.1 (*c* 0.95, $CHCl_3$); FTIR ($CHCl_3$) 2947, 1733, 1607, 1500, 1272, 1154, 1039, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.3 Hz, 2H), 7.33 (d, J = 7.3 Hz, 2H), 7.26 (t, J = 7.3 Hz, 1H), 7.12 (d, J = 8.2 Hz, 1H), 6.68−6.62 (m, 2H), 3.76 (s, 3H), 3.73 (d, J = 11.0 Hz, 1H), 3.55 (dt, J = 11.0, 3.7 Hz, 1H), 3.51 (s, 3H), 2.87−2.79 (m, 1H), 2.77−2.68 (m, 1H), 1.80−1.69 (m, 1H), 1.62−1.42 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.5, 158.0, 138.0, 137.6, 130.6, 129.8, 128.6, 128.5, 127.3, 113.8, 111.4, 57.4, 55.0, 51.6, 40.0, 28.7, 24.8, 17.6; MS (FAB) *m/z* 176.1, 333.0 (M^+ + Na); HPLC analysis 94% ee (*R*,*R*-Whelk-O1, 2% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 8.9 min, major; t_R = 13.6 min, minor). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.13; H, 7.19. Minor: R_f 0.40 (10:1 pentane/ether); FTIR ($CHCl_3$) 2947, 1734, 1608, 1501, 1258, 1153, 1039, 734, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.26−7.17 (m, 5H), 6.56 (d, J = 2.4 Hz, 1H), 6.24 (dd, J = 8.5, 2.4 Hz, 1H), 6.05 (d, J = 8.5 Hz, 1H), 3.78 (d, J = 10.4 Hz, 1H), 3.69 (s, 3H), 3.68 (s, 3H), 3.41−3.36 (m, 1H), 2.88−2.81 (m, 1H), 2.81−2.71 (m, 1H), 2.03−1.91 (m, 2H), 1.88−1.74 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.9, 157.7, 138.1, 137.8, 130.8, 129.17, 129.14, 128.2, 127.2, 113.4, 110.5, 57.0, 55.0, 41.5, 29.2, 27.0, 18.7; MS (FAB) *m/z* 161.0, 333.0 (M^+ + Na); HPLC analysis 74% ee (*R*,*R*-Whelk-O1, 2% *i*-PrOH in hexane, 1.0 mL/min, λ = 254 nm, t_R = 7.7 min, major; t_R = 9.2 min, minor). Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.09; H, 7.13.

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Supporting Information Available: Experimental procedure for the competition reaction, full data of **3b**−**e**,**g**, **4b**−**e**,**g**, **11** (*n* = 0, 1), **12** (*n* = 0, 1), **14** (R = Br), and **15** (R = Br), and X-ray crystallographic data for **15** (R = Br). This material is available free of charge via the Internet at http://pubs.acs.org.

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