Influence of a β-Alkoxy Substituent on the C–H Activation Chemistry of Alkyl Ethers

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Abstract: C–H activation reactions of 1,2-dimethoxyethane and methyl *tert*-butyl ether with methyl aryldiazoacetates or styryldiazoacetate catalyzed by Rh_2(*S*-DOSP)$_4$ result in the formation of 2-aryl- or 2-styryl-substituted propanoic acids with asymmetric induction up to 95% ee.

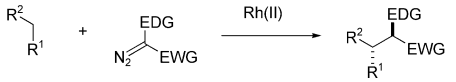
Keywords: asymmetric catalysis; C–H activation; C–H insertion; carbenoid; diazo compounds; homogeneous catalysis; rhodium

Introduction

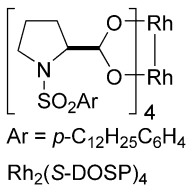
The development of practical C–H activation methods is of considerable current interest.[1,2] Such methods could have an immense impact on the functionalization of common hydrocarbon feedstocks and offer novel opportunities and strategies for the synthesis of natural products and pharmaceutical targets. One very effective catalytic and asymmetric method for C–H activation is by means of the C–H insertion chemistry of metal carbenoid intermediates (Scheme 1).[3] The catalytic asymmetric intramolecular C–H insertion is very well-established, but until very recently the intermolecular version was of limited synthetic utility.[3a, b] The major difficulty was the high reactivity of the traditional carbenoid intermediates derived from diazoacetate derivatives. Some progress has been made in taming this reactivity by the use of very bulky catalysts[4] but the major breakthrough in this area came about with the development of donor/acceptor substituted carbenoids.[3c, d] These carbenoids display much greater selectivity than the traditional carbenoids and enable the intermolecular C–H insertion to be a very general C–H activation process.[3c, d]

Over the last five years a wide variety of substrates have been shown to be effectively functionalized by means of the intermolecular C–H activation.[3c, d] Dirhodium tetraprolinates such as Rh_2(*S*-DOSP)$_4$ are exceptional chiral catalysts for these reactions (Figure 1). By now a number of highly enantioselective, diastereoselective, and regioselective transformations have been reported. The reactions display subtle chemoselectivity due to a delicate balance of steric and electronic effects. The C–H activation is considered to occur in a concerted non-synchronous manner and carbon centers that can stabilize positive charge build-up are very prone to C–H activation. The rhodium-carbenoid intermediates behave as sterically demanding species and in crowded sites the steric effects can dominate over any electronic effects. Consequently, numerous examples are known of selective C–H activation at methyl, methylene and methine C–H bonds.[3c, d] In general, methine sites tend to be most often favored because such sites display a favorable combination of electronic and steric effects.[5]

C–H activation is especially favored α to alkoxy or silyloxy groups because of the electronic stabilization of the transition state during the C–H activation.[6] A representative example of this is the reaction with tetrahydrofuran (Scheme 2).[7] The high preference for C–H activation α to oxygen is readily seen because the optimum conditions used 2 equiv. of tetrahydrofuran at –50 °C in hexane as solvent without any competing C–H insertion into the solvent. Under these conditions, the Rh_2(*S*-DOSP)$_4$-catalyzed reaction of phenyldiazoacetate gave the C–H activation product as a 2.8:1 mixture of diastereomers in 67% yield, in which the major diastereomer was formed in 97% ee. An even



Scheme 1. C–H Activation by carbenoid induced C–H insertion.



Ar = *p*-$C_{12}H_{25}C_6H_4$

Rh_2(*S*-DOSP)$_4$

Figure 1. Rh_2(*S*-DOSP)$_4$.

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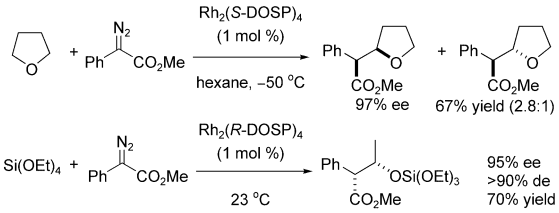
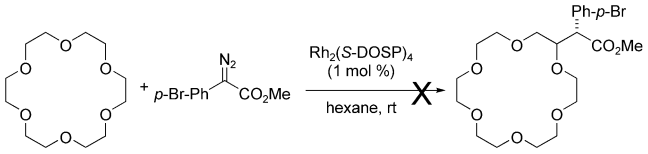


Scheme 2. C–H Activation reactions of tetrahydrofuran and tetraethoxysilane.



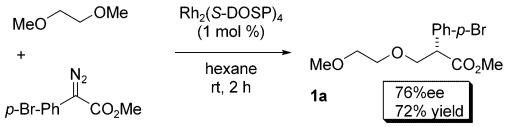
Scheme 3. Attempted C–H activation reaction of 18-crown-6 ether.

more impressive example of this chemistry is the reaction of phenyldiazoacetate with tetraethoxysilane which gave the C–H activation product in high enantioselectivity and diastereoselectivity (Scheme 2).[8a]

Having discovered the remarkable selectivity α to oxygen of the C–H activation by the donor/acceptor substituted carbenoids, my group has been exploring avenues for the exploitation of this chemistry for the rapid synthesis of useful target molecules. A reaction that appeared especially attractive was the functionalization of crown ethers by means of a C–H activation protocol (Scheme 3) because the resulting chiral crown ethers could have many applications.[9] In any event, the attempts at the asymmmetric C–H activation of crown-ethers were uniformly unsuccessful. Puzzled by the failure of this apparently straightforward reaction, especially as the crown ether would not be expected to be sterically crowded, we have carried out a systematic study to explore the factors that control the reactivity of alkyl ethers towards C–H activation. The results of this study are described in this paper.

Results and Discussion

A reasonable model substrate to explore the reactivity of the crown ethers was considered to be 1,2-dimethoxyethane (DME). Even though the oxygen substituent was expected to make DME a very active substrate towards C–H activation, this proved not to be the case and in order to achieve good yields of C–H activation products it was best to use DME as the solvent for the reaction. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of *p*-bromophenyldiazoacetate in DME gave a 72% yield of the C–H activation product **1a** (76% ee), in which the C–H activation had occurred into the methyl site rather than the methylene site (Scheme 4). The stereochemistry of the newly generated chiral center was tentatively



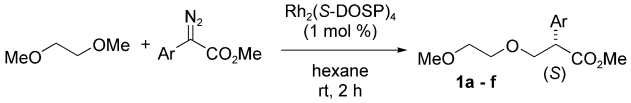
Scheme 4. C–H activation reaction of 1,2-dimethoxyethane.

assigned as (*S*) based on the predictive model.[8a] Clean C–H activation into a methyl site only occurs when the rest of the molecule is sterically protected or lacks any other activated sites.[10] In this case, the result is indicative that a β-alkoxy susbtituent has a strong deactivating effect on the C–H activation reaction. Presumably oxygen β to a C–H activation site would inductively destabilizes the positive charge build up in the transition state.[5]

The reaction is applicable to a range of aryldiazoacetates as illustrated in Table 1. In all instances C–H activation only occurs at the methyl site, generating the C–H activation product in 59 – 76% ee. The reaction of methyl *p*-methoxyphenyldiazoacetate (entry 4), which would be expected to generate the least electrophilic carbenoid intermediate was sluggish at room temperature and was more effective when the reaction was conducted at 70 °C. A most notable example is the reaction with methyl styryldiazoacetate (entry 6) which resulted in the formation of the C–H activation product in 87% ee. Although carbenoids derived from vinyldiazoacetates have commonly been less studied in C–H activation chemistry than the carbenoids derived from aryldiazoacetates, in general, vinyldiazoacetates tend to result in the highest levels of asymmetric induction.[8a,10b]

In order to determine if the methoxy C–H activation could be extended further, the reactions using methyl *tert*-butyl ether (MTBE) were examined.[11] Again, the best results were obtained when MTBE was used as solvent and the reaction was applicable to a range of aryldiazoacetates and a vinyldiazoacetate as summarized in Table 2. The utility of this method is illustrated in

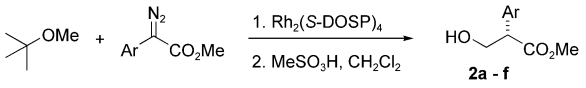
Table 1. C–H activation of 1,2-dimethoxyethane with various aryldiazoacetates.



Entry	Ar	Product	Yield [%]	ee [%]
1	*p*-Br-Ph	**1a**	72	76
2	Ph	**1b**	63	75
3	*p*-CH_3-Ph	**1c**	69	67
4[a]	*p*-MeO-Ph	**1d**	56	65
5	2-Naph	**1e**	72	59
6	(*E*)-PhCH=CH	**1f**	53	87

[a] Reaction at 70 °C.

Table 2. C–H activation of methyl *tert*-butyl ether with various aryldiazoacetates.[a]



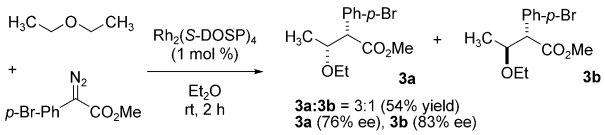
Entry	Ar	Product	Yield [%]	ee [%]
1	*p*-Br-Ph[b]	**2a**	39	85
2	Ph	**2b**	34	79
3	*p*-CH_3-Ph	**2c**	21	82
4	*p*-MeO-Ph	**2d**	36	82
5	2-Naph	**2e**	25	76
6	(*E*)-PhCH=CH[b]	**2f**	38	95

[a] Reactions were run at rt with 1 – 2 mol % Rh_2(*S*-DOSP)$_4$.
[b] Product was isolated as a *tert*-butyl ether.

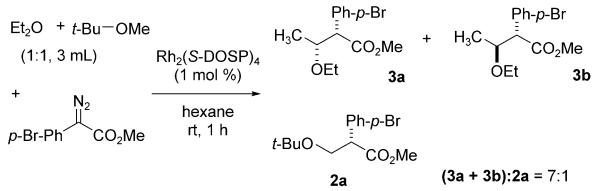
a 2-step sequence of C–H activation followed by acid-induced hydrolysis of the *tert*-butyl group leading to the formation of a series of methyl tropinate **2b** and its aryl derivatives.[12] The tentatively assigned (*S*) configuration for the C–H activation products was confirmed for **2b**, whose optical rotation {$[\alpha]_D^{25}$: –57.6 (*c* 0.50, acetone) for 79% ee} was in agreement with the literature value for (*S*)-**2b** {$[\alpha]_D^{23}$: –69.8 (*c* 0.875, acetone) for >98% ee}.[12b] In general, the yields were lower for the reactions of MTBE compared to DME but the asymmetric induction was higher. Once again, the highest asymmetric induction was obtained with methyl styryldiazoacetate (entry 6), which resulted in the formation of the C–H activation product **2f** in 95% ee.

A further evaluation of the influence of the β-alkoxy group was conducted by exploring a control reaction with diethyl ether as substrate. Rh_2(*S*-DOSP)$_4$-catalyzed decomposition of methyl *p*- bromophenyldiazoacetate in ether at room temperature resulted in the formation of **3a/3b** as a 3:1 mixture of diastereomers by ^{1}H NMR spectroscopy[13] in 54% yield (Scheme 5). The major diasteromer **3a** was formed in 76% ee while the minor diasteromer **3b** was formed in 83% ee.

Having achieved a successful reaction with diethyl ether, it was now possible to conduct a competition reaction between diethyl ether and MTBE. Rh_2(*S*-DOSP)$_4$-catalyzed reaction of *p*-bromophenyldiazoacetate in a 1:1 mixture of diethyl ether and MTBE resulted in a 7:1 mixture of products favoring C–H functionalization of diethyl ether (Scheme 6). The demonstration that the methylene site in diethyl ether is favored over



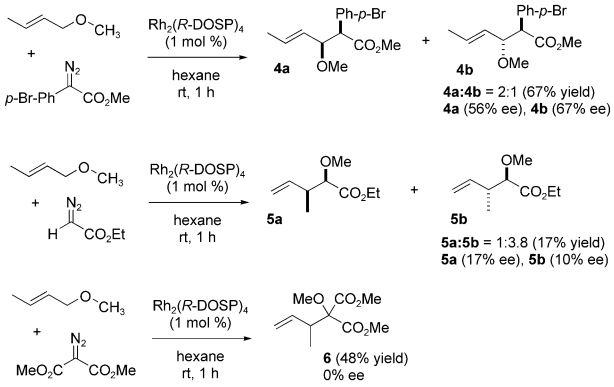
Scheme 5. C–H activation reaction of diethyl ether.



Scheme 6. Competition study on the C–H activation reactions between diethyl ether and methyl *tert*-butyl ether.

the methyl site in MTBE whereas no reaction was observed at the methylene site in DME, is indicative that the β-methoxy group has a very negative influence on the C–H activation.

The emergence of donor/acceptor-substituted carbenoids has been a major factor in enabling the asymmetric intermolecular C–H activation to become a viable synthetic process.[3c, d] We have shown in comparison studies that the chemoselectivity of the donor/acceptor substituted carbenoids is very different from that of the traditional carbenoids lacking the donor group.[14] A further demonstration of this reactivity difference is seen in the reaction with crotyl methyl ether. The reaction with *p*-bromophenyldiazoacetate led to a clean C–H activation at the methylene site (Scheme 7). A 2:1 mixture of diastereomers **4a** and **4b** was formed in 67% yield, in which the major diastereomer **4a** was formed in 56% ee and the minor diastereomer **4b** was formed in 67% ee. No C–H insertion into the methyl group was observed, indicating that the allylic methylene is highly activated towards the C–H insertion. The low diastereoselectivity in this case compared to the reaction of crotyl silyl ethers[8b] is presumably because the size differentiation between the crotyl and methoxy groups is not sufficient to induce high diastereoselctivity. In contrast, the reactions of crotyl methyl ether with ethyl diazoacetate[15] and dimethyl diazomalonate[16] led to very different results (Scheme 7). No products resulting from a C–H insertion reaction were formed. Instead of C–H



Scheme 7. C–H activation reactions of crotyl methyl ether with different diazo compounds.

activation, the products were **5** and **6** derived from a [2,3]-sigmatropic rearrangement of the corresponding oxonium ylides.

Conclusion

In summary, these studies demonstrate that electronic effects on the C–H activation chemoselectivity are very influential. An alkoxy group at the C–H activation site strongly favors the reaction but a β-alkoxy substituent is strongly deactivating. These effects offer further controlling strategies for the chemoselectvity of the C–H activation chemistry of donor/acceptor-substituted rhodium carbenoids. Furthermore, these studies again demonstrate that the donor/acceptor substituted carbenoids are uniquely suited for the C–H activation chemistry.

Experimental Section

Reactions were performed under an atmosphere of argon. Methyl aryldiazoacetates[7b] and methyl styryldiazoacetate[17] were prepared according to the published procedures. 1,2-Dimethoxyethane (DME), methyl *tert*-butyl ether (MTBE), diethyl ether, and hexane were distilled from sodium-benzophenone ketyl prior to use.

General Procedure for the Rhodium(II)-Catalyzed Decomposition of Aryldiazoacetates in the Presence of Alkyl Ethers

The procedure for the preparation of **1a** is representative. A solution of methyl *p*-bromophenyldiazoacetate (128 mg, 0.5 mmol) in hexane (2 mL) was added into a green solution of $Rh_2(S\text{-DOSP})_4$ (9 mg, 1 mol %) in 1,2-dimethoxyethane (1.5 mL) over 30 min at rt. Stirring continued for another hour under argon. The reaction mixture was concentrated under vacuum and the residue was purified by flash chromatography (silica gel, PE:Et_2O, 2:1) to give pure product **1a** as an oil; yield: 114 mg (72%).

Deprotection of *tert*-butyl ethers was achieved by treating appropriate *tert*-butyl ethers with $MeSO_3H$ (12 equiv.) in CH_2Cl_2 at rt for 30 min.

1a: R_f 0.31 (PE:ether, 2:1) [UV, $KMnO_4$]; IR (neat): ν = 1739, 1736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.4 Hz, 2H, Ar**H**), 7.19 (d, *J* = 8.4 Hz, 2H, Ar**H**), 4.02 (t, *J* = 9.0 Hz, 1H, OC**H**$_2$CH), 3.89 (dd, *J* = 9.0, 5.2 Hz, 1H, OC**H**$_2$CH), 3.70 (m, 4H, $OCH_2C\mathbf{H}$, $CO_2C\mathbf{H}_3$), 3.64–3.58 (m, 2H, $OC\mathbf{H}_2CH_2O$), 3.52–3.38 (m, 2H, $OC\mathbf{H}_2CH_2O$), 3.35 (s, 3H, $OC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.4, 134.8, 131.7, 129.8, 121.6, 72.5, 71.7, 70.6, 58.9, 52.1, 51.3; HRMS (EI): calcd. for $C_{13}H_{17}BrO_4$: 316.0305; found: 316.0310; anal. calcd.: C 49.23, H 5.40; found: C 49.45 H 5.40; 76% ee by HPLC: CHIRALCEL OD-H column, 8% 2-propanol in hexanes, 1 mL/min, t_R (minor) 6.6 min, t_R (major) 7. 8 min; $[\alpha]_D^{25}$: −30.5 (*c* 0.39, $CHCl_3$).

1b: R_f 0.36 (PE:ether, 2:1) [UV, $KMnO_4$]; IR (neat): ν = 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (m, 5H, Ar**H**), 4.07 (t, *J* = 9.3 Hz, 1H, OC**H**$_2$CH), 3.94 (dd, *J* = 9.6, 5.1 Hz, 1H, OC**H**$_2$CH), 3.69 (m, 4H, $OCH_2C\mathbf{H}$, $CO_2C\mathbf{H}_3$), 3.60 (m, 2H, $OC\mathbf{H}_2CH_2O$), 3.53–3.49 (m, 2H, $OC\mathbf{H}_2CH_2O$), 3.36 (s, 3 H, $OC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 135.8, 128.7, 128.0, 127.6, 72.9, 71.8, 70.6, 59.0, 52.03, 51.98; HRMS (EI): calcd. for $C_{13}H_{18}O_4$: 239.1278; found: 239.1277; anal. calcd.: C 65.53, H 7.61; found: C 65.69 H 7.62; 75% ee by HPLC: CHIRALCEL OD-H column, 8% 2-propanol in hexanes, 1 mL/min, t_R (minor) 6.5 min, t_R (major) 7. 1 min; $[\alpha]_D^{25}$: −41.5 (*c* 2.35, $CHCl_3$).

1c: R_f 0.24 (PE:ether, 2:1) [UV, $KMnO_4$]; IR (neat): ν = 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.1 Hz, 2H, Ar**H**), 7.12 (d, *J* = 8.4 Hz, 2H, Ar**H**), 4.06 (t, *J* = 9.6 Hz, 1H, OC**H**$_2$CH), 3.91 (dd, *J* = 9.6, 5.1 Hz, 1H, OC**H**$_2$CH), 3.68–3.61 (m, 6H, $OCH_2C\mathbf{H}$, $CO_2C\mathbf{H}_3$, $OC\mathbf{H}_2CH_2O$), 3.53–3.49 (m, 2H, $OC\mathbf{H}_2CH_2O$), 3.36 (s, 3H, $OC\mathbf{H}_3$), 2.32 (s, 3H, $ArC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 137.3, 132.7, 129.4, 127.9, 73.0, 71.8, 70.6, 58.9, 52.0, 51.5, 21.0; HRMS (EI): calcd. for $C_{14}H_{21}O_4$: 253.1434; found: 253.1429; anal. calcd.: C 66.65, H 7.99; found: C 66.88 H 7.99; 67% ee by HPLC: CHIRALCEL OD-H column, 2% 2-propanol in hexanes, 1 mL/min, t_R (minor) 8.9 min, t_R (major) 9.6 min; $[\alpha]_D^{25}$: −37.6 (*c* 1.82, $CHCl_3$).

1d: R_f 0.27 (PE:ether, 2:1) [UV, $KMnO_4$]; IR (neat): ν = 1738, 1513 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 9.0 Hz, 2H, Ar**H**), 6.85 (d, *J* = 9.0 Hz, 2H, Ar**H**), 4.04 (t, *J* = 10.0 Hz, 1H, OC**H**$_2$CH), 3.91 (dd, *J* = 9.5, 5.0 Hz, 1H, OC**H**$_2$CH), 3.78 (s, 3H, $CO_2C\mathbf{H}_3$), 3.68–3.60 (m, 6H, $OCH_2C\mathbf{H}$, $OC\mathbf{H}_2CH_2O$, $ArOC\mathbf{H}_3$), 3.55–3.47 (m, 2H, $OC\mathbf{H}_2CH_2O$), 3.36 (s, 3H, $OC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 159.1, 129.1, 127.8, 114.1, 73.0, 71.8, 70.6, 59.0, 55.2, 52.0, 51.1; LRMS (EI): *m/z* = 269 $[M+H]^+$; anal. calcd.: C 62.67, H 7.51; found: C 62.95, H 7.38; 65% ee by HPLC: (R,R)-Whelk-O 1 column, 2% 2-propanol in hexanes, 1 mL/min, t_R (major) 9.0 min, t_R (minor) 9.6 min; $[\alpha]_D^{25}$: −32.77 (*c* 1.30, $CHCl_3$).

1e: R_f 0.23 (PE:ether, 2:1) [UV, $KMnO_4$]; IR (neat): ν = 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.80 (m, 4H, Ar**H**), 7.47 (m, 3H, Ar**H**), 4.23–4.10 (m, 2H, OC**H**$_2$CH), 3.80 (dd, *J* = 9.0, 4.5 Hz, 1H, $OCH_2C\mathbf{H}$), 3.71 (s, 3H, $CO_2C\mathbf{H}_3$), 3.60 (m, 2H, $OC\mathbf{H}_2CH_2O$), 3.58–3.48 (m, 2H, $OC\mathbf{H}_2CH_2O$), 3.37 (s, 3H, $OC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 133.4, 133.2, 132.7, 128.4, 127.8, 127.6, 127.0, 126.2, 126.0, 72.9, 71.8, 70.7, 58.9, 52.06, 52.03; HRMS (EI): calcd. for $C_{17}H_{21}O_4$: 289.1434; found 289.1434; anal. calcd.: C 70.81, H 6.99; found C 71.05, H 7.02; 59% ee by HPLC: CHIRALCEL OD-H column, 2% 2-propanol in hexanes, 1 mL/min, t_R (minor) 8.9 min, t_R (major) 9.9 min; $[\alpha]_D^{25}$: −34.4 (*c* 1.56, $CHCl_3$).

1f: R_f 0.19 (PE:ether, 2:1) [UV, $KMnO_4$]; IR (neat): ν = 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.18 (m, 5H, Ar**H**), 6.50 (d, *J* = 15.9 Hz, 1H, C**H**=CH), 6.12 (dd, *J* = 15.9, 8.4 Hz, 1H, C**H**=CH), 3.83 (t, *J* = 9.0 Hz, 1H, OC**H**$_2$CH), 3.69 (s, 3H, $CO_2C\mathbf{H}_3$), 3.66–3.44 (m, 6H, OC**H**$_2$CH, $OCH_2C\mathbf{H}$ $OC\mathbf{H}_2C\mathbf{H}_2O$), 3.33 (s, 3H, $OC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.8, 136.5, 133.6, 128.5, 127.7, 126.4, 123.7, 72.1, 71.8, 70.6, 59.0, 52.0, 49.9; HRMS (EI): calcd. for $C_{15}H_{21}O_4$: 265.1434; found: 265.1434; anal. calcd.: C 68.16, H 7.63; found: C 68.19, H 7.62; 87% ee by HPLC: (R,R)-Whelk-O 1 column, 5% 2-propanol in hexanes, 1 mL/min, t_R (minor) 19.0 min, t_R (major) 21.7 min; $[\alpha]_D^{25}$: −42.3 (*c* 2.75, $CHCl_3$).

2a: R_f 0.42 (PE:ether, 2:1) [UV, $KMnO_4$]; IR (neat): ν = 1741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.21 (d, *J* = 8.5 Hz, 2H, Ar**H**), 3.90 (t, *J* = 8.5 Hz, 1H, OC**H**$_2$CH), 3.75 (dd, *J* = 8.5, 5.5 Hz, 1H, OC**H**$_2$CH), 3.68 (s, 3H, $CO_2C\mathbf{H}_3$), 3.51 (dd, *J* = 8.5, 5.5 Hz, 1H, $OCH_2C\mathbf{H}$), 1.14 [s, 9H, $C(C\mathbf{H}_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 135.4, 131.7, 130.0, 121.5, 73.3, 63.8, 52.1, 52.0, 27.3; HRMS (EI): calcd. for $C_{14}H_{19}BrO_3Na$: 337.0410; found: 337.0399; 85% ee for corresponding *tert*-butyl ether by HPLC: (R,R)-Whelk-O 1 column, 2% 2-propanol in hexanes, 1 mL/min, t_R (minor) 5.3 min, t_R (major) 5.8 min; $[\alpha]_D^{25}$: −14.0 (*c* 0.25, $CHCl_3$).

2b: R_f 0.20 (PE:ether, 1:1) [UV, PMA]; IR (neat): ν = 3413, 1735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36 (m, 5H, Ar**H**), 4.14 (t, *J* = 9.2 Hz, 1H, OC**H**$_2$CH), 3.87 (m, 2H, OC**H**$_2$CH, $OCH_2C\mathbf{H}$), 3.72 (s, 3H, $CO_2C\mathbf{H}_3$), 2.25 (br m, 1H, D_2O exch, O**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 135.6, 128.9, 128.2, 127.8, 64.6,, 53.9, 52.2; HRMS (CI): calcd. for $C_{10}H_{12}O_3$: 181.0859; found: 181.0866; anal. calcd.: C 66.65, H 6.71; found: C 66.44, H 6.74; 79% ee for corresponding *tert*-butyl ether by HPLC: CHIRALCEL OD-H column, 3% 2-propanol in hexanes, 1 mL/min, t_R (major) 4.3 min, t_R (minor) 4.7 min; $[\alpha]_D^{25}$: −57.6 (*c* 0.50, acetone), −77.4 (*c* 0.54, $CHCl_3$), lit.[12b] {$[\alpha]_D^{23}$: −69.8 (*c* 0.875, acetone) for >98% ee}.

2c: R_f 0.27 (PE:ether, 1:1) [UV, PMA]; IR (neat): ν = 3436, 1739 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.15 (s, 4H, Ar**H**), 4.12 (ddd, *J* = 11.7, 11.7, 6.0 Hz, 1H, OC**H**$_2$CH), 3.85–3.76 (m, 2H, OC**H**$_2$CH, $OCH_2C\mathbf{H}$), 3.70 (s, 3H, $CO_2C\mathbf{H}_3$), 2.33 (s, 3H, $ArC\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 137.5, 132.5, 129.6, 128.0, 64.6, 53.5, 52.2, 21.0; HRMS (EI): calcd. for $C_{11}H_{15}O_3$ [M + H]: 195.1011; found: 195.1016; anal. calcd.: C 68.02, H 7.27; found: C 67.91, H 7.28; 71% ee for corresponding *tert*-butyl ether by HPLC: CHIRALCEL OD-H column, 3% 2-propanol in hexanes, 1 mL/min, t_R (minor) 3.9 min, t_R (major) 4.3 min; $[\alpha]_D^{25}$: 70.8 (*c* 0.72, $CHCl_3$) [product with Rh_2(*R*-DOSP)$_4$].

2d: R_f 0.19 (PE:ether, 1:1) [UV, PMA]; IR (neat): ν = 3412, 1733, 1513 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.7 Hz, 2H, Ar**H**), 6.88 (d, *J* = 9.0 Hz, 2H, Ar**H**), 4.10 (dd, *J* = 12.6, 10.8 Hz, 1H, OC**H**$_2$CH), 3.79 (m, 5H, OC**H**$_2$CH, $OCH_2C\mathbf{H}$, $ArOC\mathbf{H}_3$), 3.70 (s, 3H, $CO_2C\mathbf{H}_3$), 2.26 (br m, 1H, O**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 159.2, 129.2, 127.6, 114.3, 64.7, 55.3, 53.0, 52.1; HRMS (EI): calcd. for $C_{11}H_{14}O_4Na$: 233.0791; found: 233.0784; anal. calcd.: C 62.85, H 6.71; found: C 63.01, H 6.31; 79% ee for corresponding *tert*-butyl ether by HPLC: CHIRALCEL OD-H column, 3% 2-propanol in hexanes, 1 mL/min, t_R (minor) 4.7 min, t_R (major) 5.5 min; $[\alpha]_D^{25}$: 71.0 (*c* 0.555, $CHCl_3$) [product with Rh_2(*R*-DOSP)$_4$].

2-(3-*tert*-Butyl-4-methoxyphenyl)-3-hydroxypropionic acid methyl ester **2d'** was also formed (**2d:2d'** = 3:1) during deprotection: R_f 0.24 (PE:ether, 1:1) [UV, PMA]; IR (neat): ν = 3421, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.14 (d, *J* = 2.1 Hz, 1H, Ar**H**), 7.08 (dd, *J* = 8.4, 2.1 Hz, 1H, Ar**H**), 6.83 (d, *J* = 8.4 Hz, 1H, Ar**H**), 4.10 (dd, *J* = 12.6, 10.8 Hz, 1H, OC**H**$_2$CH), 3.80 (m, 5H, OC**H**$_2$CH, $OCH_2C\mathbf{H}$, $ArOC\mathbf{H}_3$), 3.71 (s, 3H, $CO_2C\mathbf{H}_3$), 1.36 [s, 9H, $ArC(C\mathbf{H}_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 158.1, 138.7, 126.9, 126.7, 126.3, 111.7, 64.8, 55.0, 53.4, 52.1, 34.8, 29.6; HRMS (EI): calcd. for $C_{15}H_{22}O_4Na$: 289.1410; found: 289.1410.

2e: R_f 0.18 (PE:ether, 1:1) [UV, PMA]; IR (neat): ν = 3523, 1735, 1719 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.82 (m, 3H, Ar**H**), 7.73 (s, 1H, Ar**H**), 7.49 (m, 2H, Ar**H**), 7.38 (dd, *J* = 8.8, 1.6 Hz, 1H, Ar**H**), 4.25 (m, 1H, OC**H**$_2$CH), 4.03 (dd, *J* = 8.8, 5.6 Hz, 1H, OC**H**$_2$CH), 3.90 (m, 1H $OCH_2C\mathbf{H}$), 3.73 (s, 3H, $CO_2C\mathbf{H}_3$), 2.29 (br m, 1H, O**H**); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.6, 133.4, 133.0, 132.8, 128.7, 127.8, 127.7, 127.2, 126.4, 126.2, 125.9, 64.6, 54.0, 52.3; HRMS (EI): calcd. for $C_{14}H_{14}O_3$: 230.0940; found: 230.0937; anal. calcd.: C 73.03, H 6.13; found: C 73.25, H 6.26; 76% ee for corresponding *tert*-butyl ether by HPLC: CHIRALCEL OD-H column, 3% 2-propanol in hexanes, 1 mL/min, t_R (minor) 4.7 min, t_R (major) 5.5 min; $[\alpha]_D^{25}$: 69.1 (*c* 0.39, $CHCl_3$) [product with Rh_2(*R*-DOSP)$_4$].

2f: R_f 0.37 (PE:ether, 9:1) [UV, $KMnO_4$]; IR (neat): ν = 1738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.16 (m, 5H, Ar**H**), 6.50 (d, *J* = 15.9 Hz, 1H, C**H**=CH), 6.14 (dd, *J* = 15.9, 8.7 Hz, 1H, C**H**=CH), 3.68 (m, 4H, OC**H**$_2$CH, $CO_2C\mathbf{H}_3$), 3.48 (dd, *J* = 6.6, 5.4 Hz, 1H, OC**H**$_2$CH), 3.42–3.35 (m, 1H, $OCH_2C\mathbf{H}$), 1.13 [s, 9 H, $O(C\mathbf{H}_3)_3$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 136.7, 133.3, 128.5, 127.7, 126.4, 124.4, 73.2, 63.3, 51.8, 50.8, 27.4; HRMS (EI): calcd. for $C_{16}H_{22}O_3Na$: 285.1467; found: 285.1461; anal. calcd.: C 73.25, H 8.45; found: C 73.25, H 8.46; 76% ee for corresponding *tert*-butyl ether by HPLC: CHIRALCEL OD-H column, 3% 2-propanol in hexanes, 1 mL/min, t_R (minor) 4.9 min, t_R (major) 5.5 min; $[\alpha]_D^{25}$: 30.9 (*c* 0.39, $CHCl_3$) [product with Rh_2(*R*-DOSP)$_4$].

3a/3b: R_f 0.35 (PE:ether, 9:1) [UV, $KMnO_4$]; IR (neat): ν = 1736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (a 3:1 mixture of diastereomers): δ = 7.43 (m, 2H, Ar**H**), 7.23 (m, 2H, Ar**H**), 3.94 (m, 1H, $CH_3C\mathbf{H}$), 3.67 (s, 3H, $CO_2C\mathbf{H}_3$), 3.56–3.11 (m, 3H, OC**H**$_2$CH$_3$, $C\mathbf{H}CO_2CH_3$), 1.19 and 0.92 (2d, *J* = 6.0 Hz, 3H, $CH_3C\mathbf{H}$), 1.17 and 0.96 (2 t, *J* = 7.0 Hz, 3H, $OCH_2C\mathbf{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) a 3:1 mixture of diastereomers): δ = 173.0, 172.4, 135.5, 135.0, 131.8, 131.3, 130.8, 130.3, 121.8, 121.3, 77.1, 76.4, 65.0, 64.8, 58.7, 57.8, 52.0, 51.9, 18.5, 17.2, 15.5, 15.2; LRMS (EI): *m/z* = 302 [M^+]; anal. calcd.: C 51.84, H 5.69; found: C 51.76, H 5.55; 83% ee for minor isomer and 76% ee for major isomer by HPLC: (R,R)-Whelk-O 1 column, 2% 2-propanol in hexanes, 1 mL/min: minor isomer, t_R (minor) 5.7 min, t_R (major) 6.3 min: major isomer, t_R (major) 6.0 min, t_R (minor) 7.4 min.; $[\alpha]_D^{25}$: 28.3 (*c* 1.075, $CHCl_3$).

4a, *syn*-isomer: R_f 0.48 (hexane:ether, 9:1, ×2) [UV, PMA]; IR (neat): ν = 1737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.4 (d, *J* = 8.5 Hz, 2H, Ar**H**), 7.25 (d, *J* = 8.5 Hz, 2H, Ar**H**), 5.74 (m, 1H, C**H**=CH), 5.30 (ddd, *J* = 15.5, 8.5, 1.5 Hz, 1H, C**H**=CH), 4.04 (t, *J* = 8.5 Hz, 1H, $C\mathbf{H}OCH_3$), 3.65 (d, *J* = 8.5 Hz, 1H, $C\mathbf{H}CO_2CH_3$), 3.63 (s, 3H, $CO_2C\mathbf{H}_3$), 3.14 (s, 3H, $OC\mathbf{H}_3$), 1.71 (dd, *J* = 6.0, 1.5 Hz, 3H, $C\mathbf{H}_3CH$=CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.7, 135.0, 131.6, 131.4, 130.7, 128.3, 121.4, 82.9, 56.9, 56.4, 52.0, 17.7; HRMS (EI): calcd. for $C_{14}H_{17}BrO_3$: 312.0356; found: 312.0362; 56% ee by HPLC: CHIRALCEL OD-H column, 2% 2-propanol in hexanes, 1 mL/min, t_R (minor) 7.1 min, t_R (major) 8.6 min; $[\alpha]_D^{25}$: 6.2 (*c* 4.00, $CHCl_3$).

4b, *anti*-isomer: R_f 0.36 (hexane:ether, 9:1, ×2) [UV, PMA]; IR (neat): ν = 1739 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6): δ = 7.43 (d, *J* = 8.0 Hz, 2H, Ar**H**), 7.23 (d, *J* = 8.0 Hz, 2H, Ar**H**), 5.47 (m, 1H, C**H**=CH), 5.05 (m, 1H, C**H**=CH), 4.02 (t, *J* = 9.2 Hz, 1H, $C\mathbf{H}OCH_3$), 3.58 (m, 4H, $C\mathbf{H}CO_2CH_3$, $CO_2C\mathbf{H}_3$), 3.15 (s, 3H, $OC\mathbf{H}_3$), 1.46 (d, *J* = 6.4 Hz, 3H, $C\mathbf{H}_3CH$=CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.7, 134.4, 131.6, 131.5, 130.6, 127.7, 121.6, 83.9, 57.1, 56.5, 52.1, 17.6; HRMS (EI): calcd. for $C_{14}H_{17}BrO_3$: 312.0352; found: 312.0356; anal. calcd.. C 53.69, H 5.47; found: C 54.05, H 5.59; 67% ee by HPLC: CHIRALPAK AD-RH column, 3% 2-propanol in

hexanes, 1 mL/min, t_R (minor) 3.8 min, t_R (major) 4.2 min; $[\alpha]_D^{25}$: 45.0 (*c* 1.60, $CHCl_3$).

5: An inseparable mixture of **5a** (*syn*) and **5b** (*anti*) was obtained in 39% yield [with $Rh_2(OAc)_4$, **5a**: **5b** = 1:4.12 by chiral GC] and 17% yield [with Rh_2(*R*-DOSP)$_4$, **5a**: **5b** = 1:3.76 by chiral GC], respectively. The relative stereochemistry was assigned based on the literature[15a], but the absolute stereochemistry was not determined.; R_f 0.38 (PE:ether, 9:1) [PMA]; IR (neat). $\nu = 1725\ cm^{-1}$; ^1H NMR (500 MHz, $CDCl_3$): δ = 5.81 (m, 1H, C**H**=CH_2), 5.06 (m, 2H, CH=C**H**$_2$), 4.23 (m, 2H, $CO_2C\mathbf{H}_2CH_3$), 3.63 (d, *J* = 5.2 Hz, 1H, C**H**OCH_3), 3.40 (s, 3H, O**CH**$_3$), 2.64 (m, 1H, C**H**CH_3), 1.30 (t, *J* = 6.4 Hz, 3H, $CO_2CH_2C\mathbf{H}_3$), 1.10 and 1.07 (2 d, 3:1, *J* = 6.4 Hz, 3H, CHC**H**$_3$); GC/MS: *m/z* = 172 [M^+]; 17% ee for minor diastereomer (**5a**, *syn*) and 10% ee for major (**5b**, *anti*) diastereomer by GC: 30-m chiraldex B-DM column, flow rate 1 mL/min, 80 °C isothermal, t_R (minor diastereomer) 15.9 and 16.3 min, t_R (major diastereomer) 16.6 and 17.3 min; $[\alpha]_D^{25}$: 0.0 (*c* 0.60, $CHCl_3$).

6: The racemic compound is known.[16]; R_f 0.31 (PE:ether, 9:1) [PMA]; IR (neat): $\nu = 1741\ cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 17.6, 10.4, 8.4 Hz, 1H, C**H**=CH_2), 5.08 (d, *J* = 17.6 Hz, 1H, CH=C**H**$_2$), 5.07 (d, *J* = 10.4 Hz, 1H, CH=C**H**$_2$), 3.797 and 3.794 (2 s, 6H, $CO_2C\mathbf{H}_3$), 3.49 (s, 3H, O**CH**$_3$), 2.99 (q, *J* = 7.2 Hz, 1H, C**H**CH_3), 1.10 (d, *J* = 7.2 Hz, 3H, CHC**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.57, 168.52, 137.8, 116.4, 88.1, 55.4, 52.27, 52.19, 44.3, 14.7; HRMS (EI): calcd. for $C_9H_{12}O_4$ [M – CH_3OH]; 184.0730; found: 184.0737; 0% ee by ^1H NMR spectroscopy using europium [tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate] [Eu(hfc)$_3$]; $[\alpha]_D^{25}$: −0.36 (*c* 3.935, $CHCl_3$).

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