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Diastereoselective Hydroalkylation of Aryl Alkenes Enabled by Remote Hydride Transfer

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ABSTRACT

Leveraging of 1,5-hydride shift enabled diastereoselective hydroalkylation of aryl alkenes, allowing for construction of consecutive vicinal stereogenic centers in a single process. The transformation is triggered by electrophilic alkylation of aryl alkenes with *in-situ* generated carbocations, that is followed by diastereoselective 1,5-hydride shift to the resulting benzylic carbocation through a rigid 6-membered ring chair-like transition state.

1. Introduction

Intramolecular 1,5-hydride shift is an event in which a hydride is shifted from a relatively electron-rich aliphatic C-H bond to an electrophilic carbon such as an *in-situ* generated carbocation or an electrophilically activated α,β-unsaturated carbonyl moiety (Scheme 1A).[1,2] This process is known to proceed via a rigid 6-membered ring chair-like transition state, and has thus been utilized for the construction of new stereogenic centers by transferring the preinstalled stereochemical information of the substrates.[3] For example, we recently reported that alkyl ethers are capable in performing intramolecular 1,5-hydride shift to carbocation intermediates generated from protonation or electrophilic bromination of aryl alkenes. This allowed for the construction of vicinal stereogenic centers in a stereocontrolled manner as shown in Schemes 1B and 1C.[4] These processes took advantage of a stereogenic center preinstalled at the allylic position of the *exo*-alkene starting materials to create a new stereogenic center during the 1,5-hydride shift event. We wondered if benzylic carbocations, and more specifically benzylic ones, formed by electrophilic alkylation of prochiral *endo*-aryl alkenes with *in-situ* generated external carbocations,[5,6] could analogously be captured by ensuing 1,5-hydride shift (Scheme 1D). Thus, this hydroalkylation of aryl alkenes would allow for the construction of consecutive vicinal stereogenic centers in a single process. The optimization as well as the scope and limitations of this concept are described herein.

2. Results and Discussion

We embarked on our investigations using aryl alkene **1aa** having a methyl ether tether as a potential hydride donor and diphenylmethanol (**2a**) as a source of carbocation (Table 1, entry 1). Treatment of **1aa** and **2a** (1.5 equiv) with 10 mol% of TsOH in trifluoroethanol at 50 °C[7] promoted smooth conversion of alkene **1aa** within 2 h and provided the desired hydroalkylated ketone **3aa** in 80% yield as a pure diastereomer.[8] We observed that the reaction of benzyl ether **1ab** did not improve the yield of **3aa** (entry 2), whereas that of alcohol **1ac** was a fast process (0.5 h), providing **3aa** in 73% yield (entry 3). As the direct use of alcohol **1ac** as the hydride donor would be beneficial from the view points of overall process efficiency, we further screened a series of Brønsted acids to improve the process using alcohol **1ac** as the substrate. Among the Brønsted acids tested (entries 4-6), the reaction with triflimide[9] resulted in the formation of **3aa** in the highest yield within 0.3 h (entry 5).

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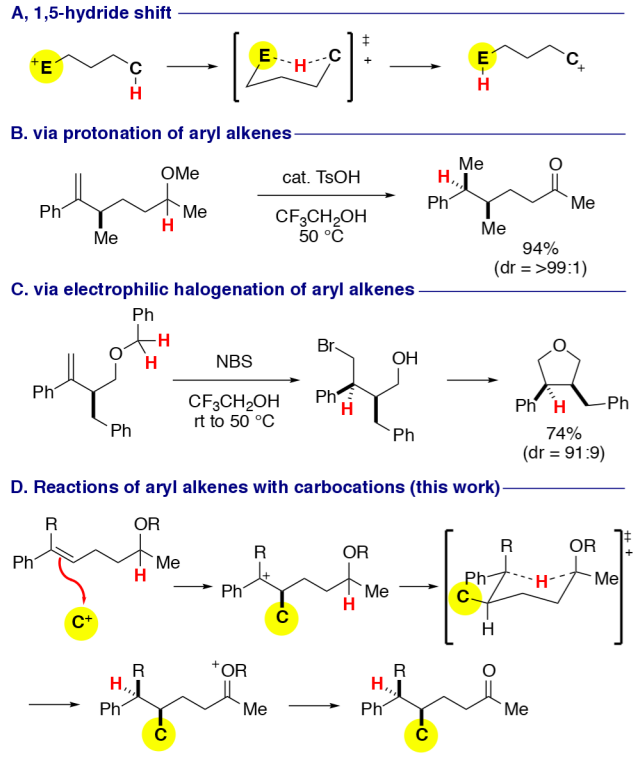
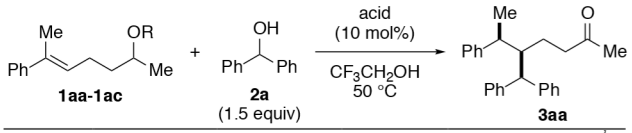


Scheme 1. 1,5-hydride shift for the construction of contiguous stereogenic centers.

Table 1. Reaction optimization[a]



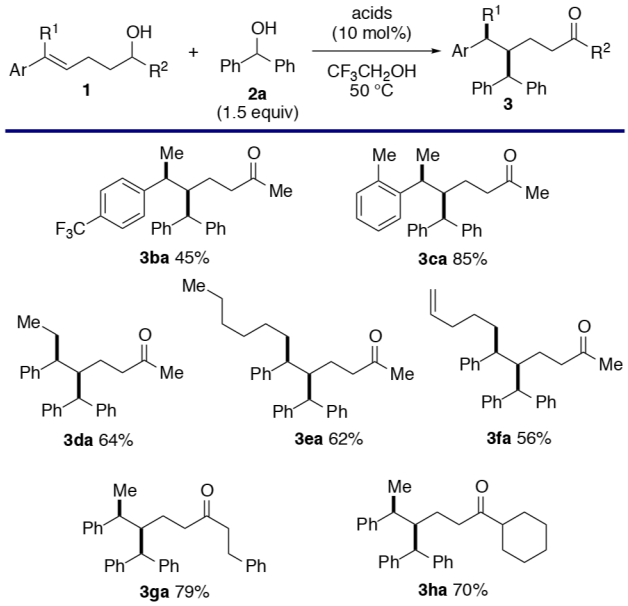
Entry	R	Acid	Time (h)	Yield of **3aa** (%)[b]
1	Me (**1aa**)	TsOH	2	80 (77)[c]
2	Bn (**1ab**)	TsOH	3	69
3	H (**1ac**)	TsOH	0.5	73 (71)[c]
4	H (**1ac**)	TfOH	0.3	75 (67)[c]
5	H (**1ac**)	Tf_2NH	0.3	88 (80)[c]
6	H (**1ac**)	CF_3CO_2H	19	50

[a] The reaction was conducted using 0.3 mmol of **1a**.

[b] ^1H NMR yields based on the internal standard.

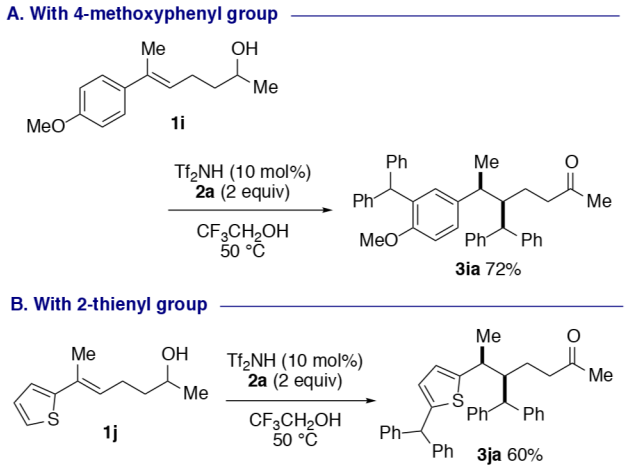
[c] Isolated yields.

With the optimized reaction conditions in hands, we next investigated the substituent compatibility on the aryl alkenes **1** in the reactions with diphenylmethanol (**2a**) (Scheme 2). The reaction of alkene **1b** having an electron-deficient 4-trifluoromethylphenyl group provided **3ba** in moderate yield (45%), whereas the process is compatible with the presence of a sterically demanding 2-methylphenyl group (for **3ca**). As for the substituent R^1, ethyl, *n*-hexyl, and pentenyl groups could be installed, affording **3da**, **3ea**, and **3fa**, respectively, as single diastereomers.[10] We also found that the process was not disturbed by the installation of a bulkier phenethyl and cyclohexyl groups at the carbinol position (for **3ga** and **3ha**).



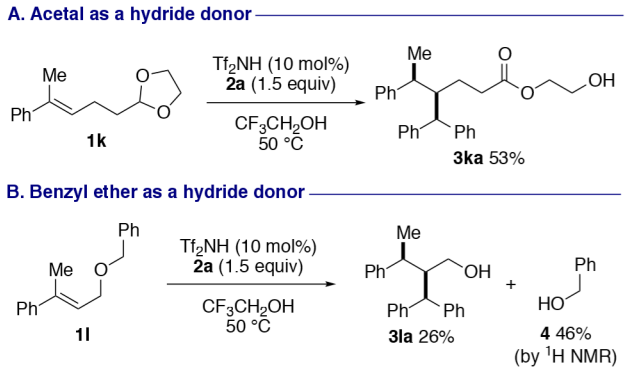
Scheme 2. Substrate scope on aryl alkenes **1**.

Substrates **1i** and **1j** possessing an electron-rich aryl group on the alkenyl moiety underwent not only the desired hydroalkylation but also an additional Friedel-Crafts type aromatic C-H alkylation with the transient carbocation derived from **2a** (used in 2 equiv). Thus, the corresponding products **3ia** and **3ja** could be isolated in 72% and 60% yield, respectively (Scheme 3).



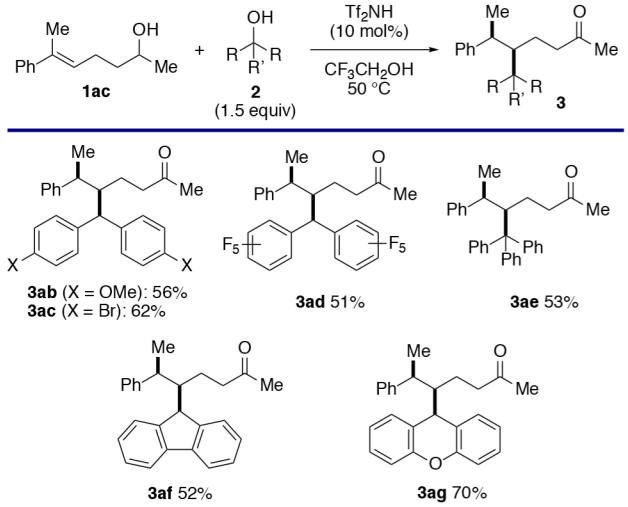
Scheme 3. The reactions of **1i** and **1j** having an electron-rich aryl group on the alkenyl moiety.

In seeking for an alternative hydride donor, a 1,3-dioxolane moiety in substrate **1k** was found capable in inducing the diastereoselective hydroalkylation with **2a**. Under the optimized reaction conditions, the process led to the formation of **3ka** in 53% yield (Scheme 4A). The reaction of allylic alcohol *O*-benzyl ether **1l** also resulted in formation of **3la** as a pure diastereomer despite a poor yield (26%) (Scheme 4B). The formation of several side products including benzyl alcohol (**4**) in 46% yield was observed probably due to the more acid sensitive character of the allyl benzyl ether motif of substrate **1l**.



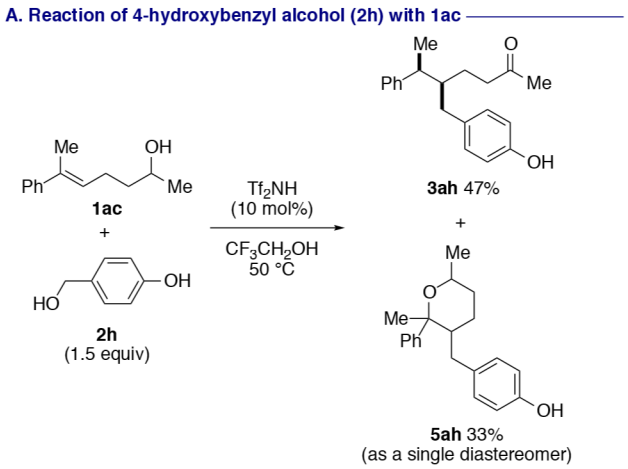
Scheme 4. Use of other hydride donors.

Various alcohols were also screened as the potential carbocation source (Scheme 5). Symmetrical bisarylmethanols **2b-2d** having 4-methoxyphenyl, 4-bromophenyl or pentafluorophenyl motifs were found to be suitable reaction partners, leading to the formation of the corresponding hydroalkylated products **3ab-3ad**, respectively in good to moderate yields. The reaction with triphenylmethanol (**2e**) delivered **3ae** having a trityl group in 53% yield. The method also allowed for the installation of fluorene and xanthene moieties, as exemplified by the formation of **3af** and **3ag**, respectively.



Scheme 5. Substrate scope with alcohols **2** as carbocation sources.

Interestingly, the reaction of aryl alkene **1ac** with 4-hydroxybenzyl alcohol (**2h**) provided not only the expected hydrobenzylated product **3ah** in 47% yield but also tetrahydropyran **5ah** in 33% yield as a single diastereomer (Scheme 6A). The processes should be mediated by a transient protonated *p*-quinone methide **A**[11] as an electrophilic intermediate. The formation of **5ah** is proposed to occur most likely in a concerted fashion by oxyalkylation of the alkene with **A** (Scheme 6B).



Scheme 6. A reaction with 4-hydroxybenzyl alcohol (**2h**).

3. Conclusions

This work demonstrated the diastereoselective construction of vicinal stereogenic centers by hydroalkylation of aryl alkenes with activated alcohols such as diphenylmethanol (**2a**) under simple Brønsted acid catalysis. The process involves the regioselective electrophilic alkylation of aryl alkenes with external carbocations generated *in situ* and ensuing 1,5-hydride shift in a single process. We are now exploring an enantioselective variant of this process by taking advantage of chiral Brønsted acid catalysis.

4. Experimental section

4.1. General experimental methods

^{1}H NMR spectra (400 or 500 MHz) were recorded on a Bruker Avance 400 or 500 spectrometer in $CDCl_3$ [using TMS (for ^{1}H, δ = 0.00) as internal standard]. ^{13}C NMR spectra (100 or 125 MHz) were recorded on a Bruker Avance 400, or 500 spectrometers in $CDCl_3$ [using $CDCl_3$ (for ^{13}C, δ = 77.00) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, brs = broad, m = multiplet. High-resolution mass spectra were obtained with a Waters Q-Tof Premier mass spectrometer. IR spectra were recorded on a Shimadzu IR Prestige-21 FT-IR spectrometer. IR spectra were taken to identify the key functional groups of alkenes **1** (see the supplementary material for their synthesis and characterization) and the respective products **3** and **5ah** to trace key functional group interconversions. All the reactions were conducted using flame dried reaction vessels under a N_2 atmosphere. 2,2,2-Trifluoroethanol was purchased from Fluorochem Ltd. and used as received.

4.2. Brønsted acid-catalyzed diastereoselective hydroalkylation of aryl alkenes

General Procedure: To a solution of aryl alkene **1** (0.30 mmol) and alcohol **2** (0.450 mmol, 1.5 equiv) in 2,2,2-

trifluoroethanol (2.9 mL) was added a solution of trifluoromethanesulfonimide (Tf_2NH) (0.30 M, 0.1 mL, 10 mol%) (the solution was prepared from 36.5 mg of Tf_2NH with 0.43 mL of 2,2,2-trifluoroethanol), and then the reaction mixture was stirred at 50 °C before it was quenched with water. The organic materials were extracted thrice with Et_2O and the combine extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The resulting crude material was purified by flash column chromatography on silica gel, using the solvent system indicated, to give product **3**.

4.2.1. (5R,6S*)-5-benzhydryl-6-phenylheptan-2-one (**3aa**)*

According to the General Procedure, (*E*)-6-phenylhept-5-en-2-ol (**1ac**) (57.0 mg, 0.30 mmol) and diphenylmethanol (**2a**) (82.8 mg, 0.450 mmol) gave **3aa** (85.8 mg, 0.241 mmol) in 80% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (20 min reaction time). Recrystallization from MeOH:CH_2Cl_2 gave a single crystal, the structure of which could be confirmed by X-ray crystallographic analysis (CCDC-1992396). IR (neat, cm^{-1}): 1713 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.30 – 7.29 (m, 4H), 7.25 – 7.16 (m, 8H), 7.13 – 7.10 (m, 1H), 7.06 (d, *J* = 7.1 Hz, 2H), 3.75 (d, *J* = 10.7 Hz, 1H), 3.03 (qd, *J* = 7.2, 3.8 Hz, 1H), 2.44 – 2.39 (m, 1H), 1.86 – 1.75 (m, 2H), 1.73 (s, 3H), 1.57 – 1.50 (m, 1H), 1.37 – 1.30 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 208.9, 144.2, 143.8, 143.7, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, , 126.3, 126.12, 126.10, 55.9. 47.0, 43.0, 40.2, 29.4, 22.8, 19.7; MS (HRMS ESI): Calcd for $C_{26}H_{29}O$ $[M+H]^+$ 357.2218, Found: 357.2227.

4.2.2. (5R,6S*)-5-benzhydryl-6-(4-(trifluoromethyl)phenyl)heptan-2-one (**3ba**)*

According to the General Procedure, (*E*)-6-(4-(trifluoromethyl)phenyl)hept-5-en-2-ol (**1b**) (77.2 mg, 0.299 mmol) and diphenylmethanol (**2a**) (83.7 mg, 0.454 mmol) gave **3ba** (58.0 mg, 0.137 mmol) in 45% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1706 [ν(C=O)], 1240[ν(C-F)].; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.47 (d, *J* = 8.2 Hz, 2H), 7.29 – 7.24 (m, 5H), 7.21 – 7.13(m, 5H), 7.13 (d, *J* = 8.2 Hz, 2H) 3.65 (d, *J* = 11.0 Hz, 1H), 3.14 (qd, *J* = 7.2, 3.4 Hz, 1H), 2.51 – 2.45 (m, 1H), 1.88 – 1.79 (m, 2H), 1.78 (s, 3H), 1.66 – 1.60 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 208.6, 148.1, 143.7 (overlapped, 2C), 128.8, 128.7, 128.6, 128.53 (q, *J* = 38.0 Hz), 128.50, 128.2, 126.4, 126.3, 124.7 (q, *J* = 4.0 Hz, 1C), 124.4 (q, *J* = 275.0 Hz), 56.1, 46.8, 42.9, 40.1, 29.5, 23.2, 18.7; ^{19}F NMR (376 MHz, $CDCl_3$): δ(ppm) -62.2 (s, 3F); MS (HRMS ESI): Calcd for $C_{27}H_{28}F_3O$ $[M+H]^+$ 425.2092, Found: 425.2088.

4.2.3. (5R,6S*)-5-benzhydryl-6-(o-tolyl)heptan-2-one (**3ca**)*

According to the General Procedure, (*E*)-6-(o-tolyl)hept-5-en-2-ol (**1c**) (61.3 mg, 0.300 mmol) and diphenylmethanol (**2a**) (83.5 mg, 0.453 mmol) gave **3ca** (94.6 mg, 0.255 mmol) in 85% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1713 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.33 – 7.27 (m, 4H), 7.24 (d, *J* = 7.0 Hz, 1H)7.21 – 7.18 (m, 3H), 7.13 – 7.09 (m, 4H), 7.04 – 7.03 (m, 2H), 4.10 (d, *J* = 8.0 Hz, 1H), 3.13 (dq, *J* = 7.0, 7.0 Hz, 1H), 2.47 – 2.42 (m, 1H), 1.97 (s, 3H), 1.78 – 1.73 (m, 3H), 1.69 (s, 3H), 1.65 – 1.60 (m, 1H), 1.20 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 208.8, 144.2, 144.1, 142.6, 135.8, 130.4, 129.4, 128.42, 128.41, 128.3, 126.9, 126.4, 126.0, 125.9, 125.7, 54.5, 47.9, 44.0, 37.1, 29.2, 24.4, 20.3, 19.6; MS (HRMS ESI): Calcd for $C_{27}H_{31}O$ $[M+H]^+$ 371.2375, Found: 371.2375.

4.2.4. (5R,6S*)-5-benzhydryl-6-phenyloctan-2-one (**3da**)*

According to the General Procedure, (*E*)-6-phenyloct-5-en-2-ol (**1d**) (61.7 mg, 0.302 mmol) and diphenylmethanol (**2a**) (82.8 mg, 0.450 mmol) gave **3da** (71.3 mg, 0.192 mmol) in 64% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1711 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.35 – 7.31 (m, 4H), 7.25 – 7.17 (m, 8H), 7.12 – 7.09 (m, 1H), 7.01 – 7.00 (m, 2H), 3.62 (d, *J* = 10.9 Hz, 1H), 2.76 (ddd, *J* = 9.2, 6.1, 3.4 Hz, 1H), 2.51 (dddd, *J* = 10.9, 6.6, 3.45, 3.45 Hz, 1H), 1.95 – 1.76 (m, 4H), 1.74 (s, 3H), 1.52 – 1.46 (m, 1H), 1.32 – 1.26 (m, 1H), 0.78 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 209.0, 144.2, 144.1, 141.8, 129.3, 128.7, 128.6, 128.5, 128.4, 127.8, 126.23, 126.17, 126.15, 56.1, 48.3, 45.0, 43.1, 29.5, 26.7, 22.8, 12.6; MS (HRMS ESI): Calcd for $C_{27}H_{30}OLi$ $[M+Li]^+$ 377.2457, Found: 377.2454.

4.2.5. (5R,6S*)-5-benzhydryl-6-phenyldodecan-2-one (**3ea**)*

According to the General Procedure, (*E*)-6-phenyldodec-5-en-2-ol (**1e**) (77.5 mg, 0.298 mmol) and diphenylmethanol (**2a**) (83.1 mg, 0.452 mmol) gave **3ea** (78.9 mg, 0.185 mmol) in 62% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (4 h reaction time). IR (neat, cm^{-1}): 1715 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.31 (m, 4H), 7.24 – 7.17 (m, 8H), 7.11 – 7.08 (m, 1H), 7.01 – 6.99 (m, 2H), 3.60 (d, *J* = 11.1 Hz, 1H), 2.85 (ddd, *J* = 9.1, 5.7, 3.4 Hz, 1H), 2.48 (dddd, *J* = 11.1, 6.6, 3.4, 3.4 Hz, 1H), 1.95 – 1.88 (m, 1H), 1.86 – 1.76 (m, 2H), 1.74 (s, 3H), 1.72 – 1.66 (m, 1H), 1.50 – 1.44 (m, 1H), 1.33 – 1.08 (m, 9H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 209.0, 144.2, 144.1, 142.1, 129.2, 128.7, 128.6, 128.5, 128.4, 127.8, 126.22, 126.17, 126.1, 56.2, 46.2, 45.4, 43.1, 33.9, 31.7, 29.5, 29.3, 27.8, 22.8, 22.6, 14.0; MS (HRMS ESI): Calcd for $C_{31}H_{39}O$ $[M+H]^+$ 427.3001, Found: 427.3005.

4.2.6. (5R,6S*)-5-benzhydryl-6-phenylundec-10-en-2-one (**3fa**)*

According to the General Procedure, (*E*)-6-phenylundeca-5,10-dien-2-ol (**1f**) (73.6 mg, 0.301 mmol) and diphenylmethanol (**2a**) (83.5 mg, 0.453 mmol) gave **3fa** (68.5 mg, 0.167 mmol) in 56% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 96:4) (30 min reaction time). IR (neat, cm^{-1}): 1715 [ν(C=O)], 1633 [ν(C=C)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.35 – 7.31 (m, 4H), 7.25 – 7.17 (m, 8H), 7.12 – 7.09 (m, 1H), 7.01 – 7.00 (m, 2H), 5.71 (ddt, *J* = 16.9, 10.2, 6.7 Hz, 1H), 4.94 – 4.88 (m, 2H), 3.60 (d, *J* = 11.1 Hz, 1H), 2.86 (ddd, *J* = 9.2, 5.6, 3.4 Hz, 1H), 2.48 (dddd, *J* = 11.1, 6.6, 3.4, 3.3 Hz, 1H), 1.98 – 1.75 (m, 5H), 1.74 (s, 3H), 1.73 – 1.69 (m, 1H), 1.51 – 1.43 (m, 1H), 1.33 – 1.18 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 209.0, 144.14, 144.07, 141.8, 138.8, 129.2, 128.7, 128.6, 128.5, 128.4, 127.9, 126.3, 126.2 (overlapped, 2C), 114.5, 56.2, 46.1, 45.5, 43.1, 33.7, 33.4, 29.5, 27.1, 22.8; MS (HRMS ESI): Calcd for $C_{30}H_{35}O$ $[M+H]^+$ 411.2688, Found: 411.2686.

4.2.7. (6R,7S*)-6-benzhydryl-1,7-diphenyloctan-3-one (**3ga**)*

According to the General Procedure, (*E*)-1,7-diphenyloct-6-en-3-ol (**1g**) (84.3 mg, 0.301 mmol) and diphenylmethanol (**2a**) (82.8 mg, 0.449 mmol) gave **3ga** (106.5 mg, 0.239 mmol) in 79% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1713 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.30 – 7.21 (m, 8H), 7.19 – 7.16 (m, 7H), 7.11 – 7.04 (m, 5H), 3.73 (d, *J* = 10.7 Hz, 1H),

3.02 (qd, *J* = 7.2, 3.7 Hz, 1H), 2.67 (t, *J* = 7.1, 2H), 2.41 – 2.36 (m, 1H), 2.27 (t, *J* = 7.3, 2H), 1.88 – 1.81 (m, 1H), 1.75 – 1.68 (m, 1H), 1.53 – 1.47 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 210.0, 144.2, 143.8, 143.6, 141.1, 128.67, 128.66, 128.5 (overlapped, 2C), 128.4, 128.3, 128.2, 127.9, 126.3, 126.13, 126.11, 126.0, 55.9, 47.0, 43.7, 42.1, 40.2, 29.6, 22.8, 19.7; MS (HRMS ESI): Calcd for $C_{33}H_{35}O$ $[M+H]^+$ 447.2688, Found: 447.2678.

4.2.8. (4R,5S*)-4-benzhydryl-1-cyclohexyl-5-phenylhexan-1-one (**3ha**)*

According to the General Procedure, (*E*)-1-cyclohexyl-5-phenylhex-4-en-1-ol (**1h**) (77.5 mg, 0.300 mmol) and diphenylmethanol (**2a**) (83.1 mg, 0.451 mmol) gave **3ha** (88.9 mg, 0.209 mmol) in 70% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 96:4) (30 min reaction time). IR (neat, cm^{-1}): 1712 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.304 – 7.295 (m, 4H), 7.25 – 7.15 (m, 8H), 7.13 – 7.09 (m, 1H), 7.06 (d, *J* = 7.1 Hz, 2H), 3.74 (d, *J* = 10.7 Hz, 1H), 3.03 (qd, *J* = 7.2, 3.8 Hz, 1H), 2.43 – 2.38 (m, 1H), 1.89 – 1.72 (m, 3H), 1.65 – 1.63 (m, 2H), 1.58 – 1.52 (m, 2H), 1.51 – 1.43 (m, 2H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.31 – 1.25 (m, 1H), 1.14 – 1.01 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 214.1, 144.3, 143.9, 143.7, 128.72, 128.66, 128.5, 128.4, 128.3, 127.9, 126.2, 126.10, 126.06, 56.0, 50.4, 47.2, 40.3, 40.1, 28.30, 28.25, 25.8, 25.6 (overlapped, 2C), 22.9, 19.7; MS (HRMS ESI): Calcd for $C_{31}H_{37}O$ $[M+H]^+$ 425.2844, Found: 425.2841.

4.2.9. (5R,6S*)-5-benzhydryl-6-(3-benzhydryl-4-methoxyphenyl)heptan-2-one (**3ia**)*

According to the General Procedure, (*E*)-6-(4-methoxyphenyl)hept-5-en-2-ol (**1i**) (66.2 mg, 0.300 mmol) and diphenylmethanol (**2a**) (111.3 mg, 0.604 mmol) gave **3ia** 109.9 mg, 0.216 mmol) in 72% yield (dr = >99:1 by ^{1}H NMR) as a white solid after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1710 [ν(C=O)], 1030 [ν(C-O)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.36 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.23 (m, 3H), 7.20 – 7.14 (m, 7H), 7.14 – 7.08 (m, 6H), 6.99 – 6.95 (m, 3H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 5.97 (s, 1H), 3.69 (s, 3H), 3.54 (d, *J* = 11.3 Hz, 1H), 2.84 (qd, *J* = 7.2, 2.3 Hz, 1H), 2.31 – 2.26 (m, 1H), , 1.74 – 1.68 (m, 1H), 1.71 (s, 3H), 1.65 – 1.58 (m, 1H), 1.43 – 1.36 (m, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 1.18 – 1.11 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 208.9, 155.5, 144.5, 144.2, 144.0, 143.6, 134.8, 132.0, 131.1, 129.50, 129.45, 128.6, 128.5, 128.4, 128.2, 128.10, 128.07, 126.63, 126.2, 126.1, 126.0, 125.9, 110.3, 55.9, 55.7, 49.3, 46.7, 42.6, 38.8, 29.4, 22.4, 20.0; MS (HRMS ESI): Calcd for $C_{40}H_{41}O_2$ $[M+H]^+$ 553.3107, Found: 553.3114.

4.2.10. (5S,6S*)-5-benzhydryl-6-(5-benzhydrylthiophen-2-yl)heptan-2-one (**3ja**)*

According to the General Procedure, (*E*)-6-(thiophen-2-yl)hept-5-en-2-ol (**1j**) (59.3 mg, 0.302 mmol) and diphenylmethanol (**2a**) (111.2 mg, 0.604 mmol) gave **3ja** (95.7 mg, 0.181 mmol) in 60% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1712 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.32 – 7.26 (m, 7H), 7.25 – 7.20 (m, 11H), 7.15 - 7.11 (m, 2H), 6.46 (d, *J* = 3.5 Hz, 1H), 6.43 (d, *J* = 3.5 Hz, 1H), 3.85 (d, *J* = 11.1 Hz, 1H), 3.18 (qd, *J* = 7.2, 3.0 Hz, 1H), 2.38 (dtd, *J* = 11.1, 4.9, 3.0 Hz, 1H) , 1.93 – 1.86 (m, 1), 1.80 – 1.73 (m, 1H), 1.78 (s, 3H), 1.69 – 1.64 (m, 1H), 1.44 – 1.37 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 208.7, 146.1, 145.2, 143.84, 143.79, 143.77, 128.8, 128.6, 128.51, 128.48, 128.32, 128.25, 126.6, 126.3, 126.2, 125.7, 124.0, 56.0, 52.3, 46.9, 42.9, 36.6, 29.5, 23.1, 21.2; MS (HRMS ESI): Calcd for $C_{37}H_{37}OS$ $[M+H]^+$ 529.2565, Found: 529.2562.

4.2.11. 2-Hydroxyethyl (4R,5S*)-4-benzhydryl-5-phenylhexanoate (**3ka**)*

According to the General Procedure, (*E*)-2-(4-phenylpent-3-en-1-yl)-1,3-dioxolane (**1k**) (65.3 mg, 0.299 mmol) and diphenylmethanol (**2a**) (82.8 mg, 0.449 mmol) gave **3ka** (63.9 mg, 0.159 mmol) in 53% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 80:20) (2 h reaction time). IR (neat, cm^{-1}): 3435 [ν(O-H)], 1732 [ν(C=O)].; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.29 (m, 3H), 7.26 – 7.15 (m, 9H), 7.14 – 7.10 (m, 1H), 7.06 (d, *J* = 7.0Hz, 2H), 4.07 – 4.05 (m, 2H), 3.75 (d, *J* = 10.8 Hz, 1H), 3.72 – 3.70 (m, 2H), 3.06 (qd, *J* = 7.2, 3.6 Hz, 1H), 2.48 (dddd, *J* = 10.8, 6.6, 3.6, 3.6 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.77 – 1.69 (m, 1H), 1.63 – 1.55 (m, 1H), 1.45 – 1.37 (m, 1H), 1.34 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 173.8, 144.2, 143.7, 143.6, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 126.3, 126.15, 126.13, 65.7, 61.2, 56.0, 47.0, 40.1, 33.4, 24.3, 19.5; MS (HRMS ESI): Calcd for $C_{27}H_{31}O_3$ $[M+H]^+$ 403.2273, Found: 403.2268.

4.2.12. (2R,3S*)-2-benzhydryl-3-phenylbutan-1-ol (**3la**)*

According to the General Procedure, (*E*)-(4-(benzyloxy)but-2-en-2-yl)benzene (**1l**) (71.6 mg, 0.300 mmol) and diphenylmethanol (**2a**) (83.2 mg, 0.452 mmol) gave **3la** (25.1 mg, 0.079 mmol) in 26% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 91:9) (20 min reaction time). IR (neat, cm^{-1}): 3370 [ν(O-H)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.39 (d, *J* = 7.7 Hz, 2H), 7.34 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.30 – 7.18 (m, 8H), 7.15 – 7.09 (m, 3H), 3.92 (d, *J* = 11.5 Hz, 1H), 3.55 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.52 (dd, *J* = 12.0, 4.3 Hz, 1H), 3.07 (qd, *J* = 7.3, 3.9 Hz, 1H), 2.63 (dddd, *J* = 11.5, 4.3, 4.3, 3.9 Hz, 1H), 1.40 (d, *J* = 7.3 Hz, 3H), 0.57 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 143.9, 143.7 (overlapped, 2C), 128.9, 128.7, 128.30, 128.28, 128.2, 128.1, 126.44, 126.41, 126.3, 61.9, 53.5, 50.4, 39.0, 20.4; MS (HRMS ESI): Calcd for $C_{23}H_{25}O$ $[M+H]^+$ 317.1905, Found: 317.1906.

4.2.13. (5R,6S*)-5-(bis(4-methoxyphenyl)methyl)-6-phenylheptan-2-one (**3ab**)*

According to the General Procedure, (*E*)-6-phenylhept-5-en-2-ol (**1ac**) (57.0 mg, 0.300 mmol) and bis(4-methoxyphenyl)methanol (**2b**) (109.5 mg, 0.448 mmol) gave **3ab** (69.7 mg, 0.167 mmol) in 56% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 97:3) (30 min reaction time). IR (neat, cm^{-1}): 1711 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.23 (d, *J* = 7.3 Hz, 2H), 7.19 – 7.16 (m, 3H), 7.10 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 7.3 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 3.78 (s, 3H), 3.73 (s, 3H), 3.67 (d, *J* = 10.5 Hz, 1H), 3.01 (qd, *J* = 7.2, 4.1 Hz, 1H), 2.34 – 2.29 (m, 1H), 1.82 – 1.77 (m, 1H), 1.76 (s, 3H), 1.62 – 1.57 (m, 2H), 1.40 – 1.34 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 209.0, 157.9, 157.7, 143.9, 136.7, 136.3, 129.4, 129.0, 128.4, 127.9, 126.0, 114.0, 113.8, 55.2, 55.1, 53.9, 47.3, 43.1, 40.2, 29.5, 22.9, 19.6; MS (HRMS ESI): Calcd for $C_{28}H_{33}O_3$ $[M+H]^+$ 417.2430, Found: 417.2432.

4.2.14. (5R,6S*)-5-(bis(4-bromophenyl)methyl)-6-phenylheptan-2-one (**3ac**)*

According to the General Procedure, (*E*)-6-phenylhept-5-en-2-ol (**1ac**) (57.6 mg, 0.303 mmol) and bis(4-bromophenyl)methanol (**2c**) (153.7 mg, 0.449 mmol) gave **3ac** (95.8 mg, 0.186 mmol) in 62% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 96:4) (30 min reaction time). IR (neat, cm^{-1}): 1713 [ν(C=O)].; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.38 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), , 7.25 – 7.18 (m, 3H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 6.6 Hz, 2H), 3.69 (d, *J* = 10.6 Hz, 1H), 2.96 (qd, *J* = 7.2, 3.5 Hz, 1H), 2.42 – 2.36 (m, 1H), 1.90 – 1.84 (m, 1H), 1.82 (s, 3H), 1.80 – 1.65 (m, 2H), 1.41 – 1.35 (m, 1H), 1.32 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 208.2, 143.5, 142.7, 142.3, 131.8, 131.7, 130.2, 129.8, 128.2, 128.1, 126.3, 120.4, 120.2, 54.6, 46.9, 42.8, 40.3, 29.6, 23.0, 19.0; MS (HRMS ESI): Calcd for $C_{26}H_{27}O^{79}Br_2$ $[M+H]^+$ 513.0429, Found: 513.0435.

4.2.15. (5R,6S*)-5-(bis(perfluorophenyl)methyl)-6-phenylheptan-2-one (**3ad**)*

According to the General Procedure, (*E*)-6-phenylhept-5-en-2-ol (**1ac**) (57.4 mg, 0.302 mmol) and bis(perfluorophenyl))methanol (**2d**) (164.3 mg, 0.451 mmol) gave **3ad** (82.7 mg, 0.154 mmol) in 51% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1717 [ν(C=O)], 1358 [ν(C-F)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.28 (dd, *J* = 7.7, 7.7 Hz, 2H), 7.19 – 7.16 (m, 3H), 6.50 (d, *J* = 10.0 Hz, 1H), 3.50 – 3.47 (m, 1H), 2.68 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.39 – 2.36 (m, 2H), 2.08 (s, 3H), 1.58 – 1.52 (m, 1H~~3H~~), 1.45 – 1.40 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 209.2, 147.2, 144.7 (dm, *J* = 237 Hz, 4C), 141.5 (dm, *J* = 254 Hz, 2C), 137.8 (dm, *J* = 249 Hz, 4C), 128.4, 126.9, 126.0, 114.0 (m, 2C), 61.0, 43.8, 39.9, 37.8, 29.7, 22.2, 22.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ(ppm) -143.1 (d, *J* = 15.0 Hz, 4F), -152.7 (t, *J* = 18.8 Hz, 2F), -160.7 (dd, *J* = 18.8, 15.0 Hz, 4F); MS (HRMS ESI): Calcd for $C_{26}H_{19}OF_{10}$ $[M+H]^+$ 537.1276, Found: 537.1271.

4.2.16. (5R,6S*)-6-phenyl-5-tritylheptan-2-one (**3ae**)*

According to the General Procedure, (*E*)-6-phenylhept-5-en-2-ol (**1ac**) (57.1 mg, 0.300 mmol) and triphenylmethanol (**2e**) (117.4 mg, 0.451 mmol) gave **3ae** (69.2 mg, 0.160 mmol) in 53% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1717 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.31 – 7.23 (m, 17H), 7.18 – 7.16 (m, 3H), 2.92 – 2.90 (m, 1H), 2.67 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.37 – 2.34 (m, 2H), 2.06 (s, 3H), 1.58 – 1.52 (m, 1H), 1.46 – 1.40 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 209.2, 147.3, 146.9, 128.4, 127.98, 127.95, 127.3, 127.0, 126.0, 82.0, 43.8, 39.9, 37.8, 29.8, 22.3, 22.1; MS (HRMS ESI): Calcd for $C_{32}H_{33}O$ $[M+H]^+$ 433.2531, Found: 433.2534.

4.2.17. (5R,6S*)-5-(9H-fluoren-9-yl)-6-phenylheptan-2-one (**3af**)*

According to the General Procedure, (*E*)-6-phenylhept-5-en-2-ol (**1ac**) (57.0 mg, 0.300 mmol) and fluoren-9-ol (**2f**) (82.3 mg, 0.452 mmol) gave **3af** (55.5 mg, 0.157 mmol) in 52% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 95:5) (30 min reaction time). IR (neat, cm^{-1}): 1714 [ν(C=O)].; 1H NMR (500 MHz, CDCl3): δ(ppm) 7.64 – 7.62 (m, 4H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.32 – 7.25 (m, 4H), 7.19 – 7.15 (m, 3H), 5.56 (d, *J* = 9.5 Hz, 1H), 2.67 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.37 – 2.34 (m, 2H), 2.06 (s, 3H), 1.57 – 1.50 (m, 2H), 1.45 – 1.39 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 209.2, 147.3, 145.7, 140.0, 129.1, 128.4, 127.8, 127.0, 126.0, 125.2, 120.0, 75.2, 43.8, 39.9, 37.8, 29.8, 22.3, 22.1; MS (HRMS ESI): Calcd for $C_{26}H_{27}O$ $[M+H]^+$ 355.2062, Found: 355.2063.

4.2.18. (5R,6S*)-6-phenyl-5-(9H-xanthen-9-yl)heptan-2-one (**3ag**)*

According to the General Procedure, (*E*)-6-phenylhept-5-en-2-ol (**1ac**) (57.0 mg, 0.300 mmol) and xanthydrol (**2g**) (89.0 mg, 0.449 mmol) gave **3ag** (77.8 mg, 0.210 mmol) in 70% yield (ca. 90% purity with inseparable minor impurities) (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 94:6) (30 min reaction time). IR (neat, cm^{-1}): 1715 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.60 – 7.59 (m, 2H), 7.37 – 7.33 (m, 2H), 7.28 (t, *J* = 7.7 Hz, 2H), 7.18 – 7.15 (m, 7H), 5.82 (d, *J* = 8.4 Hz, 1H), 2.67 (dq, *J* = 6.9, 6.9 Hz, 1H), 2.37 – 2.35 (m, 2H), 2.07 (s, 3H), 1.58 – 1.52 (m, 2~~3~~H), 1.46 – 1.40 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 209.2, 150.7, 147.2, 129.7, 129.6, 128.4, 127.0, 126.0, 123.5, 122.7, 116.7, 63.7. 43.8, 39.9, 37.8, 29.8, 22.3, 22.1; MS (HRMS ESI): Calcd for $C_{26}H_{27}O_2$ $[M+H]^+$ 371.2011, Found: 371.2014.

4.2.19. (5S,6S*)-5-(4-hydroxybenzyl)-6-phenylheptan-2-one (**3ah**)*

According to the General Procedure, (*E*)-6-phenylhept-5-en-2-ol (**1ac**) (57.2 mg, 0.301 mmol) and 4-hydroxybenzyl alcohol (**2h**) (56.1 mg, 0.452 mmol) gave **3ah** (41.8 mg, 0.141 mmol) in 47% yield (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 80:20) (23 h reaction time). IR (neat, cm^{-1}): 3352 [ν(O-H)], 1701 [ν(C=O)].; ^{1}H NMR (500 MHz, $CDCl_3$): δ(ppm) 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.19 (m, 3H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 5.04 (s, 1H), 2.83 (dq, *J* = 7.1, 7.1 Hz, 1H), 2.64 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.35 – 2.21 (m, 3H), 1.95 (s, 3H), 1.86 – 1.79 (m, 1H), 1.61 – 1.55 (m, 1H), 1.46 – 1.40 (m, 1H), 1.29 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ(ppm) 209.6, 153.7, 145.7, 133.2, 130.0, 128.2, 127.8, 126.0, 115.2, 46.0, 41.5, 41.4, 35.6, 29.6, 25.0, 16.5; MS (HRMS ESI): Calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855, Found: 297.1857.

*4.2.20. 4-((2,6-dimethyl-2-phenyltetrahydro-2H-pyran-3-yl)methyl)phenol (**5ah**)*

5ah was formed as a side product (29.3 mg, 0.099 mmol, 33% yield) (dr = >99:1 by ^{1}H NMR) as a colorless oil after purified by flash column chromatography (silica gel, hexane:EtOAc = 92:8) in the formation of **3ah** (see *4.2.19*). IR (neat, cm^{-1}): 3410 [ν(O-H)], 1186 [ν(C-O)].; ^{1}H NMR 7.62 (d, *J* = 7.4 Hz, 2H), 7.36 (dd, *J* = 7.4, 7.4 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 6.68 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 8.6 Hz, 2H), 4.66 (brs, 1H), 3.90 (dqd, *J* = 12.0, 6.0, 2.3 Hz, 1H), 2.40 (dd, *J* = 12.9, 2.1 Hz, 1H), 1.90 (dd, *J* = 12.9, 11.6 Hz, 1H), 1.78 (dddd, J = 11.6, 11.6, 3.4, 2.1 Hz, 1H), 1.68 – 1.59 (m, 2H), 1.62 (s, 3H), 1.45 – 1.34 (m, 1H), 1.31 – 1.22 (m, 1H), 1.18 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 153.6, 147.2, 133.1, 129.9, 127.9, 127.0, 126.3, 115.0, 78.9, 66.4, 48.8, 36.6, 34.2, 25.1, 22.7, 15.0; MS (HRMS ESI): Calcd for $C_{20}H_{25}O_2$ $[M+H]^+$ 297.1855, Found: 297.1856.

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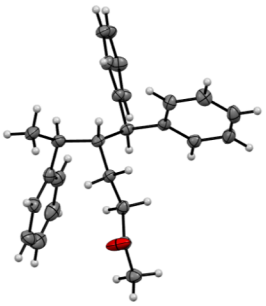
6. For a review on functionalization of carbocations, see: R. R. Naredla, D. A. Klumpp, *Chem. Rev.* **2013**, *113*, 6905.
7. See the supplementary material for the additional optimization on solvents and reaction temperature.
8. The stereochemistry of **3aa** was confirmed by the X-ray crystallographic analysis (CCDC-1992396).



ORTEP drawing of **3aa**

9. Zhao, W.; Sun, J. *Chem. Rev.* **2018**, *118*, 10349.
10. The relative steric demands of the substituents are evaluated on the basis of the A-values for a phenyl group (2.8 kcal/mol), a methyl group (1.74 kcal/mol), and an ethyl group (1.79 kcal/mol). For the A-values, see: Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry*, Wiley, 2001, p. 444.
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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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