Proximity- and Chelation-Induced S_NAr 1,4-Aromatic *ortho*-Substitution of *ortho*-Methoxyphenyl 2-Alkyl Ketones

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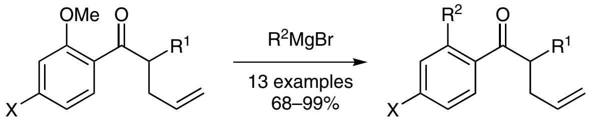

X = H, OMe, Br, Cl
R^1 = alkyl, cycloalkyl
R^2 = alkyl, alkenyl, aryl

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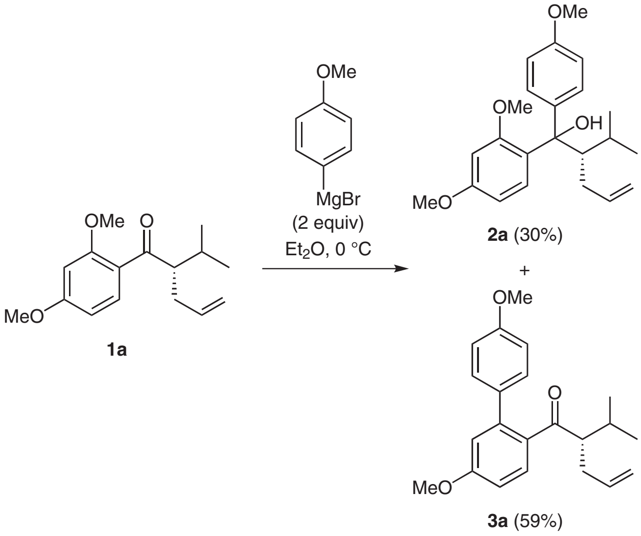
Abstract The direct displacement of an *o*-methoxy group in *o*-methoxyaryl ketones with aryl, alkyl, and alkenyl Grignard reagents to provide a series of *o*-substituted ketones is described. Application of this reaction to the synthesis of a *C*-methyl analogue of a cyclooxygenase inhibitor is shown. The scope and limitations are discussed.

Key words aromatic substitution, biaryls, Grignard reaction in aryl ketones, steric hindrance, transition-metal-free reactions

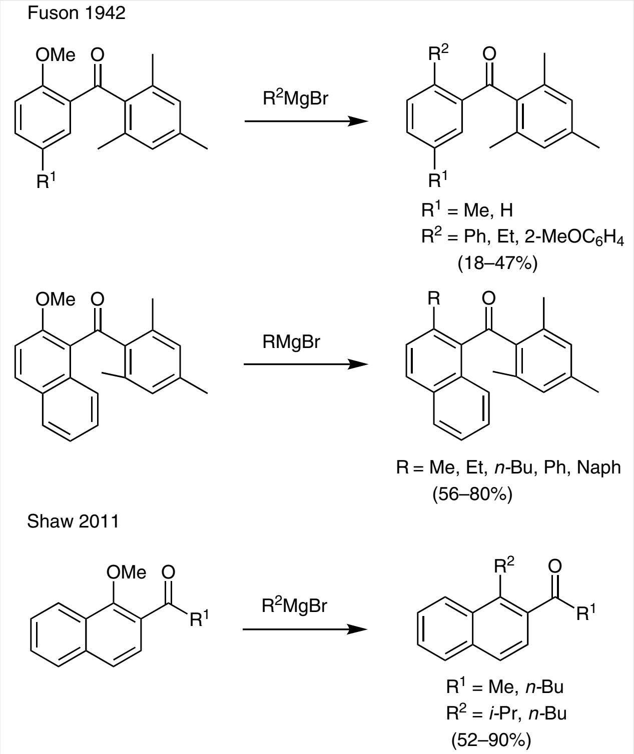
In the course of our synthetic studies on the diastereoselective arylation of 2-alkylbenzylic alcohols,[1] ketone **1a** was treated with *p*-methoxyphenylmagnesium bromide with the intention of obtaining the corresponding benzylic tertiary alcohol **2a** (Scheme 1).

We were initially surprised to find that the biaryl adduct **3a** was formed in 59% yield, in addition to the expected alcohol **2a** (30%). In this reaction, we had effectively replaced the *o*-methoxy group with an aryl group. Intrigued by this result, we were led through a literature search to the pioneering work by Fuson and Speck, who in 1942 had reported that *o*-methoxybenzoylmesitylene reacted with phenylmagnesium bromide in refluxing benzene to afford 2-phenylbenzoylmesitylene in 35% yield.[2] The reaction was extended to *o*-methoxynaphthoylmesitylene with higher yields (Scheme 2). Further examples included the direct *o*-arylation of hindered aromatic ketones and esters in what amounts to a replacement of an aromatic C–H with an aryl moiety provided by the Grignard reagent.[3] Since then, several examples of S_NAr displacement of *o*-methoxy groups with Grignard reagents in aromatic esters[4] and oxazolines[5] have been reported. In 2011, Shaw and co-workers[6] revisit-



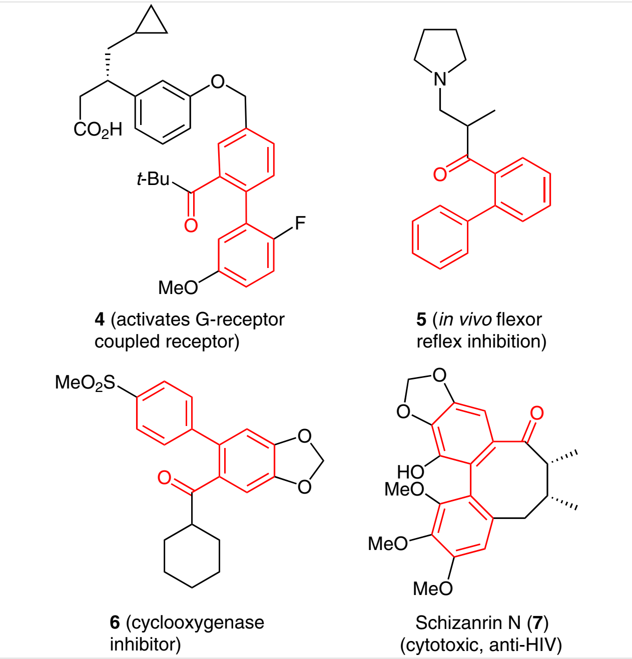
Scheme 1 Unexpected 1,4-aromatic substitution of *o*-methoxyaryl alkyl ketones

ed the Fuson chemistry with a detailed study of the direct displacement of *o*-methoxy groups in *o*-methoxynaphthalene methyl esters and ketones (Scheme 2).



Scheme 2 Previous work towards the 1,4-aromatic substitution reaction of o-methoxynaphthyl 2-ketones with Grignard reagents

Remarkably, the corresponding tosylate esters were unreactive, indicating the possible intermediacy of a magnesium chelate between the carbonyl group of the ester and the *o*-methoxy group in the naphthalene moiety. That the reaction was energetically feasible in spite of the disruption of aromaticity of the naphthalene moiety was contrasted with its failure in the case of isopropyl *o*-methoxybenzoate.[4e] The mechanism of this unique, albeit long neglected, transformation was recently reported by Houk and Shaw,[7] and clarified based on theoretical calculations. Indeed, they showed that an inner sphere attack of nucleophilic groups from the reagent involved magnesium chelates. Although the reaction is not catalytic in nature, it is an attractive alternative to a transition-metal-catalyzed transformation with applications in pharmaceutical synthetic processes.[8] The biphenyl moiety is a prevalent subunit in a number of bioactive compounds such as pivaloylbiaryl **4**,[9] biphenyl ketone **5**,[10] cyclohexyl biaryl ketone **6**[11] as well as natural products such as schizanrin N (**7**), a member of the dibenzocyclooctadiene-type lignan family[12] (Figure 1).



4 (activates G-receptor coupled receptor)

5 (*in vivo* flexor reflex inhibition)

6 (cyclooxygenase inhibitor)

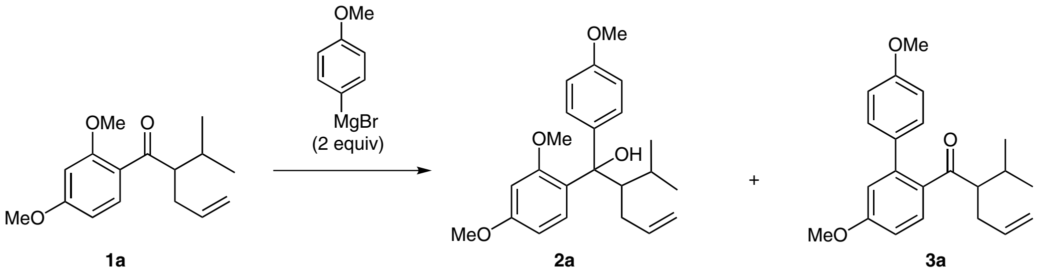
Schizanrin N (**7**) (cytotoxic, anti-HIV)

Figure 1 Bioactive compounds featuring an o-biaryl ketone motif

Herein, we report an extension of the original Fuson[3,4a] and more recent Shaw and Houk[6,7] 1,4-aromatic substitution reaction of *o*-methoxyaryl alkyl ketones. As shown in Scheme 1, the reaction of enantiomerically enriched 1-(2′,4′-dimethoxyphenyl)-2-isopropylpent-4-en-1-one (**1a**) (80% ee)[13] with 2 equivalents of *p*-methoxyphenylmagnesium bromide resulted in a 59:30 ratio for the ketone **3a** as the 1,4-substitution product over the tertiary alcohol **2a** (Scheme 1, Table 1, entry 1). Remarkably no erosion of enantiopurity was observed in the product **3a**. Optimization of this reaction with the racemic ketone **1a** revealed a ratio of **3a**/**2a** = 84:16 using dichloromethane as solvent instead of diethyl ether. Although lowering the temperature to –78 °C did not improve the ratio (entry 2), changing the solvent to dichloromethane (entry 3) had a positive effect, and decreasing the concentration to 0.01 M showed a further improvement to 87:10 in favor of the 1,4-displacement product **3a** (entry 4). Additionally, the effect of Lewis acids as additives was investigated and showed an improved selectivity [**3a**/**2a** = 93:7 using equimolar CuI, but incomplete conversion (80%), entry 5]. Therefore, the scope of the reaction was investigated without the use of any additive under the optimized conditions [2 equiv of Grignard reagent, dichloromethane (0.01 M), r.t., 45 min].[14]

A less electron-rich aromatic substrate lacking the 4-methoxy substituent showed decreased selectivity (**3b**/**2b** = 54:14) and yield (Table 2, entry 1). Increasing the steric bulk of the alkyl side chain to *tert*-butyl resulted in the exclusive formation of the biaryl ketone **3c** in excellent yield, although five equivalents of *p*-methoxyphenylmagnesium

Table 1 Grignard Reactions Using *o*-Methoxyaryl 2-Ketone **1a**



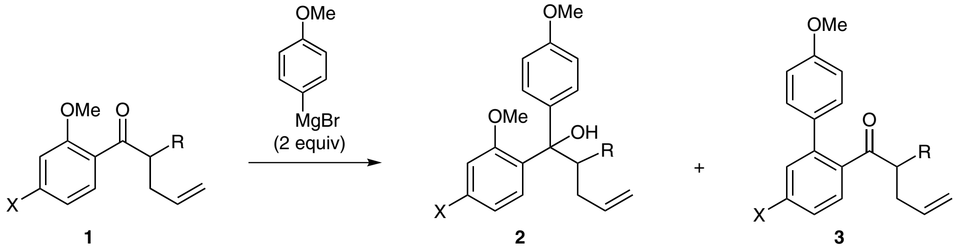
Entry	Solvent (c)	Temp	Yield (%)[a] of **2a**	Yield (%)[a] of **3a**
1[b]	Et_2O (0.1 M)	0 °C to r.t.	30	59
2	Et_2O (0.03 M)	–78 °C to r.t.	40[c]	60[c]
3	CH_2Cl_2 (0.03 M)	r.t.	16[c]	84[c]
4	CH_2Cl_2 (0.01 M)	r.t.	10	87
5[d]	CH_2Cl_2 (0.01 M)	r.t.	7[c]	93[c]

[a] Isolated yield, if not otherwise indicated.
[b] Enantiomeric excess: **1a**, 80%; **3a**, 78%.
[c] Crude ^1H NMR ratio.
[d] CuI (2 equiv), 80% conversion.

bromide were necessary for full conversion in this case (entry 2). The cyclopentyl group is large enough to yield the 1,4-product **3d** exclusively (entry 3), while the smaller cyclopropyl group enabled the 1,4-displacement reaction giving the major product in a ratio of **3e**/**2e** = 55:26 (entry 4). A methyl group or aryl substituent gave exclusively the tertiary alcohol **2f** and **2g** in good to excellent yields (entries 5, 6).

The scope of the Grignard reagent was investigated using 1-(2′,4′-dimethoxyphenyl)-2-*tert*-butylpent-4-en-1-one (**1c**) as the starting material, which can be prepared in two steps from 1,3-dimethoxybenzene (**8**) (Scheme 3).[14,15]

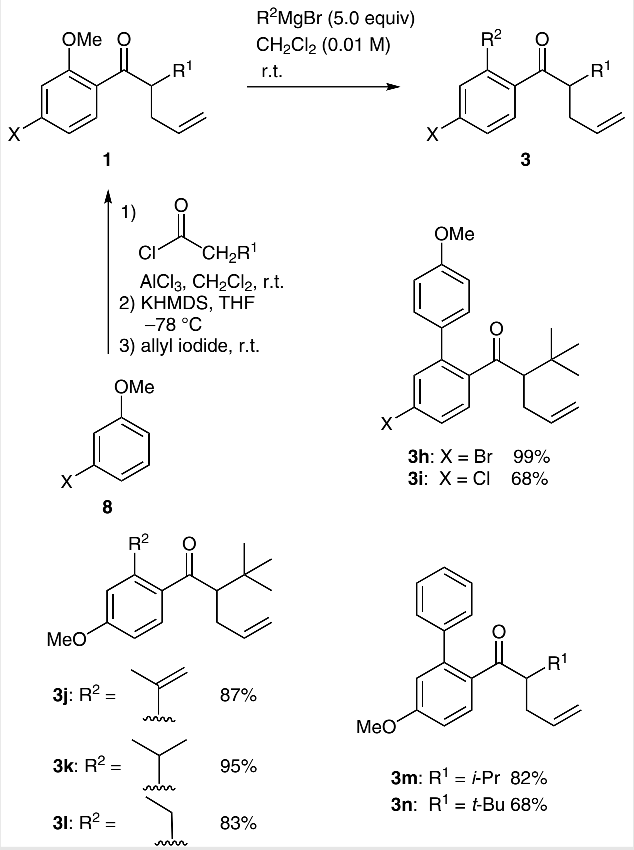
Table 2 Grignard Reactions Using *o*-Methoxyaryl 2-Ketones **1**



Entry	Ketone	R	X	Yield (%)[a] of **2**	Yield (%)[a] of **3**
1[b]	**1b**	*i*-Pr	H	**2a**, 14	**3b**, 54
2[b,c]	**1c**	*t*-Bu	OMe	**2c**[d]	**3c**, 99
3[b]	**1d**	cyclopentyl	OMe	**2d**[d]	**3d**, 87
4[b]	**1e**	cyclopropyl	OMe	**2e**, 26	**3e**, 55
5[e]	**1f**	Me	OMe	**2f**, 92	**3f**[d]
6[b]	**1g**	Ph	OMe	**2g**, 97	**3g**[d]

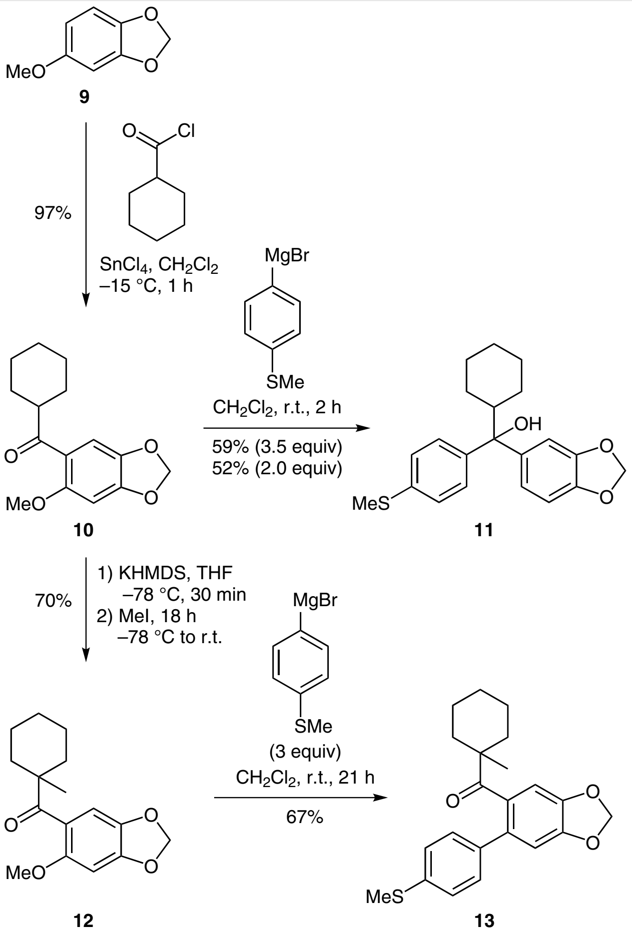
[a] Isolated yield.
[b] Optimized conditions (0.01 M in CH_2Cl_2, r.t., 45 min).
[c] Grignard reagent used: 5 equiv.
[d] Not observed.
[e] Et_2O (0.1 M), 0 °C to r.t.

Thus, halogenated aryls such as 1-(4′-bromo-2′-methoxyphenyl)-2-*tert*-butylpent-4-en-1-one (**1h**) and 1-(4′-chloro-2′-methoxyphenyl)-2-*tert*-butylpent-4-en-1-one (**1i**) are well tolerated, affording the 1,4-displacement products **3h** and **3i** in good to excellent yields. This shows as well that for 2′-methoxy-4′-halophenyl 2-alkyl ketones, the addition-elimination reaction is faster than a metal exchange and it enables the subsequent functionalization of these halides. Simple alkyl and alkenyl Grignard reagents could be utilized in very good to excellent yields to provide **3j**–**l**. Less electron-rich Grignard reagents like PhMgBr allowed the exclusive formation of the *o*-biaryl 2-alkyl ketones **3m** and **3n**. However, substrates bearing *o*,*o*-dimethoxy groups in the aromatic core were recovered unchanged, presumably due to an additional chelation opportunity with the two vicinal methoxy groups.[16] Also, electron-poor aryl Grignard reagents were not reactive enough (3-pyridinyl and 3-furanyl, results not shown).



Scheme 3 Scope of the nucleophiles

Finally, this 1,4-aromatic substitution method was applied to the synthesis of a *C*-methyl analogue of the cyclooxygenase inhibitor **6** (Scheme 4).[11]



Scheme 4 Synthesis of *C*-methyl cyclooxygenase precursor **13**

Sesamol was methylated to its methyl ether **9**, which was acylated in a Friedel–Crafts reaction with tin(IV) chloride and cyclohexylcarbonyl chloride to give ketone **10** in excellent yield. Surprisingly, the attempted aromatic substitution with *p*-methylthiophenylmagnesium bromide gave exclusively the tertiary alcohol **11**, probably due to a lack of sufficient steric bulk by the cyclohexyl moiety. However, the α-methyl cyclohexyl ketone **12**, easily prepared by enolate methylation, gave the expected 1,4-displacement product **13**, a C-methylated analogue of the cyclooxygenase inhibitor **6**, in excellent yield. Additionally, this reaction was monitored by ^1H NMR experiments. While addition of 1 equivalent Grignard reagent gave no conversion after 24 hours, the reaction with 2 equivalents led to full conversion overnight. The reaction profile suggests second order kinetics (Grignard reagent) in agreement with an addition/elimination mechanism. Following the computational studies by Houk and co-workers with *o*-methoxynaphthyl esters and ketones,[7] the more bulky ketone **12** requires at least a second equivalent of Grignard reagent to deliver the nucleophile while the first equivalent chelates the carbonyl and methoxy oxygens.

In conclusion, based on the pioneering work of Fuson and co-workers[3,4a] and the latest results by Shaw and Houk[7] who explored *o*-methoxynaphthalene core alkyl ketones, we were able to expand the scope of this very mild and practical 1,4-aromatic substitution reaction of *o*-methoxyphenyl 2-alkyl ketones to include different aryl, alkenyl, and alkyl appendages at the site originally occupied by the *o*-methoxyaryl group. The 1,4-aromatic substitution of *o*-methoxyphenyl 2-alkyl ketones at room temperature, gives direct transition-metal-free access[17] to biaryl 2-alkyl ketones of which just a few examples are described in the literature and can complement ruthenium- and palladium-catalyzed cross-couplings[18] or decarboxylative cross-couplings between aryl carboxylic acids.[19] Utilizing this method, a *C*-methyl analogue **13** of the cyclooxygenase inhibitor **6** was synthesized in three steps from *O*-methyl sesamol in 45% overall yield.

All nonaqueous reactions were run in flame-dried glassware under a positive pressure of argon with exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained using standard drying techniques. Unless stated otherwise, commercial grade reagents were used without further purification. Reactions were monitored by analytical TLC performed on pre-coated, glass-backed silica gel plates. Visualization of the developed chromatogram was performed by UV absorbance, aq cerium ammonium molybdate, or aq potassium permanganate. Flash chromatography was performed on 230–400 mesh silica gel with the indicated solvent systems. Melting points are uncorrected. Routine NMR spectra were recorded on an AV-300, AV-400, or AV-500 spectrometer. Chemical shifts for ^{1}H NMR spectra are given in parts per million from TMS with the solvent resonance as the internal standard ($CDCl_3$, δ = 7.27). Data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant in Hz, and integration. Chemical shifts for ^{13}C NMR spectra are given in parts per million from TMS using the central peak of the solvent resonance as the internal standard ($CDCl_3$, δ = 77.16). All spectra were obtained with complete proton decoupling. Optical rotations were determined with a polarimeter at 589 nm, using a 1 dm cell as well as 1 mL $CHCl_3$ at r.t. and are reported in units of $deg \cdot cm^3 \cdot g^{-1} \cdot dm^{-1}$. IR spectra were recorded on a FT-IR spectrometer equipped with an integrated ATR unit and are reported in cm^{-1}. High-resolution mass spectra were performed on a LC-TOF instrument using electrospray ionization (ESI) techniques. Analytical chiral SFC traces were obtained from a UV detector, with wavelengths set at 254 or 220 nm and the SFC separation conditions are described as follows: gradient, column, flow, column temperature, back pressure (BP, psi), retention time (t_R), ratio. Analytical chiral HPLC were performed with a chiralcel OD-H column. The column size was 4.6 mm diameter × 250 mm height. HPLC traces were obtained from a UV detector, with wavelengths set at 254 and/or 210 nm. The HPLC separation conditions and results are described as follows: gradient, column, flow, retention time (t_R), ratio.

For the preparation of starting materials **1** (GP1 and GP2) and tertiary alcohols **25** and **26** (GP3), see the Supporting Information.

Grignard Reactions; General Procedure 3 (GP3)

To a solution of *o*-methoxyaryl alkyl ketone **1** (1.0 equiv) [either with or without a Lewis acid (1.0 equiv)] in anhydrous CH_2Cl_2 (0.01 M) was added a solution of the Grignard reagent (2.0 equiv) in one portion at r.t. After stirring for 45 min, the reaction mixture was quenched by the addition of sat. aq NH_4Cl. The aqueous layer was extracted with CH_2Cl_2 (2 ×), the organic layers were combined and washed with brine (2 ×), dried ($MgSO_4$), filtered, and concentrated.

1′-(4″,5′-Dimethoxybiphenyl-2′-yl)-2-isopropylpent-4-en-1-one (3a) and 1-(2′,4′-Dimethoxyphenyl)-2-isopropyl-1-(4″-methoxyphenyl)pent-4-en-1-ol (2a) (*racemic*)

The reaction was performed according to the GP3 using 1-(2′,4′-dimethoxyphenyl)-2-isopropylpent-4-en-1-one (**1a**; 10 mg, 0.038 mmol), 4-methoxyphenylmagnesium bromide (151 µL, 0.5 M in THF, 0.076 mmol), and anhydrous CH_2Cl_2 (4.00 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 9:1) to yield **3a** (11 mg, 0.033 mmol, 87%) as a yellow oil and **2a** (1.4 mg, 0.005 mmol, 10%) as a colorless oil.

3a

R_f = 0.38 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 2959, 1673, 1599, 1578, 1515, 1499, 1440, 1247, 1175, 1024 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.6 Hz, 1 H), 7.24–7.18 (m, 2 H), 6.96–6.91 (m, 2 H), 6.89 (dd, *J* = 8.6, 2.6 Hz, 1 H), 6.81 (d, *J* = 2.6 Hz, 1 H), 5.45 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1 H), 4.92–4.84 (m, 2 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 2.47 (dt, *J* = 8.0, 5.2 Hz, 1 H), 2.29 (ddd, *J* = 12.4, 9.6, 5.2 Hz, 1 H), 2.01–1.92 (m, 1 H), 1.82–1.72 (m, 1 H), 0.74 (d, *J* = 6.9 Hz, 3 H), 0.63 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 207.3, 161.0, 159.4, 142.6, 136.9, 133.8, 133.6, 130.8, 130.1, 115.9, 115.8, 114.0, 112.5, 55.4, 55.4, 55.4, 31.0, 29.2, 20.5, 18.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{26}O_3$ $[M + H]^+$: 339.19547; found: 339.19558.

2a

R_f = 0.20 (*n*-hexane–EtOAc. 4:1).

IR (ATR): 3521, 2954, 2871, 1609, 1582, 1505, 1463, 1249, 1208, 1173, 1036 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.6 Hz, 1 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 6.54 (dd, *J* = 8.6, 2.5 Hz, 1 H), 6.39 (d, *J* = 2.5 Hz, 1 H), 5.45–5.33 (m, 1 H), 4.84–4.77 (m, 1 H), 4.74–4.69 (m, 1 H), 3.79 (s, 3 H), 3.75 (s, 3 H), 3.60 (s, 3 H), 2.47–2.37 (m, 1 H), 2.30–2.17 (m, 2 H), 2.08–2.00 (m, 1 H), 1.04 (t, *J* = 6.7 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5, 158.3, 157.7, 140.8, 140.3, 127.8, 127.4, 127.0, 113.7, 112.7, 104.2, 100.5, 83.0, 55.8, 55.3, 55.2, 50.6, 29.8, 29.0, 24.6, 18.5.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{30}O_4$ + Na $[M + Na]^+$: 393.20363; found: 393.20410.

(2*S*)-1′-(4″,5′-Dimethoxybiphenyl-2′-yl)-2-isopropylpent-4-en-1-one [(*S*)-3a] and (2*S*)-1-(2′,4′-Dimethoxyphenyl)-2-isopropyl-1-(4″-methoxyphenyl)pent-4-en-1-ol [(*S*)-2a] (enantiomerically enriched)

The reaction was performed according to the GP3 using (2*S*)-1-(2′,4′-dimethoxyphenyl)-2-isopropylpent-4-en-1-one [(*S*)-**1a**; 40 mg, 0.15 mmol, 80% ee], 4-methoxyphenylmagnesium bromide (600 µL, 0.5 M in THF, 0.300 mmol), and anhydrous Et$_2$O (3.00 mL) (solvent different from GP3). The Grignard reagent was added at 0 °C and the solution was stirred for 20 h and slowly warmed up to r.t. The residue was purified by flash chromatography (*n*-hexane–EtOAc, 9:1) to yield (*S*)-**3a** {30 mg, 0.089 mmol, 59%, 78% ee, $[\alpha]_D^{20}$ –37 (*c* 1.5, CDCl$_3$)}; ee was determined by chiral SFC (2% *i*-PrOH–hexanes, chiralcel OD, 1.0 mL/min, t_R = 8.04 min and 9.31 min, ratio 11.6:88.4) as a yellow oil and (*S*)-**2a** (17 mg, 0.045 mmol, 30%) as a colorless oil.

The analytical data of enantiomerically enriched (*S*)-**3a** and (*S*)-**2a** are in full agreement with the data of the racemic compounds.

2-Isopropyl-1-(4″-methoxybiphenyl-2′-yl)pent-4-en-1-one (3b) and 2-Isopropyl-1-(2′-methoxyphenyl)-1-(4″-methoxyphenyl)pent-4-en-1-ol (2b)

The reaction was performed according to the GP3 using 1-(2′-methoxyphenyl)-2-isopropylpent-4-en-1-one (**1b**; 50 mg, 0.22 mmol,), 4-methoxyphenylmagnesium bromide (863 µL, 0.5 M in THF, 0.431 mmol), and anhydrous CH$_2$Cl$_2$ (22.0 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 95:5) to yield **3b** (36 mg, 0.12 mmol, 54%) as a yellow oil and **2b** (10 mg, 0.028 mmol, 14%) as a yellow oil.

3b

R_f = 0.57 (*n*-hexane–EtOAc, 9:1).

IR (ATR): 2949, 1677, 1609, 1514, 1472, 1242, 1178, 1035, 831, 760 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.50–7.42 (m, 2 H), 7.40–7.31 (m, 2 H), 7.25–7.19 (m, 2 H), 6.98–6.90 (m, 2 H), 5.42 (ddt, *J* = 17.0, 10.1, 7.1 Hz, 1 H), 4.91–4.82 (m, 2 H), 3.84 (s, 3 H), 2.45–2.38 (m, 1 H), 2.30 (dt, *J* = 14.4, 7.2 Hz, 1 H), 2.01–1.91 (m, 1 H), 1.83–1.71 (m, 1 H), 0.74 (d, *J* = 6.9 Hz, 3 H), 0.62 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, CDCl$_3$): δ = 209.0, 159.4, 141.1, 139.9, 136.8, 133.2, 130.4, 130.3, 130.2, 128.4, 127.0, 115.9, 114.1, 55.9, 55.4, 30.5, 28.7, 20.5, 18.5.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{25}O_2$ [M + H]$^+$: 309.18491; found: 309.18393.

2b

R_f = 0.40 (*n*-hexane–EtOAc, 9:1).

IR (ATR): 3509, 2942, 1606, 1582, 1507, 1460, 1246, 1174, 1028, 750 cm^{-1}.

^{1}H NMR (300 MHz, CDCl$_3$): δ (rotamers) = 7.56–7.46 (m, 1 H), 7.26–7.16 (m, 3 H), 7.06–6.97 (m, 1 H), 6.86–6.72 (m, 3 H), 5.96 (ddt, *J* = 16.8, 9.9, 6.8 Hz, 0.3 H), 5.45–5.28 (m, 0.7 H), 5.06–4.64 (m, 3 H), 3.76 (s, 3 H), 3.61 (s, 3 H), 2.54–2.36 (m, 1.7 H), 2.29–2.13 (m, 1.5 H), 2.09–1.94 (m, 0.8 H), 1.08–1.02 (m, 4 H), 0.95–0.86 (m, 2 H).

^{13}C NMR (76 MHz, CDCl$_3$): δ (rotamers) = 157.9, 157.7, 157.6, 141.0, 140.9, 140.1, 139.9, 135.7, 135.3, 128.1, 128.1, 127.3, 127.2, 127.0, 126.9, 121.0, 120.9, 114.5, 113.8, 113.0, 112.9, 83.8, 83.5, 77.2, 56.0, 55.3, 55.3, 50.6, 49.8, 31.2, 29.9, 29.2, 27.9, 24.9, 24.7, 18.7, 18.6.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{28}O_3$ + Na [M + Na]$^+$: 363.19307 found: 363.19139.

2-*tert*-Butyl-1-(4″,5′-dimethoxybiphenyl-2′-yl)pent-4-en-1-one (3c)

The reaction was performed according to the GP3 using 1-(2′,4′-dimethoxyphenyl)-2-*tert*-butylpent-4-en-1-one (**1c**; 31 mg, 0.11 mmol), 4-methoxyphenylmagnesium bromide (1.12 mL, 0.5 M in THF, 0.560 mmol), and anhydrous CH$_2$Cl$_2$ (5.00 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 95:5) to yield **3c** (39 mg, 0.11 mmol, 99%) as a colorless oil; R_f = 0.34 (*n*-hexane–Et$_2$O, 9:1).

IR (ATR): 2959, 1671, 1597, 1515, 1465, 1247, 1214, 1175, 1024, 834, 631 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.67 (d, *J* = 8.7 Hz, 1 H), 7.24–7.17 (m, 2 H), 6.96–6.84 (m, 3 H), 6.75 (d, *J* = 2.6 Hz, 1 H), 5.49 (ddt, *J* = 17.0, 10.1, 7.4 Hz, 1 H), 4.93 (dd, *J* = 17.0, 1.7 Hz, 1 H), 4.86 (dd, *J* = 10.1, 2.1 Hz, 1 H), 3.85 (s, 3 H), 3.84 (s, 3 H), 2.84 (dd, *J* = 9.5, 4.0 Hz, 1 H), 2.43 (ddd, *J* = 9.5, 8.8, 7.4 Hz, 1 H), 2.20–2.08 (m, 1 H), 0.78 (s, 9 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 205.9, 161.1, 159.0, 143.7, 138.0, 134.4, 134.2, 131.6, 130.3, 116.8, 115.7, 113.6, 112.4, 57.4, 55.4, 55.3, 34.5, 32.8, 28.6.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{29}O_3$ [M + H]$^+$: 353.21112; found: 353.21182.

2-Cyclopentyl-1-(4″,5′-dimethoxybiphenyl-2′-yl)pent-4-en-1-one (3d)

The reaction was performed according to the GP3 using 1-(2′,4′-dimethoxyphenyl)-2-cyclopentylpent-4-en-1-one (**1d**; 115 mg, 0.398 mmol), 4-methoxyphenylmagnesium bromide (1.60 mL, 0.5 M in THF, 0.800 mmol), and anhydrous CH$_2$Cl$_2$ (40.0 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 9:1) to yield **3d** (127 mg, 0.349 mmol, 87%) as a colorless oil. The reaction was also carried out with a sequential addition of Grignard reagent (2 × 1.0 equiv, stirring overnight at r.t. in between); but ^{1}H NMR analysis of the crude product showed no conversion; R_f = 0.47 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 2946, 1673, 1599, 1513, 1246, 1215, 1175, 1029, 912, 832 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.53 (d, *J* = 8.6 Hz, 1 H), 7.26–7.22 (m, 2 H), 6.97–6.93 (m, 2 H), 6.89 (dd, *J* = 8.6, 2.6 Hz, 1 H), 6.80 (d, *J* = 2.6 Hz, 1 H), 5.56–5.44 (m, 1 H), 4.90–4.84 (m, 2 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 2.59 (td, *J* = 7.6, 4.7 Hz, 1 H), 2.27 (dt, *J* = 14.3, 7.2 Hz, 1 H), 2.10–2.01 (m, 1 H), 1.93 (tddd, *J* = 9.9, 7.6, 7.6, 7.6 Hz, 1 H), 1.63–1.52 (m, 3 H), 1.50–1.34 (m, 3 H), 0.99–0.84 (m, 2 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 207.1, 160.6, 158.9, 142.5, 135.8, 133.3, 133.1, 130.8, 129.7, 115.7, 115.6, 113.5, 112.0, 55.0, 55.0, 53.5, 41.0, 33.9, 30.3, 29.4, 24.7, 24.5.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{29}O_3$ [M + H]$^+$: 365.21112; found: 365.21279.

2-Cyclopropyl-1-(4″,5′-dimethoxybiphenyl-2′-yl)pent-4-en-1-one (3e) and 2-Cyclopropyl-1-(2′,4′-dimethoxyphenyl)-1-(4″-methoxyphenyl)pent-4-en-1-ol (2e)

The reaction was performed according to the GP3 using 1-(2′,4′-dimethoxyphenyl)-2-cyclopropylpent-4-en-1-one (**1e**; 54 mg, 0.21 mmol), 4-methoxyphenylmagnesium bromide (828 µL, 0.5 M in THF, 0.414 mmol), and anhydrous CH$_2$Cl$_2$ (21.0 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 95:5) to yield **3e** (38 mg, 0.11 mmol, 55%) and **2e** (19 mg, 0.052 mmol, 26%) as colorless oils.

3e

R_f = 0.40 (*n*-hexane–EtOAc, 4:1).

IR (ATR): 3002, 2936, 2837, 1677, 1600, 1513, 1216, 1175, 1027, 831 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.50 (d, J = 8.6 Hz, 1 H), 7.27–7.22 (m, 2 H), 6.98–6.94 (m, 2 H), 6.89 (dd, J = 8.6, 2.6 Hz, 1 H), 6.82 (d, J = 2.6 Hz, 1 H), 5.69–5.56 (m, 1 H), 4.94–4.87 (m, 2 H), 3.89 (s, 3 H), 3.86 (s, 2 H), 2.32 (dt, J = 13.8, 6.9 Hz, 1 H), 2.22 (dt, J = 13.8, 6.9 Hz, 1 H), 1.79 (dt, J = 9.7, 6.6 Hz, 1 H), 0.79–0.69 (m, 1 H), 0.48–0.39 (m, 1 H), 0.33–0.25 (m, 1 H), –0.10 (td, J = 9.9, 5.0 Hz, 1 H), –0.26 (td, J = 9.9, 5.0 Hz, 1 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 208.2, 161.1, 159.5, 142.4, 136.4, 133.9, 133.4, 130.8, 130.1, 116.2, 115.6, 114.2, 112.5, 55.6, 55.5, 55.2, 36.4, 13.7, 4.6, 3.9.

HRMS (ESI): m/z calcd for $C_{22}H_{25}O_3$ [M + H]$^+$: 337.17982; found: 337.18039.

2e

R_f = 0.30 (n-hexane–EtOAc, 4:1).

IR (ATR): 3495, 2942, 1606, 1500, 1300, 1246, 1205, 1174, 1032, 824 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ (rotamers) = 7.38–7.33 (m, 1.4 H), 7.32–7.26 (m, 1 H), 7.21–7.15 (m, 0.6 H), 6.83–6.77 (m, 1.4 H), 6.74–6.70 (m, 0.6 H), 6.53 (d, J = 2.5 Hz, 0.3 H), 6.45–6.41 (m, 1 H), 6.38 (d, J = 2.5 Hz, 0.7 H), 6.15–5.93 (m, 1 H), 5.07–4.87 (m, 2 H), 4.83 (s, 0.3 H), 4.36 (s, 0.6 H), 3.84 (s, 0.8 H), 3.82 (s, 1.8 H), 3.80 (s, 1.9 H), 3.80 (s, 0.8 H), 3.67 (s, 1.8 H), 3.62 (s, 0.8 H), 2.66–2.52 (m, 0.3 H), 2.45–2.33 (m, 1 H), 2.28–2.13 (m, 0.7 H), 2.07–1.91 (m, 0.7 H), 0.93–0.78 (m, 1.3 H), 0.50–0.29 (m, 1 H), 0.20 (td, J = 10.0, 5.5 Hz, 0.7 H), 0.12 to –0.02 (m, 1 H), –0.16 to –0.23 (m, 0.3 H), –0.24 to –0.33 (m, 0.7 H), –0.80 to –0.89 (m, 0.3 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ (rotamers) = 159.6, 159.5, 157.9, 157.9, 139.5, 139.5, 139.4, 128.5, 128.1, 128.0, 127.7, 127.1, 114.7, 112.7, 112.3, 104.0, 103.9, 99.7, 82.1, 55.9, 55.5, 55.4, 55.3, 55.2, 55.1, 51.4, 50.0, 37.5, 36.6, 12.5, 12.1, 5.0, 4.8, 3.5.

HRMS (ESI): m/z calcd for $C_{23}H_{28}O_4$ + Na [M + Na]$^+$: 391.18798; found: 391.18811.

1-(2′,4′-Dimethoxyphenyl)-1-(4″-methoxyphenyl)-2-methylpent-4-en-1-ol (2f)

The reaction was performed according to the GP3 using 1-(2′,4′-dimethoxyphenyl)-2-methylpent-4-en-1-one (**1f**; 40 mg, 0.17 mmol), 4-methoxyphenylmagnesium bromide (678 μL, 0.5 M in THF, 0.339 mmol), and anhydrous Et_2O (1.50 mL) (solvent different from GP3). The Grignard reagent was added at 0 °C and stirred for 1 h at 0 °C (conditions different from GP3). The residue was purified by flash chromatography (n-hexane–EtOAc, 9:1) to yield **2f** (53 mg, 0.16 mmol, 92%) as a colorless oil; R_f = 0.17 (n-hexane–EtOAc, 9:1).

IR (ATR): 3515, 2942, 1606, 1500, 1453, 1293, 1242, 1205, 1032, 821 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ (rotamers) = 7.38 (d, J = 8.5 Hz, 1 H), 7.30–7.21 (m, 2 H), 6.82–6.78 (m, 2 H), 6.53 (dd, J = 8.5, 2.4 Hz, 1 H), 6.41 (d, J = 2.4 Hz, 1 H), 5.99–5.85 (m, 0.5 H), 5.78–5.65 (m, 0.5 H), 5.09–4.88 (m, 2 H), 4.70 (s, 1 H), 3.79 (s, 3 H), 3.76 (s, 3 H), 3.60 (s, 3 H), 2.61–2.38 (m, 1.5 H), 2.07–1.79 (m, 1.5 H), 1.06 (d, J = 6.6 Hz, 1.5 H), 0.74 (d, J = 6.6 Hz, 1.5 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ (rotamers) = 159.7, 159.7, 158.7, 158.5, 157.8, 157.7, 140.1, 139.9, 138.7, 138.7, 128.0, 127.7, 127.3, 127.2, 127.0, 126.9, 115.4, 115.4, 112.9, 112.8, 104.4, 100.7, 100.5, 80.7, 80.6, 55.9, 55.9, 55.5, 55.4, 55.3, 55.2, 40.6, 40.5, 37.1, 36.0, 14.9, 13.9.

HRMS (ESI): m/z calcd for $C_{21}H_{26}O_4$ + Na [M + Na]$^+$: 365.17233; found: 365.17341.

1-(2′,4′-Dimethoxyphenyl)-1-(4″-methoxyphenyl)-2-phenylpent-4-en-1-ol (2g)

The reaction was performed according to the GP3 using 1-(2′,4′-dimethoxyphenyl)-2-phenylpent-4-en-1-one (**1g**; 75 mg, 0.25 mmol), 4-methoxyphenylmagnesium bromide (1.01 mL, 0.5 M in THF, 0.500 mmol), and anhydrous CH_2Cl_2 (25.0 mL). The residue was purified by flash chromatography (n-hexane–EtOAc, 9:1) to yield **2g** (98 mg, 0.24 mmol, 97%) as a yellow oil; R_f = 0.15 (n-hexane–EtOAc, 9:1).

IR (ATR): 3488, 2928, 1606, 1502, 1249, 1205, 1161, 1025, 913, 831 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.50–7.46 (m, 2 H), 7.32–7.28 (m, 2 H), 7.20–7.07 (m, 4 H), 6.91–6.87 (m, 2 H), 6.31 (dd, J = 8.7, 2.5 Hz, 1 H), 6.20 (d, J = 2.5 Hz, 1 H), 5.55 (ddt, J = 17.0, 10.1, 6.9 Hz, 1 H), 5.03 (s, 1 H), 4.87–4.78 (m, 2 H), 3.83 (s, 3 H), 3.71 (s, 3 H), 3.69–3.62 (m, 1 H), 3.43 (s, 3 H), 2.69–2.59 (m, 1 H), 2.53–2.45 (m, 1 H), 1.28 (s, 1 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 158.8, 157.6, 157.2, 141.0, 138.8, 137.3, 130.0, 128.5, 127.5, 127.0, 126.7, 125.6, 114.9, 112.6, 103.7, 99.1, 81.2, 55.1, 54.8, 54.8, 53.7, 34.9.

HRMS (ESI): m/z calcd for $C_{26}H_{28}O_4$ + Na [M + Na]$^+$: 427.18798; found: 427.18905.

1-(5′-Bromo-4″-methoxybiphenyl-2′-yl)-2-*tert*-butylpent-4-en-1-one (3h)

The reaction was performed according to the GP3 using 1-(4′-bromo-2′-methoxyphenyl)-2-*tert*-butylpent-4-en-1-one (**1h**; 50 mg, 0.15 mmol), 4-methoxyphenylmagnesium bromide (1.53 mL, 0.5 M in THF, 0.766 mmol), and anhydrous CH_2Cl_2 (1.50 mL). The residue was purified by flash chromatography (n-hexane–EtOAc, 99:1 → 98:2 → 97:3 → 96:4) to yield **3h** (59 mg, 0.15 mmol, 98%) as an orange oil; R_f = 0.59 (n-hexane–EtOAc, 95:5).

IR (ATR): 2922, 1659, 1618, 1484, 1420, 1255, 1195, 1033, 1008, 934 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.54 (dd, J = 8.4, 1.9 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.47 (d, J = 1.9 Hz, 1 H), 7.24–7.21 (m, 2 H), 6.97–6.94 (m, 2 H), 5.43 (ddt, J = 17.0, 10.0, 7.1 Hz, 1 H), 4.93 (ddd, J = 17.0, 3.4, 1.5 Hz, 1 H), 4.90–4.86 (m, 1 H), 3.87 (s, 3 H), 2.73 (dd, J = 8.5, 4.2 Hz, 1 H), 2.41 (ddd, J = 14.5, 8.5, 4.2 Hz, 1 H), 2.20–2.13 (m, 1 H), 0.77 (s, 9 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 206.9, 159.4, 142.9, 140.5, 137.7, 134.2, 132.3, 130.8, 130.5, 130.2, 127.7, 124.9, 116.0, 114.2, 113.9, 58.4, 55.4, 34.6, 32.6, 28.6.

HRMS (ESI): m/z calcd for $C_{22}H_{26}BrO_2$ [M + H]$^+$: 401.11107; found: 401.11179.

1-(5′-Chloro-4″-methoxybiphenyl-2′-yl)-2-*tert*-butylpent-4-en-1-one (3i)

The reaction was performed according to the GP3 using 1-(4′-chloro-2′-methoxyphenyl)-2-*tert*-butylpent-4-en-1-one (**1i**; 60 mg, 0.21 mmol), 4-methoxyphenylmagnesium bromide (2.14 mL, 0.5 M in THF, 1.07 mmol), and anhydrous CH_2Cl_2 (2.10 mL). The residue was purified by preparative TLC (n-hexane–EtOAc, 9:1) to yield **3i** (52 mg, 0.15 mmol, 68%) as a colorless oil. The reaction was repeated with sequential addition of the Grignard reagent (4 × 1.0 equiv, stirring overnight at r.t. in between additions); but ^{1}H NMR analysis of the crude product showed just the starting material **1i**; R_f = 0.66 (n-hexane–EtOAc, 9:1).

IR (ATR): 2956, 1671, 1609, 1582, 1514, 1464, 1297, 1245, 1093, 835 cm^{-1}.

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.58 (d, *J* = 8.4 Hz, 1 H), 7.38 (dd, *J* = 8.4, 2.1 Hz, 1 H), 7.30 (d, *J* = 2.1 Hz, 1 H), 7.24–7.21 (m, 2 H), 6.98–6.93 (m, 2 H), 5.44 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1 H), 4.95–4.91 (m, 1 H), 4.88 (ddt, *J* = 10.1, 2.0, 1.0 Hz, 1 H), 3.87 (s, 3 H), 2.74 (dd, *J* = 9.0, 4.2 Hz, 1 H), 2.46–2.38 (m, 1 H), 2.20–2.14 (m, 1 H), 0.77 (s, 9 H).

^{13}C NMR (125 MHz, CDCl$_3$): δ = 206.8, 159.4, 142.8, 140.1, 137.6, 136.4, 132.4, 131.3, 130.7, 130.5, 127.2, 116.0, 113.9, 58.3, 55.3, 34.6, 32.7, 28.6.

HRMS (ESI): *m*/*z* calcd for C$_{22}$H$_{26}$ClO$_2$ [M + H]$^+$: 357.16276; found: 357.16158.

2-*tert*-Butyl-1-[4′-methoxy-2′-(prop-1″-en-2″-yl)phenyl]pent-4-en-1-one (3j)

The reaction was performed according to the GP3 using **1c** (30 mg, 0.11 mmol), 2-propenylmagnesium bromide (1.09 mL, 0.5 M in THF, 0.554 mmol), and anhydrous CH$_2$Cl$_2$ (5.00 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 95:5) to yield **3j** (27 mg, 0.094 mmol, 87%) as a colorless oil; R_f = 0.65 (*n*-hexane–EtOAc, 9:1).

IR (ATR): 2957, 1670, 1595, 1467, 1309, 1223, 1086, 1037, 908, 799 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.73 (d, *J* = 8.7 Hz, 1 H), 6.82 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.70 (d, *J* = 2.7 Hz, 1 H), 5.68 (ddt, *J* = 17.0, 10.1, 7.1 Hz, 1 H), 5.07–5.04 (m, 1 H), 5.01 (dd, *J* = 17.0, 1.5 Hz, 1 H), 4.90–4.84 (m, 1 H), 4.75–4.71 (m, 1 H), 3.85 (s, 3 H), 3.30 (dd, *J* = 10.7, 3.3 Hz, 1 H), 2.60 (ddd, *J* = 13.7, 10.7, 6.9 Hz, 1 H), 2.33–2.24 (m, 1 H), 2.12–2.08 (m, 3 H), 0.93 (s, 9 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 204.3, 161.9, 147.9, 147.4, 137.5, 132.2, 131.9, 116.1, 115.9, 113.3, 111.8, 56.2, 55.5, 34.6, 33.4, 28.6, 24.7.

HRMS (ESI): *m*/*z* calcd for C$_{19}$H$_{27}$O$_2$ [M + H]$^+$: 287.20056; found: 287.20130.

2-*tert*-Butyl-1-(2′-isopropyl-4′-methoxyphenyl)pent-4-en-1-one (3k)

The reaction was performed according to the GP3 using **1c** (34 mg, 0.12 mmol), isopropylmagnesium chloride–lithium chloride complex (472 μL, 1.3 M in THF, 0.614 mmol), and anhydrous CH$_2$Cl$_2$ (4.00 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 98:2) to yield **3k** (34 mg, 0.12 mmol, 95%) as a colorless oil; R_f = 0.56 (*n*-hexane–EtOAc, 9:1).

IR (ATR): 2956, 1670, 1602, 1565, 1463, 1300, 1229, 1167, 1032, 733 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.53 (d, *J* = 8.7 Hz, 1 H), 6.92 (d, *J* = 2.6 Hz, 1 H), 6.71 (dd, *J* = 8.7, 2.6 Hz, 1 H), 5.73 (ddt, *J* = 17.1, 10.0, 7.2 Hz, 1 H), 5.06 (dd, *J* = 17.1, 1.7 Hz, 1 H), 4.98–4.88 (m, 1 H), 3.84 (s, 3 H), 3.49 (qq, *J* = 6.9, 6.7 Hz, 1 H), 3.22 (dd, *J* = 11.5, 2.9 Hz, 1 H), 2.74–2.52 (m, 1 H), 2.38–2.21 (m, 1 H), 1.29 (d, *J* = 6.7 Hz, 3 H), 1.20 (d, *J* = 6.9 Hz, 3 H), 0.95 (s, 9 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 206.9, 161.8, 151.8, 137.3, 134.3, 130.7, 116.6, 113.2, 109.7, 58.6, 55.3, 34.7, 33.4, 29.5, 28.4, 25.2, 23.8.

HRMS (ESI): *m*/*z* calcd for C$_{19}$H$_{29}$O$_2$ [M + H]$^+$: 289.21621; found: 289.21498.

2-*tert*-Butyl-1-(2′-ethyl-4′-methoxyphenyl)pent-4-en-1-one (3l)

The reaction was performed according to the GP3 using **1c** (33 mg, 0.12 mmol), ethylmagnesium bromide (199 μL, 3 M in Et$_2$O, 0.597 mmol), and anhydrous CH$_2$Cl$_2$ (5.00 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 98:2) to yield **3l** (27 mg, 0.099 mmol, 83%) as a yellow oil; R_f = 0.34 (*n*-hexane–EtOAc, 98:2).

IR (ATR): 2956, 1670, 1605, 1568, 1467, 1368, 1233, 1133, 1031, 919 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.64 (d, *J* = 8.7 Hz, 1 H), 6.79 (d, *J* = 2.6 Hz, 1 H), 6.73 (dd, *J* = 8.7, 2.6 Hz, 1 H), 5.71 (ddt, *J* = 17.2, 10.0, 7.2 Hz, 1 H), 5.09–4.99 (m, 1 H), 4.95–4.88 (m, 1 H), 3.84 (s, 3 H), 3.26 (dd, *J* = 11.5, 2.9 Hz, 1 H), 2.91 (dq, *J* = 14.8, 7.5 Hz, 1 H), 2.76 (dq, *J* = 14.8, 7.5 Hz, 1 H), 2.68–2.57 (m, 1 H), 2.32–2.22 (m, 1 H), 1.28 (t, *J* = 7.5 Hz, 3 H), 0.94 (s, 9 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 206.0, 161.6, 147.3, 137.1, 133.6, 131.4, 116.3, 116.1, 110.0, 57.4, 55.2, 34.5, 33.3, 28.3, 27.4, 15.8.

HRMS (ESI): *m*/*z* calcd for C$_{18}$H$_{27}$O$_2$ [M + H]$^+$: 275.20056; found: 275.20020.

2-Isopropyl-1-(5′-methoxybiphenyl-2′-yl)pent-4-en-1-one (3m)

The reaction was performed according to the GP3 using **1a** (34 mg, 0.13 mmol), phenylmagnesium bromide (128 μL, 2 M in THF, 0.256 mmol), and anhydrous CH$_2$Cl$_2$ (13.0 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 95:5) to yield **3m** (32 mg, 0.10 mmol, 82%) as a yellow oil; R_f = 0.42 (*n*-hexane–EtOAc, 9:1).

IR (ATR): 2962, 1674, 1596, 1460, 1297, 1212, 1174, 1018, 913, 699 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.53 (d, *J* = 8.6 Hz, 1 H), 7.43–7.35 (m, 3 H), 7.32–7.27 (m, 2 H), 6.92 (dd, *J* = 8.6, 2.6 Hz, 1 H), 6.83 (d, *J* = 2.6 Hz, 1 H), 5.40 (ddt, *J* = 17.1, 10.1, 7.1 Hz, 1 H), 4.91–4.81 (m, 2 H), 3.86 (s, 3 H), 2.43 (dt, *J* = 7.9, 4.8 Hz, 1 H), 2.28 (ddd, *J* = 14.5, 7.9, 6.7 Hz, 1 H), 2.01–1.86 (m, 1 H), 1.83–1.72 (m, 1 H), 0.73 (d, *J* = 6.9 Hz, 3 H), 0.63 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 207.1, 161.1, 143.2, 141.4, 136.9, 133.9, 131.0, 129.1, 128.6, 127.8, 116.1, 116.0, 113.0, 55.6, 55.5, 31.2, 29.2, 20.6, 18.9.

HRMS (ESI): *m*/*z* calcd for C$_{21}$H$_{24}$O$_2$ + Na [M + Na]$^+$: 331.16685; found: 331.16782.

2-*tert*-Butyl-1-(5′-methoxybiphenyl-2′-yl)pent-4-en-1-one (3n)

The reaction was performed according to the GP3 using **1c** (33 mg, 0.12 mmol), phenylmagnesium bromide (198 μL, 3 M in Et$_2$O, 0.597 mmol), and anhydrous CH$_2$Cl$_2$ (5.00 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 95:5) to yield **3n** (26 mg, 0.082 mmol, 68%) as a colorless oil; R_f = 0.43 (*n*-hexane–EtOAc, 9:1).

IR (ATR): 2958, 1672, 1598, 1480, 1298, 1215, 1038, 1018, 913, 702 cm^{-1}.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.59 (d, *J* = 8.7 Hz, 1 H), 7.35–7.12 (m, 5 H), 6.81 (dd, *J* = 8.7, 2.7 Hz, 1 H), 6.66 (d, *J* = 2.7 Hz, 1 H), 5.48 (ddt, *J* = 17.1, 10.0, 7.1 Hz, 1 H), 4.99–4.86 (m, 1 H), 4.76–4.71 (m, 1 H), 3.75 (s, 3 H), 2.72 (dd, *J* = 9.5, 3.4 Hz, 1 H), 2.42–2.22 (m, 1 H), 2.07–1.96 (m, 1 H), 0.68 (s, 9 H).

^{13}C NMR (101 MHz, CDCl$_3$): δ = 205.6, 161.1, 144.1, 141.9, 137.9, 134.2, 131.6, 129.1, 128.1, 127.3, 116.8, 115.8, 112.6, 57.3, 55.5, 34.5, 32.9, 28.6.

HRMS (ESI): *m*/*z* calcd for C$_{22}$H$_{27}$O$_2$ [M + H]$^+$: 323.20056; found: 323.20071.

Cyclohexyl(6′-methoxybenzo[*d*][1,3]dioxol-5′-yl)[4″-(methylthio)phenyl]methanol (11)

The reaction was performed according to the GP3 using cyclohexyl(6′-methoxybenzo[*d*][1,3]dioxol-5′-yl)methanone (**10**; 56 mg, 0.21 mmol), 4-thioanisolemagnesium bromide (1.5 mL, 0.5 M in THF, 0.75 mmol), and anhydrous CH_2Cl_2 (11.0 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 98:2 → 97:3 → 96:4 → 95:5) to yield **11** (49 mg, 0.13 mmol, 59%) as a colorless oil; R_f = 0.44 (*n*-hexane–EtOAc, 9:1).

IR (ATR): 3502, 2921, 1481, 1418, 1259, 1188, 1093, 1038, 824, 732 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.26–7.22 (m, 2 H), 7.17–7.13 (m, 2 H), 7.03 (s, 1 H), 6.48 (s, 1 H), 5.98–5.96 (m, 2 H), 4.86 (s, 1 H), 3.49 (s, 3 H), 2.47 (s, 3 H), 2.14–2.07 (m, 1 H), 1.97–1.91 (m, 1 H), 1.83–1.78 (m, 1 H), 1.73–1.65 (m, 2 H), 1.61–1.59 (s, 1 H), 1.46–1.27 (m, 3 H), 1.24–1.13 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.8, 146.7, 145.0, 141.5, 135.3, 127.4, 127.0, 126.7, 126.3, 125.7, 107.5, 101.4, 96.9, 80.1, 57.0, 45.7, 27.8, 27.1, 27.0, 26.8, 26.6, 15.9.

MS (ESI): *m*/*z* = 369.1 $[M - OH]^+$.

(1-Methylcyclohexyl){6′-[(4″-methylthio)phenyl]benzo[*d*][1,3]dioxol-5′-yl}methanone (13)

The reaction was performed according to the GP3 using (6-methoxybenzo[*d*][1,3]dioxol-5-yl)(1-methylcyclohexanone)methanone (**12**; 24 mg, 0.088 mmol), 4-thioanisolemagnesium bromide (523 μL, 0.5 M in THF, 0.262 mmol) and anhydrous CH_2Cl_2 (9.00 mL). The residue was purified by flash chromatography (*n*-hexane–EtOAc, 99.5:0.5 → 99:1 → 98.5:1.5 → 98:2) to yield **13** (22 mg, 0.058 mmol, 67%) as a yellow oil. [The reaction was repeated under the same conditions using 2.0 equiv and 2.5 equiv Grignard reagent, only ketone **12** could be reisolated in both cases. This reaction was also monitored by ^{1}H NMR (see the Supporting Information)]; R_f = 0.51 (*n*-hexane–EtOAc, 9:1).

IR (ATR): 3092, 2860, 1718, 1449, 1365, 1208, 1155, 1077, 926, 818 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (s, 4 H), 6.82 (s, 1 H), 6.65 (s, 1 H), 6.04 (s, 2 H), 2.51 (s, 3 H), 1.53–1.44 (m, 3 H), 1.44–1.36 (m, 2 H), 1.36–1.26 (m, 2 H), 1.24–1.17 (m, 2 H), 1.15–1.06 (m, 1 H), 0.85 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.9, 147.8, 146.3, 137.9, 137.4, 134.5, 132.1, 130.1, 126.2, 110.0, 106.4, 101.5, 48.6, 34.5, 25.6, 21.7, 21.3, 15.7.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}O_3S$ $[M + H]^+$: 369.15189; found: 369.15310.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1379992.

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