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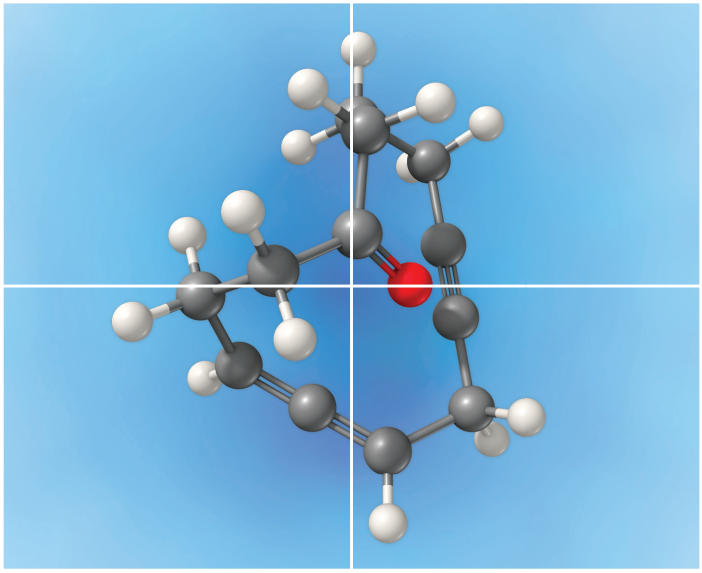

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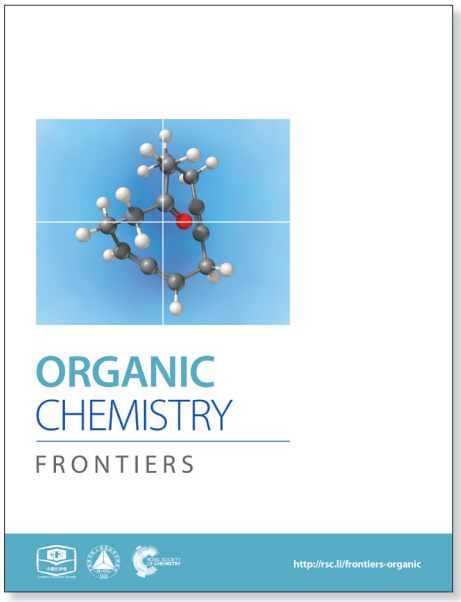

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Kinetic Resolution of Racemic 5-Alkylcyclohexenones via Pd(II)-Catalyzed 1, 4-Additions of Arylboronic Acids - Access to *trans* 3-Alkyl-5-Arylcyclohexanones

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Abstract:

The kinetic resolution of racemic 5-substituted alkylcyclohexenones *via* 1, 4-conjugate addition with a variety of arylboronic acids was achieved by utilizing a ferrocenyl phosphapalladacycle catalyst. The addition reaction proceeded smoothly to afford *trans*-3-alkyl-5-arylcyclohexanones in good yields and selectivities.

Introduction:

Optically active multi-substituted cycloalkanones are valuable precursors for a myriad of synthetic chiral building blocks and biologically relevant compounds.[1]

The preparation of these molecular motifs typically engages the conjugate addition of *C* nucleophiles to enantiomerically pure cycloalkenones.[2] Such scalemic cycloalkenones in turn lack an extensive natural library and thus require laborious synthetic protocols for their procurement.[1a, 2e, 3] Therefore, much focus in this field converges upon the kinetic resolution of readily available racemic mono-substituted cycloalkenones *via* catalyzed 1, 4-additions.[4]

Of particular interest amongst this class of compounds is 3, 5-disubstituted cyclohexanones by virtue of their utility in further synthetic manipulations that yield linear chiral building blocks as well as spiro-oxindole skeletons of interest (Scheme 1).[1a, c, d]

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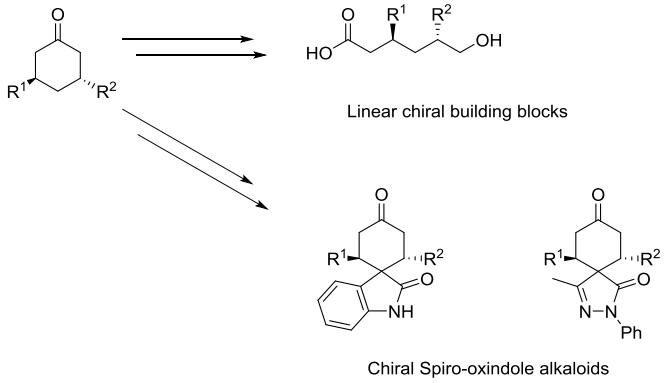
Scheme 1. Further elaborations based on 3,5-disubstituted cyclohexenones



Seminal endeavors by Tomioka[4a] and Feringa[4b] *et*. *al*. have established remarkably efficient resolution of 5-substituted cyclohexenones using Cu(I) / (II) phosphoramidite complexes with Zn *C* nucleophiles. However, ensuing advances employing Rh(I) systems on similar substrates are plagued with low diastereoselectivity in spite of excellent enantioselectivity due to the predominance of catalyst control.[4a, 4c] Similarly, the utilization of Cu systems in which substrate control predominates, suffers from moderate enantioselectivities.[4b, 4e] These examinations are also limited to the collegial reliance on either thermal activation, or the administration of moisture sensitive organo-*alkyl*zinc reagents.

The propensity of 3, 6-disubstituted cycloalkanones to undergo subsequent epimerization yielding thermodynamically stable *trans* products justifies the use of aforementioned Rh(I) / Cu protocols. The kinetic resolution of 6-monosubstituted cyclohexenones thus yields *trans*-2, 5-disubstituted cycloalkanones exclusively upon subsequent treatment with bases.[4g - 4j]

It is thus prudent to develop a methodology which allows facile access to optically active 3, 5-disubstituted cycloalkanones, specifically 3-alkyl-5-*aryl* cycloalkanones utilizing moisture / air stable reagents.

The preference of Pd catalysts to promote the competitive and (in this instance) undesirable Heck reaction pathway have contributed to their relative lack of prominence in the field of

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Michael additions.[5] As part of our continuing interest in the development and application of palladacycles in C-C[6] and C-X[7] (X = P, N) bond formation reactions, we have recently reported their efficacy for the 1, 4-addition of arylboronic acids to acyclic enones[8] as well as a preliminary study on the catalytic potential of a novel ferrocenyl phosphapalladacycle for the addition of (*p*-methoxy)phenyl boronic acid to cyclohexenone.[9] Encouraged by these preliminary results, we sought to evaluate a series of palladacycles for the kinetic resolution of racemic 5-alkylcyclohexenones *via* arylboronic acid additions that provides facile access to optically active 3, 5-disubstituted cycloalkanones, specifically 3-alkyl-5-*aryl* cycloalkanones utilizing moisture / air stable reagents.

Results and discussion:

Adopting prior optimized reaction conditions, we screened a series of palladacycles for the kinetic resolution of racemic 5-methyl cyclohexenone (**1a**) with 0.6 equivalents of phenylboronic acid (**2a**) in toluene. (Table 1) To our delight, the resolution proceeded smoothly when the ferrocenyl phosphapalladacycle (R_c S_{pl})-**C4** was employed, affording *trans*-(3*R*, 5*R*)-3-methyl-5-phenylcyclohexanone (**3a**) as the major adduct in 48 % isolated yield, 95 : 5 *dr* and 70 % *ee*[10] after 18 hours at RT. (Table 1, Entry 1) The palladacycles **C1** and **C2** only furnished trace products even after extended reaction times (48 hrs) while **C3** afforded 19 % conversion after 18 hours. Further examination revealed K_3PO_4 (5M in H_2O) to be the base of choice. In an attempt to enhance selectivity, a series of low temperature studies were conducted (Table, Entries 7 - 9) and *trans*-(3*R*, 5*R*)-**3a** was attained in 45 % isolated yield, with accompanying 97 : 3 *dr* and 81 % *ee* when the addition was conducted at 0 °C. In addition, (*S*)-**1a** was recovered in 47 % yield and 71 % *ee*, thus ruling out a simultaneous parallel kinetic resolution.

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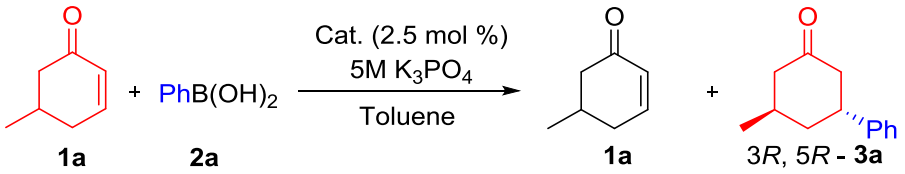
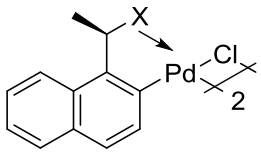
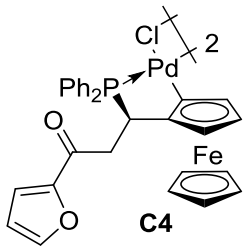
Table 1. Kinetic Resolution of racemic 5-methylcyclohexenone **1a** with phenylboronic acid **2a**.[a]





C1: X = NH_2
C2: X = NMe_2
C3: X = PPh_2



C4

Entry	Cat.	Base[b]	Temp.	Time (hrs)	Conv.[c] (%)	Yield (%)	*dr*[d]	*ee*[e] (%)
1	C4	K_3PO_4	RT	18	49	47	95:5	70
2	C4	KOH	RT	18	34	32	99:1	66
3	C4	KF	RT	18	33	32	95:5	73
4	C4	K_2CO_3	RT	18	37	35	97:3	70
5	C4	NEt_3	RT	18	13	10	99:1	73
6	C4	t-BuOK	RT	18	17	15	95:1	55
7	**C4**	**K_3PO_4**	**0**	**24**	**47**	**45**	**97:3**	**82**
8	C4	K_3PO_4	-25	48	35	34	99:1	83
9	C4	K_3PO_4	-40	72	30	28	99:1	84

[a]Reactions were performed with 12.2 mg $PhB(OH)_2$ (0.1 mmol), 16.3 mg **1a** (0.17 mmol), 5.4 mg **C4** (4.25×10^{-3} mmol) and 20.0 µL 5M base (0.1 mmol) in 0.1 mL toluene at the stated temperature. [b]5M aqueous solution. [c]Determined by integration of crude ^{1}H NMR in toluene-d8. [d]*dr* of (3*R*, 5*R*)-**3a** determined by integration of crude ^{1}H NMR in toluene-d8. *cis* / *trans* assignment of **3a** was based on comparison of ^{1}H NMR spectra with previous reports.[4c] [e]*ee* of (3*R*, 5*R*)-**3a**. Determined *via* HPLC using a chiral column, chirality determined *via* comparison of HPLC elution times with known dossiers.[4c]

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Having now determined the optimized conditions (Table 1, Entry 7) we next concerted our efforts toward the addition of various functionalized arylboronic acid derivatives onto monosubstituted racemic cyclohexenones and these results are displayed in Table 2.

In general, satisfactory conversions were achieved with excellent *dr* (up to >99 : 1) and moderate to good *ee* values (up to 87 %). The influence of the aryl fragment (Table 2, Entries 1 - 10) on yields and selectivities are typically homogenous, with deviations observed due to increased sterics (Table 2, Entry 2: *o-tolylboronic acid* with 5-methyl cyclohexenone; Entry 11: phenylboronic acid with *4-methyl cyclohexenone*) and when *p*-hydroxyphenylboronic acid was employed. Interestingly, both electron-withdrawing and donating groups are well tolerated in this protocol and yield similar results (Table 2, Entries 8 & 9). The poor result obtained when *p*-hydroxylphenyl boronic acid was used (Table 2, Entry 10) could be attributed to its poor solubility in toluene, thus requiring MeOH as a co-solvent and the addition to be conducted at RT. Increasing the bulkiness of the 5-substituted position led to lower yields, improved *de* and slightly diminished *ee* when phenylboronic acid was used (Table 2, Entry 1 *vs.* Entries 12 - 14).

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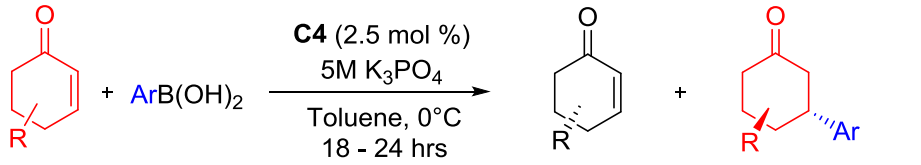
Table 2. Kinetic Resolution of racemic monosubstituted cyclohexenones with functionalized arylboronic acids.[a]



1a-e
a: 5-Me b: 4-Me
c: 5-Et d: 5-*n*Pr
e: 5-*n*Bu

(*S*)-**1a-e**

(3*R*, 5*R*)-**3a-q**

Entry	Ar	R	Yield[b] (**1**:**3**) (%)	*dr*[c]	*ee*[d] (**1**:**3**) (%)	*s*[e]
1	Ph	5-Me	47:47	97:3	71:81	20
2	o-tolyl	5-Me	50:42	99:1	51:70	9
3	m-tolyl	5-Me	43:45	99:1	64:78	15
4	p-tolyl	5-Me	42:48	97:3	76:85	29
5	1-nap	5-Me	44:50	96:4	84:87	41
6	2-nap	5-Me	44:50	98:2	79:80	22
7	Biphenyl-4-	5-Me	50:44	99:1	50:64	7
8	(p-OMe)C_6H_4	5-Me	46:50	98:2	84:86	37
9	(p-F)C_6H_4	5-Me	40:51	99:1	40:82	27
10[f]	(p-OH)C_6H_4	5-Me	60:35	97:3	38:71	9
11[g]	Ph	4-Me	56:39	99:1	44:70	9
12	Ph	5-Et	44:46	96:4	62:77	15
13	Ph	5-*n*Pr	44:44	99:1	nd:73	11
14	Ph	5-*n*Bu	52:40	97:3	50:75	11
15	(p-OMe)C_6H_4	5-Et	50:45	99:1	62:76	14
16	(p-OMe)C_6H_4	5-*n*Pr	52:42	98:2	nd:74	11
17	(p-OMe)C_6H_4	5-*n*Bu	56:39	97:3	47:75	11

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[a]Reactions were performed with 0.1 mmol $ArB(OH)_2$, 16.3 mg **1a** (0.17 mmol), 5.4 mg **C4** (4.25×10^{-3} mmol), 20.0 µL 5M K_3PO_4 (0.1 mmol) in 0.1 mL toluene at 0 °C over 24 hrs. [b]Isolated yield. [c]*dr* of (3*R*, 5*R*)-**3** determined by integration of crude ^{1}H NMR in toluene-d8. *cis* / *trans* assignment of **3a**, **b**, **k**, **l**, **n** was based on comparison of ^{1}H NMR spectra with previous reports.[4c] [d]*ee* of **1a** - **e** determined *via* optical rotation. *ee* of *trans*-**3a** - **q** determined *via* HPLC using a chiral column. [e]See supporting information for calculation of Selectivity Factor. [f]Reaction conducted in 1:1 MeOH:Toluene at RT. [g]Reaction conducted at RT.

Intrigued by the efficacy of this protocol, we decided to investigate the basis of the observed catalyst-substrate selectivity control by computational studies. The mechanism of Pd-catalyzed conjugate addition of arylboronic acids to enones has been comprehensively examined,[11] and is widely acknowledged to involve transmetalation, carbopalladation (β-insertion) and protonation steps. Although no report concerning phosphapalladacycles has been established, we postulate an analogous catalytic cycle is followed by our system. We base our supposition on the following: i) A recent publication by Fairlamb *et*. *al*. substantiates the hypotheses that the aryl moiety attunes itself to the position *cis* to the carbon ligand after transmetalation.[11b] ii) The β-insertion step involves a square-planar four-membered cyclic transition state. With these fundamental requirements in mind, there are four possible isomeric alkene insertion transition states. The 3D structures of these reaction intermediates and transition states are shown in Scheme 2.

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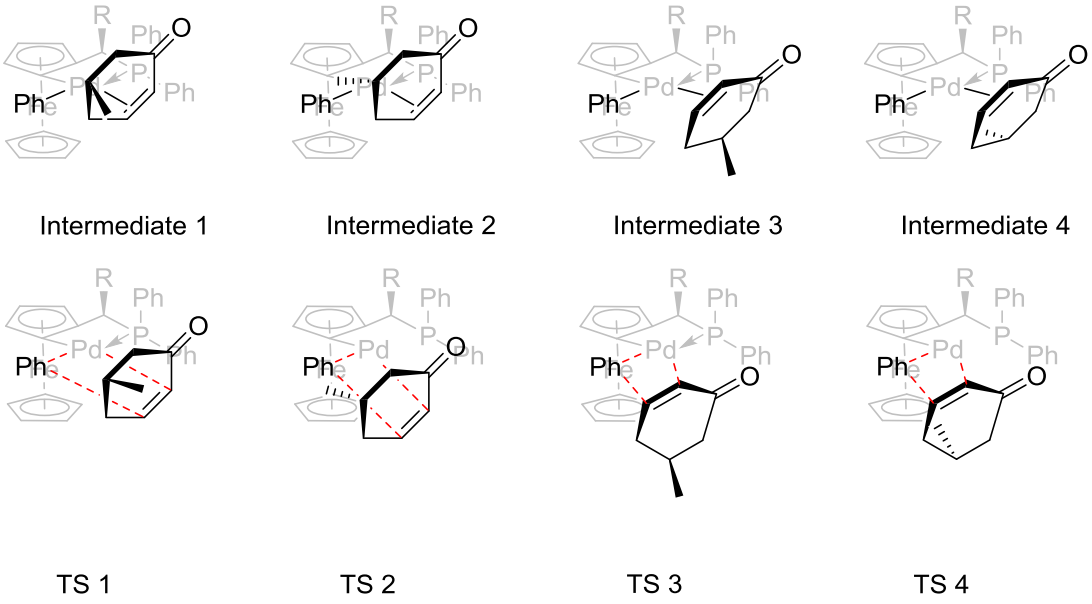
Scheme 2. Reaction intermediates and Transition states



Square-planar, 4-membered cyclic TS highlighted in red

Transition States	Activation Barrier	Product
1	**9.10**	**3*R*, 5*R***
2	9.35	3*R*, 5*S*
3	11.29	3*S*, 5*S*
4	11.04	3*S*, 5*R*

In all the transition states, the aryl group is situated *cis* to the carbon ligand. The discrimination of substrate by the catalyst is due to the steric hindrance that exists between the sp_3 carbons of cyclohexenone (TS 3 and 4) and the ferrocene scaffold or between the alkyl pendant and the ferrocene sandwich (TS 2). The combination of these 2 steric effects thus favours the addition to proceed preferentially *via* TS 1, with the lowest computed activation barrier of 9.10 kcal / mol, leading to a product with 3*R*, 5*R* configurations as seen in our studies.

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In summary, we have developed a kinetic resolution of racemic 5-alkylcyclohexenones *via* arylboronic acid additions that provides facile access to optically active *trans*-3-alkyl-5-*aryl* cycloalkanones utilizing moisture / air stable reagents with excellent diastereomeric ratios and good enantiocontrol. This is the first instance in literature that a desirable balance between catalyst control and substrate control has been achieved using a Pd(II) catalyst at ambient temperatures for this synthetic protocol. Examination of possible transition states revealed the source of diastereo-/ enantioselectivity control, which is in agreement with experimental observations.

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Experimental Section

General information

Thin layer chromatography was performed on Merck silica gel 60 F254 aluminum backed plates and visualized under UV. Flash chromatography was performed using Merck silica gel 60. NMR spectra were recorded on a Bruker AV 300 spectrometer (^{1}H at 300 MHz, ^{13}C at 75 MHz, ^{31}P at 121 MHz, ^{19}F {^{1}H} at 282 MHz), Bruker AV 400 spectrometer (^{1}H at 400 MHz, ^{13}C at 100 MHz, ^{31}P at 162 MHz) or Bruker AV 500 spectrometer (^{1}H at 500 MHz, ^{13}C at 125 MHz, ^{31}P at 202 MHz). ^{1}H spectra are referenced to an internal $SiMe_4$ standard at δ 0 ppm or to $CDCl_3$ at δ 7.26 ppm. Optical rotations were measured on the specified solution in a 0.1 dm cell at 20 °C with a Perkin - Elmer 341 polarimeter. Melting points were documented on a SRS Optimelt MPA 100 point system. Mass spectrometry was obtained in ESI mode on a Thermo Finnigan LCQ Deca XP MAX system. HRMS (ESI) were recorded on a time-of-flight (TOF) LC/MS instrument.

General procedure for the synthesis of 3-Alkyl-5-Arylcyclohexanones

To a 5 ml vial were placed boronic acid (0.1 mmol, 0.6 eq.) and catalyst (4.17×10^{-3} mmol, 2.5 mol %). The orange solution was allowed to stir for 10 mins at 0 °C before racemic cyclohexenone (0.17 mmol, 1 eq.) and 5M K_3PO_4 (0.1 mmol, 0.6 eq.) was sequentially added. Upon stirring for 18 or 24 hrs, the resulting solution was passed through a short plug of silica gel (5 *n* - Hexanes : 1 EA) to yield both 3-aryl, 5-alkyl cyclohexanone (R_f : 0.40) and 5-alkyl cyclohexenone (R_f : 0.45) as colorless oils.

3-methyl-5-phenyl cyclohexanone (**3a**):

Colorless oil. **3a** was determined to be *trans* by comparison with previous literature.[4c] The ^{1}H and ^{13}C NMR spectra are in accordance with literature data.[4c] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.03 (d, 3H, -C*H*$_3$, ^{3}J = 5.6 Hz), 1.84 - 1.89 (m, 1H), 2.05 - 2.10 (m, 1H), 2.15 - 2.19 (m, 1H), 2.26 - 2.29 (m, 1H), 2.54 - 2.64 (m, 3H), 3.36 - 3.40 (m, 1H, -C*H*Ph), 7.20 - 7.24 (m, 3H, -

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CH*Ph*), 7.30 - 7.33 (m, 2H, -CH*Ph*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3, 29.3, 39.4, 39.6, 47.2, 48.5, 126.5, 127.0, 128.6, 144.4, 211.6 MS (*M* / *Z*) 189.07 HRMS (ESI) calcd for $C_{13}H_{17}O$ $[M + H]^+$ 189.1279, found 189.1282 $[\alpha]_D$ = -22.32 (*c* 0.50, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2, 0.5 ml / min, 210 nm, 28.9 mins (major), 32.2 (minor), 33.3 (minor), 35.4 (minor).

For **1a**:

$[\alpha]_D$ = 66.2 (*c* 0.50, $CHCl_3$) for 71 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

3-methyl-5-(*o*-tolyl)cyclohexanone (**3b**):

Colorless oil. **3b** was determined to be *trans* by comparison with previous literature.[4c] The ^{1}H and ^{13}C NMR spectra are in accordance with literature data.[4c] ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05 (d, 3H, -C*H*$_3$, ^3J = 6.8 Hz), 1.76 - 1.82 (m, 1H), 1.95 - 2.02 (m, 1H), 2.18 - 2.22 (m, 1H), 2.34 (s, 3H, -Ar*Me*), 2.47 - 2.63 (m, 3H), 3.53 - 3.60 (m, 1H, -C*H*Ar), 7.11 - 7.21 (m, 4H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.3, 20.1, 29.4, 35.2, 38.1, 47.0, 48.4, 125.7, 126.3, 126.4, 130.7, 135.2, 142.4, 211.9 MS (*M* / *Z*) 203.05 HRMS (ESI) calcd for $C_{14}H_{19}O$ $[M + H]^+$ 203.1436, found 203.1433 $[\alpha]_D$ = -25.99 (*c* 0.4, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2, 210 nm, 0.5 ml / min, 23.1 mins (major), 26.4 mins (minor).

For **1a**:

$[\alpha]_D$ = 47.6 (*c* 0.50, $CHCl_3$) for 51 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

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3-methyl-5-(*m*-tolyl)cyclohexanone (**3c**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (d, 3H, -C*H*$_3$, *J* = 7.2 Hz), 1.81 - 1.86 (m, 1H), 2.02 - 2.09 (m, 1H), 2.12 - 2.17 (m, 1H), 2.25 - 2.31 (m, 1H), 2.33 (s, 3H, -Ar*Me*), 2.52 - 2.62 (m, 3H), 3.29 - 3.36 (m, 1H, -C*H*Ar), 6.99 - 7.03 (m, 3H, -*Ar*), 7.17 - 7.21 (m, 1H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3, 21.5, 29.3, 39.5, 47.3, 48.4, 124.0, 127.3, 127.8, 128.5, 138.2, 144.4, 211.7 MS (*M* / *Z*) 203.03 HRMS (ESI) calcd for $C_{14}H_{19}O$ $[M + H]^+$ 203.1436, found 203.1437 $[\alpha]_D$ = -20.04 (*c* 0.3, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2, 0.5 ml / min, 210 nm, 21.5 mins (major), 22.8 mins (minor), 24.4 mins (minor), 24.8 mins (minor).

For **1a**:

$[\alpha]_D$ = 59.7 (*c* 0.50, $CHCl_3$) for 64 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

3-methyl-5-(*p*-tolyl)cyclohexanone (**3d**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.02 (d, 3H, -C*H*$_3$, *J* = 6.92 Hz), 1.85 - 1.87 (m, 1H), 2.02 - 2.09 (m, 1H), 2.13 - 2.18 (m, 1H), 2.23 - 2.29 (m, 1H), 2.33 (s, 3H, -Ar*Me*), 2.52 - 2.60 (m, 3H), 3.31 - 3.38 (m, 1H, -C*H*Ar), 7.09 - 7.14 (m, 4H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3, 21.0, 29.3, 39.2, 39.5, 47.3, 48.5, 76.7, 77.0, 77.4, 126.8, 129.3, 136.1, 141.4, 211.7 MS (*M* / *Z*) 203.03 HRMS (ESI) calcd for $C_{14}H_{19}O$ $[M + H]^+$ 203.1436, found 203.1443 $[\alpha]_D$ = -16.65 (*c* 0.4, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2, 0.5 ml / min, 210 nm, 24.5 mins (major), 27.2 mins (minor), 28.5 mins (minor), 31.1 mins (minor).

For **1a**:

$[\alpha]_D$ = 70.9 (*c* 0.50, $CHCl_3$) for 76 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

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3-methyl-5-(1-naphthalene)cyclohexanone (**3e**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04 (d, 1H, -C*H*$_3$, *J* = 6.4 Hz), 1.94 - 2.00 (m, 1H), 2.13 - 2.23 (m, 3H), 2.56 - 2.62 (m, 1H), 2.74 (d, 2H, *J* = 6.8 Hz), 4.19 - 4.52 (m, 1H, -C*H*Ar), 7.28 (d, 1H, -*Ar*, *J* = 7.2 Hz), 7.41 (t, 1H, -*Ar*, *J* = 7.8 Hz), 7.46 - 7.54 (m, 2H, -*Ar*), 7.72 (d, 1H, -*Ar*, *J* = 8.0 Hz), 7.85 (d, 1H, -*Ar*, *J* = 8.0 Hz), 8.04 (d, 1H, -*Ar*, *J* = 8.4 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.6, 29.2, 34.9, 38.6, 46.7, 48.9, 122.9, 123.5, 125.4, 125.6, 126.2, 127.3, 129.2, 131.0, 134.0, 140.1, 212.0 MS (*M* / *Z*) 237.21 HRMS (ESI) calcd for $C_{17}H_{19}O$ $[M + H]^+$ 239.1436, found 239.1443 $[\alpha]_D$ = -19.74 (*c* 1.0, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 34.1 mins (major), 37.0 mins (minor), 40.7 mins (minor), 42.9 mins (minor).

For **1a**:

$[\alpha]_D$ = 78.3 (*c* 0.50, $CHCl_3$) for 84 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

3-methyl-5-(2-naphthalene)cyclohexanone (**3f**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.05 (d, 3H, -C*H*$_3$, *J* = 6.8 Hz), 1.91 - 1.97 (m, 1H), 2.15 - 2.31 (m, 3H), 2.56 - 2.78 (m, 3H), 3.52 - 3.59 (m, -C*H*Ar), 7.36 (dd, 1H, *J* = 1.6 Hz, 8.4 Hz, -*Ar*), 7.43 - 7.49 (m, 2H, -*Ar*), 7.63 (s, 1H, -*Ar*), 7.81 (d, 3H, *J* = 6.8 Hz, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.4, 29.2, 39.3, 39.7, 47.0, 48.6, 125.2, 125.6, 125.7, 126.2, 127.6, 127.8, 128.3, 132.2, 133.5, 141.8, 211.5 MS (*M* / *Z*) 239.04 HRMS (ESI) calcd for $C_{17}H_{19}O$ $[M + H]^+$ 239.1436, found 239.1441 $[\alpha]_D$ =-5.42 (*c* 0.7, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2, 0.5 ml / min, 254 nm, 37.9 mins (major), 39.8 mins (minor), 45.7 mins (minor), 48.6 mins (minor).

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For **1a**:

$[\alpha]_D$ = 73.7 (*c* 0.50, $CHCl_3$) for 79 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*)

3-methyl-5-(Biphenyl-4)cyclohexanone (**3g**):

White solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.04 (d, 3H, - C*H*$_3$, *J* = 6.8 Hz), 1.87 - 1.93 (m, 1H), 2.08 - 2.21 (m, 2H), 2.28 - 2.32 (m, 1H), 2.55 - 2.65 (m, 3H), 3.39 - 3.46 (m, 1H, -C*H*Ar), 7.25 - 7.35 (m, 3H, -*Ar*), 7.41 - 7.45 (m, 2H, -*Ar*), 7.53 - 7.58 (m, 4H, -*Ar*) ^{13}C NMR ($CDCl_3$, 125 MHz): δ 20.4, 29.3, 39.3, 39.4, 47.2, 48.5, 127.0, 127.2, 127.3, 127.4, 128.8, 139.5, 140.8, 143.4, 211.5 MS (*M* / *Z*) 265.11 HRMS (ESI) calcd for $C_{19}H_{21}O$ $[M + H]^+$ 265.1592, found 254.1581 $[\alpha]_D$ = -10.99 (*c* 0.9, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 95 : 5, 270 nm, 0.5 ml / min, 30.6 mins (major), 31.5 mins (minor), 33.5 mins (minor), 34.1 mins (minor).

For **1a**:

$[\alpha]_D$ = 46.6 (*c* 0.50, $CHCl_3$) for 50 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

3-methyl-5-*p*-methoxyphenylcyclohexanone (**3h**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.01 (d, 3H, -C*H*$_3$, *J* = 6.8 Hz), 1.80 - 1.86 (m, 1H), 2.00 - 2.06 (m, 1H), 2.12 - 2.17 (m, 1H), 2.22 - 2.29 (m, 1H), 2.51 - 2.57 (m, 3H), 3.30 - 3.36 (m, 1H, -C*H*Ar), 3.78 (s, 3H, -Ar*OMe*), 6.85 (d, 2H, -*Ar*, *J* = 8.4 Hz), 7.12 (d, 2H, -*Ar*, *J* = 8.8 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3, 29.2, 38.8, 39.6, 47.5, 48.5, 55.3, 113.9, 127.9, 136.5, 158.2, 211.7 MS (*M* / *Z*) 218.90 HRMS (ESI) calcd for $C_{14}H_{19}O_2$ $[M + H]^+$ 219.1385, found 219.1395 $[\alpha]_D$ = -20.00 (*c* 0.3, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 90 : 10, 280 nm, 0.5 ml / min, 24.7 mins (major), 27.1 mins (minor), 28.8 mins (minor), 29.9 mins (minor).

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For **1a**:

$[\alpha]_D$ = 78.4 (*c* 0.50, $CHCl_3$) for 84 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

3-methyl-5-*p*-fluorophenylcyclohexanone (**3i**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.00 (d, 3H, -C*H*$_3$, *J* = 6.9 Hz), 1.83 - 1.86 (m, 1H), 1.98 - 2.05 (m, 1H), 2.12 - 2.17 (m, 1H), 2.20 - 2.26 (m, 1H), 2.50 - 2.56 (m, 3H), 3.31 - 3.38 (m, 1H, -C*H*Ar), 6.96 - 6.70 (m, 2H, -*Ar*), 7.13 - 7.17 (m, 2H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.3, 29.2, 38.9, 39.5, 47.3, 48.4, 115.2, 115.5, 128.3, 128.4, 140.0, 140.0, 160.3, 162.7, 211.3 ^{19}F NMR ($CDCl_3$, 300 MHz): δ - 116.6 MS (*M* / *Z*) 207.08 HRMS (ESI) calcd for $C_{13}H_{16}OF$ $[M + H]^+$ 207.1185, found 207.1188 $[\alpha]_D$ = -18.04 (*c* 0.5, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 99 : 1, 280 nm, 0.5 ml / mins, 40.9 mins (major), 47.5 mins (minor), 49.3 mins (minor).

For **1a**:

$[\alpha]_D$ = 37.3 (*c* 0.50, $CHCl_3$) for 40 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

3-methyl-5-*p*-hydroxylphenylcyclohexanone (**3j**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.00 (d, 3H, -C*H*$_3$, *J* = 6.8 Hz), 1.79 - 1.85 (m, 1H), 1.98 - 2.05 (m, 1H), 2.12 - 2.25 (m, 2H), 2.51 - 2.58 (m, 3H), 3.29 - 3.36 (m, 1H, -C*H*Ar), 5.46 (s, 1H, -O*H*), 6.78 (d, -*Ar*, *J* = 8.4 Hz), 7.05 (d, -*Ar*, *J* = 8.4 Hz) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.4, 29.2, 38.8, 39.5, 47.4, 48.5, 115.4, 128.1, 136.3, 154.3, 212.6 MS (*M* / *Z*) 203.00 HRMS (ESI) calcd for $C_{13}H_{17}O_2$ $[M + H]^+$ 205.1229, found 205.1239 $[\alpha]_D$ = -12.19 (*c* 0.4, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 90 : 10, 280 nm, 0.5 ml / min, 33.6 (major), 35.6 mins (minor), 40.1 mins (minor), 45.4 mins (minor).

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For **1a**:

$[\alpha]_D$ = 35.4 (*c* 0.50, $CHCl_3$) for 38 % *ee*, lit[2h] $[\alpha]_D$ = -74.6 (*R*) (*c* 0.5, $CHCl_3$, 80 % *ee*).

3-methyl-4-phenylcyclohexanone (**3k**):

Colorless oil. **3k** was determined to be *trans* by comparison with previous literature.[4c] The ^1H and ^{13}C NMR spectra are in accordance with similar transformations in literature.[4c] ^1H NMR ($CDCl_3$, 500 MHz): δ 0.78 (d, 3H, -C*H*$_3$, 6.5 Hz), 1.50 - 1.59 (m, 2H), 2.09 (m, 1H), 2.13 - 2.18 (m, 1H), 2.45 - 2.58 (m, 5H), 7.17 - 7.27 (m, 3H, -*Ar*), 7.32 - 7.35 (m, 2H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 19.3, 34.6, 36.8, 14.4, 49.2, 52.1, 126.7, 127.2, 129.8, 143.6, 211.0 MS (*M* / *Z*) 189.03 HRMS (ESI) calcd for $C_{13}H_{17}O$ $[M + H]^+$ 189.1279, found 189.1282 $[\alpha]_D$ = 36.76 (*c* 0.1, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 95 : 5, 210 nm, 0.5 ml / min, 25.5 (major), 27.0 (minor).

For **1b**:

$[\alpha]_D$ = 54.9 (*c* 0.60, $CHCl_3$) for 44 % *ee*, lit[12a] $[\alpha]_D$ = -74.6 (*S*) (*c* 0.6, $CHCl_3$, 93 % *ee*).

3-ethyl-5-phenylcyclohexanone (**3l**):

Colorless oil. **3l** was determined to be *trans* by comparison with previous literature.[4a] The ^1H and ^{13}C NMR spectra are in accordance with literature data.[4a] ^1H NMR ($CDCl_3$, 400 MHz): δ 0.88 - 0.91 (m, 3H), 1.36 - 1.40 (m, 2H), 1.93 - 2.08 (m, 3H), 2.21 - 2.26 (m, 1H), 2.53 - 2.62 (m, 3H), 3.31 - 3.33 (m, 1H, -C*H*Ar), 7.20 - 7.24 (m, 3H, -*Ar*), 7.30 - 7.34 (m, 2H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.6, 27.0, 36.1, 37.0, 39.5, 46.5, 47.4, 126.5, 126.9, 128.6, 144.4, 211.7 MS (*M* / *Z*) 203.07 HRMS (ESI) calcd for $C_{14}H_{19}O$ $[M + H]^+$ 203.1436, found 203.1433 $[\alpha]_D$ = - 19.39 (*c* 0.1, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral

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column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2, 210 nm, 0.5 ml / min, 25.3 mins (major), 28.2 mins (minor), 29.4 mins (minor), 30.8 mins (minor).

For **1c**:

$[\alpha]_D$ = 28.4 (*c* 0.50, $CHCl_3$) for 62 % *ee*, lit[2h] $[\alpha]_D$ = -43.1 (*R*) (*c* 0.6, $CHCl_3$, 94 % *ee*).

3-propyl-5-phenylcyclohexanone (**3m**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.85 - 0.88 (m, 3H), 1.30 - 1.31 (m, 4H), 1.88 - 1.94 (m, 1H), 2.00 - 2.10 (m, 2H), 2.19 - 2.24 (m, 1H), 2.51 - 2.60 (m, 3H), 3.27 - 3.34 (m, 1H, -C*H*Ar), 7.19 - 7.25 (m, 3H, -*Ar*), 7.29 - 7.33 (m, 2H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0, 20.2, 34.1, 36.3, 37.3, 39.5, 46.7, 47.5, 126.5, 126.9, 128.6, 144.4, 211.7 MS (*M* / *Z*) 217.07 HRMS (ESI) calcd for $C_{15}H_{21}O$ $[M + H]^+$ 217.1592, found 217.1600 $[\alpha]_D$ = 2.04 (*c* 0.1, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2, 210 nm, 0.5 ml / min, 21.4 mins (major), 24.4 mins (minor), 26.3 mins (minor), 28.4 mins (minor).

3-butyl-5-phenylcyclohexanone (**3n**):

Colorless oil. **3n** was determined to be *trans* by comparison with previous literature.[12b] The ^{1}H and ^{13}C NMR spectra are in accordance with literature data.[12b] ^{1}H NMR 0.86 - 0.89 (m, 3H), 1.26 - 1.34 (m, 6H), 1.92 - 1.96 (m, 1H), 2.02 - 2.08 (m, 2H), 2.21 - 2.26 (m, 1H), 2.53 - 2.61 (m, 3H), 3.28 - 3.35 (m, 1H, -C*H*Ar), 7.20 - 7.24 (m, 3H, -*Ar*), 7.30 - 7.34 (m, 2H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.0, 14.1, 22.7, 22.7, 29.3, 31.6, 33.8, 34.4, 37.3, 39.5, 46.8, 47.5, 126.5, 126.9, 128.6, 144.4, 211.7 MS (*M* / *Z*) 231.09 HRMS (ESI) calcd for $C_{16}H_{23}O$ $[M + H]^+$ 231.1749, found 231.1756 $[\alpha]_D$ = -1.60 (*c* 0.5, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 98 : 2,

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210 nm, 0.5 ml / min, 20.0 mins (major), 22.7 mins (minor), 25.0 mins (minor), 27.1 mins (minor).

For **1e**:

$[\alpha]_D$ = 24.4 (*c* 0.50, $CHCl_3$) for 50 % *ee*, lit[2h] $[\alpha]_D$ = -44.9 (*R*) (*c* 0.5, $CHCl_3$, 92 % *ee*).

3-ethyl-5-*p*-methoxyphenylcyclohexanone (**3o**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.89 (t, 3H, *J* = 7.4 Hz), 1.33 - 1.40 (m, 2H), 1.89 - 2.04 (m, 3H), 2.19 - 2.24 (m, 1H), 2.51 - 2.58 (m, 3H), 3.24 - 3.31 (m, 1H, -C*H*Ar), 3.789 (s, 3H, -ArO*Me*), 6.84 - 6.86 (m, 2H, -*Ar*), 7.11 - 7.14 (m, 2H, -*Ar*) ^{13}C NMR ($CDCl_3$, 100 MHz): δ 11.6, 27.1, 36.0, 37.2, 38.7, 46.5, 47.7, 55.3, 114.0, 127.8, 136.5, 158.2, 211.8 MS (*M* / *Z*) 233.02 HRMS (ESI) calcd for $C_{15}H_{21}O_2$ $[M + H]^+$ 233.1542, found 233.1545 $[\alpha]_D$ = -13.15 (*c* 0.5, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 95 : 5, 280 nm, 0.5 ml / min, 30.0 mins (major), 33.5 mins (minor), 36.6 (minor), 37.9 (minor).

For **1c**:

$[\alpha]_D$ = 28.5 (*c* 0.50, $CHCl_3$) for 62 % *ee*, lit[2h] $[\alpha]_D$ = -43.1 (*R*) (*c* 0.6, $CHCl_3$, 94 % *ee*).

3-propyl-5-*p*-methoxyphenylcyclohexanone (**3p**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.88 (m, 3H), 1.31 (m, 4H), 1.87 - 1.92 (m, 1H), 1.98 - 2.04 (m, 1H), 2.07 - 2.08 (m, 1H), 2.18 - 2.23 (m, 1H), 2.51 - 2.58 (m, 3H), 3.25 - 3.30 (m, 1H, -C*H*Ar), 3.79 (s, 3H, -Ar*OMe*), 6.85 - 6.86 (m, 2H, -*Ar*), 7.12 - 7.14 (m, 2H, -*Ar*) ^{13}C NMR: ($CDCl_3$, 100 MHz): δ 14.0, 20.2, 34.1, 36.4, 37.5, 38.8, 46.7, 47.8, 55.3, 114.0, 127.8, 136.5, 158.2, 211.8. MS (*M* / *Z*) 247.01 HRMS (ESI) calcd for $C_{16}H_{23}O_2$ $[M + H]^+$ 247.1698, found 247.1694 $[\alpha]_D$ = -5.80 (*c* 0.3, DCM) The diastereomeric and enantiomeric ratios were determined via

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HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 95 : 5, 280 nm, 0.5 ml / min, 26.8 mins (major), 30.7 mins (minor), 34.7 mins (minor), 35.6 mins (minor).

3-butyl-5-*p*-methoxyphenylcyclohexanone (**3q**):

Colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.86 - 0.89 (m, 3H), 1.27 - 1.33 (m, 6H), 1.89 - 1.92 (m, 1H), 1.98 - 2.06 (m, 2H), 2.19 - 2.24 (m, 1H), 2.51 - 2.57 (m, 3H), 3.28 - 3.29 (m, 1H, -C*H*Ar), 3.79 (s, 3H, -Ar*OMe*), 6.85 - 6.86 (m, 2H, -*Ar*), 7.12 - 7.14 (m, 2H, -*Ar*) ^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.0, 22.7, 29.3, 33.9, 34.4, 37.5, 38.8, 46.8, 47.8, 55.3, 114.0, 127.8, 136.5, 158.2, 211.8. MS (*M* / *Z*) 261.01 HRMS (ESI) calcd for $C_{17}H_{25}O_2$ $[M + H]^+$ 261.1855, found 261.1849 $[\alpha]_D$ = -1.00 (*c* 0.5, DCM) The diastereomeric and enantiomeric ratios were determined via HPLC using a chiral column (Daicel Chiralpak IC), *n* - Hexanes : IPA = 95 : 5, 280 nm, 0.5 ml / min, 24.0 mins (major), 27.1 mins (minor), 33.8 mins (minor), 34.4 mins (minor).

For **1e**:

$[\alpha]_D$ = 22.9 (*c* 0.50, $CHCl_3$) for 47 % *ee*, lit[2h] $[\alpha]_D$ = -44.9 (*R*) (*c* 0.5, $CHCl_3$, 92 % *ee*).

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