Highly Efficient and Enantioselective α-Arylation of Cycloalkanones by Scandium-Catalyzed Diazoalkane–Carbonyl Homologation

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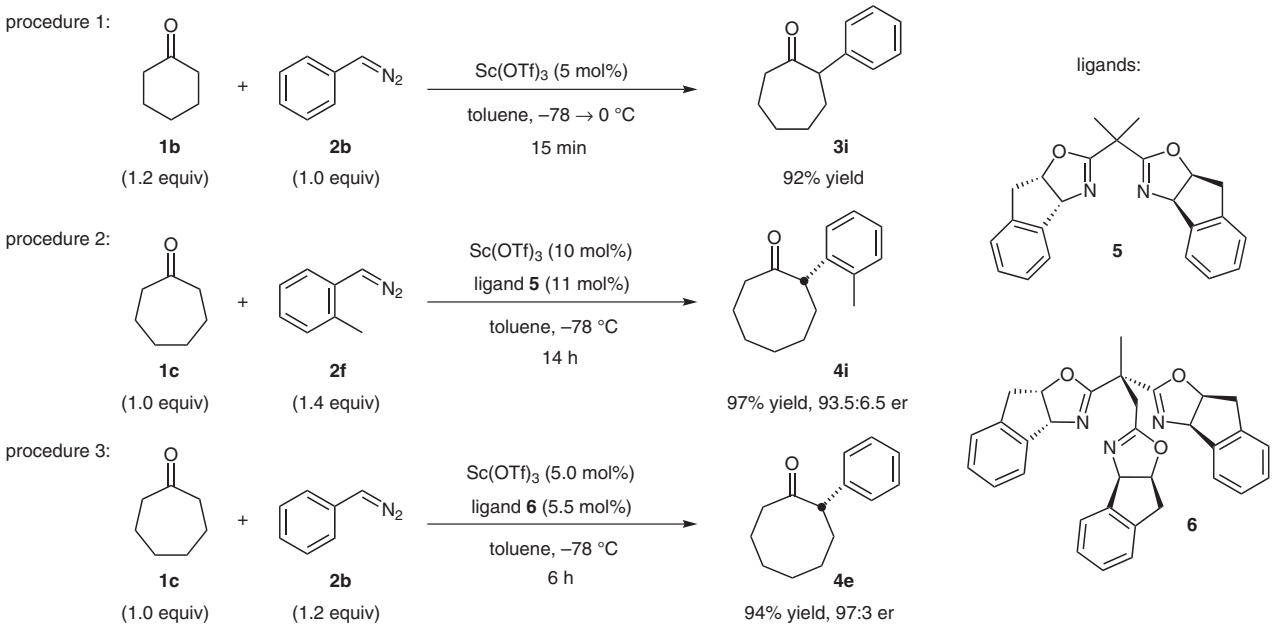
Abstract: Functionalized α-tertiary and -quaternary 2-arylcycloalkanones are rapidly accessed by scandium(III) triflate-catalyzed diazoalkane-carbonyl homologations. Recent developments have allowed for carbon insertion reactions to be performed with catalyst loadings as low as 0.5 mol% on scales up to 5 mmol. Pairing readily available bis- and tris(oxazoline) based ligands with scandium triflate allows access to arylated medium ring carbocycles with enantioselectivities up to 98:2 er and >98% yield. The formal C–C insertion of aryldiazomethanes into unsubstituted cycloalkanones provides a single-step solution to the ongoing challenge of α-arylation.

Key words: diazo compounds, scandium, asymmetric catalysis, ring expansion, arylation



Scheme 1 Racemic and enantioselective α-arylation of cycloalkanones

Introduction

Efficient and selective strategies for the preparation of α-substituted carbonyl compounds remain an ongoing challenge in modern chemical synthesis.[1] Traditional approaches[2] based on enolate alkylation rely on costly stoichiometric preformation of the nucleophile and must be carried out in an iterative fashion when an α-quaternary carbon atom is desired. In addition, the more specialized methods of α-vinylation[3] and -arylation[4] require harsh and basic reaction conditions. Thus far, direct access to tertiary aryl ketones in enantiopure form[5] has been precluded by the problem of facile racemization due to enhanced acidity of the α-proton. We recently developed a new mild and catalytic entry to α-arylalkanones based on formal carbon insertion into the α-C–C (or C–H) bonds of ketones and aldehydes.[6] The transformations take place by 1,2-rearrangement in Sc-complexed diazonium betaine intermediates, cleanly affording α-tertiary and -quaternary carbonyls in one step with dinitrogen as the only by-product (Scheme 2).[7] With mild reagents now available for hydrazone oxidation,[8] along with a safe and convenient procedure for titrating stock solutions of nonstabilized diazoalkanes,[9] large scale homologations are now

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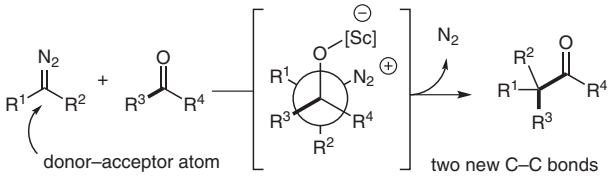
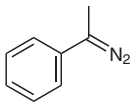
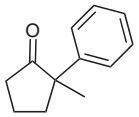
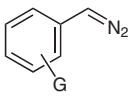
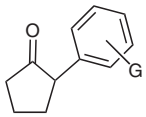
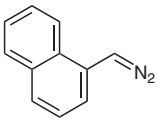
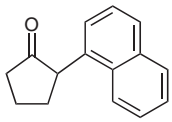
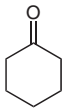
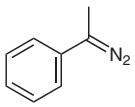
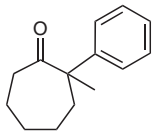
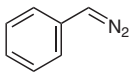
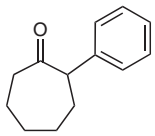
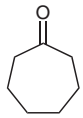
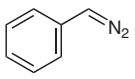
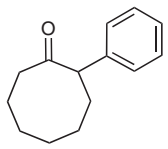
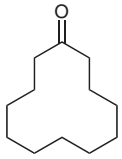
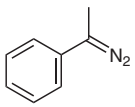
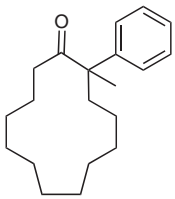
safer and more practical. Herein, we report improved procedures (Scheme 1, Procedures 1–3) for the preparation of racemic and optically active α-arylcycloalkanones on scales up to 5 mmol and with catalyst loadings as low as 0.5 mol%.



Scheme 2 Pathway for diazoalkane insertion reactions

Table 1 Catalytic Ring Expansion of Cycloalkanones with Aryldiazomethanes[a]

Entry	Cycloalkanone		Aryldiazoalkane		Catalyst loading	Product		Yield (%)[b]
1	**1a**		**2a**		1 mol%	**3a**		>98
								
2	**1a**		**2b**	G = H	1 mol%	**3b**	G = H	>98
3	**1a**		**2c**	G = 2-Br	1 mol%	**3c**	G = 2-Br	95
4	**1a**		**2d**	G = 4-CF_3	1 mol%	**3d**	G = 4-CF_3	92
5	**1a**		**2e**	G = 3-OMe	1 mol%	**3e**	G = 3-OMe	88
6	**1a**		**2f**	G = 2-Me	1 mol%	**3f**	G = 2-Me	93
7	**1a**		**2g**		1 mol%	**3g**		95
8	**1b**		**2a**		1 mol%	**3h**		>98
9	**1b**		**2b**		0.5 mol%	**3i**		92
10	**1c**		**2b**		1 mol%	**3j**		89
11	**1d**		**2a**		7 mol%	**3k**		84

[a] Conditions: 0.2–1.0 M in toluene or CH_2Cl_2; 1.0 equiv of diazoalkane **2** for reactions with **1a**,**b**; 1.1 equiv of **2** for reactions with **1c**,**d**; <1 h in every case.
[b] Isolated yield of analytically pure product as determined by ^{1}H NMR spectroscopy.

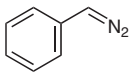
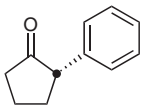
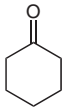
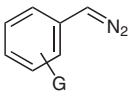
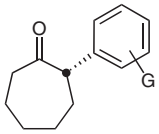
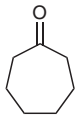
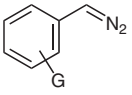
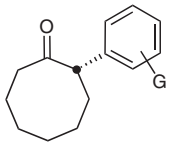
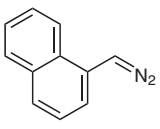
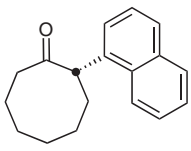
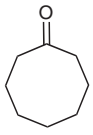
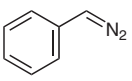
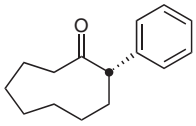
Scope and Limitations

Table 1 illustrates the results of our recent efforts to reduce catalyst loadings and improve the efficiency of α-arylation reactions. A variety of substitution patterns and electronic modifications of the diazoalkane nucleophile are readily tolerated. Even sterically congested *ortho*-substituted nucleophiles (Table 1, entries 3, 6, and 7) afford the homologation products in excellent yields. Additionally, α-quaternary carbon centers are readily prepared by insertion of disubstituted diazomethanes (entries 1, 8, and 11). By careful tuning of reaction stoichiometry, ring expansion products for 4-, 6-, 7-, and 12-membered electrophiles are all obtained in high yield. Noticeably absent from Table 1 is the homologation of cyclopentanone; the cyclohexanone product from insertion of phenyldiazomethane (**2b**) is considerably more reactive towards ring expansion than the starting cyclopentanone, leading to a complex mixture derived from overhomologation. Not surprisingly, strongly Lewis basic functionality such as free alcohols and amines are not well tolerated, and by-products from O–H insertion have been observed for substrates containing hydroxy groups.[10]

Catalyst loadings of 1 mol% and lower were achieved by the rigorous exclusion of moisture from all reagents and the removal of any trace of Lewis basic impurities introduced during preparation of the diazoalkane solutions. By vacuum drying $Sc(OTf)_3$ at 200 °C and storing diazoalkane solutions over 3 Å molecular sieves, dramatic improvements in reaction rate and chemical yield are observed. Applying these practices, we are able to extend the methodology to include asymmetric reactions with monosubstituted aryldiazomethanes.

After extensive optimization of reaction conditions with regard to solvent, temperature, ligand, and catalyst load-

Table 2 Asymmetric Arylation by Diazoalkane Ring Expansion[a]

Entry	Cycloalkanone		Aryldiazoalkane		Product		Yield (%)[b]	er[c]
1	**1a**		**2b**		**4a**		>98	85.5:14.5
	1b							
2	**1b**		**2b**	G = H	**4b**	G = H	94	95:5
3	**1b**		**2h**	G = 4-Me	**4c**	G = 4-Me	96	94:6
4	**1b**		**2i**	G = 3-Br	**4d**	G = 3-Br	>98	94.5:5.5
	1c							
5	**1c**		**2b**	G = H	**4e**	G = H	94	97:3
6[d]	**1c**		**2c**	G = 2-Br	**4f**	G = 2-Br	85	92.5:7.5
7	**1c**		**2d**	G = 4-CF_3	**4g**	G = 4-CF_3	78	98:2
8	**1c**		**2e**	G = 3-OMe	**4h**	G = 3-OMe	>98	97:3
9[d]	**1c**		**2f**	G = 2-Me	**4i**	G = 2-Me	97	93.5:6.5
10	**1c**		**2h**	G = 4-Me	**4j**	G = 4-Me	>98	98.5:1.5
11[d]	**1c**		**2g**		**4k**		94	93:7
12[e]	**1e**		**2b**		**4l**		>98	93:7

[a] Reaction conditions: 0.1–0.2 M in toluene, $Sc(OTf)_3$ (5–10 mol%), ligand **6** (5.5–11 mol%), 1.5–14 h.
[b] Isolated yield of analytically pure product as determined by ^1H NMR spectroscopy.
[c] By chiral SFC analysis.
[d] Run with ligand **5**.
[e] Run at -45 °C.

ings, we arrived at pseudo C3-symmetric[11] **6** (Scheme 1) as the premier ligand for the arylation of medium ring cycloalkanones. As previously mentioned, the introduction of Lewis basic functionality to the catalyst significantly slows reaction rates. Thus, when coordinated to an oxazoline-based ligand, catalyst loadings of 5–10 mol% are required to maintain productive reaction efficiencies. At lower loadings, Lewis acid catalyzed decomposition of the nucleophile[6a] becomes more problematic. Gratifyingly, the functional group tolerance of the asymmetric reaction is comparable to the racemic variant. With regard to substrate scope, higher levels of enantioselectivity are observed for insertion reactions with cycloheptanone compared to the other ring sizes evaluated (Table 2, entries 1, 2, 5, and 12). More sterically demanding *ortho*-substituted substrates are tolerated when the parent bis(oxazoline) ligand **5** (Scheme 1) is utilized (entries 6, 9, and 11). To demonstrate scalability, (*S*)-2-phenylcyclooctanone has been produced on a 250 mg scale in 94% yield and 97:3 er with a 5 mol% catalyst loading.

In summary, we have demonstrated that the formal carbon insertion of aryldiazomethane carbon nucleophiles into the α-C–C bond of naked cycloalkanones is efficient, scalable, and amenable to asymmetric synthesis with simple bis- and tris(oxazoline) chiral ligands. Work is currently underway to expand the scope of the enantioselective process to include α-quaternary products and to generate the diazoalkane reagents for use in situ.

Unless stated otherwise, all reactions were carried out in flame-dried glassware under an atmosphere of N_2. Toluene and CH_2Cl_2 were dispensed under argon from a Glass Contour solvent purification system custom manufactured by SG Waters, LLC (Nashua, NH). $Sc(OTf)_3$ (99%) was purchased from Aldrich and then finely powdered and dried at 200 °C over P_2O_5 for 24 h under high vacuum (0.1 mm Hg) before being taken directly into a glove box under inert atmosphere. Diazoalkanes and ligands were prepared according to the previously reported literature procedures.[6c,12] Unsubstituted cycloalkanones were obtained from commercial sources and purified by distillation according to the literature procedures before use.[13] Silica gel chromatography was performed with ZEOPrep 60 Eco 40–63 μm silica gel. Analytical TLC was performed using 0.25 mm silica gel 60 F254 plates purchased from EMD Chemicals. TLC plates were visualized by exposure to ultraviolet light and/or exposure to ceric ammonium molybdate, *p*-anisaldehyde, or $KMnO_4$ stains. ^{1}H NMR spectra were recorded on a 400 or 500 MHz instrument and referenced using the residual solvent as an internal standard ($CHCl_3$: δ = 7.26 ppm). ^{13}C NMR spectra were recorded on a 100 or 125 MHz instrument and referenced using the solvent as an internal standard ($CDCl_3$: δ = 77.16 ppm). High-resolution mass spectra were obtained at the Boston College Mass Spectrometry facility. Supercritical fluid chromatography (SFC) data were obtained on a Berger Instruments system using Daicel CHIRALPAK AS-H or AD-H columns (φ 4.6 mm, 25 cm length).

2-Phenylcycloheptanone (3i); Typical Procedure 1 for Racemic Homologations

In an inert atmosphere glovebox, $Sc(OTf)_3$ (6.2 mg, 0.012 mmol, 0.48 mol%) was suspended in toluene (0.4 mL). The suspension was moved to a N_2 manifold and cyclohexanone (311 μL, 3.00 mmol, 1.19 equiv) was added in a single portion. The solution was stirred for 5 min at r.t., then cooled to –78 °C. Phenyldiazomethane (**2b**; 2.10 mL, 2.52 mmol, 1.20 M in toluene, 1.00 equiv) was added and the reaction mixture was warmed to 0 °C. An 18 gauge exit needle was used to relieve excess pressure generated by the copious amounts of N_2 gas evolved. After 15 min, the pale yellow solution was diluted with Et_2O (30 mL), washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated. Purification by column chromatography (8% EtOAc in hexanes v/v) afforded the desired compound **3i** as a colorless oil (436 mg, 92%) that solidified just below r.t.; R_f = 0.20 (10% EtOAc in hexanes).

IR (neat): 3028 (w), 2929 (m), 2855 (w), 1702 (s), 1495 (w), 1452 (m), 719 (w), 698 cm^{-1} (m).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 2 H), 7.27–7.21 (m, 3 H), 3.73 (dd, *J* = 11.3, 4.1 Hz, 1 H), 2.70 (ddd, *J* = 13.3, 13.3, 3.1 Hz, 1 H), 2.57–2.49 (m, 1 H), 2.20–2.11 (m, 1 H), 2.10–1.91 (m, 4 H), 1.72–1.58 (m, 1 H), 1.54–1.40 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.6, 140.5, 128.6, 128.0, 127.0, 58.9, 42.8, 32.1, 30.1, 28.7, 25.4.

HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{17}O$ [M + H]$^+$: 189.1279; found: 189.1277.

2-Methyl-2-phenylcyclopentanone (3a)

Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (24.6 mg, 0.050 mmol, 1.00 mol%) suspended in CH_2Cl_2 (16.1 mL), cyclobutanone (411 μL, 5.50 mmol, 1.10 equiv), and **2a** (11.4 mL, 5.0 mmol, 0.44 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3a** as a colorless oil (857 mg, 98%); R_f = 0.33 (10% EtOAc in hexanes).

IR (neat): 2965 (br m), 2870 (br w), 1735 (s), 1496 (m), 1445 (m), 1156 (m), 1056 (m), 760 (m), 670 (m), 545 cm^{-1} (br m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.30 (m, 4 H), 7.25–7.21 (m, 1 H), 2.58–2.53 (m, 1 H), 2.37–2.33 (m, 2 H), 2.05–1.84 (m, 3 H), 1.39 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 220.77, 142.75, 128.69, 126.78, 126.41, 53.23, 38.22, 37.76, 25.16, 18.86.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{15}O$ [M + H]$^+$: 175.1123; found: 175.1128.

2-Phenylcyclopentanone (3b)

Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (24.6 mg, 0.0500 mmol, 1.00 mol%) suspended in CH_2Cl_2 (6.2 mL), cyclobutanone (392 μL, 5.25 mmol, 1.05 equiv), and **2b** (3.76 mL, 5.0 mmol, 1.33 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3b** as a white solid (794 mg, 99%); mp 37–39 °C; R_f = 0.33 (20% EtOAc in hexanes).

IR (neat): 2961 (br w), 1737 (s), 1495 (m), 1452 (m), 1269 (br w), 1141 (m), 756 (m), 698 (s), 535 cm^{-1} (m).

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.31 (m, 2 H), 7.27–7.23 (m, 1 H), 7.21–7.18 (m, 2 H), 3.33 (dd, *J* = 11.7, 8.8 Hz, 1 H), 2.55–2.44 (m, 2 H), 2.30 (ddd, *J* = 19.5, 10.7, 8.8 Hz, 1 H), 2.21–2.08 (m, 2 H), 1.99–1.89 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 218.20, 138.57, 128.73, 128.27, 127.03, 55.45, 38.58, 31.89, 21.00.

HRMS (ESI+): *m*/*z* calcd for $C_{11}H_{13}O$ [M + H]$^+$: 161.0966; found: 161.0960.

2-(2-Bromophenyl)cyclopentanone (3c)

Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol%) suspended in CH_2Cl_2 (0.4 mL), cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2c** (1.6 mL, 1.0 mmol, 0.64 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3c** as a white solid (228 mg, 95%); mp 50–53 °C; R_f = 0.35 (20% EtOAc in hexanes).

IR (neat): 2964 (br m), 2879 (br w), 1740 (s), 1474 (m), 1438 (m), 1163 (m), 1146 (m), 1022 (m), 825 (w), 754 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.57 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.27 (ddd, *J* = 7.6, 7.6, 1.5 Hz, 1 H), 7.11 (ddd, *J* = 7.6, 7.6, 1.7 Hz, 1 H), 7.07 (dd, *J* = 7.6, 1.7 Hz, 1 H), 3.80–3.74 (m, 1 H), 2.60–2.49 (m, 2 H), 2.41–2.32 (m, 1 H), 2.22–2.15 (m, 1 H), 2.08–1.92 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 217.54, 138.90, 133.20, 129.80, 128.67, 127.89, 125.23, 56.32, 38.74, 31.92, 21.03.

HRMS (ESI+): *m*/*z* calcd for $C_{11}H_{12}BrO$ $[M + H]^+$: 239.0072; found: 239.0079.

2-(4-Trifluoromethylphenyl)cyclopentanone (3d)
Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol%) suspended in CH_2Cl_2 (1.1 mL), cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2d** (943 μL, 1.0 mmol, 1.06 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3d** as a white solid (209 mg, 92%); mp 33–35 °C; R_f = 0.30 (20% EtOAc in hexanes).

IR (neat): 2967 (br w), 2883 (br w), 1743 (m), 1619 (w), 1326 (s), 1163 (m), 1120 (br s), 1069 (m), 840 cm^{-1} (w).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.3 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 1 H), 3.39 (dd, *J* = 12.0, 8.8 Hz, 1 H), 2.58–2.47 (m, 2 H), 2.31 (ddd, *J* = 19.3, 10.5, 8.5 Hz, 1 H), 2.24–2.08 (m, 2 H), 2.02–1.92 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 216.98, 142.41, 129.35 (q, $J_{C,F}$ = 32.2 Hz), 128.64, 125.63 (q, $J_{C,F}$ = 4.1 Hz), 124.31 (q, $J_{C,F}$ = 272.0 Hz), 55.19, 38.44, 31.57, 20.94.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{12}F_3O$ $[M + H]^+$: 229.0840; found: 229.0848.

2-(3-Methoxyphenyl)cyclopentanone (3e)
Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol%) suspended in CH_2Cl_2 (1.1 mL), cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2e** (943 μL, 1.0 mmol, 1.06 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3e** as a colorless oil (167 mg, 88%); R_f = 0.24 (20% EtOAc in hexanes).

IR (neat): 2961 (br m), 2875 (br w), 1739 (s), 1601 (m), 1583 (m), 1490 (m), 1245 (br m), 1159 (m), 1041 (br m), 779 (br m), 695 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 7.8, 7.8 Hz, 1 H), 6.81–6.77 (m, 2 H), 6.75 (dd, *J* = 2.2, 2.2 Hz, 1 H), 3.80 (s, 3 H), 3.30 (dd, *J* = 11.7, 9.0 Hz, 1 H), 2.54–2.43 (m, 2 H), 2.30 (ddd, *J* = 19.5, 11.0, 9.0 Hz, 1 H), 2.20–2.07 (m, 2 H), 1.98–1.87 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 217.95, 159.85, 140.10, 129.68, 120.58, 114.30, 112.26, 55.39, 55.32, 38.57, 31.85, 20.98.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{15}O_2$ $[M + H]^+$: 191.1072; found: 191.1081.

2-(2-Methylphenyl)cyclopentanone (3f)
Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol%) suspended in CH_2Cl_2 (1.2 mL), cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2f** (769 μL, 1.00 mmol, 1.30 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3f** as a colorless oil (162 mg, 93%); R_f = 0.36 (20% EtOAc in hexanes).

IR (neat): 2963 (br m), 2879 (br w), 1740 (s), 1493 (w), 1461 (br w), 1146 (m), 756 (m), 727 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.20–7.13 (m, 3 H), 7.01–6.99 (m, 1 H), 3.53 (dd, *J* = 11.7, 8.0 Hz, 1 H), 2.54–2.45 (m, 2 H), 2.33 (ddd, *J* = 19.5, 10.8, 8.9 Hz, 1 H), 2.32 (s, 3 H), 2.22–2.15 (m, 1 H), 2.09–1.91 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 218.81, 137.68, 136.90, 130.67, 127.46, 127.01, 126.40, 53.12, 38.82, 31.82, 21.17, 20.04.

HRMS (ESI+): *m*/*z* calcd for $C_{12}H_{15}O$ $[M + H]^+$: 175.1123; found 175.1122.

2-(Napthalen-1-yl)cyclopentanone (3g)
Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol%) suspended in CH_2Cl_2 (0.3 mL), cyclobutanone (82 μL, 1.1 mmol, 1.1 equiv), and **2g** (1.7 mL, 1.0 mmol, 0.58 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3g** as a white solid (200 mg, 95%); mp 93–95 °C; R_f = 0.27 (20% EtOAc in hexanes).

IR (neat): 2964 (br w), 1738 (s), 1510 (w), 1400 (m), 1142 (m), 1114 (m), 798 (m), 778 cm^{-1} (s).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.91–7.85 (m, 2 H), 7.77 (d, *J* = 8.3 Hz, 1 H), 7.53–7.47 (m, 2 H), 7.43 (dd, *J* = 8.3, 7.3 Hz, 1 H), 7.25 (dd, *J* = 7.3, 1.0 Hz, 1 H), 4.08 (dd, *J* = 8.8, 8.8 Hz, 1 H), 2.68–2.56 (m, 2 H), 2.52–2.43 (m, 1 H), 2.28–2.17 (m, 2 H), 2.13–2.02 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 218.73, 135.58, 134.23, 132.20, 129.10, 127.78, 126.20, 125.78, 125.62, 125.18, 123.75, 52.44, 39.13, 32.56, 21.30.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{15}O$ $[M + H]^+$: 211.1123; found: 211.1129.

2-Methyl-2-phenylcycloheptanone (3h)
Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (4.9 mg, 0.010 mmol, 1.0 mol%), cyclohexanone (114 μL, 1.10 mmol, 1.10 equiv), and **2a** (2.3 mL, 1.0 mmol, 0.44 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3h** as a colorless oil (206 mg, quant); R_f = 0.43 (10% EtOAc in hexanes).

IR (neat): 2930 (br m), 2858 (br w), 1702 (s), 1495 (w), 1458 (m), 764 (m), 700 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 2 H), 7.25–7.20 (m, 3 H), 2.55 (ddd, *J* = 13.7, 11.2, 2.7 Hz, 1 H), 2.34–2.28 (m, 1 H), 2.22–2.17 (m, 2 H), 1.99–1.91 (m, 1 H), 1.88–1.80 (m, 2 H), 1.57–1.39 (m, 2 H), 1.35 (s, 3 H), 1.33–1.24 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 215.16, 145.09, 128.83, 126.74, 126.09, 55.97, 41.05, 36.77, 30.78, 27.10, 26.68, 24.49.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{19}O$ $[M + H]^+$: 203.1436; found: 203.1443.

2-Phenylcyclooctanone (3j)
Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (24.6 mg, 0.050 mmol, 1.0 mol%) suspended in toluene (5.8 mL), cycloheptanone (710 μL, 6.00 mmol, 1.2 equiv), and **2b** (4.17 mL, 5.0 mmol, 1.2 M in toluene, 1.0 equiv). Purification by column chromatography afforded **3j** as a white solid (903 mg, 89%); mp 36–38 °C; R_f = 0.33 (10% EtOAc in hexanes).

IR (neat): 2927 (s), 2855 (w), 1698 (s), 1494 (w), 1449 (m), 700 cm^{-1} (m).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.36–7.28 (m, 4 H), 7.26–7.20 (m, 1 H), 3.79 (dd, *J* = 12.3, 2.7 Hz, 1 H), 2.61 (ddd, *J* = 12.5, 12.5, 4.3 Hz, 1 H), 2.42–2.30 (m, 1 H), 2.29–2.22 (m, 1 H), 2.04–1.86 (m, 3 H), 1.83–1.70 (m, 2 H), 1.65–1.55 (m, 2 H), 1.53–1.37 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.57, 139.49, 128.64, 127.91, 127.12, 57.53, 40.40, 31.67, 26.98, 26.88, 26.85, 24.76.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{19}O$ $[M + H]^+$: 203.1436; found: 203.1439.

2-Methyl-2-phenylcyclotridecanone (3k)

Prepared according to Typical Procedure 1 using $Sc(OTf)_3$ (24.6 mg, 0.050 mmol, 7.00 mol%), however, rather than suspending the $Sc(OTf)_3$ in solvent, cyclododecanone (145 mg, 0.715 mmol, 1.00 equiv) was introduced to the $Sc(OTf)_3$ as a solution in CH_2Cl_2 (1.8 mL). The rest of the procedure was carried out as usual with **2a** (1.8 mL, 0.79 mmol, 0.44 M in toluene, 1.1 equiv). Purification by column chromatography afforded **3k** as a colorless semi-solid (191 mg, 84%); R_f = 0.43 (10% EtOAc in hexanes).

IR (neat): 2930 (br s), 2860 (br m), 1706 (s), 1495 (m), 1463 (m), 1445 (m), 763 (m), 700 cm^{-1} (m).

^1H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.29 (m, 2 H), 7.27–7.20 (m, 3 H), 2.37 (ddd, *J* = 18.3, 9.0, 4.2 Hz, 1 H), 2.24 (ddd, *J* = 12.9, 12.9, 3.2 Hz, 1 H), 1.98 (dddd, *J* = 18.3, 4.6, 4.6, 4.6 Hz, 1 H), 1.90 (ddd, *J* = 13.2, 13.2, 5.6 Hz, 1 H), 1.84–1.76 (m, 1 H), 1.61–1.54 (m, 1 H), 1.51–1.39 (m, 2 H), 1.38–1.22 (m, 11 H), 1.36 (s, 3 H), 1.21–1.14 (m, 1 H), 1.14–1.03 (m, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 213.65, 145.55, 128.73, 126.79, 126.50, 56.04, 36.86, 36.13, 27.56, 26.92, 26.64, 25.84, 25.72, 25.22, 24.75, 24.24, 22.26, 22.13.

HRMS (ESI+): *m*/*z* calcd for $C_{20}H_{31}O$ $[M + H]^+$: 287.2375; found: 287.2376.

(*S*)-2-Phenylcyclooctanone (4e); Typical Procedures 2 and 3 for Asymmetric Homologation

In an inert atmosphere glove box, $Sc(OTf)_3$ (30.4 mg, 0.0618 mmol, 5.00 mol%) was weighed into a 25 mL scintillation vial. Ligand **6** (35.0 mg, 0.0679 mmol, 5.50 mol%) was transferred to the vial containing $Sc(OTf)_3$ with toluene (6.2 mL). The suspension was sealed with a rubber septum and stirred for 1.5 h, then removed from the glove box and to a N_2 manifold. Cycloheptanone (146 μL, 1.24 mmol, 1.00 equiv) was added to the cloudy gray suspension and stirred for 15 min at which point the reaction mixture became clear and homogeneous. The mixture was cooled to –78 °C and phenyldiazomethane (**2b**; 1.20 mL, 1.48 mmol, 1.20 M in toluene, 1.20 equiv) was added in a single portion. After 6 h, the cold reaction mixture was quickly poured into H_2O (20 mL) and diluted with Et_2O (30 mL). The organic layer was washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), and concentrated to a crude yellow oil. Purification by column chromatography (10% EtOAc in hexanes) yielded **4f** as a white solid (235 mg, 94%) with 97:3 er [AS-H, 50 °C, 150 psi, 3.0 mL/min, 4% MeOH, λ = 220 nm; t_R = 1.85 min (minor), 2.07 min (major)]. Characterization data were in agreement with those tabulated above for the racemic compound; $[\alpha]_D^{20}$ –138.8 (*c* 1.26, $CHCl_3$).

(*S*)-2-Phenylcyclopentanone (4a)

Run for 1.5 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **6** (8.5 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cyclobutanone (16 μL, 0.18 mmol, 1.2 equiv), and **2b** (203 μL, 0.15 mmol, 0.74 M in toluene, 1.0 equiv). The crude reaction mixture was not purified by column chromatography,[14] but instead poured into pentane (15 mL) and filtered through a cotton plug. The organics were washed with H_2O (10 mL), brine (10 mL), and dried (Na_2SO_4). Concentration under high vacuum afforded a crude yellow oil that was taken up in hexanes (1.5 mL) and again filtered through a cotton plug. Concentration afforded **4a** as a pale yellow oil (26.2 mg, quant) with 85.5:14.5 er [AS-H, 50 °C, 150 psi, 1.5 mL/min, 2% MeOH, λ = 220 nm; t_R = 4.02 min (minor), 4.67 min (major)]. Characterization data were in agreement with those tabulated above for the racemic compound.

(*S*)-2-Phenylcycloheptanone (4b)

Run for 1.5 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **6** (8.5 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cyclohexanone (19 μL, 0.18 mmol, 1.2 equiv), and **2b** (203 μL, 0.15 mmol, 0.74 M in toluene, 1.0 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4b** as a colorless oil (26.5 mg, 94%) with 95:5 er [AS-H, 50 °C, 150 psi, 3.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 2.35 min (minor), 2.70 min (major)]. Characterization data were in agreement with those tabulated above for the racemic compound; $[\alpha]_D^{20}$ –138.2 (*c* 0.80, $CHCl_3$).

(*S*)-2-(4-Methylphenyl)cycloheptanone (4c)

Run for 1.5 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **6** (8.5 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cyclohexanone (19 μL, 0.18 mmol, 1.2 equiv), and **2h** (227 μL, 0.15 mmol, 0.66 M in toluene, 1.0 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4c** as a colorless oil (29.2 mg, 96%) with 94:6 er [AS-H, 50 °C, 150 psi, 3.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 2.49 min (minor), 2.90 min (major)]; $[\alpha]_D^{20}$ –154.5 (*c* 0.47, $CHCl_3$); R_f = 0.18 (10% EtOAc in hexanes).

IR (neat): 3022 (br w), 2927 (br m), 2856 (w), 1702 (s), 1513 (m), 1454 (br m), 1163 (w), 1129 (w), 825 (w), 789 (w) cm^{-1}.

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.16–7.10 (m, 4 H), 3.69 (dd, *J* = 11.3, 4.1 Hz, 1 H), 2.73–2.64 (m, 1 H), 2.55–2.47 (m, 1 H), 2.32 (s, 3 H), 2.18–2.08 (m, 1 H), 2.08–1.89 (m, 4 H), 1.70–1.56 (m, 1 H), 1.52–1.40 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 213.77, 137.46, 136.61, 129.35, 127.80, 58.56, 42.71, 32.04, 30.18, 28.63, 25.51.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{19}O$ $[M + H]^+$: 203.1436; found: 203.1445.

(*S*)-2-(3-Bromophenyl)cycloheptanone (4d)

Run for 3 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **6** (8.5 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cyclohexanone (19 μL, 0.18 mmol, 1.2 equiv), and **2i** (125 μL, 0.15 mmol, 1.20 M in toluene, 1.0 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4d** as a colorless oil (41.1 mg, quant) with 94.5:5.5 er [AS-H, 50 °C, 150 psi, 3.0 mL/min, 3% MeOH, λ = 220 nm; t_R = 3.02 min (minor), 3.58 min (major)]; $[\alpha]_D^{20}$ –102.7 (*c* 1.05, $CHCl_3$); R_f = 0.27 (10% EtOAc in hexanes).

IR (neat): 2928 (m), 2855 (w), 1702 (s), 1593 (w), 1566 (w), 1475 (w), 1454 (w), 1129 (w), 1074 (w), 937 (w), 779 (w), 690 cm^{-1} (w).

^1H NMR ($CDCl_3$, 400 MHz): δ = 7.38–7.34 (m, 2 H), 7.20–7.12 (m, 2 H), 3.70 (dd, *J* = 11.2, 3.7 Hz, 1 H), 2.69–2.60 (m, 1 H), 2.59–2.51 (m, 1 H), 2.14–1.86 (m, 5 H), 1.72–1.59 (m, 1 H), 1.54–1.38 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 212.67, 142.80, 131.11, 130.10, 130.07, 126.83, 122.63, 58.57, 43.06, 32.19, 29.87, 28.82, 25.10.

HRMS (ESI+): *m*/*z* calcd for $C_{13}H_{16}BrO$ $[M + H]^+$: 269.0364; found: 269.0401.

(*S*)-2-(2-Bromophenyl)cyclooctanone (4f)

Run for 14 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **5** (5.9 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2c** (370 μL, 0.21 mmol, 0.57 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4f** as a colorless oil (35.9 mg, 85%) with 92.5:7.5 er [AS-H, 50 °C, 150 psi, 2.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 4.65 min (major), 5.09 min (minor)]; $[\alpha]_D^{20}$ –1.9 (*c* 0.99, $CHCl_3$); R_f = 0.21 (10% EtOAc in hexanes).

IR (neat): 3063 (br w), 2927 (br m), 2856 (br w), 1705 (s), 1467 (m), 1440 (m), 1326 (w), 1157 (w), 1021 (m), 743 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.54–7.48 (m, 2 H), 7.34–7.28 (m, 1 H), 7.12–7.05 (m, 1 H), 4.67 (dd, *J* = 11.5, 3.3 Hz, 1 H), 2.74 (ddd, *J* = 14.9, 7.4, 3.1 Hz, 1 H), 2.49–2.40 (m, 1 H), 2.39–2.25 (m, 1 H), 2.15–2.04 (m, 1 H), 2.03–1.88 (m, 2 H), 1.86–1.66 (m, 3 H), 1.65–1.52 (m, 2 H), 1.37–1.24 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.99, 139.78, 132.55, 130.04, 128.33, 127.68, 124.54, 52.89, 44.67, 35.56, 28.61, 25.74, 25.08, 23.87.

HRMS (ESI+): *m*/*z* calcd for $C_{14}H_{18}BrO$ [M + H]$^+$: 281.0541; found: 281.0571.

(*S*)-2-(4-Trifluromethylphenyl)cyclooctanone (4g)

Run for 14 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **6** (8.5 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2d** (320 μL, 0.21 mmol, 0.66 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4g** as a colorless oil (31.7 mg, 78%) with 98:2 er [AD-H, 50 °C, 150 psi, 1.0 mL/min, 3% MeOH, λ = 220 nm; t_R = 8.69 min (minor), 9.44 min (major)]; $[\alpha]_D^{20}$ –93.52 (*c* 0.88, $CHCl_3$); R_f = 0.18 (10% EtOAc in hexanes).

IR (neat): 2935 (br w), 2860 (br w), 1703 (m), 1617 (w), 1466 (w), 1447 (w), 1419 (w), 1325 (s), 1163 (m), 1122 (m), 1069 (m), 1019 (m), 838 cm^{-1} (br w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56 (d, *J* = 8.0 Hz, 1 H), 7.46 (d, *J* = 8.0 Hz, 1 H), 3.92 (dd, *J* = 12.1, 2.9 Hz, 1 H), 2.55 (ddd, *J* = 12.5, 12.5, 3.7 Hz, 1 H), 2.38–2.22 (m, 2 H), 2.10–1.97 (m, 2 H), 1.96–1.86 (m, 1 H), 1.84–1.69 (m, 2 H), 1.64–1.46 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.72, 143.67 (q, $J_{C,F}$ = 1.5 Hz), 129.40 (q, $J_{C,F}$ = 32.2 Hz), 128.44, 125.50 (q, $J_{C,F}$ = 3.7 Hz), 124.30 (q, $J_{C,F}$ = 271.5 Hz), 56.73, 41.40, 32.97, 27.22, 26.44, 26.18, 24.75.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{18}F_3O$ [M + H]$^+$: 271.1310; found: 271.1341.

(*S*)-2-(3-Methoxyphenyl)cyclooctanone (4h)

Run for 3 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **6** (8.5 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2e** (200 μL, 0.21 mmol, 1.05 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4h** as a colorless oil (35.1 mg, quant) with 97:3 er [AS-H, 50 °C, 150 psi, 2.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 2.05 min (minor), 2.26 min (major)]; $[\alpha]_D^{20}$ –116.3 (*c* 0.99, $CHCl_3$); R_f = 0.16 (10% EtOAc in hexanes).

IR (neat): 2929 (s), 2856 (w), 1697 (s), 1598 (m), 1583 (m), 1491 (m), 1465 (m), 1286 (s), 1048 (m), 767 (w), 696 cm^{-1} (w).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.24–7.18 (m, 1 H), 6.94–6.88 (m, 2 H), 6.80–6.75 (m, 1 H), 3.80 (s, 3 H), 3.75 (dd, *J* = 12.5, 2.7 Hz, 1 H), 2.62 (ddd, *J* = 11.7, 4.7 Hz, 1 H), 2.41–2.29 (m, 1 H), 2.29–2.21 (m, 1 H), 2.03–1.84 (m, 3 H), 1.82–1.69 (m, 2 H), 1.64–1.53 (m, 2 H), 1.53–1.34 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.41, 159.79, 140.98, 129.53, 120.21, 113.81, 112.41, 57.60, 55.31, 40.25, 31.44, 27.10, 26.87, 26.80, 24.74.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{21}O_2$ [M + H]$^+$: 233.1542; found: 233.1560.

(*S*)-2-(2-Methylphenyl)cyclooctanone (4i)

Run for 14 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **5** (5.9 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2f** (180 μL, 0.21 mmol, 1.18 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4i** as a colorless oil (31.3 mg, 97% yield) with 93.5:6.5 er [AS-H, 50 °C, 150 psi, 2.5 mL/min, 2% MeOH, λ = 220 nm; t_R = 2.74 min (minor), 3.11 min (major)]; $[\alpha]_D^{20}$ –98.1 (*c* 1.26, $CHCl_3$); R_f = 0.21 (10% EtOAc in hexanes).

IR (neat): 3096 (w), 3020 (w), 2927 (br s), 2856 (w), 1697 (s), 1488 (w), 1464 (m), 1446 (m), 1325 (m), 1160 (w), 1123 (w), 845 (w), 755 (br m), 730 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.45–7.41 (m, 1 H), 7.23–7.17 (m, 1 H), 7.16–7.10 (m, 2 H), 4.06 (dd, *J* = 12.1, 2.7 Hz, 1 H), 2.72 (ddd, *J* = 13.1, 11.7, 4.3 Hz, 1 H), 2.46–2.35 (m, 1 H), 2.40 (s, 3 H), 2.33–2.23 (m, 1 H), 2.01–1.87 (m, 3 H), 1.84–1.71 (m, 2 H), 1.67–1.46 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.22, 138.06, 136.47, 130.63, 127.04, 126.83, 126.33, 53.04, 40.77, 32.02, 27.21, 27.15, 27.04, 24.91, 20.21.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{21}O$ [M + H]$^+$: 217.1591; found: 217.1592.

(*S*)-2-(4-Methylphenyl)cyclooctanone (4j)

Run for 3 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **6** (8.5 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2h** (320 μL, 0.21 mmol, 0.66 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4j** as a colorless oil (32.5 mg, quant) with 98.5:1.5 er [AS-H, 50 °C, 150 psi, 3.0 mL/min, 4% MeOH, λ = 220 nm; t_R = 1.90 min (minor), 2.13 min (major)]; $[\alpha]_D^{20}$ –148.9 (*c* 0.98, $CHCl_3$); R_f = 0.37(10% EtOAc in hexanes).

IR (neat): 3021 (br w), 2926 (br s), 2856 (br m), 1698 (s), 1513 (m), 1465 (w), 1446 (w), 1159 (w), 818 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.22 (d, *J* = 8.2 Hz, 2 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 3.74 (dd, *J* = 12.3, 2.7 Hz, 1 H), 2.61 (ddd, *J* = 12.7, 11.7, 4.5 Hz, 1 H), 2.42–2.29 (m, 1 H), 2.31 (s, 3 H), 2.26–2.20 (m, 1 H), 2.00–1.85 (m, 3 H), 1.81–1.70 (m, 2 H), 1.63–1.54 (m, 2 H), 1.53–1.36 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.75, 136.78, 136.44, 129.37, 127.76, 57.26, 40.16, 31.46, 27.13, 26.92, 26.82, 24.78, 21.13.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{21}O$ [M + H]$^+$: 217.1592; found: 217.1599.

(*S*)-2-(Napthalen-1-yl)cyclooctanone (4k)

Run for 14 h at –78 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **5** (5.9 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cycloheptanone (18 μL, 0.15 mmol, 1.0 equiv), and **2g** (396 μL, 0.21 mmol, 0.53 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4k** as a pale yellow solid (35.5 mg, 94%) with 93:7 er [AD-H, 50 °C, 150 psi, 2.0 mL/min, 3% MeOH, λ = 220 nm; t_R = 21.52 min (major), 25.15 min (minor)]; mp 97–100 °C; $[\alpha]_D^{20}$ +48.3 (*c* 0.82, $CHCl_3$); R_f = 0.20 (10% EtOAc in hexanes).

IR (neat): 3042 (w), 2924 (br m), 2898 (br w), 1689 (s), 1510 (w), 1397 (w), 1117 (m), 800 (m), 780 cm^{-1} (br s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.33–8.28 (m, 1 H), 7.87–7.83 (m, 1 H), 7.79–7.74 (m, 1 H), 7.64–7.60 (m, 1 H), 7.60–7.54 (m, 1 H), 7.51–7.45 (m, 2 H), 4.65 (dd, *J* = 12.1, 2.6 Hz, 1 H), 2.82 (ddd, *J* = 12.3, 12.3, 3.9 Hz, 1 H), 2.68–2.55 (m, 1 H), 2.30 (ddd, *J* = 12.9, 5.7, 3.7 Hz, 1 H), 2.11–1.94 (m, 3 H), 1.90–1.79 (m, 2 H), 1.78–1.63 (m, 2 H), 1.61–1.49 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 215.91, 135.62, 134.07, 131.86, 129.01, 127.75, 126.46, 125.70, 125.59, 124.63, 123.68, 52.49, 39.88, 31.66, 27.41, 27.30, 26.91, 24.92.

HRMS (ESI+): *m*/*z* calcd for $C_{18}H_{21}O$ [M + H]$^+$: 253.1592; found: 253.1622.

(*S*)-2-(4-Phenyl)cyclononanone (4l)

Run for 14 h at –45 °C according to the general procedure with $Sc(OTf)_3$ (7.4 mg, 0.015 mmol, 10 mol%), ligand **6** (8.5 mg, 0.016 mmol, 11 mol%), toluene (1.5 mL), cyclooctanone (18.9 mg, 0.15 mmol, 1.0 equiv) in toluene (0.15 mL), and **2b** (284 μL, 0.21 mmol, 0.74 M in toluene, 1.4 equiv). The crude reaction mixture was directly purified by column chromatography to afford **4l** as a colorless oil (33.0 mg, quant) with 93:7 er [AD-H, 50 °C, 150 psi, 2.0 mL/min, 2% MeOH, λ = 220 nm; t_R = 9.04 min (minor), 9.82 min (major)]; $[\alpha]_D^{20}$ –43.9 (*c* 0.94, $CHCl_3$); R_f = 0.25 (10% EtOAc in hexanes).

IR (neat): 3061 (br w), 3026 (br w), 2926 (br m), 1702 (s), 1495 (w), 1451 (m), 698 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.29–7.14 (m, 5 H), 3.88 (dd, *J* = 11.9, 2.7 Hz, 1 H), 2.46–2.34 (m, 1 H), 2.34–2.24 (m, 2 H), 1.95–1.34 (m, 11 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 216.28, 139.72, 128.68, 128.02, 127.12, 58.94, 41.80, 31.78, 25.97, 25.68, 25.49, 24.22, 24.02.

HRMS (ESI+): *m*/*z* calcd for $C_{15}H_{21}O$ [M + H]$^+$: 217.1592; found: 217.1589.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. ^{1}H and ^{13}C NMR data are included.

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References

(1) (a) Dolling, U. F.; Davis, P.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1984**, *106*, 446. (b) Corey, E. J.; Xu, F.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (c) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (d) Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 62. (e) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (f) Braun, M.; Meier, T. *Synlett* **2005**, 2968. (g) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192. (h) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc.* **1994**, *116*, 8829. For unrelated catalytic entries to such products, see: (i) Luchaco-Cullis, C.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 8192. (j) Shen, Y.-M.; Wang, B.; Shi, Y. *Tetrahedron Lett.* **2006**, *47*, 5455. For a lead reference on the α-derivatization of aldehydes by organocatalysis, see: (k) Mastracchio, A.; Warkentin, A. A.; Walji, A. M.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20648.

(2) (a) Meyers, A. I.; Williams, D. R.; Druelinger, M. *J. Am. Chem. Soc.* **1976**, *98*, 3032. (b) Job, A.; Janeck, C. F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* **2002**, *58*, 2253.

(3) (a) Alexander, M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900. (b) Chieffi, A.; Kamikawa, K.; Åhman, J.; Fox, J. M.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 1897.

(4) (a) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918. (b) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (c) Chae, J.; Yun, J.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 4809. (d) Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195.

(5) (a) Ishihara, K.; Nakamura, S.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 12854. (b) Yanagisawa, A.; Inanami, H.; Yamamoto, H. *Chem. Commun.* **1998**, 1573. (c) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *122*, 8120. (d) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24. (e) Cheon, C. H.; Yamamoto, H. *J. Am. Chem. Soc.* **2008**, *130*, 9246. (f) Yanagisawa, A.; Touge, T.; Arai, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 1546.

(6) (a) Moebius, D. C.; Kingsbury, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 878. (b) Wommack, A. J.; Moebius, D. C.; Travis, A. L.; Kingsbury, J. S. *Org. Lett.* **2009**, *11*, 3202. (c) Rendina, V. L.; Moebius, D. C.; Kingsbury, J. S. *Org. Lett.* **2011**, *13*, 2004.

(7) (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364. (b) Gutsche, C. D.; Redmore, D. In *Carbocyclic Ring Expansion Reactions*; Hart, H.; Karabatsos, G. J., Eds.; Academic Press: New York, **1968**, 81–98.

(8) (a) Javed, M. I.; Brewer, M. *Org. Lett.* **2007**, *9*, 1789. (b) Furrow, M. E.; Myers, A. G. *J. Am. Chem. Soc.* **2004**, *126*, 12222. (c) Holton, T. L.; Shechter, H. *J. Org. Chem.* **1995**, *60*, 4725.

(9) Rendina V. L.; Kingsbury, J. S. Submitted to *J. Org. Chem.* for publication.

(10) Though not studied in the context of cycloalkanone ring expansions, heteroaromatic substrates are well tolerated in the Sc-catalyzed homologation of aldehydes. See reference 6b.

(11) (a) Tang, Y.; Zhou, J. *J. Am. Chem. Soc.* **2002**, *124*, 9030. (b) Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2005**, *34*, 664.

(12) Davies, I. W.; Gerena, L.; Castonguay, L.; Senanayake, C. H.; Larsen, R. D.; Verhoevena, T. R.; Reidera, P. J. *Chem. Commun.* **1996**, 1753.

(13) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th ed.; Butterworth-Heinemann: Oxford, **2003**.

(14) Tertiary 2-arylcyclopentanones are known to racemize on silica gel. See: Shen, Y.-M.; Wang, B.; Shi, Y. *Angew. Chem. Int. Ed.* **2006**, *45*, 1429.