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Enantioselective One-Pot Conjugate Addition of Grignard Reagents to Cyclic Enones Followed by Amidomethylation

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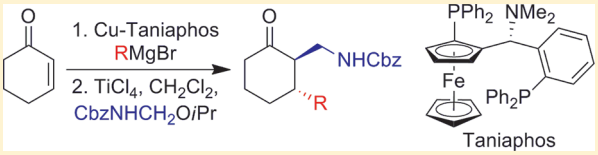
Supporting Information

ABSTRACT: Enantioselective conjugate addition of Grignard reagents to enones, catalyzed by Cu-Taniaphos or Josiphos complex, affords chiral enolates. Ensuing one-pot Mannich reaction with $TiCl_4$-generated imine leads to aminocarbonyl compounds with benzyloxycarbonyl-protected nitrogen. Both diastereomers of these compounds are isolated in moderate yields but high enantiomeric purities (up to er 97.5:2.5).



There is a growing demand for synthesis of compounds with multiple stereogennic centers and functional groups. However, efficient and stereocontrolled construction of complex molecules is still a considerable challenge. Stepwise processes, in which each reaction step is followed by a purification operation, are slow and laborious. Therefore, stereoselective domino reactions or one-pot arrangements of reactions constitute a significant improvement in terms of step economy.[1] Performing such transformations in a catalytic manner adds to the benefits. Domino reactions require appropriate initiator reaction which provides a reactive intermediate for the subsequent step. A convenient starting reaction is a metal-catalyzed conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds.[2−10] The 1,4-addition of organometallic nucleophiles affords reactive metal enolates, which can be advantageously reacted with a broad range of electrophilic reagents.[11,12] Such enolate trapping reactions work well with aldehydes,[13−17] alkyl halides,[18,19] allylic bromides and acetates,[20−23] nitroso compounds.[24] Metal enolates also open epoxides,[25] take part in cross-coupling,[26] or cyclopropanation reactions.[27] The concept was also utilized in an intramolecular fashion with another unsaturated carbonyl compound.[28−30] Imines also acted as electrophilic trapping reagents for zinc enolates formed by conjugate addition of dialkylzinc reagents.[31−33] Zinc enolates are most commonly used because of their easy formation and appropriate reactivity. However, structural variability is difficult to obtain because of limited availability of dialkylzinc reagents. On the other hand, magnesium enolates can be formed by conjugate addition with a broad range of Grignard reagents. Nevertheless, magnesium enolates were used in trapping reactions to much lesser extent.[16,34,35] We have showed that Mg enolates resulting from Cu-catalyzed addition of Grignard reagents can be trapped with imines derived from aromatic aldehydes.[36,37] Although seemingly simple, enolate trapping with formaldehyde-derived imines is unknown, because of instability of such imines. Such methodology, however, would broaden the scope of enolate trapping by opening a way to new β-aminocarbonyl compounds in a catalytic manner. We were inspired by the work of Evans[38] and Seebach[39,40] on diastereoselective synthesis of β-amino acids. In this methodology, a titanium enolate, usually obtained by a soft enolization of an acyl oxazolidone, reacted with formaldehyde imine equivalent, formed in situ from $CbzNHCH_2OR$ by the action of $TiCl_4$. In this context, we asked whether amidomethylation can be performed also with enolates formed by enantioselective conjugate addition. This report shows the results using cyclic and linear enones with several Grignard reagents.

Conjugate additions of Grignard reagents to cyclic enones,[41−44] and our own studies[36] of enolate trapping with imines, served as a starting point for our investigation. The conjugate addition of ethylmagnesium bromide was catalyzed by a complex formed in situ from CuCl and ferrocene ligand Taniaphos in an ethereal solvent. Imine was generated by treating amidomethylation reagent with $TiCl_4$ in a separate flask. We quickly discovered that the projected enolate trapping with formaldehyde imine equivalent would not be compatible with oxygenated solvents, such as Et_2O or *t*-BuOMe, because of high oxophilicity of titanium. It is, however, possible to perform the conjugate addition in ethereal solvents such as *t*-BuOMe or Et_2O and then add a solution of amidomethylation reagent with $TiCl_4$ in CH_2Cl_2. In this way, the reaction of cyclohex-2-enone (**1**) with EtMgBr catalyzed by Cu−Taniaphos complex afforded Cbz-protected aminocarbonyl compound **2** (Scheme 1).

The conjugate addition of organometallic reagents can be performed also in CH_2Cl_2 at low temperatures.[45] Therefore, we also tried conjugate addition of EtMgBr followed by amidomethylation in CH_2Cl_2. This reaction set up led to the best outcome of the enolate trapping. By this way, compound **2** was isolated in overall 64% yield (sum of isolated *trans*- and *cis*-**2**). Product **2** always formed as a mixture of *trans*- and *cis*-diastereomers. It was, however, surprising that diastereoselectivity was relatively low with typical ratio *trans*/*cis* 2:1. On the

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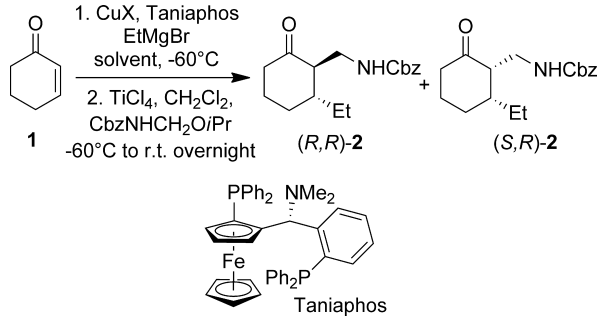
Scheme 1



other hand, both diastereoisomers can be separated by column chromatography. Enantiomeric purity of both *trans*- and *cis*-**2** was high (up to e.r. of 97:3). The most reliable results were obtained with CuCl as copper source. Table 1 summarizes the results of screening for optimal solvent and copper source.

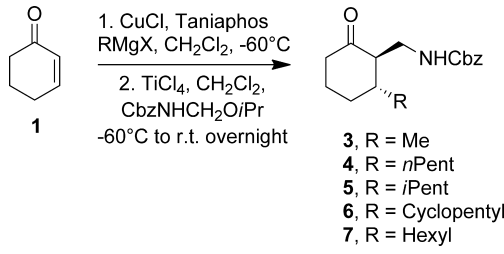
Table 1. Screening for Conditions for the One-Pot Reaction of Ketone 1 with EtMgBr[a]

CuX	solvent	yield (%) (*trans*/*cis*)	dr[b]	er (*trans*/*cis*)[c]
CuCl	*t*-BuOMe	28/20	2.4:1	96:4/95:5
CuCl	Et_2O	28/16	2:1	93:7/88:12
CuCl[d]	CH_2Cl_2	37/21	2.1:1	96:4/95:5
CuCl[e]	CH_2Cl_2	41/23	1.6:1	96.5:3.5/97:3
CuCl	mTHF[f]	32/2	2.3:1	79:21/60:40
CuCl	THF	21/23	3.2:1	52:48/60:40 (-)
CuBr.SMe_2	CH_2Cl_2	36/18	2.5:1	95:5/92:8
CuTC	CH_2Cl_2	34/16	2.3:1	95:5/84:16
$Cu(OTf)_2$	CH_2Cl_2	22/15	2.3:1	92:8/88:12
$[Cu(MeCN)_4]PF_6$	CH_2Cl_2	32/19	2:1	86:14/92:8
CuI	CH_2Cl_2	23/17	2.2:1	94:6/91:9
CuF_2	CH_2Cl_2	20/12	2.3:1	53.5:46.5/52:48

[a]All reactions were carried out with 375 μmol of cyclohex-2-enone, 563 μmol of MeMgBr, 18.8 μmol of CuX (5 mol %), and 22.5 μmol of Taniaphos (6 mol %) in 3.75 mL of solvent. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Determined by HPLC. [d]Average of two parallel runs. [e]Catalyst loading 10 mol %. [f]mTHF stands for 2-methyltetrahydrofuran.

With proper experimental conditions, we tested a variety of alkyl Grignard reagents in the reaction with cyclohex-2-enone (**1**) (Scheme 2). Compounds **3**–**7** were also obtained as

Scheme 2



separable *trans*- and *cis*-isomers, with similarly modest diastereomeric ratios, typically 2:1. Enantiomeric ratios were usually high (up to er of 97.5:2.5) with the exception of cyclopentylmagnesium bromide, which afforded compound **6** in moderate enantiomeric purity (er 87:13). Arylmagnesium halides were not used in the one-pot reaction because they are unreactive in the conjugate addition catalyzed by Cu–Taniaphos complex.[36,41] We also verified conjugate addition with methylmagnesium bromide in CH_2Cl_2 without subsequent amidomethylation. GC analysis of the reaction mixture showed 98% conversion and 77% of the 1,4-addition product. Table 2

Table 2. One-Pot Reaction of Enone 1 with Various Grignard Reagents[a]

RMgX	yield (%) (*trans*/*cis*)	dr[b]	er (*trans*/*cis*)[c]
MeMgBr	47/19	2:1	96:4/97.5:2.5
MeMgI	20/7	2.7:1	92:8/94:6
EtMgBr	37/21	2.1:1	96:4/95:5
n-PentMgBr	33/30	2.4:1	96:4/80:20
i-PentMgBr	21/13	2.2:1	96:4/80:20
CpMgBr	10/6	n.d.	87:13/87:13
HexMgBr	26/15	1.8:1	96:4/96:4

[a]All reaction were carried out with 375 μmol of enone, 563 μmol of RMgBr, 18.8 μmol of CuCl (5 mol %), and 22.5 μmol of Taniaphos (6 mol %) in 3.75 mL of CH_2Cl_2. [b]Determined by ^{1}H NMR of the crude reaction mixture. [c]Determined by HPLC.

summarizes the results of the one-pot reaction of enone **1** with several Grignard reagents.

The scope of the reaction with respect to enone was evaluated on several cyclic α,β-unsaturated ketones. 4,4,-Dimethylcyclohex-2-enone afforded expected product **8** of the one-pot reaction with MeMgBr. Yields and enantioselectivities were slightly lower, probably because of higher steric crowding near C-3 atom (Figure 1). This notion is also supported by the fact

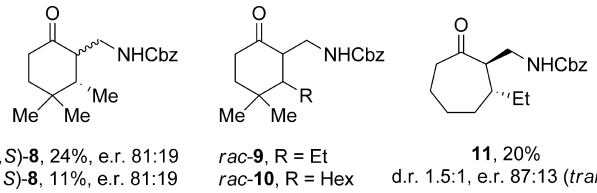


Figure 1. Products of one-pot reactions with other cyclic enones.

that, the reaction with EtMgBr and HexMgBr did not proceed with chiral Cu–Taniaphos catalyst. Corresponding products **9** and **10** were only isolated from racemic reactions carried out with a stoichiometric amount of copper and PBu_3 as ligand. Using cyclopent-2-enone as substrate, we isolated only traces of the desired product. All additions to 4,4-dimethylcyclohex-2-enone were accompanied by a significant amount of 1,2-addition product, which is inactive in amidomethylation reaction. On the other hand, with cyclohept-2-enone, a one-pot reaction product **11** was isolated in 20% yield and with an er of 87:13 (*trans*). In this case, however, we were not able to isolate diastereomers (Figure 1).

Relative configuration of both diastereomers of compound **9** was determined by 2D NMR techniques. Assignment of signals was performed from gDQCOSY and gHSQCAD experiments, and then the spatial relationship of relevant protons was deduced from NOESY experiments. All other compounds were assigned by comparison of H–H coupling constants between COCH and CHNH. For *trans*-isomers J_{HH} = 6.5–6.9 Hz and for *cis*-isomers J_{HH} = 9.0–10.0 Hz.

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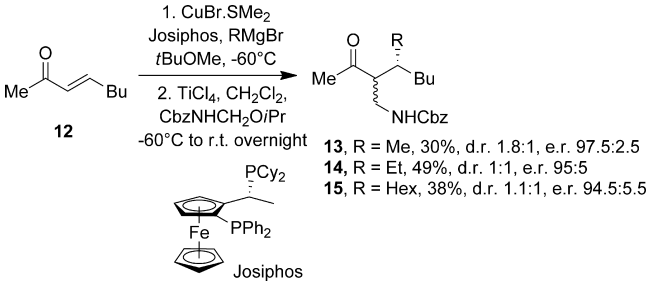
We also tested the one-pot reaction on linear enones (Scheme 3). In contrast to the one-pot reaction with cyclic enones,

Scheme 3



conjugate addition on linear enones performed in CH_2Cl_2 was less enantioselective. Therefore, we performed the reaction of oct-2-enone (**10**) with methyl-, ethyl-, and hexylmagnesium bromide in *t*-BuOMe, and only amidomethylating reagent was added in CH_2Cl_2. In this case, we used Josiphos ligand because it works well in the conjugate addition of Grignard reagents to linear enones.[46] Products **13**−**15** were isolated in slightly lower yields and as diastereomeric mixtures. Enantioselectivities were, however, high, up to 97.5:2.5.

The one-pot conjugate addition and amidomethylation, both on cyclic and linear enones, affords products with diastereoselectivity lower than expected. We proposed that it can be the result of $TiCl_4$-mediated epimerization of the product. Control experiments proved this conjecture. Stirring pure diastereomers, either (*R*,*R*)-**2** or (*R*,*S*)-**2**, in the presence of $TiCl_4$ at −60 °C lead in both cases to diastereomeric mixtures *trans*/*cis* 2:1. Attempts at thermodynamic equilibration either in acidic (*p*TsOH in refluxing toluene) or basic (DBU in CH_2Cl_2) conditions also afforded similar results.

We have also investigated the nature of amidomethylating reagent by ^{1}H NMR. Addition of $TiCl_4$ led to downfield shift of protons indicating only complexation of titanium to oxygen. The corresponding imine was not detected.

In summary, we report here a catalytic one-pot conjugate addition followed by amidomethylation. Magnesium enolates, formed by enantioselective copper-catalyzed conjugate addition of Grignard reagents to enones, can be trapped with $TiCl_4$-generated imine. In this way, Cbz-protected aminocarbonyl compounds were prepared in moderate yields. Diastereoselectivities were relatively low because of Ti-mediated epimerization of the products, but diastereomers (from cyclic enones) were separated by column chromatography. Enantiomeric purities of obtained compounds were high (up to e.r. 97.5:2.5) in the majority of examples.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under nitrogen using standard Schlenk techniques. Commercially available reagents were used without further purification. Solvents were dried according to the standard procedures.

General Procedure for One-Pot Reaction on Cyclic Ketones. Ligand Taniaphos (15.5 mg, 22.5 μmol) and CuCl (1.9 mg, 18.8 μmol) were dissolved in CH_2Cl_2 (3.75 mL), and the resulting solution was stirred 1 h at rt. The reaction mixture was then cooled at −60 °C, and ketone (375 μmol) was added via syringe. The resulting mixture was stirred for an additional 10 min at −60 °C. Into this mixture, Grignard reagent (563 μmol) was added during 5 min and the mixture was stirred for 2 h at −60 °C. In another flask, $TiCl_4$ (35 μL, 330 μmol) was added into a solution of CbzNHCH$_2$O-*i*-Pr (300 μmol) dissolved in CH_2Cl_2 (2.5 mL) at −40 °C. This solution was stirred for 2 h at −40 °C, and then it was added via canula to the solution of conjugate addition at −60 °C. The temperature of the resulting mixture was allowed to rise to rt overnight. The reaction was quenched with aq NH_4Cl and then extracted with CH_2Cl_2. Combined organic extracts were concentrated. Column chromatography (SiO_2, hexane/EtOAc/CH_2Cl_2 83:14:3) of the crude product afforded pure diastereomers of the product. The nantiomeric ratio was determined by HPLC with chiral stationary phase and detected by UV at 211 nm.

*(R,R)-Benzyl ((2-Ethyl-6-oxocyclohexyl)methyl)carbamate ((R,R)-**2**).* Following general procedure for cyclic ketones with EtMgBr: colorless oil: $[\alpha]_D$ −8.2 (*c* 1.0, $CHCl_3$, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.40−7.27 (m, 5H), 5.39 (br, 1H), 5.15−4.98 (m, 2H), 3.55 (ddd, *J* = 13.8, 6.7, 2.6 Hz, 1H), 3.28 (ddd, *J* = 13.9, 7.5, 6.4 Hz, 1H), 2.46−2.20 (m, 3H), 2.14−1.98 (m, 1H), 1.98−1.84 (m, 1H), 1.80−1.32 (m, 5H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.8 (CO), 156.4 (qC), 136.7 (qC), 128.5 (CH), 128.00 (CH), 127.98 (CH), 66.5 (CH_2), 55.2 (CH), 42.3 (CH), 42.0 (CH_2), 37.8 (CH_2), 29.7 (CH_2), 25.95 (CH_2), 25.94 (CH_2), 10.0 (CH_3); HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{24}NO_3$ 290.1751, found 290.1725; HPLC (OD-H, hexane/*i*-PrOH = 85:15, 0.6 mL min^{-1}) t_R(major) 13.6 min, t_R(minor) 17.7 min; IR (ATR) ν_{max} (cm^{-1}) 3455, 3390 (m, N−H), 1699 (s, C═O).

*(S,R)-Benzyl ((2-Eethyl-6-oxocyclohexyl)methyl)carbamate ((S,R)-**2**).* Following the general procedure for cyclic ketones with EtMgBr: colorless oil; $[\alpha]_D$ +2.8 (*c* 1.0, $CHCl_3$, 92% ee); ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.39−7.27 (m, 5H), 5.12 (br, 1H), 5.10−5.02 (m, 2H), 3.38 (ddd, *J* = 14.2, 9.9, 4.5 Hz, 1H), 3.27 (ddd, *J* = 13.4, 8.2, 4.0 Hz, 1H), 2.78−2.70 (m, 1H), 2.41−2.33 (m, 1H), 2.31−2.22 (m, 1H), 2.17−2.09 (m, 1H), 1.94−1.71 (m, 4H), 1.36−1.26 (m, 1H), 1.09−0.98 (m, 1H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.1 (CO), 156.4 (qC), 136.6 (qC), 128.5 (CH), 128.05 (CH), 128.02 (CH), 66.6 (CH_2), 55.4 (CH), 42.0 (CH), 41.5 (CH_2), 39.0 (CH_2), 27.0 (CH_2), 22.4 (CH_2), 20.2 (CH_2), 11.5 (CH_3); HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{17}H_{24}NO_3$ 290.1751, found 290.1750; HPLC (OJ-H, hexane/*i*-PrOH = 95:5, 0.6 mL min^{-1}): t_R(major) 36.8 min, t_R(minor) 40.6 min; IR (ATR) ν_{max} (cm^{-1}) 3342 (m, N−H), 1698 (s, C═O).

*(R,R)-Benzyl ((2-Methyl-6-oxocyclohexyl)methyl)carbamate ((R,R)-**3**).* Following the general procedure for cyclic ketones with MeMgBr: colorless oil; $[\alpha]_D$ −1.5 (*c* 1.0, $CHCl_3$, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.42−7.27 (m, 5H), 5.39 (br s, 1H), 5.07 (s, 2H), 3.56 (ddd, *J* = 13.7, 6.6, 2.7 Hz, 1H), 3.30 (td, *J* = 13.8, 6.9 Hz, 1H), 2.44−2.25 (m, 2H), 2.25−2.13 (m, 1H), 2.10−1.98 (m, 1H), 1.93−1.79 (m, 1H), 1.75−1.40 (m, 3H), 1.16 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.4 (CO), 156.4 (qC), 136.7 (qC), 128.5 (CH), 128.01 (CH), 127.99 (CH), 66.5 (CH_2), 57.6 (CH), 41.9 (CH_2), 37.9 (CH_2), 36.7 (CH), 34.1 (CH_2), 26.1 (CH_2), 20.5 (CH_3); HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{16}H_{22}NO_3$, 276.1594, found 276.1622; HPLC (OD-H, hexane/*i*-PrOH 85:15; 0.7 mL.min^{-1}) t_R(major) 14.0 min, t_R(minor) 17.1 min; IR (ATR) ν_{max} (cm^{-1}) 3454, 3373 (m, NH), 1699 (s, C═O).

*(S,R)-Benzyl ((2-Methyl-6-oxocyclohexyl)methyl)carbamate ((S,R)-**3**).* Following the general procedure for cyclic ketones with MeMgBr: colorless crystalline solid; $[\alpha]_D$ +4.6 (*c* 0.9, $CHCl_3$, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.40−7.27 (m, 5H), 5.17 (br s, 1H), 5.12−5.00 (m, 2H), 3.38−3.17 (m, 2H), 2.78−2.66 (m, 1H), 2.52−2.39 (m, 1H), 2.39−2.17 (m, 2H), 2.02−1.81 (m, 3H), 1.77−1.58 (m, 1H), 0.81 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.2 (CO), 156.4 (qC), 136.6 (qC), 128.5 (CH), 128.1 (CH), 128.0 (CH), 66.6 (CH_2), 54.9 (CH), 41.8 (CH_2), 39.4 (CH_2), 35.1 (CH), 32.0 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HPLC (OD-H, hexane/*i*-PrOH 95:5; 0.6 mL min^{-1}) t_R(major) 29.5 min, t_R(minor) 32.6 min; IR (ATR) ν_{max} (cm^{-1}) 3321 (s, NH), 1708, 1681 (s, C═O). Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.48; H, 7.65; N, 5.04.

*(R,R)-Benzyl ((2-Oxo-6-pentylcyclohexyl)methyl)carbamate ((R,R)-**4**).* Following the general procedure for cyclic ketones with nPentMgBr: colorless oil; $[\alpha]_D$ −5.6 (*c* 1.0, $CHCl_3$, 92% ee); ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.40−7.32 (m, 4H), 7.32−7.27 (m, 1H),

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5.42−5.32 (m, 1H), 5.14−5.02 (m, 2H), 3.57 (ddd, J = 13.7, 6.8, 2.6 Hz, 1H), 3.28 (ddd, J = 13.9, 7.6, 6.3 Hz, 1H), 2.41−2.34 (m, 1H), 2.33−2.24 (m, 2H), 2.10−2.02 (m, 1H), 1.99−1.91 (m, 1H), 1.70−1.63 (m, 1H), 1.63−1.53 (m, 2H), 1.48−1.38 (m, 2H), 1.38−1.18 (m, 6H), 0.89 (t, J = 7,0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.8 (CO), 156.4 (qC), 136.7 (qC), 128.5 (CH), 128.01 (CH), 127.98 (CH), 66.5 (CH_2), 55.8 (CH), 42.0 (CH_2), 41.3 (CH), 38.0 (CH_2), 33.4 (CH_2), 32.0 (CH_2), 30.3 (CH_2), 26.0 (CH_2), 25.7 (CH_2), 22.6 (CH_2), 14.1 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{20}H_{30}NO_3$ 332.2220, found 332.2230; HPLC (OD-H, hexane/i-PrOH = 85:15, 0.6 mL min^{-1}) t_R(major) 11.4 min, t_R(minor) 17.0 min; IR (ATR) ν_{max} (cm^{-1}) 3457 (m, N−H), 1722, 1704 (s, C═O).

*(S,R)-Benzyl ((2-Oxo-6-pentylcyclohexyl)methyl)carbamate ((S,R)-**4**).* Following the general procedure for cyclic ketones with nPentMgBr: colorless oil; $[\alpha]_D$ −5.5 (c 1.0, $CHCl_3$, 60% ee); ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.42−7.28 (m, 5H), 5.19−5.00 (m, 3H), 3.38 (ddd, J = 14.1, 10.0, 4.4 Hz, 1H), 3.30−3.23 (m, 1H), 2.77−2.68 (m, 1H), 2.41−2.32 (m, 1H), 2.32−2.17 (m, 2H), 1.93−1.70 (m, 4H), 1.36−0.97 (m, 8H), 0.87 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.2 (CO), 156.4 (qC), 136.6 (qC), 128.5 (CH), 128.06 (CH), 128.03 (CH), 66.6 (CH_2), 55.4 (CH), 41.5 (CH_2), 40.3 (CH), 39.1 (CH_2), 31.7 (CH_2), 27.6 (CH_2), 27.2 (CH_2), 26.6 (CH_2), 22.54 (CH_2), 22.51 (CH_2), 14.0 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{20}H_{30}NO_3$ 332.2220, found 332.2262; HPLC (OD-H, hexane/i-PrOH = 95:5, 0.7 mL min^{-1}) t_R(major) 20.4 min, t_R(minor) 23.2 min; IR (ATR) ν_{max} (cm^{-1}) 3387, 3328 (s, N−H), 1715, 1690 (s, C═O).

*(S,S)-Benzyl 6-(3-Methylbutyl)-2-oxocyclohexyl)methyl)-carbamate ((S,S)-**5**).* Following the general procedure for cyclic ketones with i-PentMgBr: colorless oil; $[\alpha]_D$ −6.7 (c 1.0, $CHCl_3$, 60% ee); ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.39−7.27 (m, 5H), 5.17−5.03 (m, 3H), 3.39 (ddd, J = 14.2, 10.0, 4.5 Hz, 1H), 3.31−3.23 (m, 1H), 2.76−2.69 (m, 1H), 2.41−2.34 (m, 1H), 2.31−2.22 (m, 1H), 2.22−2.14 (m, 1H), 1.91−1.71 (m, 4H), 1.52−1.40 (m, 1H), 1.27−1.09 (m, 2H), 1.09−0.96 (m, 2H), 0.86 (d, J = 6.6 Hz, 3H), 0.83 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.2 (CO), 156.4 (qC), 136.5 (qC), 128.5 (CH), 128.04 (CH), 128.01 (CH), 66.6 (CH_2), 55.4 (CH), 41.5 (CH_2), 40.6 (CH), 39.1 (CH_2), 36.2 (CH_2), 28.0 (CH), 27.6 (CH_2), 24.9 (CH_2), 22.9 (CH_3), 22.4 (CH_2), 22.2 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{20}H_{30}NO_3$ 332.2220, found 332.2212; HPLC (OJ-H, hexane/i-PrOH = 92:8, 0.7 mL .min^{-1}) t_R(minor) 12.6 min, t_R(major) 14.9 min; IR (ATR) ν_{max} (cm^{-1}) 3345 (m, N−H), 1704 (s, C═O).

*(R,S)-Benzyl 6-(3-Methylbutyl)-2-oxocyclohexyl)methyl)-carbamate ((R,S)-**5**).* Following the general procedure for cyclic ketones with i-PentMgBr: colorless oil; $[\alpha]_D$ −6.7 (c 1.0, $CHCl_3$, 92% ee); ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.38−7.32 (m, 4H), 7.32−7.27 (m, 1H), 5.40−5.33 (m, 1H, NH), 5.14−5.01 (m, 2H, CH_2O), 3.57 (ddd, J = 13.7, 6.8, 2.7 Hz, 1H), 3.28 (ddd, J = 13.8, 7.6, 6.3 Hz, 1H), 2.41−2.35 (m, 1H), 2.34−2.24 (m, 2H), 2.10−2.02 (m, 1H), 1.98−1.90 (m, 1H), 1.70−1.63 (m, 1H), 1.63−1.48 (m, 3H), 1.48−1.39 (m, 1H), 1.39−1.30 (m, 1H), 1.30−1.21 (m, 1H), 1.18−1.09 (m, 1H), 0.94−0.84 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.8 (CO), 156.4 (qC), 136.7 (qC), 128.5 (CH), 128.00 (CH), 127.97 (CH), 66.5 (CH_2), 55.7 (CH), 42.0 (CH_2), 41.5 (CH), 38.0 (CH_2), 35.1 (CH_2), 31.1 (CH_2), 30.3 (CH_2), 28.2 (CH), 26.0 (CH_2), 23.0 (CH_3), 22.3 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{20}H_{30}NO_3$ 332.2220, found 332.2220; HPLC (OD-H, hexane/i-PrOH = 85:15, 0.6 mL min^{-1}) t_R(major) 11.2 min, t_R(minor) 16.6 min; IR (ATR) ν_{max} (cm^{-1}) 3455, 3390 (m, N−H), 1703 (s, C═O).

*(S,S)-Benzyl ((6-Cyclopentyl-2-oxocyclohexyl)methyl)carbamate ((S,S)-**6**).* Following the general procedure for cyclic ketones with CpMgBr: colorless crystalline solid; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.40−7.27 (m, 5H), 5.06 (s, 2H), 4.84 (brs, 1H), 3.67−3.48 (m, 1H), 3.40 (td, J = 13.4, 5.1 Hz, 1H), 2.75−2.61 (m, 1H), 2.61−2.45 (m, 1H), 2.35−2.19 (m, 1H), 2.10−1.91 (m, 1H), 1.91−1.40 (m, 11H), 1.15−0.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.7 (CO), 156.3 (qC), 136.4 (qC), 128.5 (CH), 128.1 (CH), 128.0 (CH), 66.8 (CH_2), 55.4 (CH), 47.3 (CH), 41.6 (CH), 39.2 (CH_2), 38.8 (CH_2), 32.1 (CH_2), 30.9 (CH_2), 27.1 (CH_2), 25.03 (CH_2), 24.98 (CH_2), 24.7 (CH_2); HPLC (OD-H, hexane/i-PrOH = 95:5, 0.6 mL min^{-1}) t_R(major) 29.9 min, t_R(minor) 33.2 min; IR (ATR) ν_{max} (cm^{-1}) 3297 (m, N−H), 1723, 1694 (s, C═O). Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.61; H, 8.27; N, 4.03.

*(R,S)-Benzyl ((6-Cyclopentyl-2-oxocyclohexyl)methyl)carbamate ((R,S)-**6**).* Following the general procedure for cyclic ketones with CpMgBr: colorless oil; $[\alpha]_D$ −0.8 (c 0.8, $CHCl_3$, 74% ee); ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.38−7.27 (m, 5H), 5.35 (br, 1H), 5.09 (d, J = 12.3 Hz, 1H), 5.04 (d, J = 12.3 Hz, 1H), 3.59 (ddd, J = 13.6, 6.6, 3.3 Hz, 1H), 3.32 (ddd, J = 14.0, 8.0, 6.3 Hz, 1H), 2.45−2.35 (m, 2H), 2.28 (ddd, J = 12.8, 12.6, 6.1 Hz, 1H), 2.20−2.10 (m, 1H), 2.05 (dq, J = 9.1, 4.6 Hz, 1H), 1.89−1.82 (m, 1H), 1.78−1.69 (m, 2H), 1.69−1.45 (m, 7H), 1.32−1.23 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) 214.0 (CO), 156.4 (qC), 136.6 (qC), 128.4 (CH), 127.98 (CH), 127.94 (CH), 66.5 (CH_2), 55.4 (CH), 44.2 (CH), 41.5 (CH_2), 40.5 (CH), 38.6 (CH_2), 30.3 (CH_2), 26.2 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 24.6 (CH_2); HRMS (m/z) $[M + H]^+$ calcd for $C_{20}H_{28}NO_3$ 330.2064, found 330.2030; HPLC (OD-H, hexane/i-PrOH = 85:15, 0.6 mL min^{-1}) t_R(major) 13.9 min, t_R(minor) 17.9 min; IR (ATR) ν_{max} (cm^{-1}) 3335 (m, N−H), 1705 (s, C═O).

*(R,R)-Benzyl ((6-Hexyl-2-oxocyclohexyl)methyl)carbamate ((R,R)-**7**).* Following the general procedure for cyclic ketones with HexMgBr: colorless oil; $[\alpha]_D$ −8.4 (c 1.0, $CHCl_3$, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.42−7.27 (m, 5H), 5.43−5.30 (m, 1H), 5.15−5.01 (m, 2H), 3.57 (ddd, J = 13.8, 6.9, 2.8 Hz, 1H), 3.27 (ddd, J = 13.9, 7.7, 6.2 Hz, 1H), 2.44−2.20 (m, 3H), 2.13−2.01 (m, 1H), 2.01−1.88 (m, 1H), 1.75−1.10 (m, 13H), 0.88 (t, J = 6.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) 213.9 (CO), 156.4 (qC), 136.7 (qC), 128.5 (CH), 128.01 (CH), 127.98 (CH), 66.5 (CH_2), 55.8 (CH), 42.0 (CH_2), 41.4 (CH), 38.0 (CH_2), 33.5 (CH_2), 31.8 (CH_2), 30.3 (CH_2), 29.5 (CH_2), 26.04 (CH_2), 26.01 (CH_2), 22.65 (CH_2), 14.1 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{21}H_{32}NO_3$ 346.2377, found 346.2390; HPLC (OD-H, hexane/i-PrOH = 85:15, 0.6 mL min^{-1}) t_R(major) 11.0 min, t_R(minor) 15.6 min; IR (ATR) ν_{max} (cm^{-1}) 3455, 3379 (m, N−H), 1703 (s, C═O).

*(S,R)-Benzyl ((6-Hhexyl-2-oxocyclohexyl)methyl)carbamate ((S,R)-**7**).* Following the general procedure for cyclic ketones with HexMgBr: colorless oil; $[\alpha]_D$ −9.3 (c 1.2, $CHCl_3$, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.42−7.27 (m, 5H), 5.20−5.00 (m, 3H), 3.32 (dddd, J = 21.9, 13.6, 9.0, 4.3 Hz, 2H), 2.79−2.65 (m, 1H), 2.45−2.15 (m, 3H), 1.97−1.65 (m, 4H), 1.40−0.96 (m, 10H), 0.87 (t, J = 6.7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) 213.2 (CO), 156.4 (qC), 136.6 (qC), 128.5 (CH), 128.06 (CH), 128.03 (CH), 66.6 (CH_2), 55.4 (CH), 41.5 (CH_2), 40.3 (CH), 39.1 (CH_2), 31.8 (CH_2), 29.2 (CH_2), 27.7 (CH_2), 27.2 (CH_2), 26.9 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 14.1 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{21}H_{32}NO_3$ 346.2377, found 346.2394; HPLC (OD-H, hexane/i-PrOH = 85:15, 0.6 mL min^{-1}) t_R(major) 20.8 min, t_R(minor) 23.4 min; IR (ATR) ν_{max} (cm^{-1}) 3347 (m, N−H), 1704 (s, C═O).

*(S,S)-Benzyl ((2-Methyl-3,3-dimethyl-6-oxocyclohexyl)methyl)-carbamate ((S,S)-**8**).* Following the general procedure for cyclic ketones with MeMgBr: colorless crystalline solid; mp 73−78 °C (heptane); ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.39−7.32 (m, 4H), 7.32−7.28 (m, 1H), 5.18 (br, 1H), 5.10 (d, J = 12.2 Hz, 1H), 5.05 (d, J = 12.2 Hz, 1H), 3.33 (ddd, J = 13.3, 9.4, 3.8 Hz, 1H), 3.25−3.17 (m, 1H), 2.99−2.93 (m, 1H), 2.41 (dt, J = 14.1, 7.0 Hz, 1H), 2.21 (ddd, J = 14.5, 5.0, 1.7 Hz, 1H), 1.93−1.85 (m, 1H), 1.81 (dt, J = 13.7, 5.0 Hz, 1H), 1.55 (tdd, J = 13.6, 7.0, 1.7 Hz, 1H), 1.38 (s, 3H), 0.98 (s, 3H), 0.74 (d, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) 213.4 (qC−CO), 156.3 (qC), 136.6 (qC), 128.5 (CH-Ph), 128.04 (CH-Ph), 128.03 (CH-Ph), 66.6 (CH_2), 51.0 (CH), 45.5 (CH), 39.7 (CH_2), 38.3 (CH_2), 34.5 (CH_2), 33.7 (qC), 28.3 (CH_3), 26.8 (CH_3), 10.8 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{18}H_{26}NO_3$, 304.1907; found 304.1915. HPLC (OD-H, hexane/i-PrOH = 90:10, 0.6 mL.min^{-1}) t_R(major) 29.3 min, t_R(minor) 33.5 min; IR (ATR) ν_{max} (cm^{-1}) 3372, 3329 (m, N−H), 1715, 1697 (s, C═O).

*(R,S)-Benzyl ((2-Methyl-3,3-dimethyl-6-oxocyclohexyl)methyl)-carbamate ((R,S)-**8**).* Following the general procedure for cyclic ketones with MeMgBr: colorless oil; $[\alpha]_D$ −5.0 (c = 1.0, $CHCl_3$, 62% ee); ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.38−7.33 (m, 4H), 7.33−7.28 (m, 1H), 5.39 (br, 1H), 5.08 (s, 2H), 3.57 (ddd, J = 13.8, 6.5, 2.6 Hz, 1H),

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3.29 (td, J = 13.7, 6.8 Hz, 1H), 2.48 (dt, J = 14.2, 6.0 Hz, 1H), 2.33−2.26 (m, 1H), 2.26 (ddd, J = 13.9, 4.3, 2.8 Hz, 1H), 1.74 (ddd, J = 13.5, 5.9, 2.6 Hz, 1H), 1.59 (dt, J = 14.1, 4.3 Hz, 1H), 1.49 (qd, J = 13.2, 6.7 Hz, 1H), 1.07−1.02 (m, 6H), 0.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) 213.7 (qC−CO), 156.5 (qC), 136.7 (qC), 128.5 (CH-Ph), 128.02 (CH-Ph), 128.00 (CH-Ph), 66.5 (CH_2), 52.9 (CH), 44.1 (CH), 41.5 (CH_2), 38.8 (CH_2), 38.2 (CH_2), 33.5 (qC), 29.4 (CH_3), 19.0 (CH_3), 14.2 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{18}H_{26}NO_3$ 304.1907, found 304.1921; HPLC (OD-H, hexane/i-PrOH = 90:10, 0.6 mL min^{-1}) t_R(minor) 14.1 min, t_R(major) 19.5 min; IR (ATR) ν_{max} (cm^{-1}) 3455, 3390 (m, N−H), 1704 (s, C═O).

(S,S*)-Benzyl ((2-Ethyl-3,3-dimethyl-6-oxocyclohexyl)methyl)carbamate ((S*,S*)-**9**).* Colorless crystalline solid: mp 85−87 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.44−7.27 (m, 5H), 5.21 (br, 1H), 5.08 (m, 2H), 3.43−3.23 (m, 2H), 3.00−2.90 (m, 1H), 2.41 (dt, J = 14.0, 6.9 Hz, 1H), 2.22 (ddd, J = 14.6, 5.3, 2.3 Hz, 1H), 1.79 (dt, J = 13.5, 5.3 Hz, 1H), 1.62−1.47 (m, 2H), 1.40−1.17 (m, 1H), 1.28 (s, 3H), 1.10−0.92 (m, 1H), 1.01 (s, 3H), 0.90 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 213.6 (qC−CO), 156.4 (qC), 136.6 (qC), 128.5 (CH-Ph), 128.06 (CH-Ph), 128.05 (CH-Ph), 66.6 (CH_2), 53.2 (CH), 51.6 (CH), 39.7 (CH_2), 38.3 (CH_2), 35.7 (CH_2), 34.5 (qC), 27.5 (CH_3), 27.4 (CH_3), 19.5 (CH_2), 15.9 (CH_3); HPLC (OD-H, hexane/i-PrOH = 95:5, 0.7 mL min^{-1}) t_R 24.8 min, t_R 27.2 min; IR (ATR) ν_{max} (cm^{-1}) 3357 (m, N−H), 1706 (s, C═O). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.17; H, 8.64; N, 4.44.

(R,S*)-Benzyl ((2-Ethyl-3,3-dimethyl-6-oxocyclohexyl)methyl)carbamate ((R*,S*)-**9**).* Colorless crystalline solid: mp 73−75 °C (EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.40−7.27 (m, 5H), 5.48 (br, 1H), 5.07 (m, 2H), 3.62 (ddd, J = 13.5, 8.2, 2.7 Hz, 1H), 3.16 (ddd, J = 13.6, 8.8, 4.8 Hz, 1H), 2.56−2.33 (m, 2H), 2.26 (ddd, J = 14.0, 4.5, 2.8 Hz, 1H), 1.71 (ddd, J = 13.5, 6.1, 2.8 Hz, 1H), 1.66−1.33 (m, 3H), 1.18−1.06 (m, 1H), 1.07 (s, 3H), 0.99 (s, 3H), 0.97 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 214.1 (qC−CO), 156.4 (qC), 136.6 (qC), 128.5 (CH-Ph), 128.02 (CH-Ph), 128.01 (CH-Ph), 66.5 (CH_2), 53.0 (CH), 51.8 (CH), 41.5 (CH_2), 39.1 (CH_2), 38.6 (CH_2), 34.4 (qC), 29.2 (CH_3), 22.8 (CH_2), 20.1 (CH_3), 15.0 (CH_3); HPLC (OD-H, hexane/i-PrOH = 85:15, 0.6 mL min^{-1}) t_R 12.5 min, t_R 17.3 min; IR (ATR) ν_{max} (cm^{-1}) 3433 (m, N−H), 1716, 1702 (s, C═O). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.03; H, 8.63; N, 4.37.

(S,S*)-Benzyl ((2-Hexyl-3,3-dimethyl-6-oxocyclohexyl)methyl)carbamate ((S*,S*)-**10**).* Colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.38−7.32 (m, 4H), 7.32−7.27 (m, 1H), 5.23 (br, 1H), 5.10 (d, J = 12.3 Hz, 1H), 5.04 (d, J = 12.3 Hz, 1H), 3.30 (dd, J = 13.4, 4.1 Hz, 2H), 2.95 (td, J = 8.5, 4.2 Hz, 1H), 2.40 (dt, J = 13.8, 6.9 Hz, 1H), 2.25−2.17 (m, 1H), 1.79 (dt, J = 13.4, 5.2 Hz, 1H), 1.60−1.49 (m, 2H), 1.28 (s, 3H), 1.32−1.16 (m, 10H), 1.00 (s, 3H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) 213.7 (CO), 156.3 (qC), 136.6 (qC), 128.5 (CH), 128.03 (CH), 66.6 (CH_2), 51.5 (CH), 51.3 (CH), 39.7 (CH_2), 38.4 (CH_2), 35.6 (CH_2), 34.5 (qC), 31.58 (CH_2), 31.55 (CH_2), 29.6 (CH_2), 27.6 (CH_3), 27.2 (CH_3), 26.8 (CH_2), 26.2 (CH_2), 14.0 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{23}H_{36}NO_3$ 374.2695, found 374.2708; HPLC (OJ-H, hexane/i-PrOH = 90:10, 0.7 mL min^{-1}) t_R 9.1 min, t_R 12.0 min; IR (ATR) ν_{max} (cm^{-1}) 3454, 3348 (m, N−H), 1704 (s, C═O).

(R,S*)-Benzyl ((2-Hexyl-3,3-dimethyl-6-oxocyclohexyl)methyl)carbamate ((R*,S*)-**10**).* Colorless crystalline solid: ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.43−7.27 (m, 5H), 5.47 (br, 1H), 5.20−4.95 (m, 2H), 3.70−3.48 (m, 1H), 3.13 (ddd, J = 13.6, 9.1, 4.6 Hz, 1H), 2.56−2.32 (m, 2H), 2.25 (ddd, J = 14.0, 4.3, 2.8 Hz, 1H), 1.72 (ddd, J = 13.4, 6.0, 2.5 Hz, 1H), 1.65−1.42 (m, 2H), 1.42−1.09 (m, 10H), 1.06 (s, 3H), 0.98 (s, 3H), 0.88 (t, J = 6.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) 214.0 (CO), 156.3 (qC), 136.7 (qC), 128.5 (CH), 128.00 (CH), 127.97 (CH), 66.5 (CH_2), 53.5 (CH), 50.6 (CH), 41.5 (CH_2), 39.2 (CH_2), 38.6 (CH_2), 34.3 (qC), 31.7 (CH_2), 31.1 (CH_2), 30.4 (CH_2), 29.7 (CH_2), 29.2 (CH_3), 22.7 (CH_2), 19.8 (CH_3), 14.1 (CH_3); HPLC (OD-H, hexane/i-PrOH = 85:15, 0.6 mL min^{-1}) t_R 9.6 min, t_R 14.6 min; IR (ATR) ν_{max} (cm^{-1}) 3458, 3327 (m, N−H), 1702 (s, C═O). Anal. Calcd for $C_{23}H_{35}NO_3$: C, 73.96; H, 9.44; N, 3.75. Found: C, 74.19; H, 9.45; N, 3.61.

*Benzyl ((2-Ethyl-7-oxocycloheptyl)methyl)carbamate (**11**).* Following the general procedure for cyclic ketones with MeMgBr: colorless oil, diastereomeric mixture; ^{1}H NMR (600 MHz, $CDCl_3$, δ) signals for minor diastereomer are in italics: 7.39−7.27 (m, 5H), *5.19*; 5.18 (br, 1H), 5.11−5.02 (m, 2H), 3.45 (ddd, J = 13.6, 6.8, 3.4 Hz, 1H), 3.39−3.34 (m, 1H), 3.34−3.27 (m, 1H), *3.12−3.04* (m, 1H), 2.68−2.59 (m, 1H), *2.55−2.48* (m, 1H), 2.48−2.32 (m, 2H), *2.31−2.22* (m, 1H), *2.00−1.93* (m, 1H), 1.86−1.20 (m, 8H), *1.06−0.97* (m, 1H), 0.94 (t, J = 7.4 Hz, 3H), *0.85* (t, J = 7.3 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) signals for minor diastereomer are in italics: 215.3; *214.9* (qC−CO), 156.42; 156.41 (qC), *136.59*; 136.56 (qC), 128.5 (CH-Ph), 128.05; *128.03* (CH-Ph), 128.00 (CH-Ph), 66.59; *66.58* (CH_2), 56.8; *56.1* (CH), *43.9*; 42.5 (CH_2), 41.1; *40.8* (CH_2), *39.3*; 38.8 (CH), *32.4*; 29.74 (CH_2), 26.4 (CH_2), 24.8; *24.3* (CH_2), 23.73; *23.66* (CH_2), *21.0* (CH_2), *12.4*; 11.4 (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{18}H_{26}NO_3$ 304.1907, found 304.1881; HPLC (OJ-H, hexane/i-PrOH = 92:8, 0.7 mL min^{-1}) t_R(major-trans) 16.7 min, t_R(minor-trans) 18.0 min, t_R(cis − both enantiomers) 19.3 min; IR (ATR) ν_{max} (cm^{-1}) 3442 (m, N−H), 1694 (s, C═O).

General Procedure for One-Pot Reaction on Linear Ketones. (*R,R*)-Josiphos (19.2 mg, 0.03 mmol) and CuBr·SMe_2 (5.2 mg, 0.025 mmol) were dissolved in *t*-BuOMe, and the solution was stirred for 30 min at room temperature. The solution was then cooled to −75 °C, and ketone **12** (0.5 mmol) was added. After an additional 5 min of stirring, Grignard reagent (0.5 mmol) was added during 30 min and the resulting mixture was stirred for 1.5 h at −75 °C. A mixture of $CbzNHCH_2O$-*i*-Pr (89.3 mg, 0.4 mmol) and $TiCl_4$ (55 μL, 0.48 mmol) in CH_2Cl_2 (3 mL), which was stirred in another Schlenck tube for 2 h at −60 °C was added. The reaction temperature was then allowed to reach room temperature overnight. The reaction was then quenched with a few drops of satd solution of NH_4Cl and extracted with CH_2Cl_2. Combined organic extracts were concentrated. Column chromatography (SiO_2, Hex/AcOEt 4:1−6:1) of the residue afforded pure product (mixture of diastereoms) as colorless oil. Enantiomeric and diastereomeric ratio was determined by HPLC with chiral stationary phase and detected by UV at 211 nm.

*Benzyl 2-Acetyl-3-methylheptylcarbamate (**13**).* Following the general procedure for linear ketones with MeMgBr: colorless oil, diastereomeric mixture; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.28−7.39 (m, 5H), 4.95−5.15 (m, 3H), 3.36−3.49 (m, 1H), 3.20−3.35 (m, 1H), 2.68−2.79 (m, 1H), 2.15 (s, 3H), 1.11−1.51 (m, 7H), 0.99, *0.81*(d, J = 6.9 Hz, 3H), 0.84−0.96 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): *211.8*, 211.7 (CO); 156.3 (CONH); 136.5 (qC); 128.5; 128.1; 128.1 (CH); 66.6 (OCH_2); *58.2*, 57.2 (CH); *38.8*, 37.4 (NCH_2); 34.7,*32.9* (CH_2); *33.3*; 33.1 (CH); *30.7*, 29.7 (CH_3); *29.6*, *29.4* (CH_2); *22.70*, 22.67 (CH_2); *17.6*, 15.7 (CH_3); 14.04, *14.00* (CH_3); IR ($CHCl_3$) ν_{max} (cm^{-1}) 3454 (w, N−H), 1705 (s, C═O), 1513 (m, σ N−H), 1241 (m, C−O); HRMS (m/z) $[M + H]^+$ calcd for $C_{18}H_{28}NO_3$ 306.2064, found 306.2074.

*Benzyl 2-Acetyl-3-ethylheptylcarbamate (**14**).* Following the general procedure for linear ketones with EtMgBr: colorless oil; diastereomeric mixture. ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.28−7.39 (m, 5H), 4.99−5.11 (m, 2H), 4.85 (br s, 1H), 3.34−3.47 (m, 1H), 3.16−3.29 (m, 1H), 2.72−2.89 (m, 1H), 2.15 (s, 3H), 1.65−1.79 (m, 1H), 1.09−1.51 (m, 8H), 1.01 (t, J = 7.3 Hz, 3H) 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): *212.2*, 212.1 (CO); 156.3(CONH); 136.5 (C_q); 128.5(CH_{Ph}); 128.1(CH); 128.0 (CH); 66.6 (OCH_2); *55.4*, 55.2 (CH); 40.1; *40.0* (CH); *37.6*, 37.3; 30.8, *30.0*; 29.72, *29.67* (CH_2); 29.53, *29.50* (CH_3); *24.6*, 24.4; 22.8, *22.7* (CH_2); *14.1*, 14.0 (CH_3); 12.0, *11.9* (CH_3); HRMS (m/z) $[M + H]^+$ calcd for $C_{19}H_{30}NO_3$ 320.2220, found 320.2240; IR ($CHCl_3$) ν_{max} (cm^{-1}) 1455 (w, N−H), 1705 (s, CO), 1513 (m, σN−H), 1255 (w, C−O).

*Benzyl 2-Acetyl-3-butylnonylcarbamate (**15**).* Following the general procedure for linear ketones with HexMgBr: colorless oil, diastereomeric mixture; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.29−7.40 (m, 5H), 4.99−5.16 (m, 3H), 3.34−3.46 (m, 1H), 3.16−3.29 (m, 1H), 2.76−2.86 (m, 1H), 2.15 (s, 3H), 1.78 (m, 1H); 1.02−1.55 (m, 16H),

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0.92 (t, J = 7.3 Hz, 3H) 0.78−0.98 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 212.0 (CO); 156.3 (CONH); 136.5 (qC); 128.5; 128.1; 128.0 (CH); 66.6 (OCH_2); 55.6 (CH); 38.4 (CH); 31.8, *31.7*; *31.6*, 31.3; 30.6, *30.3*; 29.7, *29.6*; 29.58, *29.55* (CH_3); 29.5, *29.4*; *27.5*, 27.4; 24.6, *24.3*; 22.9, *22.7*; 22.7, *22.6*; *14.10*, 14.07 (CH_3); *14.0*, 13.8 (CH_3); HRMS (*m*/*z*) $[M + H]^+$ calcd for $C_{23}H_{38}NO_3$ 376.2846, found 376.2834; IR ($CHCl_3$) ν_{max} (cm^{-1}) 3455 (w, N−H), 1705 (s, CO), 1513 (m, σN−H), 1254 (w, C−O).

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra and HPLC chromatograms for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org/.

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