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Synthesis of 3-Phenyl-4-piperidones from Acetophenone by Shapiro and Aza-Michael Reactions and Their Further Derivatization

Anna Rosiak,[a][‡] Christoph Hoenke,[b] and Jens Christoffers*[a]

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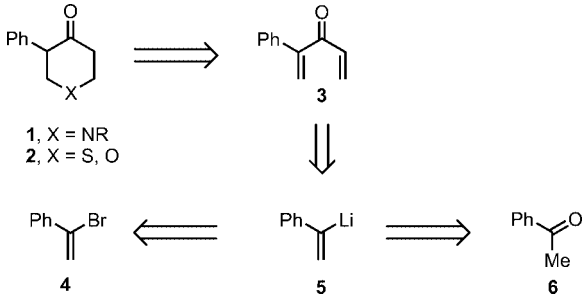
The Shapiro reaction of acetophenone is the key in a convenient three-step access to a divinyl ketone which is further transformed by double aza-Michael reactions with primary amines into *N*-substituted 3-phenyl-4-piperidones. In the case of *N*-benzyl and *N*-allyl derivatives, the piperidine nitrogen atom can be deprotected and further functionalized, for example, by carboxamide, carbamate, or urea formation.

Introduction

Successful drug development is dependent on the availability of functionalized heterocyclic building blocks with a broad variety of aromatic and heteroaromatic substituents. For example, 4-piperidinones **1** with an aromatic substituent in the 3-position are of enormous importance for the preparation of biologically active compounds, mostly with applications in medicinal chemistry.[1] Whereas the synthesis of 4-piperidone derivatives with various other substitution patterns is highly developed,[2] the preparation of congeners **1** (Scheme 1) with an aryl substituent in particular at the 3-position is almost unknown. Reliable procedures are so far only found in the patent literature.[3] The most prominent of these routes to *N*-substituted 3-aryl-4-piperidones **1** starts from 2-arylacetic acids and proceeds in several steps by α-methylenation, aza-Michael reaction, Dieckmann condensation, ester saponification and decarboxylation.[4] Since established methods for a direct α-arylation of cyclohexanones failed, largely due to E1cb eliminations in this heterocyclic series, we envisioned a double hetero-Michael reaction of divinyl ketone **3** to access these target compounds.[5] This idea is actually related to our recent work on tetrahydro-4-pyranones and -thiopyranones **2** which we have prepared by ring closure of divinyl ketone **3** with water or H_2S. In this context we have developed a short and scalable access to divinyl ketone **3** with an aryl substituent in the α-position which starts from α-bromostyrene (**4**) and proceeds via α-lithiostyrene (**5**).[6] However, bromo olefins like **4** with various residues in the aromatic moiety are not routinely accessible. In contrast to α-bromostyrenes, a broad variety of acetylbenzene derivatives and acetylated heteroaromatic compounds are readily available. Therefore, we report herein on an alternative route to ketone **3** which starts from acetophenone (**6**) and has a Shapiro reaction as the key step. Moreover, we will report on the utilization of building block **3** for the preparation of 3-phenyl-4-piperidones **1** with various *N*-substituents R by double aza-Michael reaction.



Scheme 1. Divinyl ketone **3** is accessed via α-lithiostyrene (**5**) from either α-bromostyrene (**4**) or more conveniently from acetophenone (**6**), the latter by Shapiro reaction. Compound **3** is the key building block for the preparation of 3-aryl-substituted heterocyclic ketones **1** and **2**.

Results and Discussion

Shapiro Reaction of Acetophenone

The transformation of phenylsulfonylhydrazones with at least 2 equiv. of *n*-butyllithium into lithiated alkenes is a convenient and reliable method for the synthesis of olefins from ketones.[7] When intermediate lithioalkenes such as **5** are converted with ketones or aldehydes, highly substituted

[a] Institut für Reine und Angewandte Chemie der Universität Oldenburg,
Carl von Ossietzky-Str. 9–11, 26111 Oldenburg, Germany
Fax: +49-441-798-3873
E-mail: jens.christoffers@uni-oldenburg.de
[b] Boehringer Ingelheim Pharma GmbH & Co. KG, Abteilung Chemische Forschung,
Birkendorfer Str. 65, 88397 Biberach an der Riß, Germany
[‡] New address: Degussa GmbH,
Rodenbacher Chaussee 4, 63457 Hanau-Wolfgang, Germany

allylic alcohols are obtained.[8] However, conversions with acrolein as a very reactive and, thus, problematic electrophile have, to the best of our knowledge, not been reported so far. And indeed, conversion of the common acetophenone *p*-tosylhydrazone (**7a**)[9] with acrolein yielded only 17% of allylic alcohol **8** after tedious optimization of the reaction conditions (Scheme 2). In the literature the utilization of mesitylsulfonylhydrazones is often recommended to give superior results. Therefore, we converted the corresponding hydrazone **7b**,[10] but again the results were not satisfying (33% yield) although the temperature at which N_2 evolution started was lower (5 °C instead of 23 °C). One of the major problems in Shapiro reactions is reported to be the *ortho*-lithiation of a phenylsulfonyl group or the α-lithiation of a mesitylsulfonyl moiety. To overcome this drawback it was suggested to use 2,4,6-triisopropylphenylsulfonylhydrazones ("trisylhydrazones") which are neither capable of α-lithiation nor *ortho*-lithiation.[11] The preparation of trisylhydrazine[12] and the corresponding hydrazone **7c**[13] of acetophenone are known and were well reproducible in our hands. To our delight, deprotonation of trisylhydrazone **7c** with 2.2 equiv. of *n*BuLi, subsequent nitrogen elimination and conversion with acrolein gave allylic alcohol **8** in 82% yield. Again, the temperature at which N_2 evolution started was lower (0 °C). The yield and the purity of the crude product after chromatography was better than that achieved in the preparation of alcohol **8** from α-bromostyrene **4** (78%).[6] Careful control of reaction temperatures and times is crucial for the success of these conversions which can be conveniently monitored by gas evolution upon nitrogen elimination. Optimal reaction conditions are listed in Table 1.

Table 1. Conditions and yields for the Shapiro reaction of hydrazones **7a**–**7c** giving allylic alcohol **8**.

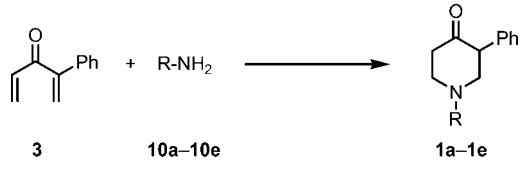
Hydrazone	Ar	Conditions[a]	Yield of **8**
7a	4-MeC_6H_4	1. –78 °C, 20 min 2. 23 °C, 20 min 3. –78 °C, 2 h	17%
7b	2,4,6-$Me_3C_6H_2$	1. –78 °C, 30 min 2. 5 °C, 30 min 3. 23 °C, 2 h	33%
7c	2,4,6-*i*$Pr_3C_6H_2$	1. –78 °C, 30 min 2. 0 °C, 15 min 3. –78 °C, 1 h	82%

[a] Steps: 1. addition of *n*BuLi; 2. nitrogen elimination; 3. addition and reaction with acrolein.

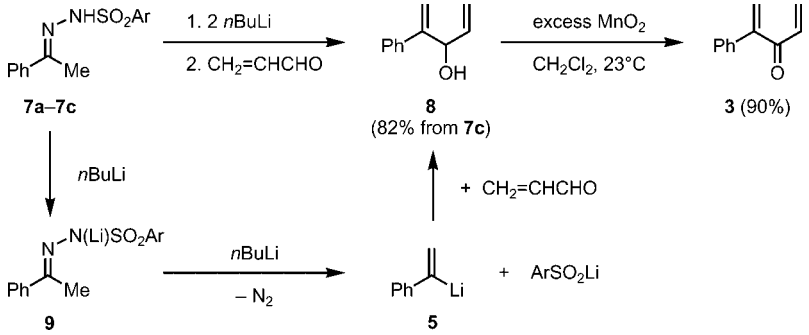
Further oxidation of alcohol **8** to ketone **3**, our key intermediate for heterocycle synthesis, was reported by us earlier.[6] A key feature of this step is the high reactivity and instability of compound **3**. It can neither be stored under ambient conditions nor at low temperatures and it cannot be purified by chromatography without loss of material and must therefore be directly converted after its preparation. For this reason, we utilized an excess of MnO_2 as a heterogeneous reagent which gives rapid conversion of alcohol **8** without the formation of any other soluble byproduct. The progress of the reaction is conveniently monitored by TLC and after full conversion has been achieved (10–60 min), the excess MnO_2 is simply removed by filtration through SiO_2 yielding about 90% of the crude divinyl ketone **3** which was used directly to yield piperidones without storage or purification.

Double Aza-Michael Reaction

Divinyl ketone **3** can be cyclized with a small excess of primary amines **10a**–**10d** as well as ammonia (**10e**) to afford the racemic 3-aryl-4-piperidones **1a**–**1e** (Scheme 3). Reaction conditions (solvent, temperature and time) were first optimized with benzylamine (**10a**). With MeCN as solvent and at 80 °C the yield of compound **1a** was 68% after a reaction time of 1.5 h (Table 2). Comparable yields were obtained with allylamine (**10b**) (73% of **1b**), aniline (**10c**) (55% of **1c**) and optically active α-phenylethylamine (**10d**) (62% of **1d**). The latter product was obtained as a mixture of two diastereoisomers (*dr* 1:1) which were not separated. Application of aqueous ammonia (**10e**) gave the *N*-unsubstituted product **1e**, however, in low yield, which could not be im-



Scheme 3. Ring closure of divinyl ketone **3** with amines **10** forming 3-aryl-4-piperidones **1**. For substituents R, conditions and yields see Table 2.



Scheme 2. Preparation of allylic alcohol **8** by Shapiro reaction and oxidation to divinyl ketone **3**. For residues Ar, the conditions and yields of the first step see Table 1.

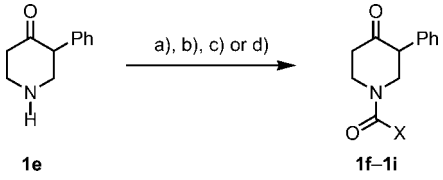
proved in our hands. In order to have direct access to the *N*-Boc-protected compound **1f** we tried to perform the cyclization with *tert*-butyl carbamate, which unfortunately failed completely.

Table 2. Conditions, products, and yields of double aza-Michael reactions of **3** with primary amines.

Product	Conditions	Yield
1a, R = Bn	80 °C, 1.5 h	68%
1b, R = Allyl	80 °C, 1.5 h	73%
1c, R = Ph	80 °C, 3 h; then 23 °C, 16 h	55%
1d, R = (*R*)-PhCH(CH_3)-	80 °C, 3 h; then 23 °C, 16 h	62% (*dr* 1:1)
1e, R = H	80 °C, 4 h	27%

N-Functionalization

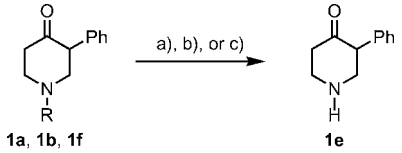
We were interested in whether the cyclic β-aminocarbonyl moiety in parent compound **1e** is stable under conditions of *N*-functionalization, namely, in carbamate, amide and urea formation. Conversion with Boc_2O under standard conditions furnished the *N*-Boc-protected compound **1f** in almost quantitative yield (Scheme 4, Table 3). DCC-mediated amide formation with diphenylacetic acid proceeded smoothly, however, the yield was somewhat lowered by chromatographic separation of the product **1g** (76%) from the dicyclohexylurea. Reaction of **1e** with PhNCO[14] gave urea **1h** in 84% yield after chromatographic purification. When treated with base and a solution of phosgene, "dimeric" urea **1i** was formed in 66% yield and as a mixture of two diastereoisomers (*dr* 1:1).



Scheme 4. *N*-Functionalization of piperidone **1e**. For reagents and conditions see Table 3.

N-Deprotection

Since the direct preparation of unsubstituted piperidone **1e** with ammonia **10e** was not satisfying at all, we decided to access this important intermediate by *N*-deprotection of the *N*-benzyl and *N*-allyl compounds **1a** and **1b**. The latter was achieved with catalytic amounts of $RhCl_3$ hydrate in $EtOH/H_2O$ at an elevated temperature,[15] however, the yield (56%) was not entirely satisfying. More successful was the hydrogenolytic cleavage of the *N*-benzyl group of compound **1a** with Pd/C and a drop of hydrochloric acid, which proceeded smoothly with 97% yield. Use of 2-propanol instead of ethanol as the solvent prevents ketal formation at the carbonyl group.[16] Finally, we showed that the *N*-Boc protective group installed in compound **1f** can be readily removed by a standard protocol[17] and in good yield (77%) (Scheme 5, Table 4).



Scheme 5. *N*-Deprotection yielding compound **1e**. For reagents and conditions see Table 4.

Conclusions

3-Aryl-substituted 4-piperidone derivatives **1** can be conveniently accessed by cyclization of divinyl ketone **3** with primary amines **10**. The *N*-unsubstituted compound **1e** is best prepared by hydrogenolysis of the benzyl derivative **1a** which proceeds in two steps and in 66% yield from **3**. *N*-Functionalization at the piperidine nitrogen atom as the carbamate, carboxamide or urea can be achieved without significant problems.

The Shapiro reaction of acetophenone is the method of choice for a convenient three-step access to key intermediate divinyl ketone **3**. This reaction proceeds with optimal results when the trisylhydrazone of acetophenone is uti-

Table 3. Products, reaction conditions and yields for the *N*-functionalization of piperidone **1e**.

Product	Reagents and conditions	Yield
1f, X = O*t*Bu	a) Boc_2O, cat. DMAP, MeOH, 23 °C, 30 min	98%
1g, X = $CHPh_2$	b) Ph_2CHCO_2H, DCC, CH_2Cl_2, 23 °C, 20 h	76%
1h, X = NHPh	c) PhNCO, toluene, 23 °C, 1 h	84%
1i, X = 4-oxo-3-phenyl-1-piperidyl	d) $COCl_2$, NEt_3, cat. DMAP, CH_2Cl_2, 0–10 °C, 3 h	66% (*dr* 1:1)

Table 4. Starting materials, reaction conditions and yields for the formation of piperidone **1e** by deprotection.

Starting material	Reagents and conditions	Yield of **1e**
1a, R = Bn	a) 1 atm H_2, cat. Pd/C, cat. HCl, *i*PrOH, 23 °C, 16 h	97%
1b, R = Allyl	b) cat. $RhCl_3$ hydrate, EtOH, H_2O, 90 °C, 5 h	56%
1f, R = Boc	c) TFA, CH_2Cl_2, 23 °C, 16 h	77%

lized. This method is superior with respect to purity and yield to a procedure published earlier starting from α-bromostyrene.

Experimental Section

General Methods: Preparative column chromatography was carried out using Merck SiO_2 (0.035–0.070 mm, type 60 A) with hexanes (PE, b.p. 40–60 °C) and ethyl acetate (EA) as eluents. TLC was performed on Merck SiO_2 F_{254} plates on aluminium sheets; we recommend use of molybdophosphoric acid reagent to visualize spots. ^1H and ^{13}C NMR spectra were recorded with Bruker Avance DRX 500, Avance DPX 300, and AC 250 spectrometers. Multiplicities were determined with DEPT experiments. EI-MS and HRMS data were obtained with a Finnigan MAT 95 spectrometer. IR spectra were recorded with a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond-ATR unit. Elemental analyses were performed with an EA 1108 from Fisons Instruments. All starting materials were commercially available except for hydrazones **7a**,[9] **7b**,[10] and **7c**[13] which were prepared according to literature procedures. Experimental data for compounds **3** and **8** were reported by us earlier.[6] Procedures using *n*BuLi (2 mol dm^{-3} solution in pentane, Aldrich) were performed in flame-dried glassware and with absolute solvents under nitrogen. Acrolein was freshly distilled prior to use. MnO_2 (active) was used as obtained from Fluka.

2-Phenyl-1,4-pentadien-3-ol (8): Under the exclusion of moisture and air, a solution of *n*BuLi (2.8 mL, 5.6 mmol, c = 2 mol dm^{-3} in pentane) was at –78 °C added dropwise to a solution of trisylhydrazone **7c** (1.00 g, 2.50 mmol) in abs. THF (8 mL). The resulting mixture was further stirred at –78 °C for 30 min, then warmed to 0 °C and stirred for 15 min at this temperature (rapid nitrogen evolution), and again cooled to –78 °C. Freshly distilled acrolein (520 mg, 9.3 mmol) was added and the resulting mixture subsequently stirred at –78 °C for 1 h. Finally, $NaHCO_3$ (15 mL sat. aqueous solution) was added and the mixture extracted with EA (3 × 20 mL). The combined organic layers were washed with brine (25 mL) and dried ($MgSO_4$). After filtration and evaporation of the solvent, the residual oil was purified by chromatography on SiO_2 [PE/EA, gradient elution from 5:1 to 2:1, R_f(5:1) = 0.35] to give the title compound **8** (327 mg, 2.04 mmol, 82%) as a colourless oil. All spectroscopic and analytical data are in accordance with the literature.[6]

2-Phenyl-1,4-pentadien-3-one (3): Active MnO_2 (3.41 g, 39.3 mmol) was added portionwise to a solution of **8** (300 mg, 1.87 mmol) in CH_2Cl_2 (10 mL) at ambient temperature. The progress of the reaction was monitored by TLC [product **3**: R_f(SiO_2, PE/EA = 5:1) = 0.44]. After being stirred for 20 min at 23 °C, the reaction mixture was filtered under vacuum through SiO_2 to separate MnO_2 and the residue was washed several times with acetone (total ca. 100 mL). The filtrate was concentrated under vacuum to give **3** as a yellow oil (280 mg, 1.77 mmol, 90%), which decomposes under ambient conditions. It can not even be stored at –5 °C. All spectroscopic and analytical data are in accordance with the literature.[6]

1-Benzyl-3-phenyl-4-piperidone (1a): $BnNH_2$ (**10a**) (400 mg, 3.73 mmol) was added to a solution of divinyl ketone **3** (400 mg, 2.53 mmol) in MeCN (3 mL). The mixture was stirred in a tightly closed reaction flask at 80 °C for 1.5 h, then water (20 mL) and CH_2Cl_2 (20 mL) were added, the layers were separated and the aqueous phase was extracted (CH_2Cl_2, 2 × 15 mL). The combined organic layers were dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue purified by chromatography on SiO_2 (PE/EA = 2:1, R_f = 0.25) to yield the title compound **1a** (454 mg, 1.71 mmol, 68%) as a light yellow solid, m.p. 56–58 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.48–2.53 (m, 1 H), 2.61–2.69 (m, 2 H), 2.77 (dd, J = 11.5, J = 10.1 Hz, 1 H), 3.05–3.08 (m, 1 H), 3.17 (ddd, J = 11.5, J = 5.7, J = 2.4 Hz, 1 H), 3.65 (s, 2 H), 3.80 (dd, J = 9.8, J = 5.7 Hz, 1 H), 7.20–7.37 (m, 10 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 40.76 (CH_2), 53.50 (CH_2), 56.40 (CH), 59.78 (CH_2), 61.98 (CH_2), 127.20 (CH), 127.40 (CH), 128.41 (2 CH), 128.43 (2 CH), 128.93 (2 CH), 128.96 (2 CH), 136.76 (C), 137.93 (C), 208.10 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3060 (w), 3028 (w), 2904 (w), 2804 (w, br.), 1717 (vs), 1602 (w), 1494 (m), 1453 (m), 1353 (m), 1183 (w), 1126 (w), 736 (w), 699 (m) cm^{-1}. MS (EI, 70 eV): m/z (%) = 265 (93) [M]$^+$, 174 (9), 146 (12), 118 (10), 104 (29), 91 (100), 65 (9), 42 (14). $C_{18}H_{19}NO$ (265.35): calcd. C 81.48, H 7.22, N 5.27; found C 81.08, H 7.25, N 5.28.

1-Allyl-3-phenyl-4-piperidone (1b): Allylamine (**10b**) (160 mg, 2.80 mmol) was added to a solution of divinyl ketone **3** (300 mg, 1.89 mmol) in MeCN (4 mL). The mixture was stirred in a tightly closed reaction flask at 80 °C for 1.5 h, then water (20 mL) and EA (20 mL) were added, the layers were separated and the aqueous phase was extracted (EA, 20 mL). The combined organic layers were dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue purified by chromatography on SiO_2 (PE/EA = 1:2, R_f = 0.31) to yield the title compound **1b** (297 mg, 1.38 mmol, 73%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.48–2.76 (m, 4 H), 3.09–3.24 (m, 4 H), 3.80 (dd, J = 10.4, J = 5.7 Hz, 1 H), 5.19 (dm, J = 10.1 Hz, 1 H), 5.22 (dq, J = 17.1, J = 1.6 Hz, 1 H), 5.92 (ddt, J = 17.1, J = 10.6, J = 6.1 Hz, 1 H), 7.19–7.36 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (62 MHz, $CDCl_3$): δ = 40.78 (CH_2), 53.54 (CH_2), 56.38 (CH), 59.83 (CH_2), 60.57 (CH_2), 118.45 (CH_2), 127.24 (CH), 128.44 (2 CH), 128.94 (2 CH), 134.72 (CH), 136.66 (C), 207.89 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3028 (w), 2906 (w), 2793 (m), 1717 (vs), 1642 (w), 1602 (w), 1495 (w), 1453 (w), 1418 (w), 1345 (w), 1188 (m, br.), 1124 (m), 993 (w), 923 (w), 699 (m) cm^{-1}. MS (EI, 70 eV): m/z (%) = 215 (100) [M]$^+$, 118 (13), 104 (63), 96 (20), 91 (13), 82 (27), 42 (21). HRMS (EI, 70 eV): calcd. for $C_{14}H_{17}NO$ [M]$^+$ 215.1310; found 215.1310.

1,3-Diphenyl-4-piperidone (1c): Aniline (**10c**) (106 mg, 1.14 mmol) was added to a solution of divinyl ketone **3** (150 mg, 0.95 mmol) in MeCN (2 mL). The mixture was stirred in a tightly closed reaction flask at 80 °C for 3 h and at 23 °C for 16 h, then water (10 mL) and EA (15 mL) were added, the layers were separated and the aqueous phase was extracted (EA, 10 mL). The combined organic layers were dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue purified by chromatography on SiO_2 (PE/EA = 5:1, R_f = 0.21) to yield the title compound **1c** (131 mg, 0.52 mmol, 55%) as a yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.58 (dt, J = 14.5, J = 4.4 Hz, 1 H), 2.67–2.74 (m, 1 H), 3.44 (ddd, J = 13.0, J = 10.9, J = 4.3 Hz, 1 H), 3.50 (dd, J = 13.7, J = 10.9 Hz, 1 H), 3.82 (dd, J = 10.5, J = 6.2 Hz, 1 H), 3.94–4.22 (m, 2 H), 6.87–6.90 (m, 1 H), 6.98–7.00 (m, 2 H), 7.17–7.22 (m, 2 H), 7.27–7.36 (m, 5 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 40.14 (CH_2), 49.24 (CH_2), 55.60 (CH_2), 55.74 (CH), 115.69 (2 CH), 119.88 (CH), 127.43 (CH), 128.59 (2 CH), 128.81 (2 CH), 129.52 (2 CH), 136.07 (C), 148.70 (C), 207.02 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3027 (w), 2821 (w, br.), 1714 (vs), 1599 (vs), 1498 (vs), 1453 (w), 1383 (w), 1283 (w), 1214 (m), 1032 (w), 994 (w), 753 (m), 698 (m) cm^{-1}. MS (EI, 70 eV): m/z (%) = 251 (100) [M]$^+$, 147 (19), 132 (16), 118 (13), 105 (63), 77 (15). HRMS (EI, 70 eV): calcd. for $C_{17}H_{17}NO$ [M]$^+$ 251.1310; found 251.1308.

3-Phenyl-1-[(*R*)-1-phenylethyl]-4-piperidone (1d): (+)-[(*R*)-1-Phenylethyl]amine (**10d**) (230 mg, 1.90 mmol) was added to a solution

of divinyl ketone **3** (200 mg, 1.26 mmol) in MeCN (2 mL). The mixture was stirred in a tightly closed reaction flask at 80 °C for 3 h and at 23 °C for 16 h, then water (15 mL) and EA (15 mL) were added, the layers were separated and the aqueous phase extracted (EA, 10 mL). The combined organic layers were dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue purified by chromatography on SiO_2 (PE/EA = 2:1, R_f = 0.38) to yield the title compound **1d** (217 mg, 0.78 mmol, 62%) as a yellow oil, which was a mixture of two optically active diastereoisomers (*dr* 1:1 according to ^1H NMR). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.43 (d, J = 6.7 Hz, 3 H), 1.44 (d, J = 6.5 Hz, 3 H), 2.43–2.52 (m, 2 H), 2.55–2.66 (m, 4 H), 2.71 (t, J = 10.4 Hz, 1 H), 2.76 (t, J = 10.4 Hz, 1 H), 3.04–3.08 (m, 1 H), 3.11–3.14 (m, 1 H), 3.17 (ddd, J = 11.6, J = 5.5, J = 2.7 Hz, 1 H), 3.27 (ddd, J = 11.6, J = 5.5, J = 2.7 Hz, 1 H), 3.67 (q, J = 6.9 Hz, 1 H), 3.68 (q, J = 6.9 Hz, 1 H), 3.74 (dd, J = 10.0, J = 5.6 Hz, 1 H), 3.79 (dd, J = 10.0, J = 5.7 Hz, 1 H), 7.19–7.36 (m, 20 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 19.12 (CH_3), 19.30 (CH_3), 40.92 (CH_2), 41.04 (CH_2), 50.41 (CH_2), 50.71 (CH_2), 56.60 (CH), 56.74 (CH), 56.89 (CH_2), 57.06 (CH_2), 63.34 (CH), 63.44 (CH), 127.11 (CH), 127.15 (CH), 127.17 (CH), 127.19 (CH), 127.32 (2 CH), 127.40 (2 CH), 128.35 (4 CH), 128.36 (4 CH), 128.91 (2 CH), 128.98 (2 CH), 136.93 (C), 136.96 (C), 142.99 (C), 143.11 (C), 208.27 (C=O), 208.30 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3027 (w), 2970 (w), 2802 (w), 1714 (vs), 1601 (w), 1492 (m), 1451 (m), 1414 (w), 1207 (m), 1127 (m), 1080 (w), 1031 (w), 763 (m), 698 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 279 (87) $[M]^+$, 264 (26), 175 (17), 105 (100), 91 (6), 77 (8). HRMS (EI, 70 eV): calcd. for $C_{19}H_{21}NO$ $[M]^+$ 279.1623; found 279.1623.

3-Phenyl-4-piperidone (1e)

(a) By Ring Closure with Ammonia: Ammonia (**10e**) (10 mmol, 680 mg of a 25% aqueous solution) was added to a solution of divinyl ketone **3** (680 mg, 4.30 mmol) in MeCN (4.5 mL). The mixture was stirred in a tightly closed reaction flask at 80 °C for 4 h, then water (10 mL) and CH_2Cl_2 (15 mL) were added, the layers were separated and the aqueous phase was extracted (CH_2Cl_2, 3 × 10 mL). The combined organic layers were dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue purified by chromatography on SiO_2 (MeOH/EA = 9:1, R_f = 0.25) to yield the title compound **1e** (202 mg, 1.15 mmol, 27%) as a light yellow solid, m.p. 97–98 °C.

(b) By Hydrogenation of 1a: A mixture of benzylpiperidone **1a** (100 mg, 0.38 mmol), Pd/C (5% Pd, 40 mg), concd. hydrochloric acid (ca. 0.02 mL) and *i*PrOH (5 mL) was degassed (three cycles of freeze, pump and thaw) and then stirred at 23 °C under 1 atm of H_2 for 16 h. After filtering off the catalyst (washing with MeOH) and evaporation of the solvent, the residue was suspended in CH_2Cl_2 (20 mL) and washed with $NaHCO_3$ (20 mL satd. aqueous solution). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$). After filtration, the solvent was evaporated to yield the title compound **1e** (65 mg, 0.37 mmol, 97%) as a light yellow solid.

(c) By *N*-Deallylation of 1b: $RhCl_3 \cdot 2.3H_2O$ (18 mg, 72 μmol) was added to a solution of allylpiperidone **1b** (100 mg, 0.46 mmol) in EtOH/H_2O (2 mL/1.5 mL). The mixture was stirred in a tightly closed reaction flask at 90 °C for 5 h, then water (5 mL), $NaHCO_3$ (10 mL satd. aqueous solution) and CH_2Cl_2 (15 mL) were added, the layers were separated and the aqueous phase was extracted (CH_2Cl_2, 3 × 10 mL). The combined organic layers were dried ($MgSO_4$). After filtration, the solvent was evaporated and the residue purified by chromatography on SiO_2 (MeOH/EA = 9:1, R_f = 0.25) to yield the title compound **1e** (45 mg, 0.26 mmol, 56%) as a yellow solid.

(d) By Boc Cleavage of 1f: A mixture of *N*-Boc-piperidone **1f** (35 mg, 0.13 mmol), CH_2Cl_2 (1 mL) and TFA (0.2 mL) was stirred at 23 °C for 16 h, then CH_2Cl_2 (5 mL) and $NaHCO_3$ (20 mL satd. aqueous solution) were added. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (20 mL). After drying ($MgSO_4$) and filtration, the combined organic layers were concentrated to yield the product **1e** (18 mg, 0.10 mmol, 77%) as a light yellow solid which was pure according to ^1H NMR and did not need further purification. ^1H NMR (250 MHz, $CDCl_3$): δ = 1.84 (br. s, 1 H,), 2.50–2.58 (m, 2 H), 3.15–3.18 (m, 1 H), 3.18 (dd, J = 12.4, J = 10.2 Hz, 1 H), 3.40–3.55 (m, 2 H), 3.67 (dd, J = 10.9, J = 5.8 Hz, 1 H), 7.16–7.19 (m, 2 H), 7.23–7.38 (m, 3 H) ppm. $^{13}C\{^1H\}$ NMR (62 MHz, $CDCl_3$): δ = 43.38 (CH_2), 47.92 (CH_2), 54.31 (CH_2), 59.33 (CH), 127.24 (CH), 128.51 (2 CH), 128.81 (2 CH), 136.38 (C), 207.87 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3332 (m), 2956 (w), 2899 (w), 2801 (m), 1700 (vs), 1601 (w), 1452 (m), 1355 (w), 1322 (w), 1221 (m), 1161 (m), 1143 (m), 1070 (w), 920 (m), 833 (m), 766 (vs), 741 (m), 701 (vs) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 175 (69) $[M]^+$, 118 (7), 104 (100), 84 (13), 77 (6), 56 (11), 42 (42). $C_{11}H_{13}NO$ (175.23): calcd. C 75.39, H 7.48, N 7.99; found C 75.10, H 7.58, N 7.71.

***tert*-Butyl 4-Oxo-3-phenylpiperidine-1-carboxylate (1f):** A solution of Boc_2O (90 mg, 0.41 mmol) in MeOH (0.7 mL) was added dropwise to a solution of piperidone **1e** (70 mg, 0.40 mmol) and DMAP (2 mg, 16 μmol) in MeOH (1 mL). After stirring the mixture at ambient temperature for 30 min, the solvent was evaporated and the residue purified by chromatography on SiO_2 (PE/EA = 2:1, R_f = 0.38) to yield the title compound **1f** (107 mg, 0.39 mmol, 98%) as a colourless solid, m.p. 93–94 °C. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.50 (s, 9 H), 2.51–2.61 (m, 2 H), 3.48–3.55 (m, 1 H), 3.50–3.66 (br. s, 1 H), 3.67–3.74 (m, 1 H), 4.12–4.20 (m, 1 H), 4.15–4.39 (br. s, 1 H), 7.17–7.21 (m, 2 H), 7.28–7.39 (m, 3 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 28.37 (3 CH_3), 40.60 (CH_2), 43.49 (br., CH_2), 49.23 (br., CH_2), 56.31 (CH), 80.63 (C), 127.52 (CH), 128.56 (2 CH), 128.64 (2 CH), 135.52 (C), 154.39 (C=O), 206.99 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 2979 (w), 1714 (m), 1683 (s), 1477 (m), 1458 (w), 1421 (m), 1365 (m), 1309 (m), 1279 (w), 1161 (s, br.), 1123 (m), 1047 (m), 974 (w), 869 (m), 701 (s) cm^{-1}. MS (EI, 70 eV): *m*/*z* (%) = 275 (21) $[M]^+$, 202 (13), 175 (37), 104 (87), 84 (10), 57 (100), 41 (14). $C_{16}H_{21}NO_3$ (275.35): calcd. C 69.79, H 7.69, N 5.09; found C 69.50, H 7.89, N 4.96.

1-(Diphenylacetyl)-3-phenyl-4-piperidone (1g): DCC (60 mg, 0.29 mmol) and diphenylacetic acid (62 mg, 0.29 mmol) were added to a solution of piperidone **1e** (50 mg, 0.29 mmol) in CH_2Cl_2 (2.5 mL). The mixture was stirred at ambient temperature for 20 h, then the solvent was evaporated and the residue purified by chromatography twice on SiO_2 (PE/EA = 1:1, R_f = 0.46) to yield the title compound **1g** (81 mg, 0.22 mmol, 76%) as a colourless oil. A doubled signal set is observed in the NMR spectra which is due to two rotamers (A/B = 1:0.7 according to ^1H NMR integration). ^1H NMR (500 MHz, $CDCl_3$); isomer A: δ = 2.54–2.57 (m, 2 H), 2.86 (dd, J = 11.2, J = 6.0 Hz, 1 H), 3.19–3.28 (m, 1 H), 3.53 (dd, J = 13.6, J = 11.3 Hz, 1 H), 4.22 (ddd, J = 13.7, J = 6.0, J = 2.7 Hz, 1 H), 4.84–4.89 (m, 1 H), 5.27 (s, 1 H), 6.71–6.74 (m, 2 H), 7.15–7.44 (m, 13 H) ppm; isomer B: δ = 2.04 (ddd, J = 15.0, J = 9.7, J = 5.8 Hz, 1 H), 2.26 (dt, J = 15.0, J = 4.7 Hz, 1 H), 3.62 (ddd, J = 13.6, J = 9.7, J = 4.2 Hz, 1 H), 3.67–3.73 (m, 2 H), 4.02 (ddt, J = 13.5, J = 2.0, J = 5.5 Hz, 1 H), 4.57–4.64 (m, 1 H), 5.30 (s, 1 H), 7.15–7.44 (m, 15 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$); isomer A: δ = 40.64 (CH_2), 42.23 (CH_2), 51.71 (CH_2), 55.11 (CH), 56.60 (CH), 127.12 (CH), 127.70 (2 CH), 128.38 (2 CH), 128.59 (2 CH), 128.72 (2 CH), 128.81 (2 CH), 129.10 (2 CH), 129.38 (2 CH), 134.82 (C), 138.56 (C), 139.13 (C), 170.47 (C=O),

205.85 (C=O) ppm; isomer B: δ = 40.11 (CH_2), 45.15 (CH_2), 47.07 (CH_2), 55.13 (CH), 55.86 (CH), 127.21 (CH), 127.44 (CH), 127.60 (CH), 128.44 (2 CH), 128.62 (2 CH), 128.69 (2 CH), 128.86 (2 CH), 128.87 (2 CH), 128.92 (2 CH), 134.96 (C), 138.78 (C), 138.91 (C), 170.64 (C=O), 206.25 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3027 (w), 2871 (w), 1714 (s), 1639 (vs), 1600 (m), 1494 (m), 1451 (m), 1427 (m, br.), 1366 (m), 1210 (m), 1125 (w), 1080 (w), 1057 (w), 1002 (w), 827 (m), 743 (m), 694 (vs), 610 (m) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 369 (38) $[M]^+$, 202 (62), 167 (100), 104 (12), 28 (29). HRMS (EI, 70 eV): calcd. for $C_{25}H_{23}NO_2$ $[M]^+$ 369.1729; found 369.1727.

3-Phenyl-1-(phenylaminocarbonyl)-4-piperidone (1h): PhNCO (68 mg, 0.65 mL, 0.57 mmol) was added to a solution of piperidone **1e** (100 mg, 0.57 mmol) in toluene (1 mL). The resulting mixture was stirred at 23 °C for 1 h, then water (5 mL) was added and the mixture extracted with EA (2 × 10 mL). The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated after filtration. The residue was purified by chromatography on SiO_2 [PE/EA, gradient elution from 5:1 to 2:1, R_f(2:1) = 0.17] to give the title compound **1h** (140 mg, 0.48 mmol, 84%) as a colourless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.64–2.74 (m, 2 H), 3.63–3.68 (m, 2 H), 3.80–3.83 (m, 1 H), 4.16–4.18 (m, 1 H), 4.26 (dd, *J* = 13.0, *J* = 5.4 Hz, 1 H), 6.54 (s, 1 H), 7.07 (t, *J* = 7.1 Hz, 1 H), 7.18 (d, *J* = 7.4 Hz, 1 H), 7.29–7.38 (m, 8 H) ppm. $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ = 40.45 (CH_2), 43.59 (CH_2), 49.52 (CH_2), 56.04 (CH), 120.17 (2 CH), 123.63 (CH), 127.80 (CH), 128.60 (2 CH), 128.81 (2 CH), 128.99 (2 CH), 135.16 (C), 138.50 (C), 154.68 (C=O), 206.27 (C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3314 (w, br.), 3031 (w), 2873 (w), 1713 (s), 1637 (s), 1595 (s), 1530 (vs), 1498 (m), 1442 (s), 1384 (m, br.), 1310 (m), 1236 (s), 1156 (w), 1133 (m), 1076 (m), 1024 (m), 998 (m), 966 (m), 922 (m), 750 (s), 693 (vs) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 294 (14) $[M]^+$, 175 (100), 119 (14), 104 (91), 84 (12). HRMS (EI, 70 eV): calcd. for $C_{18}H_{18}N_2O_2$ $[M]^+$ 294.1368; found 294.1368.

1,1′-Carbonylbis(4-oxo-3-phenylpiperidine) (1i): Under nitrogen a solution of $COCl_2$ (0.28 mL, 0.55 mmol, *c* = 2.0 mol dm^{-3} in toluene), NEt_3 (111 mg, 1.1 mmol) and DMAP (1 mg, 8 μmol) were added to a cooled (ice/water bath) solution of piperidone **1e** (180 mg, 1.0 mmol) in abs. CH_2Cl_2 (3.5 mL). After stirring at 23 °C for 3 h, the mixture was poured into water (15 mL) and extracted with CH_2Cl_2 (4 × 10 mL). After drying ($MgSO_4$) and filtration, the solvent was evaporated and the residue purified by chromatography (SiO_2, PE/EA = 1:2, R_f = 0.67) to give the title compound **1i** (123 mg, 0.33 mmol, 66%) as a yellow oil, which consisted of two racemic diastereoisomers (1:1 according to ^1H NMR). ^1H NMR (300 MHz, $CDCl_3$): δ = 2.61 (t, *J* = 5.6 Hz, 4 H), 3.52–3.78 (m, 6 H), 4.27–4.43 (m, 4 H), 7.07–7.10 (m, 4 H), 7.25–7.35 (m, 6 H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 39.82 (CH_2), 40.11 (CH_2), 44.97 (CH_2), 47.45 (CH_2), 50.03 (CH_2), 52.80 (CH_2), 55.40 (CH), 55.92 (CH), 127.98 (2 CH), 128.42 (2 CH), 128.86 (6 CH), 134.20 (2 C), 148.60 (C=O), 204.58 (2 C=O) ppm. IR (ATR): $\tilde{\nu}$ = 3031 (w), 2888 (w, br.), 1717 (vs), 1644 (w), 1498 (w), 1467 (w), 1453 (w), 1408 (m), 1383 (m), 1269 (w), 1222 (m), 1204 (m), 1178 (m), 1082 (w), 1049 (m), 854 (w), 764 (w), 701 (m), 662 (m), 631 (s) cm^{-1}. MS (EI, 70 eV): *m/z* (%) = 376 (22) $[M]^+$, 272 (6), 202 (68), 175 (21), 146 (16), 104 (100), 77 (34). HRMS (EI, 70 eV): calcd. for $C_{23}H_{24}N_2O_3$ $[M]^+$ 376.1787; found 376.1787.

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