Stereoselective Synthesis of *meso*- and *cis*-2,6-Diarylpiperidin-4-ones Catalyzed by L-Proline

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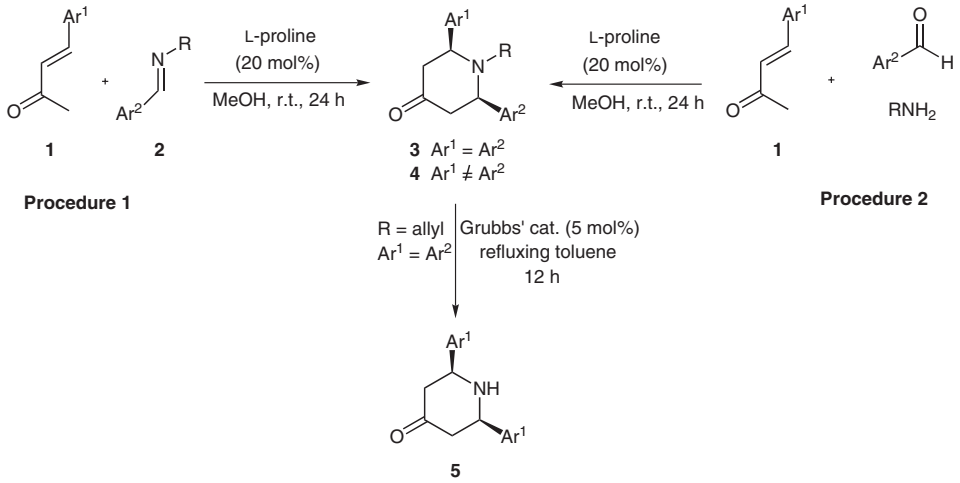
Abstract: A convenient stereoselective preparation of *meso*- and *cis*-2,6-diarylpiperidin-4-ones has been developed by aza-Diels–Alder reaction catalyzed by L-proline from simple and commercially available starting materials.

Key words: 2,6-diarylpiperidin-4-ones, organocatalysis, L-proline, aza-Diels–Alder, nitrogen heterocycles



Scheme 1

Introduction

The piperidine ring is an important framework present in a large variety of natural products.[1] In particular, piperidin-4-ones are versatile building blocks due to the easy manipulation of the carbonyl group for the introduction of different substituents into the six-membered ring.[2] Substitution at the C2 and C6 positions are very frequent and in some cases biological activity studies have shown a relationship between the biological activity and the aromatic rings present in those positions.[3] Even though synthesis of piperidin-4-ones is still a very important theme of research and several synthetic methods have been developed,[2b,c] the number of references for the synthesis of 2,6-disubstituted piperidin-4-ones are remarkably fewer and, in particular, in the case of 2,6-diarylpiperidin-4-ones very few methodologies can be found in the literature.[4] Moreover some of these methods suffer from several drawbacks such as restrictions in the choice of substituents, low yields, and elaborated starting materials. Over the past few years organocatalysis has become very popular for a wide range of enantioselective transformations. In particular, L-proline has been reported to catalyzed asymmetric aldol, Michael, Mannich, α-amination, Diels–Alder dimerization, and aza-Diels–Alder reactions with cyclic enones.[5] As part of our ongoing interests in the synthesis of piperidin-4-ones with high stereoselectivity employing the aza-Diels–Alder reaction of 2-aminobuta-1,3-dienes with unactivated aldimines,[6] we decided to combine our experience in this field and use organocatalysis to described a new synthesis of 2,6-disubstituted piperidin-4-ones by the aza-Diels–Alder reaction between an acyclic enone and an aldimine (or an aldehyde and an amine as a multi-component reaction) in the presence of L-proline as catalyst, without preformation of the aminodienes.[7] We describe here the development of an efficient single-step synthesis of a wide range of *meso*-or *cis*-N-substituted or N-unsubstituted 2,6-diarylpiperidin-4-ones **3**–**5** in good yields and high diastereoselectivity (Scheme 1). An

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attractive feature of this chemistry includes the one-pot, three-component, aza-Diels–Alder reaction.

Scope and Limitations

The optimal reaction conditions were as follows: commercially available (*E*)-4-phenylbut-3-en-2-one (**1a**, 4 mmol) and *N*-allylbenzaldimine (1 mmol) were mixed in the presence of a catalytic amount of L-proline (20 mol%) in methanol (1.5 mL). After vigorously stirring the mixture for 24 hours, the reaction was subjected to extraction and the crude product was purified by column chromatography on silica gel to furnish (2*R**,6*S**)-1-allyl-2,6-diphenylpiperidin-4-one (**3a**) in 77% yield with >93% diastereoselectivity. Solvent effects were studied for this reaction and neither anhydrous solvents nor use of inert atmosphere conditions were found to be necessary. When the reaction was performed in dimethyl sulfoxide and acetonitrile the yield decreased considerably (25% and 5%, respectively) and when other solvents were used (THF, $CHCl_3$, DMF, EtOAc, dioxane, toluene) only starting material was recovered from the reaction mixture under the same reaction conditions. Another important factor was the reaction temperature. The experiments were run from –20 °C to 40 °C and we found that those conducted at room temperature (23–25 °C) afforded higher yields, while at 40 °C some decomposition products were observed. The concentration of substrate also affects the yield of the reaction. Among all the different molar ratio of α,β-unsaturated ketone/imine (1:1; 2:1; 4:1, 6:1) tested, the best yield was found with a 4:1 ratio. The use of an excess of ketone is not an inconvenience since products **3** and **4** can be easily separated out by an acid–base extraction workup in almost all the examples (except **3h**–**k**, see experimental section for details). Two other secondary amines were also tested as the catalyst, (*S*)-2-(methoxymethyl)pyrrolidine and (*S*)-1-(pyrrolidin-2-ylmethyl)pyrrolidine but in these cases the reaction did not proceed, however, in the presence of 4-toluenesulfonic acid (20 mol%), **3a** was obtained in lower yield (58% and 61% respectively). Thus, of the three catalysts screened, L-proline was the most efficient.

This methodology, under the optimized conditions, was extended to the synthesis of a variety of *meso*-2,6-diarylpiperidin-4-ones **3a**–**k** with excellent diastereoselectivities and good yields (Table 1). The reaction is fairly general with regards to the structure of the aryl substituent, both electron-rich (Table 1, entries 6 and 7) and electron-poor (Table 1, entries 8–11) aryl groups can be utilized. However, the outcome of the cycloaddition is greatly affected by the N-substituent of the imine; with *N*-aryl (Ph, 4-$MeOC_6H_4$, Table 1, entries 4 and 5) and *N*-alkylimines (but-3-enyl, Bu, Table 1, entries 2 and 3) we observed low conversion, but still high diastereoselectivities.

We also investigated the application of this methodology using different aryl substituents on the α,β-unsaturated ketone and imine. In all cases examined, we obtained from the reaction mixture the *cis*-2,6-disubstituted piperidin-4-ones **4** as one diastereomer (Table 2) but, unfortunately, the reaction lacked promising enantioselectivity (by HPLC analysis).

An important novelty and advantage of this methodology is that the one-pot, three-component aza-Diels–Alder reaction was also successful (procedure 2). Thus, 4-phenylbut-3-en-2-one **1** (4 mmol, 4 equiv) was added to a

Table 1 1-Substituted *meso*-2,6-Diarylpiperidin-4-ones **3** Prepared

Entry	Product				Yield[a] (%)		dr[b]
	Ar^1	Ar^2	R		Proc. 1	Proc. 2	
1	Ph	Ph	$CH_2CH{=}CH_2$	**3a**	77	79	93:7
2	Ph	Ph	$(CH_2)_2CH{=}CH_2$	**3b**	59	–	97:3
3	Ph	Ph	*n*-Bu	**3c**	23	–	97:3
4	Ph	Ph	Ph	**3d**	22	–	90:10
5	Ph	Ph	4-$MeOC_6H_4$	**3e**	21	14	90:10
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	$CH_2CH{=}CH_2$	**3f**	40	55	96:4
7	3,4-$(MeO)_2C_6H_3$	3,4-$(MeO)_2C_6H_3$	$CH_2CH{=}CH_2$	**3g**	42	–	96:4
8	4-FC_6H_4	4-FC_6H_4	$CH_2CH{=}CH_2$	**3h**	66	–	95:5
9	4-ClC_6H_4	4-ClC_6H_4	$CH_2CH{=}CH_2$	**3i**	64	–	97:3
10	2-BrC_6H_4	2-BrC_6H_4	$CH_2CH{=}CH_2$	**3j**	66	61	96:4
11	2-IC_6H_4	2-IC_6H_4	$CH_2CH{=}CH_2$	**3k**	67	–	96:4

[a] Isolated yield after chromatographic purification.
[b] Determined by ^1H NMR of the crude reaction mixture.

Table 2 *cis*-1-Allyl-2,6-diarylpiperidin-4-ones **4** Prepared

Entry	Product				Yield[a] (%)		dr[b]
	Ar^1	Ar^2	R		Proc. 1	Proc. 2	
1	Ph	4-$MeOC_6H_4$	$CH_2CH{=}CH_2$	**4a**	47	48	95:5
2	Ph	4-FC_6H_4	$CH_2CH{=}CH_2$	**4b**	59	68	95:5
3	Ph	4-ClC_6H_4	$CH_2CH{=}CH_2$	**4c**	61	15	98:2
4	Ph	2-BrC_6H_4	$CH_2CH{=}CH_2$	**4d**	–	15	98:2

[a] Isolated yield after chromatographic purification.
[b] Determined by ^1H NMR of the crude reaction mixture.

mixture of an aromatic aldehyde (1 mmol, 1 equiv), allylamine (1.1 mmol, 1.1 equiv), and L-proline (20 mol%) in methanol (2 mL). After stirring the mixture for 24 hours, the mixture was subjected to acid–base extraction workup and the crude product was purified by column chromatography, furnishing the products with yields (except **4c**,**d**) and diastereoselectivities similar to those observed for the corresponding reaction with preformed aldimines (Table 1, entries 1, 5, 6, 10 and Table 2, entries 1–4).

Fortunately, the best results were obtained for *N*-allyl-substituted imines, which have the additional advantage that the allyl group can be easily removed after the cycloaddition providing the N-unsubstituted *meso*-2,6-diarylpiperidin-4-ones **5** in good yields[8] (Table 3).

Table 3 *meso*-2,6-Diarylpiperidin-4-ones **5** Prepared

Entry	Product		Yield[a] (%)
	Ar^1		
1	Ph	**5a**	67
2	4-$MeOC_6H_4$	**5b**	68
3	4-FC_6H_4	**5c**	70
4	2-IC_6H_4	**5d**	63

[a] Isolated yield after chromatographic purification.

Herein we describe two general procedures for the different substrate classes depicted in Scheme 1 and in Tables 1– 3. Compound **4d** has not been previously described; for the other compounds, see ref. 7.

1-Substituted *meso*-2,6-Diarylpiperidin-4-ones 3a–k and *cis*-1-Allyl-2-aryl-6-phenylpiperidin-4-ones 4a–d; General Procedure

Procedure 1

Method A: To a mixture of α,β-unsaturated ketone **1**[9] (4 mmol, 4 equiv) and L-proline (20 mol%) in MeOH (1.5 mL or 5 mL in the case of **1e**,**f**) was added imine **2**[10] (1 mmol, 1 equiv) and the mixture was allowed to stir at r.t. for 24 h. Then, the solvent (MeOH) was evaporated under reduce pressure and the mixture was subject to an acid–base extraction workup to eliminated the excess of ketone **1**. EtOAc (10 mL) was added to the reaction crude and the organic layer was washed with 1 M HCl (3 × 5 mL). The aqueous layers were combined and 1 M NaOH (25 mL) was added rapidly and the mixture extracted thoroughly with EtOAc (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, mixtures of hexane–EtOAc) to afford the desired pure product.

Method B: As for Method A, but in this case, acid–base extraction was unsuccessful and the product was isolated by extraction with sat. $NaHCO_3$ solution followed by column chromatography (silica gel) to give the desired pure *meso*-N-substituted 2,6-diarylpiperidin-4-ones **3h–k**.

Procedure 2

To a mixture of aromatic aldehyde (1 mmol, 1 equiv), allylamine (1.1 mmol, 1.1 equiv), and L-proline (20 mol%) in MeOH (2 mL) was added 4-phenylbut-3-en-2-one **1** (4 mmol, 4 equiv) and the mixture was allowed to stir at r.t. for 24 h. The solvent was then evaporated under reduced pressure and the mixture was subject to an acid–base extraction workup (see procedure 1, method A) to afford the desired products.

***meso*-1-Allyl-2,6-diphenylpiperidin-4-one (3a)**

Yellow oil; yield: 224 mg (77%, procedure 1, method A); 230 mg (79%, procedure 2); R_f = 0.31 (hexane–EtOAc, 10:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.30 (m, 10 H), 5.83–5.72 (m, 1 H), 5.04 (dd, *J* = 10.2, 2.0 Hz, 1 H), 4.64 (dd, *J* = 17.1, 2.0 Hz, 1 H), 3.96 (dd, *J* = 12.8, 2.3 Hz, 2 H), 3.00 (d, *J* = 7.1 Hz, 2 H), 2.81 (t, *J* = 12.8 Hz, 2 H), 2.53 (dd, *J* = 12.8, 2.3 Hz, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.1 (CO), 142.4 (2 C), 130.5 (CH), 128.6 (4 CH), 127.5 (2 CH), 127.2 (4 CH), 119.5 (CH_2), 64.4 (2 CH), 51.0 (CH_2), 50.8 (2 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{21}NO$: 291.1623; found: 291.1616.

***meso*-1-But-3-enyl-2,6-diphenylpiperidin-4-one (3b)**

Yellow oil; yield: 180 mg (59%, procedure 1, method A); R_f = 0.39 (hexane–EtOAc, 5:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.33 (m, 10 H), 5.31–5.14 (m, 1 H), 4.73–4.62 (m, 2 H), 3.99 (dd, *J* = 11.9, 2.9 Hz, 2 H), 2.85 (t, *J* = 11.9 Hz, 2 H), 2.56 (d, *J* = 11.9 Hz, 2 H), 2.44 (m, 2 H), 1.99–1.92 (m, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.3 (CO), 142.3 (2 C), 135.9 (CH), 128.6 (4 CH), 127.6 (2 CH), 127.2 (4 CH), 115.4 (CH_2), 64.8 (2 CH), 50.5 (2 CH_2), 48.7 (CH_2), 26.3 (CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{21}H_{23}NO$: 305.1780; found: 305.1781.

***meso*-1-Butyl-2,6-diphenylpiperidin-4-one (3c)**

Yellow oil; yield: 71 mg (23%, procedure 1, method A); R_f = 0.30 (hexane–EtOAc, 10:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.26 (m, 10 H), 3.92 (dd, *J* = 13.7, 2.0 Hz, 2 H), 2.81 (t, *J* = 13.7 Hz, 2 H), 2.51 (d, *J* = 13.7

Hz, 2 H), 2.35–2.29 (m, 2 H), 1.19–1.09 (m, 2 H), 0.76–0.64 (m, 2 H), 0.52 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.6 (CO), 142.6 (2 C), 128.6 (4 CH), 127.5 (2 C), 127.2 (4 CH), 64.7 (2 CH), 50.6 (2 CH_2), 40.8 (CH_2), 23.1 (CH_2), 20.1 (CH_2), 13.5 (CH_3).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{21}H_{25}NO$: 307.1936; found: 307.1932.

***meso*-1,2,6-Triphenylpiperidin-4-one (3d)**
Yellow solid; yield: 72 mg (22%, procedure 1, method A); R_f = 0.29 (hexane–EtOAc, 6:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51–7.30 (m, 13 H), 7.12 (t, *J* = 8.3 Hz, 2 H), 4.62 (dd, *J* = 12.8, 2.7 Hz, 2 H), 3.05 (t, *J* = 12.8 Hz, 2 H), 2.57 (dd, *J* = 12.8, 2.7 Hz, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.7 (CO), 143.1 (2 C), 136.0 (C), 129.9 (CH), 129.3 (4 CH), 128.7 (4 CH), 128.6 (5 CH), 128.1 (CH), 64.7 (2 CH), 50.2 (2 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{23}H_{21}NO$: 327.1623; found: 327.1619.

***meso*-1-(4-Methoxyphenyl)-2,6-diphenylpiperidin-4-one (3e)**
Yellow solid; yield: 75 mg (21%, procedure 1, method A); 50 mg (14%, procedure 2); R_f = 0.26 (hexane–EtOAc, 8:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.16 (m, 10 H), 6.82 (d, *J* = 10.5 Hz, 2 H), 6.45 (d, *J* = 10.5 Hz, 2 H), 4.52 (dd, *J* = 10.8, 3.3 Hz, 2 H), 3.56 (s, 3 H), 3.12–2.91 (m, 2 H), 2.75 (dd, *J* = 10.8, 3.3 Hz, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.4 (CO), 158.9 (C), 142.5 (2 C), 134.8 (C), 128.9 (4 CH), 128.5 (4 CH), 127.5 (2 CH), 127.1 (2 CH), 114.0 (2 CH), 64 (2 CH), 55.9 (CH_3), 50.9 (2 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{24}H_{23}NO_2$: 357.1729; found: 357.1735.

***meso*-1-Allyl-2,6-bis(4-methoxyphenyl)piperidin-4-one (3f)**
White solid, yield: 141 mg (40%, procedure 1, method A); 194 mg (55%, procedure 2); mp 142–146 °C; R_f = 0.34 (hexane–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.6 Hz, 4 H), 6.91 (d, *J* = 8.6 Hz, 4 H), 5.85–5.65 (m, 1 H), 5.03 (dd, *J* = 10.2, 2.0 Hz, 1 H), 4.65 (dd, *J* = 17.1, 2.0 Hz, 1 H), 3.85 (dd, *J* = 12.5, 2.8 Hz, 2 H), 3.83 (s, 6 H), 2.97 (d, *J* = 7.0 Hz, 2 H), 2.77 (t, *J* = 12.5 Hz, 2 H), 2.48 (dd, *J* = 12.5, *J* = 2.8 Hz, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.7 (CO), 158.9 (2 C), 134.7 (2 C), 130.9 (1 CH), 128.4 (4 CH), 119.3 (1 CH_2), 114.0 (4 CH), 63.9 (2 CH), 55.2 (2 CH_3), 51.1 (3 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{22}H_{25}NO_3$: 351.1834; found: 351.1829.

***meso*-1-Allyl-2,6-bis(3,4-dimethoxyphenyl)piperidin-4-one (3g)**
Yellow solid; yield: 173 mg (42%, procedure 1, method A); mp 109–112 °C; R_f = 0.27 (hexane–EtOAc, 6:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.02–6.81 (m, 6 H), 5.83–5.69 (m, 1 H), 5.03 (d, *J* = 10.2 Hz, 1 H), 4.67 (d, *J* = 17.2 Hz, 1 H), 3.92 (s, 6 H), 3.88 (s, 6 H), 3.85 (d, *J* = 12.9 Hz, 2 H), 3.01 (d, *J* = 6.9 Hz, 2 H), 2.79 (t, *J* = 12.9 Hz, 2 H), 2.50 (d, *J* = 12.9 Hz, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.2 (CO), 149.1 (2 C), 148.2 (2 C), 134.9 (2 C), 131.1 (CH), 119.5 (2 CH), 119.1 (CH_2), 110.9 (2 CH), 110.1 (2 CH), 64.2 (2 CH), 55.8 (2 CH_3), 55.7 (2 CH_3), 51.2 (CH_2), 50.7 (2 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{24}H_{29}NO_5$: 411.2046; found: 411.2040.

***meso*-1-Allyl-2,6-bis(4-fluorophenyl)piperidin-4-one (3h)**
Yellow solid; yield: 216 mg (66%, procedure 1, method B); mp 107–109 °C; R_f = 0.26 (hexane–EtOAc, 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.38 (m, 4 H), 7.08 (t, *J* = 8.8 Hz, 4 H), 5.83–5.63 (m, 1 H), 5.05 (dd, *J* = 10.0, 2.4 Hz, 1 H), 4.63 (dd, *J* = 17.2, 2.4 Hz, 1 H), 3.94 (dd, *J* = 12.9, 2.8 Hz, 2 H), 2.95 (d, *J* = 7.0 Hz, 2 H), 2.75 (t, *J* = 12.9 Hz, 2 H), 2.50 (dd, *J* = 12.9, 2.8 Hz, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 206.5 (CO), 162.0 (d, *J* = 244.0 Hz, 2 C), 138.0 (2 C), 130.3 (CH), 128.7 (d, *J* = 7.9 Hz, 4 CH), 119.6 (CH_2), 115.6 (d, *J* = 21 Hz, 4 CH), 63.6 (2 CH), 51.2 (CH_2), 50.7 (2 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{19}F_2NO$: 327.1435; found: 327.1419.

***meso*-1-Allyl-2,6-bis(4-chlorophenyl)piperidin-4-one (3i)**
Yellow solid; yield: 231 mg (64%, procedure 1, method B); R_f = 0.43 (hexane–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.33 (m, 8 H), 5.80–5.66 (m, 1 H), 5.07 (dd, *J* = 13.2, 2.0 Hz, 1 H), 4.67 (dd, *J* = 17.0, 2.0 Hz, 1 H), 3.94 (dd, *J* = 12.4, 2.7 Hz, 2 H), 2.97 (d, *J* = 7.1 Hz, 2 H), 2.73 (t, *J* = 12.4 Hz, 2 H), 2.50 (dd, *J* = 12.4, 2.7 Hz, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 206.0 (CO), 140.7 (2 C), 133.1 (2 C), 130.0 (CH), 128.9 (4 CH), 128.5 (4 CH), 119.9 (CH_2), 63.5 (2 CH), 51.2 (CH_2), 50.4 (2 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{19}Cl_2NO$: 359.0844; found: 359.0833.

***meso*-1-Allyl-2,6-bis(2-bromophenyl)piperidin-4-one (3j)**
Yellow oil; yield: 296 mg (66%, procedure 1, method B); 274 mg (61%, procedure 2); R_f = 0.28 (hexane–EtOAc, 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 7.3 Hz, 2 H), 7.55 (d, *J* = 7.3 Hz, 2 H), 7.40 (t, *J* = 7.3 Hz, 2 H), 7.15 (t, *J* = 7.3 Hz, 2 H), 5.83–5.75 (m, 1 H), 5.10 (d, *J* = 10.0 Hz, 1 H), 4.64 (d, *J* = 17.1 Hz, 1 H), 4.52 (dd, *J* = 12.0, 2.0 Hz, 2 H), 2.98 (d, *J* = 6.9 Hz, 2 H), 2.63–2.54 (m, 4 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 205.7 (CO), 141.2 (2 C), 133.1 (2 CH), 130.6 (CH), 129.1 (2 CH), 128.8 (2 CH), 128.1 (2 CH), 122.8 (2 C), 120.4 (CH_2), 62.0 (2 CH), 51.9 (CH_2), 48.5 (2 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{19}Br_2NO$: 446.9833; found: 446.9839.

***meso*-1-Allyl-2,6-bis(2-iodophenyl)piperidin-4-one (3k)**
Yellow solid; yield: 364 mg (67%, procedure 1, method B); mp 98–100 °C; R_f = 0.36 (hexane–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 7.8 Hz, 4 H), 7.44 (t, *J* = 7.8 Hz, 2 H), 6.99 (td, *J* = 7.4, 1.6 Hz, 2 H), 5.93–5.72 (m, 1 H), 5.15 (dd, *J* = 10.2, 1.6 Hz, 1 H), 4.66 (dd, *J* = 17.2, 1.6 Hz, 1 H), 4.33 (dd, *J* = 10.2, 4.0 Hz, 2 H), 2.98 (d, *J* = 7.1 Hz, 2 H), 2.59 (td, *J* = 13.3, 3.9 Hz, 4 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 205.2 (CO), 143.8 (2 C), 139.7 (CH), 130.4 (CH), 129.11 (4 CH), 128.8 (4 CH), 98.6 (2 C), 66.8 (2 CH), 51.6 (CH_2), 48.43 (2 CH_2).

HRMS: *m*/*z* $[M]^+$ calcd for $C_{20}H_{19}I_2NO$: 542.9556; found: 542.9560.

***cis*-1-Allyl-2-(4-methoxyphenyl)-6-phenylpiperidin-4-one (4a)**
Yellow oil; yield: 151 mg (47%, procedure 1, method A); 154 mg (48%, procedure 2); R_f = 0.26 (hexane–EtOAc, 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.49–7.28 (m, 7 H), 6.93 (d, *J* = 8.3 Hz, 2 H), 5.84–5.70 (m, 1 H), 5.04 (dd, *J* = 10.3, 1.0 Hz, 1 H), 4.65 (dd, *J* = 17.1, 1.0 Hz, 1 H), 3.96–3.84 (m, 2 H), 3.84 (s, 3 H), 2.98 (d, *J* = 7.1 Hz, 2 H), 2.79 (t, *J* = 12.7 Hz, 2 H), 2.54–2.48 (m, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.5 (CO), 158.9 (C), 142.5 (C), 134.5 (C), 130.7 (CH), 128.7 (2 CH), 128.3 (2 CH), 127.5

(CH), 127.3 (2 CH), 119.4 (CH_2), 114.0 (2 CH), 64.5 (CH), 63.8 (CH), 55.2 (CH_3), 51.1 (CH_2), 51.0 (CH_2), 50.9 (CH_2).

HRMS: *m/z* $[M]^+$ calcd for $C_{21}H_{23}NO_2$: 321.1729; found: 321.1715.

***cis*-1-Allyl-2-(4-fluorophenyl)-6-phenylpiperidin-4-one (4b)**
Yellow solid; yield: 183 mg (59%, procedure 1, method A); 211 mg (68%, procedure 2); mp 136–139 °C; R_f = 0.28 (hexane–EtOAc, 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.31 (m, 7 H), 7.10 (t, *J* = 8.6 Hz, 2 H), 5.85–5.71 (m, 1 H), 5.00 (dd, *J* = 10.1, 1.8 Hz, 1 H), 4.66 (dd, *J* = 17.1, 1.8 Hz, 1 H), 3.97 (dd, *J* = 9.2, 2.4 Hz, 2 H), 3.03–2.91 (m, 2 H), 2.82–2.71 (m, 2 H), 2.54–2.47 (m, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 206.8 (CO), 161.9 (d, *J* = 244.4 Hz, C), 142.2 (C), 138.1 (C), 130.4 (CH), 128.8 (CH), 128.7 (3 CH), 127.6 (CH), 127.2 (2 CH), 119.5 (CH_2), 115.5 (d, *J* = 21.2 Hz, 2 CH), 64.3 (CH), 63.6 (CH), 51.1 (CH_2), 50.8 (CH_2), 50.7 (CH_2).

HRMS: *m/z* $[M]^+$ calcd for $C_{20}H_{20}FNO$: 309.1529; found: 309.1522.

***cis*-1-Allyl-2-(4-chlorophenyl)-6-phenylpiperidin-4-one (4c)**
White solid; yield: 199 mg (61%, procedure 1, method A); 49 mg (15%, procedure 2); R_f = 0.27 (hexane–EtOAc, 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.28 (m, 9 H), 5.79–5.68 (m, 1 H), 5.04 (dt, *J* = 10.3, 0.9 Hz, 1 H), 4.63 (dd, *J* = 16.9, 0.9 Hz, 1 H), 3.93 (dt, *J* = 11.8, 3.7 Hz, 2 H), 3.03–2.90 (m, 2 H), 2.81–2.70 (m, 2 H), 2.53–2.46 (m, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 206.8 (CO), 142.3 (C), 141.1 (C), 133.2 (C), 130.4 (CH), 128.9 (2 CH), 128.7 (2 CH), 128.6 (2 CH), 127.6 (CH), 127.3 (2 CH), 119.8 (CH_2), 64.5 (CH), 63.8 (CH), 51.3 (CH_2), 50.8 (CH_2), 50.7 (CH_2).

HRMS: *m/z* $[M]^+$ calcd for $C_{20}H_{20}ClNO$: 325.1233; found: 325.1230.

***cis*-1-Allyl-2-(2-bromophenyl)-6-phenylpiperidin-4-one (4d)**
Yellow oil; yield: 55 mg (15%, procedure 2); R_f = 0.53 (hexane–EtOAc, 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 7.8, 1.7 Hz, 1 H), 7.46–7 (m, 9 H), 5.79–5.56 (m, 1 H), 5.06 (dd, *J* = 10.2, 2.1 Hz, 1 H), 4.65 (dd, *J* = 17.1, 2.1 Hz, 1 H), 4.48 (dd, *J* = 10, 5.1 Hz, 1 H), 4.01 (dd, *J* = 11.7, 3.3 Hz, 1 H), 2.90 (d, *J* = 7.2 Hz, 2 H), 2.78 (dd, *J* = 13.5, 11.8 Hz, 1 H), 2.57 (m, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 206.65 (CO), 142.55 (C), 141.37 (C), 133.12 (CH), 130.78 (CH), 129.30 (CH), 128.86 (2 CH), 128.82 (CH), 128.18 (CH), 127.73 (CH), 127.38 (2 CH), 122.87 (C), 120.03 (CH_2), 64.12 (CH), 62.40 (CH), 51.64 (CH_2), 50.71 (CH_2), 48.77 (CH_2).

MS EI (70 eV): *m/z* (%) = 369 $[M^+ Br^{79}]$ (10), 371 $[M^+ Br^{81}]$ (10), 368 $[M – H]^+$ (8), 290 $[M – Br]^+$ (18), 145 (bp).

***meso*-2,6-Diarylpiperidin-4-ones 5a–d; General Procedure**
Bis(tricyclohexylphosphine)benzylideneruthenium(IV) chloride (5 mol%, Grubbs'catalyst) was added in portions under argon to a solution of the corresponding *meso*-1-allyl-2,6-diarylpiperidin-4-ones **3a**,**f**,**h**,**k** (100 mg) in anhydrous toluene (5 mL) and the mixture was heated at reflux for 12 h. Then, the mixture was concentrated under reduced pressure and was purified by flash column chromatography (silica gel, mixtures of hexane–EtOAc) to afford the desired N-unprotected *meso*-2,6-diarylpiperidin-4-ones **5**.

***meso*-2,6-Diphenylpiperidin-4-one (5a)**
White solid; yield: 58 (67%); mp 102–105 °C; R_f = 0.43 (hexane–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.28 (m, 10 H), 4.11 (dd, *J* = 10.1, 4.2 Hz, 2 H), 2.71–2.58 (m, 4 H), 2.18 (br s, 1 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 208.0 (CO), 142.6 (2 C), 128.6 (4 CH), 127.8 (2 CH), 126.5 (4 CH), 61.0 (2 CH), 50.3 (2 CH_2).

HRMS: *m/z* $[M]^+$ calcd for $C_{17}H_{17}NO$: 251.1310; found: 251.1301.

***meso*-2,6-Bis(4-methoxyphenyl)piperidin-4-one (5b)**
White solid; yield: 60.2 mg (68%); R_f = 0.20 (hexane–EtOAc, 5:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.5 Hz, 4 H), 6.89 (d, *J* = 8.5 Hz, 4 H), 4.01 (dd, *J* = 10.8, 3.1 Hz, 2 H), 3.80 (s, 6 H), 2.64–2.51 (m, 4 H), 2.03 (br s, 1 H, NH).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 208.5 (CO), 159.0 (2 C), 134.8 (2 C), 127.6 (4 CH), 113.9 (4 CH), 60.5 (2 CH), 55.2 (2 CH_3), 50.4 (2 CH_2).

HRMS: *m/z* $[M]^+$ calcd for $C_{19}H_{21}NO_3$: 311.1521; found: 311.1535.

***meso*-2,6-Bis(4-fluorophenyl)piperidin-4-one (5c)**
Yellow oil; yield: 61.4 mg (70%); R_f = 0.16 (hexane–EtOAc, 10:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44 (dd, *J* = 8.1, 5.2 Hz, 4 H), 7.04 (t, *J* = 8.1 Hz, 4 H), 4.05 (dd, *J* = 9.4, 5.0 Hz, 2 H), 2.53 (m, 4 H), 2.36 (br s, 1 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 207.3 (CO), 162.1 (d, *J* = 244.2 Hz, 2 C), 138.2 (2 C), 128.0 (4 C), 115.4 (d, *J* = 20.8 Hz, 4 C), 60.2 (2 CH), 50.1 (2 CH_2).

HRMS: *m/z* $[M]^+$ calcd for $C_{17}H_{15}F_2NO$: 287.1122; found: 287.1127.

***meso*-2,6-Bis(2-iodophenyl)piperidin-4-one (5d)**
White solid; yield: 58.3 mg (63%); R_f = 0.27 (hexane–EtOAc, 6:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (dd, *J* = 7.8, 1.2 Hz, 2 H), 7.78 (d, *J* = 7.8 Hz, 2 H), 7.43 (t, *J* = 7.8 Hz, 2 H), 7.03 (td, *J* = 7.8, 2.0 Hz, 2 H), 4.41 (dd, *J* = 12.1, 2.4 Hz, 2 H), 2.78 (dd, *J* = 12.1, 2.4 Hz, 2 H), 2.46 (t, *J* = 12.1 Hz, 2 H).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 206.5 (CO), 144.0 (2 C), 139.6 (2 CH), 129.6 (2 CH), 128.8 (2 CH), 127.5 (2 CH), 98.9 (2 C), 63.7 (2 CH_2), 47.8 (2 CH).

HRMS: *m/z* $[M]^+$ calcd for $C_{17}H_{15}I_2NO$: 502.9243; found: 502.9256.

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