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Proline-Catalyzed Imino-Diels–Alder Reactions: Synthesis of *meso*-2,6-Diaryl-4-piperidones

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Abstract: Amine-catalyzed imino-Diels–Alder reactions of acyclic α,β-unsaturated ketones with imines have been developed. L-Proline catalyzed the *in situ* generation of 2-amino-1,3-butadienes to provide a stereoselective synthesis of *meso*-2,6-diaryl-4-piperidones in one direct step.

Keywords: 2-amino-1,3-butadienes; *meso*-2,6-diaryl-4-piperidones; hetero-Diels–Alder reaction; nitrogen heterocycles; organic catalysis; L-proline

Introduction

4-Oxopiperidine ring systems play an important role in heterocyclic chemistry from the chemical, biological and medicinal points of view.[1] In particular, 2,6-disubstituted-4-piperidones are found in the frameworks of many biologically active natural products.[2] The hetero-Diels–Alder reaction is well-known as a powerful tool for the construction of functionalized six-membered heterocyclic rings.[3]

One of the ongoing themes of research in our laboratory has been the synthesis of 4-piperidones with high stereoselectivity employing the imino-Diels–Alder reaction of 2-amino-1,3-butadienes with non-activated aldimines.[4] Moreover, this cycloaddition can also be carried out asymmetrically to give adducts in very high enantiomeric excesses.[5] Recently, we described an efficient method for the stereoselective synthesis of *meso*-2,6-disubstituted-4-piperidones by the imino-Diels–Alder reaction of 3-unsubstituted-2-aminodienes using $Cu(OTf)_2$ as a Lewis acid catalyst (Figure 1).[6] In this case, it was necessary to prepare and isolate the 2-amino-1,3-diene reactant in advance in order for this reaction to be successful.

In the past few years, small organic molecules such as chiral amines have been used as catalysts for a wide range of enantioselective transformations.[7] In particular, L-proline has been reported to catalyze asymmetric aldol,[8] Michael,[9] Mannich,[10] α-amination[11] and related reactions. Recently, organoamines

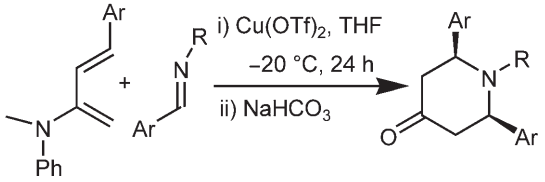


Figure 1. Preparation of *meso*-2,6-disubstituted-4-piperidones using a Lewis acid as catalyst.

have also been applied as catalysts of Diels–Alder dimerization reactions of α,β-unsaturated carbonyl compounds, by the *in situ* formation of an electron-deficient dienophile *via* iminium ion formation[12] (Figure 2, **I**) and an electronically-activated diene through enamine formation[13] (Figure 2, **II**).

Taking into consideration this latter strategy involving the *in situ* generation of 2-amino-1,3-butadienes, we considered the possibility of using chiral amines as the catalyst for the imino-Diels–Alder reaction with aldimines (Figure 3). During the preparation of this manuscript we became aware of the first enantioselective aza-Diels–Alder reaction catalyzed by an amino acid, L-proline.[14] In this report, only cyclic α,β-unsaturated ketones were used as substrates. Here we report an amine-catalyzed imino-Diels–Alder reaction between acyclic α,β-unsaturated ketones and aldimines, providing an efficient single-step route to the synthesis of *meso*-2,6-disubstituted-4-piperidones.

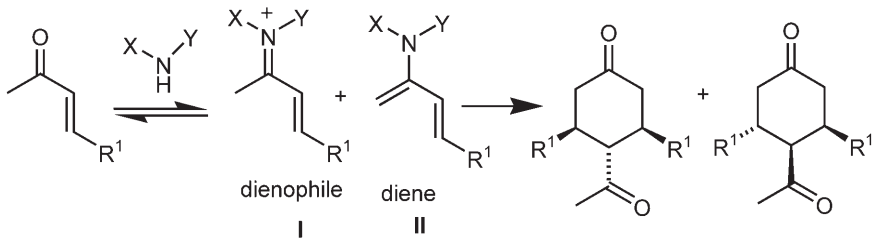


Figure 2. Amine-catalyzed Diels–Alder dimerization reactions.

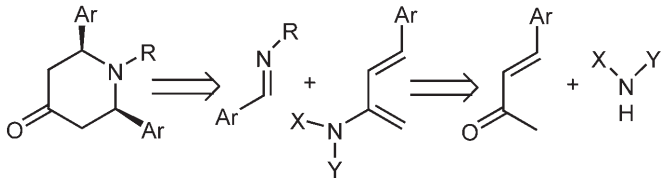
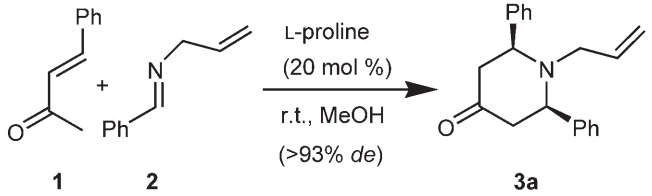


Figure 3. Retrosynthetic analysis for the synthesis of *meso*-2,6-diaryl-4-piperidones.

Results and Discussion

In an initial experiment commercially available *trans*-4-phenyl-3-buten-2-one (2 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 h, the reaction was quenched by extraction and the crude product was purified by column chromatography on silica gel to furnish the desired imino-Diels–Alder product, (2*R*,6*S*)-*N*-allyl-2,6-diphenyl-4-piperidone (**3a**), in 65% yield with >93% diastereoselectivity (Scheme 1).



Scheme 1. Imino-Diels–Alder reaction catalyzed by L-proline.

Encouraged by this experiment, we investigated different reaction conditions to optimize this process. First, we studied the solvent effect. Neither anhydrous solvents nor use of inert atmosphere conditions were found to be necessary or beneficial. We obtained the best results using MeOH as solvent; in DMSO the yield decreased to 27%, and with CH_3CN only a trace (5%) of compound **3a** was observed. When the reaction was performed in other solvents (THF, $CHCl_3$, DMF, dioxane, toluene and EtOAc), none of the desired cyclo product was obtained even after 72 h; only starting material was recovered from these reaction mixtures.

The concentration of substrate also affects the yield of the reaction (Table 1).[15] We found that changing the molar ratio of α,β-unsaturated ketone:imine from 1:1 to 4:1 increased the product yield by about 30%

Table 1. Effect of changing the molar ratios of ketone **1**:imine **2** on the formation of cycloadduct **3a** in the presence of L-proline (20 mol%) in methanol.

Entry	Compound **1** (equivs.)[a]	Temp. [°C]	Yield [%][b]
1	1	r.t.	50
2	2	r.t.	65
3	4	r.t.	77
4	6	r.t.	63

[a] Equivalents of ketone **1** to imine **2**.
[b] Yield after column chromatographic purification.

(entries 1 and 3). In this case, the use of an excess of ketone is not an inconvenience since the imino-Diels–Alder adduct can be easily separated out by an acid-base extraction work-up. However, lower or higher molar ratios led to a decrease in the product yield (entries 2 and 4).

Another important factor was the reaction temperature (Table 2). When the reaction of ketone **1** with imine **2** was carried out in methanol at −20°C, no cycloaddition product was isolated (entry 4) and at 0°C only a trace of the product **3a** was observed (entry 3). In both cases, starting materials were recovered even when the reaction mixture was allowed to stir for

Table 2. Effect of the reaction temperature on the yield of the L-proline-catalyzed imino-Diels–Alder reaction between ketone **1** and imine **2** (4:1 molar ratio) in methanol.

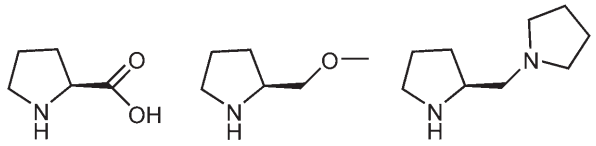
Entry	Compound **1** (equivs.)	Temp. [°C]	Yield [%][a]
1	4	40	49
2	4	r.t.	77
3	4	0	traces (<5)
4	4	−20	–

[a] Yield after column chromatography purification.

96 h. At room temperature (23–25 °C), product **3a** was obtained in 77 % yield (entry 2) but at higher temperature (40 °C) the yield decreased to only 49 % due perhaps to product decomposition (entry 1).

Besides L-proline, **A**, we also tested two other secondary amines as catalysts, (*S*)-2-methoxymethylpyrrolidine, **B**, and (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine, **C** (Table 3). Of the three catalysts screened for the reaction of ketone **1** with imine **2**, L-proline was the most efficient (entry 1). In the case of L-proline, a higher concentration of catalyst or the presence of *p*-toluenesulfonic acid did not improve the reaction yield (entries 2 and 3). When secondary amines **B** and **C** were employed, the reaction did not proceed to any measurable extent (entries 4 and 6); but in the presence of 20 mol % of *p*-TsOH, the adduct **3** was obtained in 58 % and 61 % yield, respectively (entries 5 and 7). These results suggest that both the amine catalyst and an acid catalyst are required to promote formation and equilibration of the initial iminium ion to the reactive enamine.

Table 3. Effect of catalyst on the imino-Diels–Alder reaction.



A B C

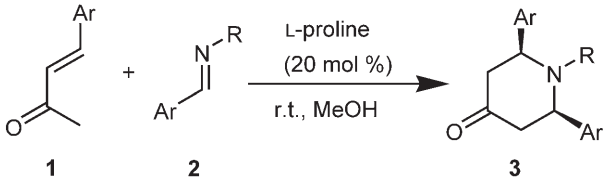
Entry	Catalyst (equivs.)[a]	Additive (equivs.)	Yield [%]
1	A (0.2)	–	77
2	A (0.4)	–	76
3	A (0.2)	*p*-TsOH (0.2)	68
4	B (0.2)	–	–
5	B (0.2)	*p*-TsOH (0.2)	58[b]
6	C (0.2)	–	–
7	C (0.2)	*p*-TsOH (0.2)	61[c]

[a] Equivalents of catalyst.
[b] *de* = 94 %.
[c] *de* = 92 %.

This methodology under these optimized conditions was then extended to the synthesis of different *meso*-2,6-diaryl-4-piperidones **3**. These adducts could be readily obtained from reactions in which the aryl substituent of the α,β-unsaturated ketone **1**[16] is properly matched with the arylimine **2**.[17] The results are summarized in Table 4.

The reaction is general and the *meso*-2,6-diaryl-4-piperidones **3** were obtained with excellent diastereoselectivities and fairly good yields regardless of the structure of the aryl substituent, from electron-rich (MeO, entries 6 and 7) to electron poor (halogen, entries 8–11). When the aryl substituent is halogen, the acid-base extraction to eliminate the excess ketone **1** was unsuccessful, but the products **3h–k** can be isolated by extraction with saturated $NaCO_3H$ solution followed by flash chromatography.

Table 4. Preparation of *meso*-2,6-diaryl-4-piperidones **3** using L-proline as catalyst.



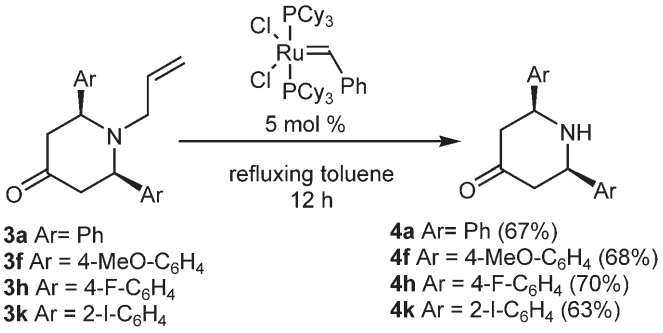
1 2 3

Entry	Compound	Ar	R	*de* [%][a]	Yield [%][b]
1	**3a**	Ph	allyl	> 93	77
2	**3b**	Ph	homoallyl	> 97	59
3	**3c**	Ph	Bu	> 97	23
4	**3d**	Ph	Ph	90	22
5	**3e**	Ph	*p*-MeO-C_6H_4	90	21
6	**3f**	*p*-MeO-C_6H_4	allyl	> 96	40
7	**3g**	3,4-di-MeO-C_6H_3	allyl	> 96	42
8	**3h**	*p*-F-C_6H_4	allyl	> 95	66
9	**3i**	*p*-Cl-C_6H_4	allyl	> 97	64
10	**3j**	*o*-Br-C_6H_4	allyl	> 96	66
11	**3k**	*o*-I-C_6H_4	allyl	> 96	67

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

On the other hand, the reaction is highly sensitive to the *N*-substituent of the imine. Although the reaction takes place for *N*-arylimines [Ph, 4-MeO-C_6H_4 (PMP), entries 4 and 5] and *N*-alkylimines (Bu, homoallyl; entries 2 and 3), in some cases we observed low conversion. The best results are obtained for *N*-allyl-substituted imines (entries 1 and 6–11), which have the additional and attractive advantage that the allyl group can be easily removed after the cycloaddition following published methods.[18] Deprotection of the *N*-allyl group of piperidones **3** using a first generation Grubbs catalyst[19] provided the *N*-unsubstituted *meso*-2,6-diaryl-4-piperidones **4** in good yields (Scheme 2).

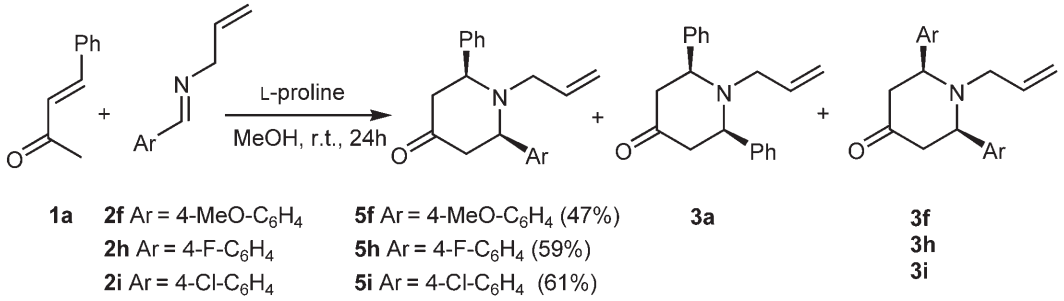
We next investigated the application of this methodology to the preparation of enantiomerically enriched 2,6-disubstituted-4-piperidones by using different aryl substituents (Ar^1, Ar^2) on the α,β-unsaturated ketone and imine (Scheme 3). In all cases examined, the *cis*-2,6-disubstituted-4-piperidones **5** were obtained from the reactions as one diastereoisomer but, unfortunately, the compound was racemic (by HPLC analysis).[20] Also, a small amount (< 5 %) of *meso*



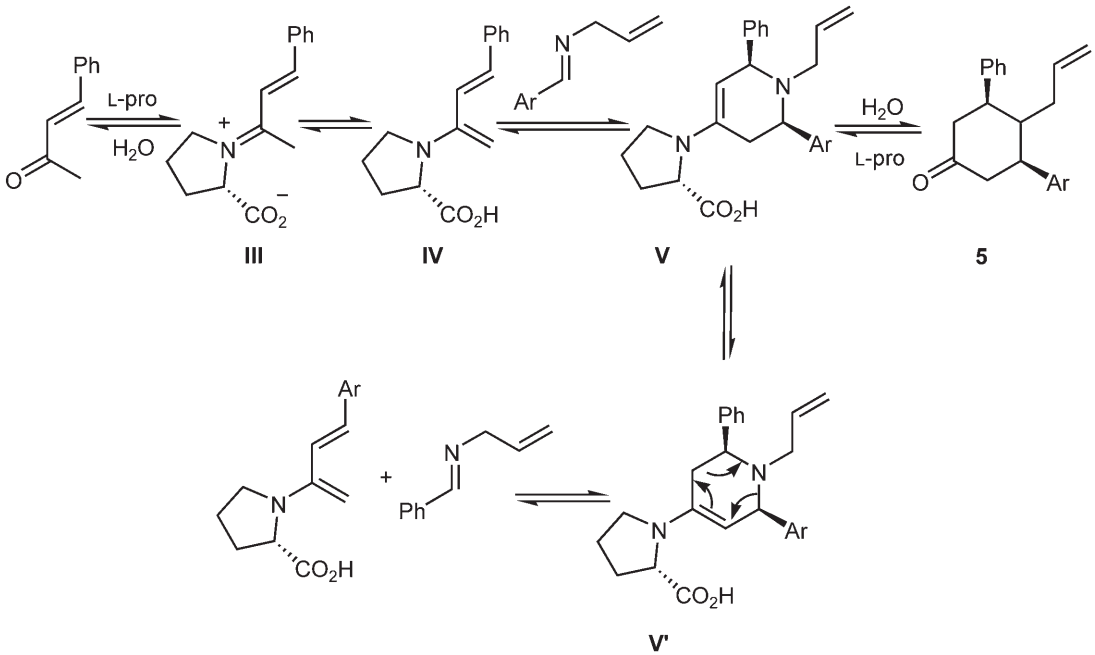
Scheme 2. Deprotection of *N*-allyl-4-piperidones using Grubbs catalyst.

compounds **3a**, **f**, **h**, **i** could be obtained from the crude reaction mixtures.

To explain the formation of these minor (*meso*) byproducts we propose a mechanism where all the intermediates are in equilibrium (Scheme 4). First, the 2-amino-1,3-butadiene **IV** is generated *in situ* by the reaction of the α,β-unsaturated ketone with L-proline, giving the iminium zwitterion **III**. Equilibration of **III** to 2-amino-1,3-butadiene **IV**, followed by cycloaddition with the imine, provides tethahydropyridine adduct **V** which hydrolyzes to the unsymetrical 4-piperidone **5**. Alternatively, intermediate **V** could undergo equilibration under the reaction conditions to its regioisomer **V'** prior to hydrolysis, and then undergo retro-imino-Diels–Alder cycloaddition to obtain the 2-amino-1,3-butadiene and the imine in which the Ar^1 and Ar^2 groups have been interchanged relative to the initial starting materials. Cycloaddition between the two sets of dienes and imines present in the media could thereby give rise to the *meso*-4-piperidones **3** byproducts observed in these reactions.



Scheme 3. Preparation of unsymmetrical 2,6-disubstituted-4-piperidones **5**.



Scheme 4. A putative pathway for the proline-catalyzed imino-Diels–Alder reaction leading to unsymmetrical 2,6-disubstituted-4-piperidones **5**.

Conclusions

In summary, we have described, to the best of our knowledge, the first synthesis of *meso*-2,6-diaryl-4-piperidones by an L-proline-catalyzed imino-Diels–Alder reaction between acyclic α,β-unsaturated ketones and aldimines. The simplicity and mildness of the reaction protocol make this a very efficient and stereoselective method to obtain *meso* or *cis*-*N*-substituted or *N*-unsubstituted-2,6-diaryl-4-piperidones in good yields. Compared to previously reported methods, this L-proline-catalyzed cycloaddition methodology has the advantages that neither the use of a metal catalyst [Cu(II)] nor the restriction of having to isolate the diene intermediate prior to the cycloaddition is required, and the reaction can easily be run on a multigram scale. Further studies aimed at exploring the applications of this strategy are underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Preparation of *meso*-*N*-Substituted-2,6-diaryl-4-piperidones 3a–k

Method A: To a mixture of α,β-unsaturated ketone **1**[16] (4 mmol, 4 equivs.) and L-proline (20 mol%) in MeOH (1.5 mL or 5 mL in the case of **1e**, **f**) was added imine **2**[17] (1 mmol, 1 equiv.) and the reaction mixture was allowed to stir at room temperature for 24 h. Then, the solvent (MeOH) was evaporated under reduced pressure and the reaction mixture was subject to an acid-base extraction work-up to eliminate the excess of ketone **1**. Ethyl acetate (10 mL) was added to the reaction crude and the organic layer was washed with HCl (1 N) (3×5 mL). The aqueous layers were combined and added quickly to a solution of 1 N NaOH (25 mL) and extracted thoroughly with EtOAc (3×20 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and purified by flash column chromatography (silca gel, mixtures of hexane/EtOAc) to afford the desired pure *meso*-*N*-substituted-2,6-diaryl-4-piperidones **3a–g**.

Method B: It is the same procedure as Method A but in this case the acid-base extraction was unsuccessful and the product could be isolated by extraction with saturated $NaHCO_3$ solution followed by flash chromatograghy column on silica gel to furnish the desired pure *meso*-*N*-substituted-2,6-diaryl-4-piperidones **3h–k**.

***meso*-*N*-Allyl-2,6-diphenyl-4-piperidone (3a):** Employing Method A, yield: 224 mg (77%); yellow oil; R_f = 0.31 (hexane/EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.49–7.30 (m, 10H), 5.83–5.72 (m, 1H), 5.04 (dd, J = 10.2, 2.0 Hz, 1H), 4.64 (dd, J = 17.1, 2.0 Hz, 1H), 3.96 (dd, J = 12.8, 2.3 Hz, 2H), 3.00 (d, J = 7.1 Hz, 2H), 2.81 (t, J = 12.8 Hz, 2H), 2.53 (dd, J = 12.8, 2.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): 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); HR-MS: m/z = 291.1616, calcd. for $C_{20}H_{21}NO$: 291.1623.

***meso*-*N*-Allyl-2,6-bis(4-fluorophenyl)-4-piperidone (3h)**: Employing Method B; yield: 216 mg (66%); yellow solid, mp 107–109 °C; R_f = 0.26 (hexane/EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48–7.38 (m, 4H), 7.08 (t, J = 8.8 Hz, 4H), 5.83–5.63 (m, 1H), 5.05 (dd, J = 10.0, 2.4 Hz, 1H), 4.63 (dd, J = 17.2, 2.4 Hz, 1H), 3.94 (dd, J = 12.9, 2.8 Hz, 2H), 2.95 (d, J = 7.0 Hz, 2H), 2.75 (t, J = 12.9 Hz, 2H), 2.50 (dd, J = 12.9, 2.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): δ = 206.5 (CO), 162.0 (d, J = 244.0; 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); HR-MS: m/z = 327.1419, calcd. for $C_{20}H_{19}F_2NO$: 327.1435.

General Experimental Procedure for the Deprotection of *meso*-*N*-Allyl-2,6-diaryl-4-piperidones. Synthesis of *meso*-2,6-Diaryl-4-piperidones 4a, f, h, k

Bis(tricyclohexylphosphine)benzylidine ruthenium(IV) chloride (5 mol%, Grubbs' catalyst) was added in portions under nitrogen to a solution of the corresponding *meso*-*N*-allyl-2,6-diaryl-4-piperidones **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-diaryl-4-piperidones **4a**, **f**, **h**, **k**.

***meso*-2,6-Diphenyl-4-piperidone (4a)**: yield: 168 mg (67%); white solid, mp 102–105 °C; R_f = 0.43 (hexane/EtOAc, 5:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.53–7.28 (m, 10H), 4.11 (dd, J = 10.1, 4.2 Hz, 2H), 2.71–2.58 (m, 4H), 2.18 (bs, 1H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): 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); HR-MS: m/z = 251.1301, calcd. for $C_{17}H_{17}NO$: 251.1310.

Typical Experimental Procedure for the Preparation of *cis*-*N*-Allyl-2,6-disubstituted-4-piperidones 5f, h, i

The same procedure described for the preparation of *meso*-*N*-substituted-2,6-diaryl-4-piperidones **3a–k** (**Method A**) has been used for the synthesis of **5f**, **h**, **i**.

***cis*-*N*-Allyl-2-(4-methoxyphenyl)-6-phenyl-4-piperidone (5f)**: yield: 151 mg (47%); yellow oil; R_f = 0.26 (hexane/EtOAc, 10:1); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.49–7.28 (m, 7H), 6.93 (d, J = 8.3 Hz, 2H), 5.84–5.70 (m, 1H), 5.04 (dd, J = 10.3, 1.0 Hz, 1H), 4.65 (dd, J = 17.1, 1.0 Hz, 1H), 3.96–3.84 (m, 2H), 3.84 (s, 3H), 2.98 (d, J = 7.1 Hz, 2H), 2.79 (t, J = 12.7 Hz, 2H), 2.54–2.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): 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); HR-MS: m/z = 321.1715, calcd. for $C_{21}H_{23}NO_2$: 321.1729.

Supporting Information

Experimental datas for compounds **3b–g**, **3i–k**, **4f**, **4h**, **4k**, **5h** and **5i**. ^{1}H and ^{13}C NMR spectra for all compounds.

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