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Three-component *anti* selective Mannich reactions in a tetrahydro-4-pyranone system by using PDAG-Co catalyst

Abstract: Catalytic quantities (2 mol%) of a complex of cobalt containing guanidine and 2,6-pyridinedicarboxylic acid ligands (PDAG-Co) were used for the efficient three-component Mannich reactions of tetrahydro-4-pyranone (**1**) with different aromatic aldehydes and aniline derivatives in a one-pot process. Reactions rapidly gave high yields of the corresponding three-substituted tetrahydro-4-pyranones at room temperature. Spectroscopic and X-ray analyses support the formation of *anti* diastereomers as the major or sole products of the reactions.

Keywords: heterocycles; Mannich reaction; multicomponent reaction; tetrahydro-4-pyranone.

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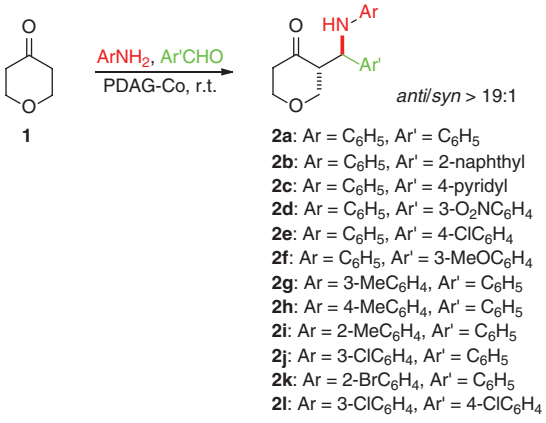
Introduction

Multicomponent reactions (MCRs) are highly successful strategies for combining several reactants in a single process and allowing direct access to diverse groups of products and libraries of compounds [1–3]. In this regard, the Mannich reaction, which comprises the one-pot combination of carbonyl compounds with aldehydes and amine derivatives [4, 5], is one of the most important MCRs in synthetic organic chemistry that provides a facile access to β-amino carbonyl structures. These products are interesting because they are the subunits of many nitrogen-containing natural products and synthetically important compounds [6]. In addition, they exhibit diverse biological activities [7, 8] and are useful intermediates in other synthetic transformations [9, 10]. Several important one-pot Mannich reactions have recently been reported. They involve the use of asymmetric inductive agents [11, 12], aqueous media [13], organocatalytic conditions [14], Lewis acids [15–17], ionic liquids [18], and solid supports [19]. Recently, we have reported the synthesis of a complex in which cobalt is chelated with guanidine and 2,6-pyridinedicarboxylic acid ligands (PDAG-Co). This complex can be used as an efficient catalyst in Biginelli and Hantzsch reactions [20]. In the framework of our studies on one-pot processes [21–23] and based on our interests in heterocyclic chemistry [24–26], we herein report a three-component Mannich process in which tetrahydropyran-4-one (**1**) undergoes a reaction with aromatic aldehydes and aniline derivatives in the presence of catalytic quantities of PDAG-Co (Scheme 1).

The pyran system is an important group of six-membered oxygen-containing heterocycles [10, 27] that possess diverse biological features and are found in the structure of many natural products [28]. Therefore, it is important to develop new strategies and synthetic methods to access various pyran derivatives. To the best of our knowledge, the Mannich reactions of tetrahydropyran-4-one (**1**) are mostly limited to two-component Mannich-type transformations [29–32]. The three-component reaction is rare and it may employ high-temperature conditions and long time periods [33, 34].

Results and discussion

Initially, we optimized the conditions by analyzing the reaction of **1** with benzaldehyde and aniline. As a result, we noted that the use of a 1:1:1 mixture of the reactants in ethanol and in the presence of PDAG-Co conveniently gives rise to product **2a** in a one-pot process at room temperature (Scheme 1). Further experiments showed that only 2 mol% of the catalyst was enough for the process to be completed within 35 min. The ^{1}H NMR analysis of the



Scheme 1 Products synthesized under the optimized conditions.

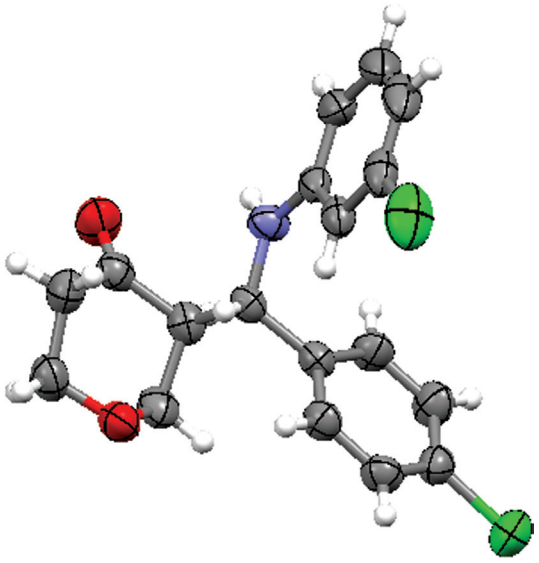


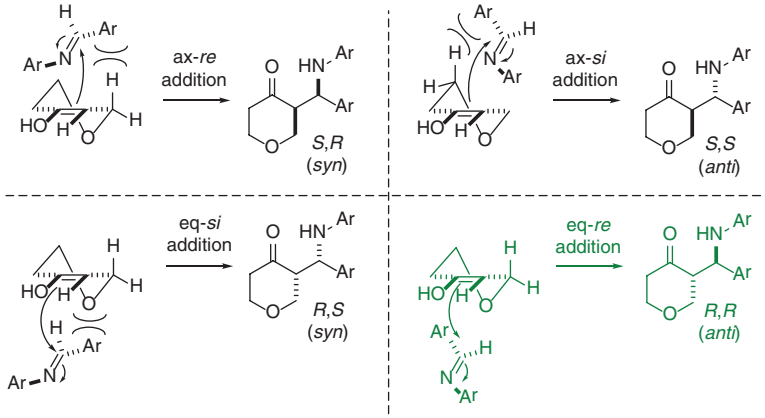
Figure 1 Crystal structure of **2l** with displacement ellipsoids at 50% probability level.

reaction mixture supported the formation of the β-amino ketone **2a** as the only product in the crude mixture. Other reactions of **1** with naphthaldehyde, a heteroaromatic aldehyde, and various derivatives of benzaldehyde and aniline proceeded equally well, leading to high yield of **2b**–**f**. When the optimized conditions were applied to the reactions with ring-substituted anilines, again complete disappearance of the reactants and formation of a single product **2g**–**l** was observed in each case.

To assign the relative stereochemistry of the two stereogenic centers in the products, a single crystal of **2l** was obtained by crystallization from ethyl acetate and analyzed by X-ray crystallography. As shown in Figure 1 the *anti* stereoisomer of product **2l** was obtained. This result can be extrapolated to the structures of other products due to the similar ^{1}H NMR pattern they show. See the supplementary material for this article please.

A mechanism that explains the observed *anti* stereoselectivity is suggested in Scheme 2. It is generally accepted that three-component Mannich reactions proceed thorough primary formation of imine species [35], which are the result of condensation between amines and aldehydes, followed by the addition of the enol of the starting ketone to imine intermediates. For such an addition, one can propose four possible modes of interaction. These four combinations are shown in Scheme 2. They arise from pseudoaxial or pseudoequatorial addition of the enol to the *re* or *si* face of the *trans* imine, respectively. The depiction suggests that among the four modes, the undesired steric congestions are minimized in the pseudoequatorial addition to the *re* face, the combination that leads to the *R*,*R* *anti* product.

Regarding the effect of the PDAG catalyst on the progress of the reaction, the catalyst primarily acts as a Lewis



Scheme 2 Four possible modes of addition and the preferred pathway leading to *R*,*R* (*anti*) product.

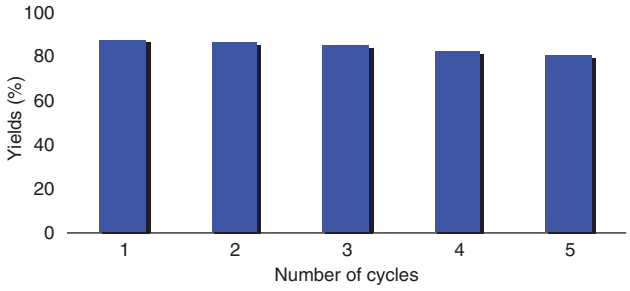


Figure 2 Efficient recycling of the catalyst illustrated for the synthesis of **2a**.

acid by assisting the enolization of the starting ketone. The next step of the addition of the enol to the imine intermediate can also be catalyzed by the Co catalyst.

By contrast, the catalyst is heterogeneous and during the process remains insoluble. Therefore, it can be easily recycled each time and reused in next reactions, as shown in Figure 2 for five efficient reactions of **1** with benzaldehyde and aniline. These features of Lewis acidity and recyclability of catalysts in heterogeneous reactions (in general) [36] and in Mannich reactions [37] (in particular) have also been observed and reported by others.

Conclusions

A direct method for efficient and diastereoselective asymmetric three-component Mannich reaction of tetrahydropyran-4-one system with aromatic aldehydes and amines is described. Simple experimental procedure, fast reaction rates, recyclability of the catalyst, and easy isolation of the major *anti* products by precipitation are characteristic features of the protocol that make this method very useful and eco-friendly.

Experimental

Reactions were monitored by thin layer chromatography (TLC) using silica gel-coated plates and ethyl acetate/hexane (1:3) solutions as the mobile phase. Melting points are uncorrected. FT-IR spectra were recorded using KBr disks on a Bruker Vector-22 infrared spectrometer. ^{1}H NMR spectra (300 MHz or 500 MHz) and ^{13}C NMR spectra (75 MHz or 125 MHz) were obtained on a FT-NMR Bruker Avance (300 MHz) or Bruker Ultra Shield™ (500 MHz) in $CDCl_3$ or DMSO-d_6 solutions. Electron-impact mass spectra (MS) were obtained on a Finnigan Mat 8430 apparatus at ionization potential of 70 eV. Elemental analyses were performed using a Thermo Finnigan Flash EA 1112 instrument. All chemicals were purchased from commercial sources and were used after purification by standard procedures. Known products were identified by the comparison of their physical and spectral data with those reported in the literature [33, 34]. New products were characterized based on their ^{1}H NMR, ^{13}C NMR, IR, and MS, and their purities were confirmed by elemental analyses. The stereoselectivity of the reactions (*anti*/*syn* ratio) was analyzed by ^{1}H NMR spectroscopy. Because no *syn* isomers were detected in the crude spectra, the *de* ratio (diastereomeric excess) was >19:1 (>95:5) in all cases. Products **2a–l** were crystallized from ethyl acetate.

General procedure

To a solution of an aniline (2.0 mmol) in ethanol (1 mL), were added an aldehyde (2.0 mmol), compound **1** (200 mg, 2 mmol), and complex PDAG-Co (21 mg, 2 mol%) successively at ambient temperature. Stirring was continued at the same temperature until TLC showed completion of the reaction (20 min for **2b**–**f**, 30 min for **2g**,**i**,**l**, 35 min for **2a**,**h**,**k**, and 40 min for **2j**). Ethyl acetate (15 mL) was added to the mixture and the organic layer was washed with saturated $NaHCO_3$ solution and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude mixture was crystallized from ethyl acetate to afford the *anti* product.

Spectral data of products

(*R)-3-[(*R**)-Phenyl(phenylamino)methyl]tetrahydro-4-pyranone (2a)** This product was obtained in 87% yield as a white solid; mp 185–187°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.32–2.38 (m, 1H), 2.59–2.66 (m, 1H), 2.71 (ddd, 1H, *J* = 4.5, 5.0, 9.0 Hz), 3.38 (dd, 1H, *J* = 5.5, 11.5 Hz), 3.57 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.77–3.82 (m, 1H), 3.95 (ddd, 1H, *J* = 5.0, 5.5, 11.5 Hz), 4.87 (dd, 1H, *J* = 9.0, 9.5 Hz), 6.17 (d, 1H, *J* = 9.0 Hz), 6.45 (dd, 1H, *J* = 7.0, 7.5 Hz), 6.54 (d, 2H, *J* = 7.5 Hz), 6.95 (dd, 2H, *J* = 7.5, 7.5 Hz), 7.18 (dd, 1H, *J* = 7.0, 7.5 Hz), 7.27 (dd, 2H, *J* = 7.0, 7.5 Hz), 7.42 (d, 2H, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.3, 54.7, 57.9, 68.2, 69.3, 113.3, 116.3, 127.1, 127.5, 128.3, 128.7, 141.3, 147.6, 206.8; MS: m/z 281 (M^+), 181, 131, 115; IR: 3340, 1656, 1431 cm^{-1}. Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.55; H, 6.67; N, 5.03.

(*R)-3-[(*R**)-Naphthalen-2-yl(phenylamino]methyl)tetrahydro-4-pyranone (2b)** This product was in 92% as a white solid; mp 187–189°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.35–2.41 (m, 1H), 2.63–2.70 (m, 1H), 2.86 (ddd, 1H, *J* = 4.0, 4.5, 8.5 Hz), 3.38 (dd, 1H, *J* = 5.0, 11.5 Hz), 3.58 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.77–3.84 (m, 1H), 3.99 (ddd, 1H, *J* = 5.0, 5.5, 11.0 Hz), 5.05 (dd, 1H, *J* = 9.0, 9.5 Hz), 6.29 (d, 1H, *J* = 9.0 Hz), 6.42 (dd, 1H, *J* = 7.0, 7.5 Hz), 6.60 (d, 2H, *J* = 8.0 Hz), 6.93 (dd, 2H, *J* = 7.5, 7.5 Hz), 7.32–7.50 (m, 2H), 7.61 (d, 1H, *J* = 8.5 Hz), 7.82–7.85 (m, 3H), 7.93 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.3, 54.9, 57.7, 68.2, 69.3, 113.3, 116.4, 125.1, 125.8, 126.2, 126.7, 127.5, 127.6, 128.2, 128.7, 132.4, 132.6, 138.7, 147.6, 206.8; MS: m/z 331 (M^+), 230, 127; IR: 3340, 1708, 1506 cm^{-1}. Anal. Calcd for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.52; H, 6.32; N, 4.25.

(*R)-3-[(*R**)-(Phenylamino)(pyridin-4-yl)methyl]tetrahydro-4-pyranone (2c)** This product was obtained in 87% as a white solid; mp 160–162°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.33–2.38 (m, 1H), 2.60–2.63 (m, 1H), 2.79–2.81 (m, 1H), 3.39–3.42 (m, 1H), 3.57 (d, 1H, *J* = 11.5 Hz), 3.77–3.80 (m, 1H), 4.00 (dd, 1H, *J* = 5.0, 10.5 Hz), 5.17 (dd, 1H, *J* = 9.5, 10.0 Hz), 6.14 (d, 1H, *J* = 9.5 Hz), 6.46–6.55 (m, 4H), 6.98 (dd, 2H, *J* = 7.5, 7.5 Hz), 7.11–7.17 (m, 2H), 7.23–7.26 (m, 1H); ^{13}C NMR

(75 MHz, DMSO-d_6): δ 41.5, 47.8, 57.4, 68.3, 69.3, 112.9, 115.1, 116.7, 125.0, 128.9, 129.2, 147.2, 206.5; MS: m/z 282 (M^+), 183, 133, 77; IR: 3335, 1700, 1602, 1509 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.51; H, 6.55; N, 10.00.

(*R)-3-[(*R**)-(3-Nitrophenyl)(phenylamino)methyl]tetrahydro-4-pyranone (2d)** This product was obtained in 95% as a white solid; mp 170–172°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.35 (dd, 1H, *J* = 6.5, 13.5 Hz), 2.52–2.59 (m, 1H), 2.69–2.80 (m, 2H), 2.93–2.97 (m, 3H), 5.16 (dd, 1H, *J* = 9.5, 9.5 Hz), 6.22 (d, 1H, *J* = 9.5 Hz), 6.48 (dd, 1H, *J* = 7.0, 7.5 Hz), 6.57 (d, 2H, *J* = 7.5 Hz), 6.95–7.05 (m, 3H), 7.29–7.37 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.5, 32.8, 42.3, 55.3, 57.6, 113.3, 114.0, 114.3, 116.6, 123.9, 128.8, 130.2, 144.5, 147.4, 164.0, 208.3; MS: m/z 326 (M^+), 227, 115, 77; IR: 3370, 1708, 1593 cm^{-1}. Anal. Calcd for $C_{18}H_{18}N_2O_4$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.01; H, 5.30; N, 8.55.

(*R)-3-[(*R**)-(4-Chlorophenyl)(phenylamino)methyl]tetrahydro-4-pyranone (2e)** This product was obtained in 85% as a white solid; mp 173–174°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.32–2.40 (m, 1H), 2.57–2.66 (m, 1H), 2.75 (ddd, 1H, *J* = 4.5, 4.5, 8.5 Hz), 3.36 (dd, 1H, *J* = 5.0, 11.0 Hz), 3.63 (dd, 1H, *J* = 4.0, 11.0 Hz), 3.77–3.83 (m, 1H), 3.93 (ddd, 1H, *J* = 5.5, 5.5, 11.0 Hz), 4.90 (dd, 1H, *J* = 9.0, 9.5 Hz), 6.20 (d, 1H, *J* = 9.0 Hz), 6.46 (dd, 1H, *J* = 7.0, 7.5 Hz), 6.53 (d, 2H, *J* = 8.0 Hz), 6.95 (dd, 2H, *J* = 7.5, 8.0 Hz), 7.34 (d, 2H, *J* = 8.5 Hz), 7.45 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.3, 54.0, 57.6, 68.1, 69.2, 113.3, 116.5, 128.3, 128.7, 129.4, 131.6, 140.3, 147.3, 206.6; MS: m/z 315 (M^+), 216, 151, 115; IR: 3360, 1700, 1504 cm^{-1}. Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.58; H, 5.69; N, 4.53.

(*R)-3-[(*R**)-(3-Methoxyphenyl)(phenylamino)methyl]tetrahydro-4-pyranone (2f)** This product was obtained in 86% as a white solid; mp 157–159°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.34–2.48 (m, 1H), 2.54–2.67 (m, 1H), 2.73–2.76 (m, 1H), 3.35–3.39 (m, 1H), 3.61 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.63 (s, 3H), 3.68–3.72 (m, 1H), 3.92–3.95 (m, 1H), 4.92 (dd, 1H, *J* = 9.0, 9.5 Hz), 6.19 (d, 1H, *J* = 9.0 Hz), 6.44–6.48 (m, 1H), 6.56 (d, 2H, *J* = 8.5 Hz), 6.94–7.05 (m, 3H), 7.26–7.37 (m, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.3, 54.2, 55.7, 57.6, 68.1, 69.2, 113.3, 114.0, 116.5, 123.9, 128.8, 130.1, 144.6, 147.4, 162.4, 206.6; MS: m/z 311 (M^+), 212, 77; IR: 3335, 1713, 1562 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.45; H, 6.66; N, 4.61.

(*R)-3-[(*R**)-Phenyl(*m*-tolylamino)methyl]tetrahydro-4-pyranone (2g)** This product was obtained in 85% as a white solid; mp 140–141°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.08 (s, 3H), 2.33 (ddd, 1H, *J* = 4.0, 9.0, 10.5 Hz), 2.59–2.73 (m, 2H), 3.35 (dd, 1H, *J* = 5.0, 11.5 Hz), 3.55 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.74–3.82 (m, 1H), 3.96 (ddd, 1H, *J* = 5.5, 5.5, 11.5 Hz), 4.86 (dd, 1H, *J* = 9.5, 9.5 Hz), 6.10 (d, 1H, *J* = 9.5 Hz), 6.27 (d, 1H, *J* = 7.5 Hz), 6.34 (d, 1H, *J* = 8.0 Hz), 6.39 (s, 1H), 6.82 (dd, 1H, *J* = 7.5, 7.5 Hz), 7.19 (d, 1H, *J* = 7.5 Hz), 7.29 (dd, 2H, *J* = 7.5, 7.5 Hz), 7.42 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 21.3, 41.2, 54.7, 58.0, 68.2, 69.3, 110.4, 114.0, 117.3, 127.1, 127.5, 128.3, 128.6, 137.6, 141.4, 147.6, 206.9; MS: m/z 295 (M^+), 194, 115, 91; IR: 3377, 1765, 1524 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.39; H, 7.25; N, 5.00.

(*R)-3-[(*R**)-Phenyl(*p*-tolylamino)methyl]tetrahydro-4-pyranone (2h)** This product was obtained in 86% as a white solid; mp 152–153°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.21 (s, 3H), 2.44–2.47 (m, 1H), 2.66–2.68 (m, 1H), 2.79–2.82 (m, 1H), 3.72 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.84–3.88 (m, 2H), 4.20–4.22 (m, 1H), 4.47 (br s, 1H), 4.86 (d, 1H, *J* = 9.5 Hz), 6.51 (d, 2H, *J* = 8.5 Hz), 6.92 (d, 2H, *J* = 8.5 Hz), 7.27–7.29 (m, 1H), 7.35–7.38 (m, 2H), 7.44 (d, 2H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.8, 41.8, 57.1, 59.7, 69.0, 70.2, 114.4, 127.7, 127.8, 128.1, 129.2, 130.0, 141.1, 144.5, 208.6; MS: m/z 295 (M^+), 194, 91; IR: 3392, 1878, 1527 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.22; H, 7.06; N, 4.70.

(*R)-3-[(*R**)-Phenyl(*o*-tolylamino)methyl]tetrahydro-4-pyranone (2i)** This product was obtained in 87% as a white solid; mp 168–169°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.10 (s, 3H), 2.34–2.42 (m, 1H), 2.58 (ddd, 1H, *J* = 6.5, 13.5, 13.5 Hz), 2.96 (ddd, 1H, *J* = 4.0, 4.5, 9.0 Hz), 3.40 (dd, 1H, *J* = 5.5, 11.5 Hz), 3.59 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.79–3.87 (m, 1H), 3.95 (ddd, 1H, *J* = 5.5, 11.0, 16.5 Hz), 4.86 (dd, 1H, *J* = 8.5, 8.5 Hz), 5.14 (d, 1H, *J* = 8.5 Hz), 6.39–6.45 (m, 2H), 6.81 (dd, 1H, *J* = 7.5, 7.5 Hz), 6.90 (d, 1H, *J* = 7.0 Hz), 7.17–7.22 (m, 1H), 7.28–7.32 (m, 2H), 7.46–7.49 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 17.6, 41.5, 55.0, 57.5, 68.0, 69.5, 110.6, 116.3, 122.2, 126.5, 127.2, 127.5, 128.4, 129.7, 141.4, 145.0, 207.4; MS: m/z 295 (M^+), 196, 115, 91. IR: 3369, 1701, 1519 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.32; H, 7.03; N, 4.72.

(*R)-3-[(*R**)-((3-Chlorophenyl)amino)(phenyl)methyl]dihydro-4-pyranone (2j)** The product was obtained in 80% as a white solid; mp 140–142°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.36 (ddd, 1H, *J* = 5.0, 5.0, 13.5 Hz), 2.63 (dd, 1H, *J* = 5.5, 13.5 Hz), 2.71 (ddd, 1H, *J* = 4.0, 8.0, 9.0 Hz), 3.31–3.36 (m, 1H), 3.55 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.78–3.85 (m, 1H), 3.93 (ddd, 1H, *J* = 5.5, 5.5, 11.0 Hz), 4.85 (dd, 1H, *J* = 9.0, 9.5 Hz), 6.44–6.55 (m, 4H), 6.95 (dd, 1H, *J* = 8.0 Hz), 7.18–7.23 (m, 1H), 7.31 (dd, 2H, *J* = 7.5, 7.5 Hz) 7.41–7.23 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.3, 54.5, 57.7, 68.2, 69.3, 111.9, 112.4, 115.7, 127.3, 127.4, 128.4, 130.2, 133.3, 140.7, 149.1, 206.6; MS: m/z 315 (M^+), 216, 138, 115; IR: 3319, 1710, 1514 cm^{-1}. Anal. Calcd for $C_{18}H_{18}ClNO_2$: C, 68.46; H, 5.75; N, 4.44. Found: C, 68.29; H, 5.65; N, 4.48.

(*R)-3-[(*R**)-((2-Bromophenyl)amino)(phenyl)methyl]tetrahydrohydro-4-pyranone (2k)** This product was obtained in 84% as a white solid; mp 149–150°C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.43–2.59 (m, 2H), 3.01–3.08 (m, 1H), 3.46 (ddd, 1H, *J* = 1.5, 6.5, 11.5 Hz), 3.73 (dd, 1H, *J* = 4.5, 11.5 Hz), 3.83–3.96 (m, 2H), 4.87 (dd, 1H, *J* = 8.0, 8.5 Hz), 5.50 (d, 1H, *J* = 8.5 Hz), 6.48 (ddd, 1H, *J* = 1.5, 7.5, 7.5 Hz), 6.60 (d, 1H, *J* = 7.5 Hz), 7.01 (ddd, 1H, *J* = 1.5, 7.0, 7.0 Hz), 7.20–7.24 (m, 1H), 7.31 (t, 2H, *J* = 7.0 Hz), 7.37 (dd, 1H, *J* = 1.5, 7.5 Hz), 7.41–7.45 (m, 2H), ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.8, 55.0, 57.0, 68.0, 69.7, 109.2, 112.9, 118.0, 127.2, 127.3, 128.4, 128.5, 132.2, 140.5, 143.7, 207.5; MS: m/z 359 (M^+), 260, 131; IR: 3348, 1716, 1586 cm^{-1}. Anal. Calcd for $C_{18}H_{18}BrNO_2$: C, 60.01; H, 5.04; N, 3.89. Found: C, 59.82; H, 4.93; N, 3.80.

(*R)-3-[(*R**)-(4-Chlorophenyl)((3-chlorophenyl)amino)methyl]tetrahydro-4-pyranone (2l)** This product was obtained in 83% as a white solid; mp 177–178°C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.39 (ddd, 1H, *J* = 5.0, 8.5, 11.0 Hz), 2.61 (dd, 1H, *J* = 5.5, 7.0, 13.5), 2.75 (ddd, 1H, *J* = 4.0, 5.0, 9.0 Hz), 3.33–3.40 (m, 1H), 3.60 (dd, 1H, *J* = 4.0, 11.5 Hz), 3.79–3.95 (m, 2H), 4.88 (dd, 1H, *J* = 9.0, 9.0 Hz), 6.47–6.57 (m, 4H), 6.96 (dd, 1H, *J* = 8.0, 8.0 Hz), 7.37 (d, 2H, *J* = 8.5 Hz), 7.44 (d, 2H, *J* = 8.5 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 41.4, 53.8, 57.4, 68.1, 69.2, 111.9, 112.4, 115.9, 128.4, 129.3, 130.3, 131.8, 133.4, 139.8, 148.9, 206.5; MS: m/z 349 (M^+), 250, 138, 115; IR: 3361, 1703, 1593 cm^{-1}. Anal. Calcd for $C_{18}H_{17}Cl_2NO_2$: C, 61.73; H, 4.89; N, 4.00. Found: C, 61.59; H, 4.85; N, 3.97.

X-ray data for 2l

$C_{18}H_{17}Cl_2NO_2$, M = 350.23 g/mol, monoclinic system, space group $P2_1/c$, a = 11.3714(11), b = 8.6096(5), c = 17.9791(18) Å, β =106.843(8), V = 1684.7(3) Å^3, Z = 2, Dc = 1.381 g/cm^{-3}, μ(Mo-Kα) = 0.394 mm^{-1}, crystal dimension of 0.25×0.20×0.18 mm. The structure was solved by using SHELXS. The structure refinement and data reduction was carried out with SHELXL. The non-hydrogen atoms were refined anisotropically by full matrix least-squares on F^2 values to final R_1 = 0.0677, wR_2 = 0.1142, and S = 1.025 with 208 parameters using 3303 independent reflection (θ range = 2.37–26.00°). Hydrogen atoms were located from expected geometry and were not refined. Crystallographic data for **2l** have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained, free of charge, on application to The Director, CCDC 929625, Union Road, Cambridge CB2 1EZ, UK. Fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk.

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