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Enantioselective Michael reaction of 2-nitropropane with substituted chalcones catalysed by chiral azacrown ethers derived from α-D-glucose

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Abstract—The chiral monoaza-15-crown-5 lariat ethers anellated to methyl-4,6-*O*-benzylidene-α-D-glucopyranoside **1a–c** showed significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to substituted chalcones. Among the catalysts bearing different side arms at the nitrogen atom, the compound with a phosphinoxidoalkyl side chain **1c** proved to be the most effective (max. 78% e.e.). The type of substituent on the chalcone was found to have a very significant influence on both the chemical yield and the enantioselectivity of the reaction. The absolute configuration of the Michael adducts **3b** and **3i** was determined by chemical methods, while that of **3d** was assigned by X-ray crystal structure determination.

1. Introduction

The Michael addition of carbon nucleophiles to conjugated enones is one of the most powerful methods for carbon–carbon bond formation. Due to its relevance in the synthesis of biologically active compounds, much effort has been directed into carrying out this reaction stereoselectively. Stereoselective variants of the addition of enolates or their analogues to the carbon–carbon double bond of α,β-unsaturated ketones and aldehydes in the presence of chiral catalysts have been extensively investigated recently.[1] The catalytic asymmetric conjugate additions of nitroalkanes to enones has been studied using various chiral catalysts. The reaction of nitroalkanes with chalcone catalysed by chiral ammonium salts,[2a,b] quinine,[2c] L-proline,[2d–f] Ni(II) complexes,[3a] La-BINOL complexes,[3b] and Al complexes of amino alcohols[3c] have been described. Recently, Corey and co-workers reported the enantioselective Michael addition of nitromethane to 4-chlorobenzylideneacetophenone catalysed by a chiral cinchoninium salt as phase transfer catalyst.[3d]

One of the most recent and interesting techniques in catalytic asymmetric synthesis is the phase transfer reaction in which the enantioselectivity is generated by a chiral crown ether catalyst.[1] A special group of optically active crown ethers contains carbohydrate moieties as the source of chirality. Although a number of chiral crown ethers have been prepared from monosaccharides,[4] only a few have been successfully used as catalysts in asymmetric reactions.[5] Recently, we have reported the asymmetric Michael addition of 2-nitropropane to chalcone catalysed by glucose-based chiral lariat ethers of the type **1**. It was observed that the substituents (alkyl-, arylalkyl-, alkoxy- and phosphonoalkyl groups) on the nitrogen atom in catalyst **1** had a significant effect on both the yield and the enantioselectivity of the 1,4-addition reaction.[6]

2. Results and discussion

Herein, the addition of 2-nitropropane to substituted chalcones is investigated in the presence of catalysts **1**

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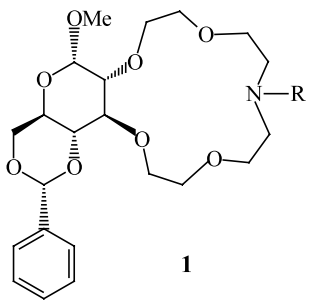
(Scheme 1). In our experiments, lariat ethers **1b** and **1c** containing a methoxyethyl or a phosphinoxidobutyl substituent on the nitrogen atom, respectively, were tested that gave the best results in the earlier examinations.[6b,7a] The unsubstituted azacrown **1a** was applied as a reference compound. The Michael addition was carried out in a solid–liquid system; using toluene, 35 mol% of solid sodium *tert*-butoxide and 7 mol% of chiral catalyst **1a**–**1c** at 22°C. After preparative TLC, the asymmetric inductions expressed in terms of enantiomeric excess (e.e.) were determined by ^{1}H NMR spectroscopy in the presence of the chiral shift reagent (+)-Eu(hfc)$_3$ (Aldrich Chem. Co.).

Table 1 contains the data obtained with chalcones substituted at only one of the phenyl rings. Entries 1–3 show the earlier results obtained for the unsubstituted chalcone **2a** ($Ar^1 = Ar^2 = Ph$). In all cases, use of the phosphinoxidobutyl azacrown **1c** led to the best enantioselectivity, while the unsubstituted counterpart **1a** proved to be the least efficient catalyst. The methoxyethyl derivative **1b** displayed an intermediate result.

The energetically favourable azacrown–sodium ion complex accompanied by the corresponding anion formed from nitropropane can be efficiently stabilised by the bending of the phosphinoxidoalkyl side arm. The steric influence of the phenyl groups may also play a role in the complexation. It can be seen that the aryl substituents have a considerable impact on the stereochemistry of the products (**3a**–**3k**). With respect to the effect of the substituents on the Ar^1 group, using the most efficient catalyst **1c**, the chloro- (**3b**), methyl- (**3c**) and methoxy- (**3a**) substituted products were formed in 56, 64 and 72% enantiomeric purity, respectively (entries 6, 9 and 11). Evaluating the effect of the substituents on the Ar^2 group, the lowest asymmetric induction (e.e. = 29%) was found with the dimethylamino model compound **3g** (entry 15), while the nitroderivative **3f** reacted with the highest enantioselectivity (78% e.e., entry 14). With the methyl- and the dimethoxy model compounds **3e** and **3h**, the e.e. values were modest (48 and 42%, entries 13 and 16, respectively).

Table 2 contains the experimental results obtained with the chalcones **3i**–**3k** having substituents on both phenyl rings. In all of the reactions, catalyst **1c** (R = $(CH_2)_4P(O)Ph_2$) was more efficient than lariat ether analogue **1b** (R = $(CH_2)_2OCH_3$) from the point of view of asymmetric induction. The Michael adducts with



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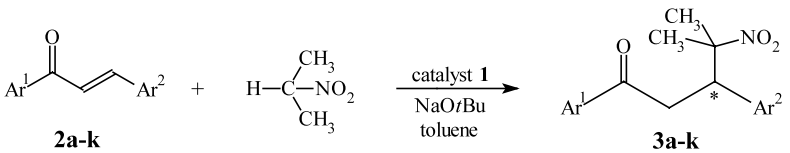
1a R = H

1b R = $CH_2CH_2OCH_3$

1c R = $(CH_2)_4P(O)Ph_2$



2a-k **3a-k**

Compound	Ar^1	Ar^2
A	Ph	Ph
B	4–Cl–Ph	Ph
c	4–CH_3–Ph	Ph
d	4–CH_3O–Ph	Ph
e	Ph	4–CH_3–Ph
f	Ph	4–NO_2–Ph
g	Ph	4–$N(CH_3)_2$–Ph
h	Ph	3,4–di–CH_3O–Ph
i	4–Cl–Ph	4–Cl–Ph
j	4–F–Ph	2–Cl–Ph
k	4–NO_2–Ph	4–CH_3O–Ph

Scheme 1.

Table 1. Asymmetric Michael reaction of 2-nitropropane with chalcones mediated by chiral azacrown ethers **1**

Entry	Ar^1	Ar^2	Catalysts	Time (h)	Yield[a] (%)	$[\alpha]_D$[b]	E.e.[c] (%)
1[7b]	Ph	Ph	**1a**	42	**3a**, 53	+49.3	61 (*R*)
2[6b]	Ph	Ph	**1b**	40	**3a**, 45	+70.3	87 (*R*)
3[7a]	Ph	Ph	**1c**	32	**3a**, 43	+76.0	94 (*R*)
4	4-Cl-Ph	Ph	**1a**	24	**3b**, 49	+45.7	42 (*R*)
5	4-Cl-Ph	Ph	**1b**	22	**3b**, 50	+49.8	46 (*R*)
6	4-Cl-Ph	Ph	**1c**	16	**3b**, 75	+58.5	56 (*R*)
7	4-CH_3-Ph	Ph	**1a**	72	**3c**, 49	+39.3	37
8	4-CH_3-Ph	Ph	**1b**	70	**3c**, 44	+41.3	40
9	4-CH_3-Ph	Ph	**1c**	48	**3c**, 45	+65.7	64
10	4-CH_3O-Ph	Ph	**1a**	86	**3d**, 23	+42.1	41 (*R*)
11	4-CH_3O-Ph	Ph	**1c**	72	**3d**, 38	+71.1	72 (*R*)
12	Ph	4-CH_3-Ph	**1b**	72	**3e**, 58	+43.3	39
13	Ph	4-CH_3-Ph	**1c**	70	**3e**, 72	+52.9	48
14	Ph	4-NO_2-Ph	**1c**	48	**3f**, 67	+99.8	78
15	Ph	4-$N(CH_3)_2$-Ph	**1c**	70	**3g**, 50	+60.2	29
16	Ph	3,4-di-CH_3O-Ph	**1c**	62	**3h**, 26	+75.0	42

[a] Based on substance isolated by preparative TLC.
[b] In CH_2Cl_2 at 22°C.
[c] Determined by ^1H NMR spectroscopy.

Table 2. Asymmetric Michael reaction of 2-nitropropane with chalcones substituted in both phenyl rings

Entry	Ar^1	Ar^2	Catalysts	Time (h)	Yield[a] (%)	$[\alpha]_D$[b]	E.e.[c] (%)
1	4-Cl-Ph	4-Cl-Ph	**1a**	70	**3i**, 51	+24.5	20 (*R*)
2	4-Cl-Ph	4-Cl-Ph	**1b**	52	**3i**, 54	–	14 (*R*)
3	4-Cl-Ph	4-Cl-Ph	**1c**	46	**3i**, 51	+50.6	39 (*R*)
4	4-F-Ph	2-Cl-Ph	**1a**	72	**3j**, 66	+34.6	32
5	4-F-Ph	2-Cl-Ph	**1b**	58	**3j**, 84	+30.1	28
6	4-F-Ph	2-Cl-Ph	**1c**	42	**3j**, 70	+46.5	43
7	4-NO_2-Ph	4-CH_3O-Ph	**1a**	20	**3k**, 56	+14.6	36
8	4-NO_2-Ph	4-CH_3O-Ph	**1b**	26	**3k**, 45	+6.4	16
9	4-NO_2-Ph	4-CH_3O-Ph	**1c**	48	**3k**, 52	+27.3	67

[a] Based on product quantity isolated by preparative TLC.
[b] In CH_2Cl_2 at 22°C.
[c] Determined by ^1H NMR spectroscopy.

two chloro substituents (**3i**), with fluoro and chloro substituents (**3j**), or with nitro and methoxy substituents (**3k**) have been obtained with 39, 43 and 67% enantiomeric excess, respectively (entries 3, 6 and 9). As can be seen, the introduction of a second chloro substituent into the chalcone molecule led to a decrease in the e.e. from 56→39% (Table 1 entry 6 and Table 2 entry 3).

It can be concluded that, in general, the presence of phenyl ring substituents is unfavourable from the point of view of asymmetric induction in these reactions. Regardless of the catalyst used, the substituted Michael adducts **3b**–**3k** were obtained in lower enantiomeric excess than the parent compound **3a**. Relatively, the highest enantioselectivities were obtained for **3d** (Ar^1 = 4-MeO-Ph, e.e. = 72%), **3f** (Ar^2 = 4-NO_2-Ph, e.e. = 78%) and **3k** (Ar^1 = NO_2-Ph, Ar^2 = MeO-Ph, e.e. = 67%). In some cases, pure enantiomers were obtained by repeated crystallisation. The specific rotations obtained in dichloromethane at 22°C are as follows: $[\alpha]_D$ = +111.2 for **3d**, $[\alpha]_D$ = +118.5 for **3f** and $[\alpha]_D$ = +45.4 for **3k**.

It is not easy to decide if the asymmetric induction is influenced by the electronic or steric effects of the substituents. To give an explanation of the effect of the Ar^1 and Ar^2 substituents on the magnitude of the enantioselectivity we have supposed that a substituent-dependent retro-Michael reaction and a deracemisation process also proceed during the **2** to **3** addition, the size of them being sensitive to the configuration of the stereogenic centre of **3** in the presence of the chiral catalyst complex formed from crown compounds **1** and potassium *tert*-butoxide. Preliminary experiments carried out with clean product enantiomers **3** as well as several racemates from **3** by imitating the Michael addition reaction conditions in the presence of chiral catalyst **1** and NaO*t*Bu substantiate the above hypothesis.

The absolute configuration of the new compounds was proven either chemically, or by single-crystal X-ray analysis. Hydrogenolysis of the chloro substituent from the aromatic ring was performed using Pd/C in the presence of sodium acetate.[8] The hydrogenation of compounds **3b** and **3i** containing the (+)-enantiomer in

excess led to product **3a** of (*R*)-configuration with a positive optical rotation.[7c] Hence **3b** and **3i** are also of (*R*)-configuration.

The positive sign of the specific rotation of compound **3d** suggested (*R*)-configuration. This was indeed corroborated by the X-ray analysis (Fig. 1). The crystal structure of **3d** has two independent molecules in the asymmetric unit, both of which are of (*R*)-configuration. A peculiar displacement of these two molecules around a pseudo-symmetry centre can be clearly seen (c.f. Fig. 1). Each one of the two symmetrically displaced methylene H atoms approaches the bridgehead carbon atoms at the methoxy wings well beyond the sum of their respective van der Waals radii (H(22B)···C(141) = 3.37 Å, H(21B)···C(142) = 3.33 Å). Interestingly these are precisely at the sites where the catalytic reaction took place, in the case of ligand **3d** with noticeable selectivity, too. Torsions and C–C bond lengths (ranging from 1.48 to 1.52 Å) around the C=O groups indicate slight delocalisation over this region. A C–H···O interaction with one of the *meta*-position H atoms indicate the only vectorial type interaction between molecules of symmetry related asymmetric units (C(92)–H(92)···O(32)$_{(-2-x,\ -1/2+y,\ -1-z)}$, d = 2.53 Å, 136°).

3. Experimental

3.1. General procedures

Melting points were determined using a Büchi 510 apparatus and are uncorrected. Specific rotation was measured on a Perkin–Elmer 241 polarimeter at 20°C, while the IR spectra were recorded on a Perkin–Elmer 237 spectrophotometer. NMR spectra were obtained on a Bruker DRX-500 instrument in $CDCl_3$. Mass spectra were obtained on a Varian MAT 312 instrument. Chemical ionisation was applied as the ionisation technique. Elemental analysis was determined on a Perkin–Elmer 240 automatic analyser. Analytical and preparative thin layer chromatography was performed on silica gel plates (60 GF-254, Merck), while column chromatography was carried out using 70–230 mesh silica gel (Merck).

3.2. General procedure for the Michael addition of 2-nitropropane to substituted chalcones in the presence of glucose-based azacrown ethers

The corresponding azacrown (0.1 mmol) and sodium *tert*-butoxide (0.05 g, 0.5 mmol) was added to a solution of chalcone (0.3 g, 1.44 mmol) and 2-nitropropane

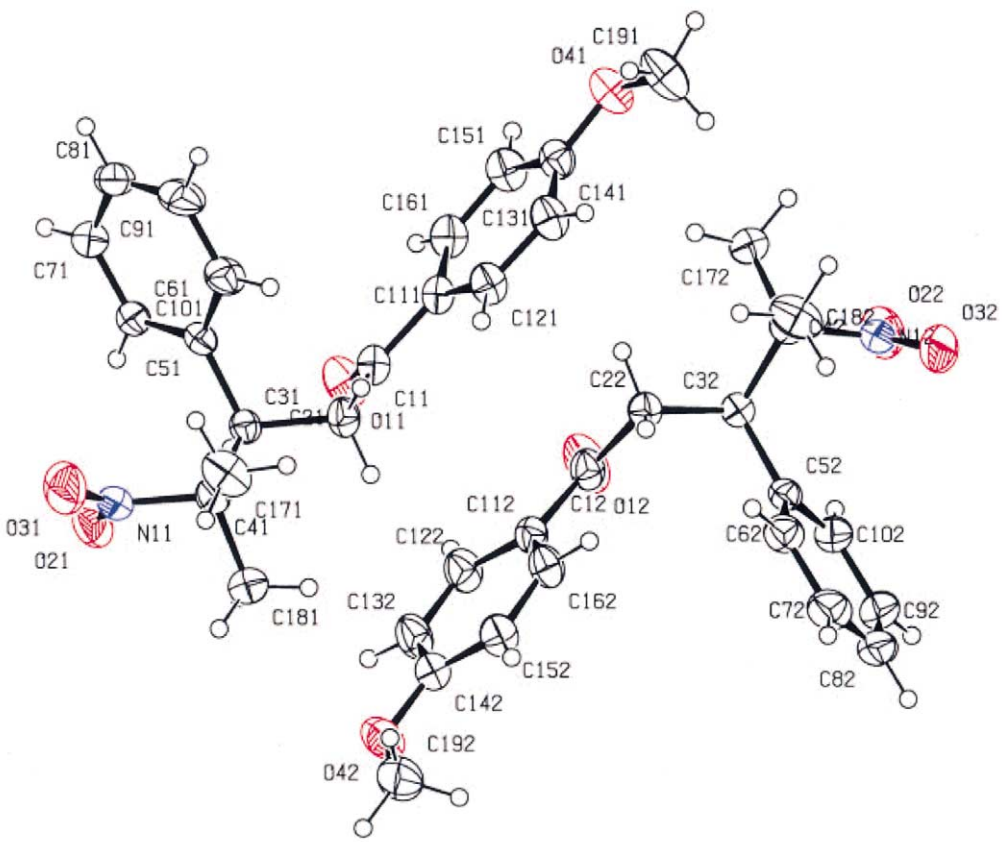


Figure 1. Asymmetric unit of the X-ray crystal structure model of **3d** with atomic numbering applied. Broken line indicates the C–H···O contact site.[14]

(0.3 mL, 3.36 mmol) in dry toluene (3 mL). The mixture was stirred under argon at room temperature. After a reaction time of 48 h, a new portion of toluene (7 mL) was added and the mixture stirred with water (10 mL). The organic phase was washed with water (7 mL) and dried (Na_2SO_4). The crude product obtained after evaporating the solvent was purified by preparative TLC (silica gel, hexane:ethyl acetate, 10:1, eluent) to give pure adducts **3a**–**3k**.

3.2.1. 1-(4-Chlorophenyl)-4-methyl-4-nitro-3-phenylpentan-1-one 3b. Yield: 75% (colourless crystals); mp 117–119°C; $[\alpha]_D^{22}$ +58.5 (*c* 1, CH_2Cl_2), 56% e.e.; IR (KBr), *v* 2997, 1689, 1589, 1529, 1452, 1344, 1231, 1094, 797, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.46 (s, 3H), 1.55 (s, 3H), 3.16 (dd, $J_{gem}=17.3$, 3.1 Hz, 1H), 3.55 (dd, $J_{gem}=17.3$, 10.4 Hz, 1H), 4.04 (dd, 1H), 7.13–7.21 (m, 5H, CHPhH), 7.32 (d, 2H, COPhH-*o*), 7.72 (d, 2H, COPhH-*m*); MS (EI) *m*/*z* 333 ($M+H^+$); anal. calcd for $C_{18}H_{18}NO_3Cl$: C, 65.16; H, 5.42; N, 4.22; Cl, 10.71. Found: C, 65.11; H, 5.44; N, 4.18; Cl, 10.73%.

3.2.2. 1-(4-Tolyl)-4-methyl-4-nitro-3-phenylpentan-1-one 3c. Yield: 45%; mp 113–114°C; $[\alpha]_D^{22}$ +65.7 (*c* 1, CH_2Cl_2); 64% e.e.; IR (KBr), *v* 2999, 1680, 1606, 1537, 1453, 1397, 1346, 1232, 818, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.55 (s, 3H), 1.64 (s, 3H), 2.40 (s, 3H), 3.25 (dd, $J_{gem}=17.2$, 3.7 Hz, 1H), 3.65 (dd, $J_{gem}=17.2$, 10.4 Hz, 1H), 4.15 (dd, 1H), 7.22–7.25 (m, 5H, CHPhH), 7.28 (d, 2H, COPhH-*m*), 7.78 (d, 2H, COPhH-*o*); MS (EI) *m*/*z* 312 ($M+H^+$); anal. calcd for $C_{19}H_{21}NO_3$: C, 73.31; H, 6.75; N, 4.50. Found: C, 73.35; H, 6.71; N, 4.52%.

3.2.3. 1-(4-Methoxyphenyl)-4-methyl-4-nitro-3-phenylpentan-1-one 3d. Yield: 38%; mp 104–105°C; $[\alpha]_D^{22}$ +71.1 (*c* 1, CH_2Cl_2); 72% e.e.; IR (KBr), *v* 2998, 1662, 1601, 1535, 1454, 1344, 1267, 1245, 1175, 1027, 833, 762, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.55 (s, 3H), 1.63 (s, 3H), 3.23 (dd, $J_{gem}=16.8$, 3.2 Hz, 1H), 3.63 (dd, $J_{gem}=16.8$, 10.4 Hz, 1H), 3.85 (s, 3H), 4.15 (dd, 1H), 6.90 (d, 2H, COPhH-*m*), 7.22–7.29 (m, 5H, CHPhH), 7.86 (d, 2H, COPhH-*o*); MS (EI) *m*/*z* 328 ($M+H^+$); anal. calcd for $C_{19}H_{21}NO_4$: C, 69.72; H, 6.42; N, 4.28. Found: C, 69.75; H, 6.40; N, 4.32%. One recrystallisation from ethanol gave the pure enantiomer of **3d**, $[\alpha]_D^{22}$ +111.2 (*c* 1, CH_2Cl_2).

3.2.4. 4-Methyl-4-nitro-3-(4-tolyl)-1-phenylpentan-1-one 3e. Yield: 72%; mp 109–110°C; $[\alpha]_D^{22}$ +52.9 (*c* 1, CH_2Cl_2); 48% e.e.; IR (KBr), *v* 2921, 1686, 1532, 1449, 1372, 1334, 1216, 814, 748, 686 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.55 (s, 3H), 1.63 (s, 3H), 2.29 (s, 3H), 3.25 (dd, $J_{gem}=17.3$, 3.3 Hz, 1H), 3.66 (dd, $J_{gem}=17.3$, 10.6 Hz, 1H), 4.12 (dd, 1H), 7.09 (d, 2H, CHPhH-*m*), 7.13 (d, 2H, CHPhH-*o*), 7.43 (t, 2H, COPhH-*m*), 7.55 (t, 1H, COPhH-*p*), 7.87 (d, 2H, COPhH-*o*); MS (EI) *m*/*z* 312 ($M+H^+$); anal. calcd for $C_{19}H_{21}NO_3$: C, 73.31; H, 6.75; N, 4.50. Found: C, 73.34; H, 6.72; N, 4.54%.

3.2.5. 4-Methyl-4-nitro-3-(4-nitrophenyl)-1-phenylpentan-1-one 3f. Yield: 67%; mp 95–97°C; $[\alpha]_D^{22}$ +99.8 (*c* 1, CH_2Cl_2); 78% e.e.; IR (KBr), *v* 2929, 1680, 1532, 1449, 1370, 1335, 1214, 820, 746, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.60 (s, 3H), 1.65 (s, 3H), 3.40 (dd, $J_{gem}=17.7$, 3.2 Hz, 1H), 3.71 (dd, $J_{gem}=17.7$, 10.6 Hz, 1H), 4.25 (dd, 1H), 7.43 (d, 2H, COPhH-*m*), 7.46 (d, 2H, CHPhH-*o*), 7.58 (t, 1H, COPhH-*p*), 7.87 (d, 2H, COPhH-*o*), 8.16 (d, 2H, CHPhH-*m*); MS (EI) *m*/*z* 343 ($M+H^+$); anal. calcd for $C_{18}H_{18}N_2O_5$: C, 63.16; H, 5.26; N, 8.19. Found: C, 63.20; H, 5.22; N, 8.22%. One recrystallisation from ethanol gave the pure enantiomer of **3f**, $[\alpha]_D^{22}$ +118.5 (*c* 1, CH_2Cl_2).

3.2.6. 4-Methyl-4-nitro-3-(4-dimethylaminophenyl)-1-phenylpentan-1-one 3g. Yield: 50%; mp 137–138°C; $[\alpha]_D^{22}$ +60.2 (*c* 1, CH_2Cl_2); 29% e.e.; IR (KBr), *v* 2996, 2899, 1678, 1616, 1530, 1366, 1343, 1232, 805, 756, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.55 (s, 3H), 1.64 (s, 3H), 2.93 (s, 6H), 3.22 (dd, $J_{gem}=17.0$, 3.1 Hz, 1H), 3.62 (dd, $J_{gem}=17.0$, 10.7 Hz, 1H), 4.07 (dd, 1H), 6.64 (d, 2H, CHPhH-*m*), 7.09 (d, 2H, CHPhH-*o*), 7.45 (t, 2H, COPhH-*m*), 7.55 (t, 1H, COPhH-*p*), 7.88 (d, 2H, COPhH-*o*); MS (EI) *m*/*z* 341 ($M+H^+$); anal. calcd for $C_{20}H_{24}N_2O_3$: C, 70.59; H, 7.06; N, 8.24. Found: C, 70.60; H, 7.02; N, 8.28%.

3.2.7. 4-Methyl-4-nitro-3-(3,4-dimethoxyphenyl)-1-phenylpentan-1-one 3h. Yield: 26%; mp 96–98°C; $[\alpha]_D^{22}$ +75.0 (*c* 1, CH_2Cl_2); 42% e.e.; IR (KBr), *v* 2991, 2964, 1684, 1531, 1345, 1258, 1242, 1146, 1024, 813, 766, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.56 (s, 3H), 1.63 (s, 3H), 3.25 (dd, $J_{gem}=17.0$, 3.8 Hz, 1H), 3.6 (dd, $J_{gem}=17.0$, 10.4 Hz, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 4.07 (dd, 1H), 6.76 (d, 3H, CHPhH-*o*,*m*), 7.42 (t, 2H, COPhH-*m*), 7.55 (t, 1H, COPhH-*p*), 7.86 (d, 2H, COPhH-*o*); MS (EI) *m*/*z* 358 ($M+H^+$); anal. calcd for $C_{20}H_{23}NO_5$: C, 67.23; H, 6.44; N, 3.92. Found: C, 67.20; H, 6.42; N, 3.96%.

3.2.8. 4-Methyl-4-nitro-3-(4-chlorophenyl)-1-(4-chlorophenyl)pentan-1-one 3i. Yield: 51%; mp 109–110°C; $[\alpha]_D^{22}$ +50.6 (*c* 1, CH_2Cl_2); 39% e.e.; IR (KBr), *v* 2996, 1682, 1590, 1533, 1398, 1345, 1231, 1095, 821, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.55 (s, 3H), 1.61 (s, 3H), 3.25 (dd, $J_{gem}=17.2$, 3.1 Hz, 1H), 3.58 (dd, $J_{gem}=17.2$, 10.5 Hz, 1H), 4.09 (dd, 1H), 7.16 (d, 2H, CHPhH-*m*), 7.27 (d, 2H, CHPhH-*o*), 7.41 (d, 2H, COPhH-*m*), 7.80 (d, 2H, COPhH-*o*); MS (EI) *m*/*z* 367 ($M+H^+$); anal. calcd for $C_{18}H_{17}NO_3Cl_2$: C, 59.02; H, 4.64; N, 4.22; Cl, 19.40. Found: C, 59.05; H, 4.62; N, 4.26; Cl, 19.38%.

3.2.9. 4-Methyl-4-nitro-3-(2-chlorophenyl)-1-(4-fluorophenyl)pentan-1-one 3j. Yield: 70%; mp 95–96°C; $[\alpha]_D^{22}$ +46.5 (*c* 1, CH_2Cl_2); 43% e.e.; IR (KBr), *v* 2993, 1683, 1597, 1542, 1343, 1229, 1160, 1037, 769 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.55 (s, 3H), 1.57 (s, 3H), 3.34 (dd, $J_{gem}=17.3$, 3.1 Hz, 1H), 3.50 (dd, $J_{gem}=17.3$, 10.7 Hz, 1H), 4.75 (dd, 1H), 7.00–7.10 (m, 4H, CHPhH-*o*,*m* and COPhH-*m*), 7.11 (t, 1H, CHPhH-*m*), 7.34 (t, 1H, CHPhH-*p*), 7.82 (d, 2H, COPhH-*o*); MS (EI) *m*/*z* 351 ($M+H^+$); anal. calcd for $C_{18}H_{17}NO_3ClF$: C, 61.80; H, 4.86; N, 4.01; Cl, 10.16; F, 5.44. Found: C, 61.85; H, 4.82; N, 4.04; Cl, 10.12; F, 5.45%.

3.2.10. 4-Methyl-4-nitro-3-(2-methoxyphenyl)-1-(4-nitrophenyl)pentan-1-one 3k. Yield: 52%; mp 106–108°C; $[\alpha]_D^{22}$ +27.3 (*c* 1, CH_2Cl_2); 67% e.e.; IR (KBr), *v* 2991, 2965, 1684, 1532, 1345, 1252, 1242, 1148, 1028, 813, 765 cm^{-1}; ^1H NMR ($CDCl_3$) δ ppm: 1.54 (s, 3H), 1.63 (s, 3H), 3.27 (dd, $J_{gem}=17.1$, 3.1 Hz, 1H), 3.64 (dd, $J_{gem}=17.1$, 10.7 Hz, 1H), 3.76 (s, 3H), 4.06 (dd, 1H), 6.81 (d, 2H, CHPhH-*m*), 7.13 (d, 2H, CHPhH-*o*), 7.98 (d, 2H, COPhH-*o*), 8.27 (d, 2H, COPhH-*m*); MS (EI) *m*/*z* 373 ($M+H^+$); anal. calcd for $C_{18}H_{17}NO_3ClF$: C, 61.29; H, 5.38; N, 7.53. Found: C, 61.33; H, 5.36; N, 7.55%.

3.2.11. Hydrogenation of compound 3b. A solution of **3b** (0.3 g, 0.9 mmol, $[\alpha]_D^{22}$ +58.5; 56% e.e.), sodium acetate (0.1 g, 1.22 mmol) and Pd/C (10%, 100 mg) in methanol (5 mL) was stirred under an atmosphere of H_2 (1 atm) at room temperature for 14 h. The reaction mixture was filtered and the filtrate was concentrated. The residue was purified by crystallisation to give **3a** as a solid (0.24 g, 80%); $[\alpha]_D^{22}$ +45.2 (*c* 1, CH_2Cl_2); 56% e.e.; mp 146–148°C ($[\alpha]_D^{22}$ +80.8 (*c* 1, CH_2Cl_2) for pure (+)-(*S*)-enantiomer). ^1H NMR ($CDCl_3$) δ ppm: 1.54 (s, 3H), 1.63 (s, 3H), 3.70 (dd, 1H, $J_{gem}=17.6$, 3.1 Hz), 4.09 (dd, 1H, $J_{gem}=17.6$, 10.0 Hz), 4.15 (dd, 1H), 7.18–7.32 (m, 5H, CHPhH), 7.42 (t, 2H, COPhH-*m*), 7.53 (t, 1H, COPhH-*p*), 7.85 (d, 2H, COPhH-*o*); MS (EI) *m*/*z* 298 ($M+H^+$).

3.3. X-Ray structure analysis of 3d

Crystal data: $C_{19}H_{21}NO_4$, formula wt.: 327.37, colourless, plate, size: 0.60×0.30×0.09 mm, monoclinic, space group $P2_1$, $a=14.698(1)$, $b=5.979(1)$, $c=20.14(2)$ Å, $\beta=107.14(1)°$, $V=1690.9(17)$ $Å^3$, $T=566(2)$ K, $Z=4$, $F(000)=696$, $D_x=1.286$ Mg/m^3, $\mu=0.736$ mm^{-1}. A crystal of **3d** was mounted on a glass fiber. Cell parameters were determined by least-squares of the setting angles of 49 ($25.04\leq\theta\leq46.15°$) reflections. Intensity data were collected on an Enraf–Nonius CAD4 diffractometer (graphite monochromator; Cu-Kα radiation, $\lambda=1.54184$ Å) at 295(2) K in the range $3.30\leq\theta\leq75.29°$ using $\omega/2\theta$ scans. Backgrounds were measured 1/2 the total time of the peak scans. The intensities of three standard reflections were monitored regularly (every 60 min). The intensities of the standard reflections remained constant within experimental error throughout the data collection. A total of 7886 reflections were collected of which 6806 were unique [$R_{int}=0.0076$, $R\sigma=0.0205$]; intensities of 5854 reflections were greater than $2\sigma(I)$,[9] completeness to $\theta=0.987$. An empirical absorption correction[10] was applied to the data (the minimum and maximum transmission factors were 0.188 and 1.00). Initial structure model was provided by direct methods.[11] Anisotropic full-matrix least-squares refinement[12] on F^2 for all non-hydrogen atoms yielded $R_1=0.0396$ and $wR_2=0.1068$ for 5854 [$I>2\sigma(I)$] and $R_1=0.0479$ and $wR_2=0.1115$ for all (6806) intensity data (number of parameters = 439, goodness-of-fit = 1.018, absolute structure parameter $x=-0.17(15)$,[13] the maximum and mean shift/esd is 0.007 and 0.001). The maximum and minimum residual electron density in the final difference map was 0.156 and –0.190 e $Å^{-3}$. Hydrogen atomic positions were calculated from assumed geometries. Hydrogen atoms were included in structure factor calculations but they were not refined. The isotropic displacement parameters of the hydrogen atoms were approximated from the $U_{(eq)}$ value of the atom they were bonded to.

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