Highly Enantioselective Organocatalytic Conjugate Addition of Nitromethane to Benzylidene Acetones

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ABSTRACT Six active 4-aryl-5-nitro-pentan-2-ones were synthesized enantioselectively from the corresponding 5-aryl-butenones by asymmetric Michael addition of nitromethane using an imidazolidine-type enantioselective organocatalyst. The ee ratio of the products were between 67 and 100%, determined by HPLC with Chiracel OD. Molecular and crystal structure of 3,4-methylenedioxy-phenyl-5-nitro-pentan-2-one has been studied by single crystal X-ray diffraction. *Chirality 20:1120–1126, 2008.*

KEY WORDS: organocatalyst; Michael addition; enantioselectivity; crystal structure; enantiomer excess

INTRODUCTION

The asymmetric conjugate addition is one of the most powerful bond-forming reactions to construct enantioenriched, highly functionalized carbon skeletons for total synthesis of natural and biological active compounds (for recent reviews see Refs. 1–6). Its importance is evident by considering that a Michael addition can represent the initiating step of more complex inter- and intramolecular tandem processes. The utility of this reaction is due, in part, to the broad spectrum of nucleophilic donors and electrophilic acceptors that can be employed in the transformation (see Refs. 7–12 for general reviews).

Nitroalkanes are particularly valuable source of stabilized carbanions, as the strongly electron withdrawing nature of the nitro group (pK_a $MeNO_2 < 10$) facilitates generation of the nitronate anion under mild conditions[13] and are suitable nucleophilic donors in Michael addition. Additionally, the nitro group is versatile functional group that can be converted to ketone (Nef reaction), reduced to amine, etc.[14] Although the γ-nitro-ketones which are the products of the conjugate addition of nitroalkanes to enones easily can be synthesized alternatively by the Michael addition of ketones to the corresponding nitroolefins, generally, the first route is preferable because of the better stability of enones than nitro olefins specially for large-scale synthesis.

In the last two decades, a variety of catalyst systems have been developed for the asymmetric conjugate addition of nitroalkanes and in particular nitromethane to chalcones. These include chiral crown ethers,[15–20] chiral Lewis acids,[21] phase transfer catalyst derived from cinchona alkaloids,[22–24] and cinchona alkaloid-derived thiourea catalysts,[25] and aluminum-salen complex.[26]

These methods, however, have good stereoselectivity either only in case of chalcones, or for other enones needed complicate bidentate catalysts (sometimes with metal-complexes) which mostly can be synthesized on lengthy, multistep routes.

Simple metal-free organocatalysts[27–31] having chiral pyrrolidine or imidazolidine skeleton, easily made from such common L-amino acids as L-proline or L-phenylalanine, developed in the last years by several groups,[32–38] seem to be the most successful enantioselective catalysts for a range of reactions. Proline (**1**) has been first used as its rubidium salt in the addition of nitroalkanes to enones with moderate to good enantioselectivities (41–84%).[39–42] The use of proline with amine additives for addition to enones was investigated by Hanessian and Pham[43] than Ley and coworkers improved the method using tetrazole derivatives of proline, in every case with piperazin derivatives as base additives, reaching 72–89% ee.[44–49]

Macmillan and coworkers have introduced the chiral imidazolidinone type catalyst **2** and **3** (Scheme 1), readily available from L-phenylalanine, methylamine, and acetone or pivalaldehyde, respectively,[50–55] but these catalysts have not been used in conjugate addition of nitroalkanes to enones.

Jørgensen and coworkers developed the simple chiral imidazolidine catalyst **4** (Scheme 1), which without any additives gave 34–86% enantioselectivities for conjugate addition of nitroalkanes to simple enones, for example, in case of nitrometane and benzylidene acetone the ee was

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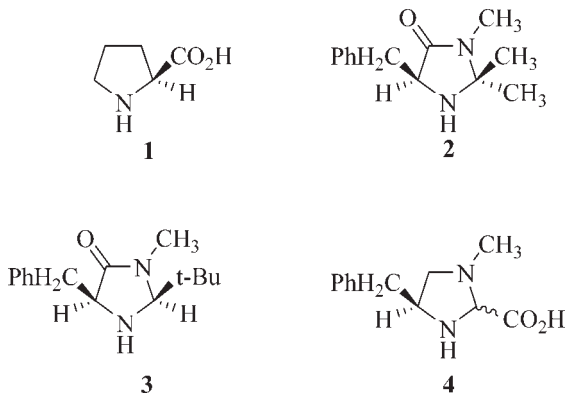


Scheme 1. The metal-free organocatalysts **1–4**.

73%.[56] Their catalyst gave good enantioselectivities in other type Michael reactions, too, for example, they developed a method for the synthesis of the anticoagulant warfarin and analogues.[57–60]

In our ongoing studies directing toward the synthesis of phenantridine alkaloids and their analogues we extended the application of the Jørgensen catalyst **4** for the enantioselective Michael addition of nitromethane to hydroxy, alkoxy, and methylenedioxy substituted benzylidene acetones **5a–f** and have reached in every case similar or better enantioselectivites than can be reached with the unsubstituted enone.[56] The synthesized six active 4-aryl-5-nitropentan-2-ones **6a–f** are suitable intermediates for our alkaloid synthesis (Scheme 2).

4-Aryl-5-nitro-pentan-2-ones as chiral compounds can be synthesized by Michael addition either from the prochiral 4-arylbutenones and nitromethane or from the prochiral β-nitrostyrenes and acetone. Both reactions are known for a long time using unsubstituted[61–69] or substituted[61–71] phenyl derivatives. Although it is obvious that both reactions can be performed enantioselectively; they were not described in the literature until recently.

The alternative way of preparation of the *R*-enantiomer of this compound **(6a)** from nitrostyrene and acetone[26,44–49,72] with bidentate or mixture catalysts was reported recently. The *R*-enantiomer of 4-(4-methoxyphenyl)-5-nitro-pentan-2-one was also synthesized,[26,72] anyhow none of other substituted active nitropentanones were prepared and published until now.

EXPERIMENTAL

General Procedures

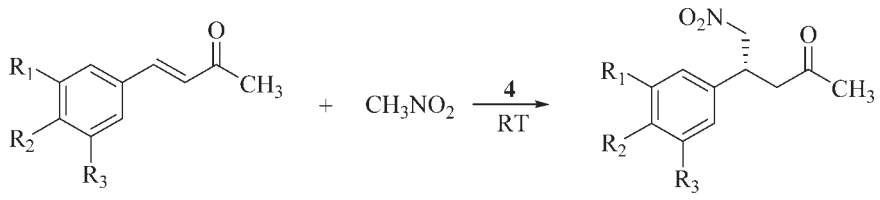
Melting points were determined using a Büchi 510 apparatus and are uncorrected. The optical rotation was measured with the help of a Perkin-Elmer 241 polarimeter at 20°C. NMR spectra were obtained in $CDCl_3$ on a Brucker DRX-500 instrument. Mass spectra were obtained on a Varian MAT312 instrument. Column chromatography was carried out using 70–230 mesh silica gel (Merck). The ee values were determined by HPLC (detector: JASCO UV-1575, pump: PU-1580).

Preparation of Starting Compounds 5a–f

Aryl-butenones **5a–f**[73–79] were synthesized from the corresponding aromatic aldehydes and acetone in diluted NaOH solution,[80] and were purified by distillation in reduced pressure or in some cases by crystallization from methanol.

General Method for Preparation of Michael Adducts 6a–f

The corresponding aryl-butenone (10.5 mmol) was dissolved in nitromethane (20 ml, 369.3 mmol) and catalyst **4** (2.1 mmol) was added to the solution. Then, the reaction mixture was stirred for 168 h in room temperature. The solvent was evaporated and the product was isolated by FC on silica gel using ether-pentane (1:1) as eluant.



5a-f **6a-f**

Compound	R^1	R^2	R^3
a	CH_3O	H	H
b	CH_3O	CH_3O	H
c	CH_3O	CH_3O	CH_3O
d		$-OCH_2O-$	H
e	CH_3O	HO	H
f	CH_3O	$PHCH_2O$	H

Scheme 2. The enantioselective synthesis of the 4-aryl-5-nitropentan-2-ones.

4-(3-Methoxyphenyl)-5-nitro-pentane-2-one (6a)

Yield: 68%; $[\alpha]_D^{20}$: −1.2° (*c* = 1, $CHCl_3$), 74% ee. The enantiomer excess was determined by HPLC analysis with Chiralcel OD (Daicel Chemical Industries); eluent: hexane:isopropanol = 8:2; flow rate: 1 ml/min; detection: UV 286 nm; temperature: 20°C. Oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.05 (s, 3H, 1-CH_3), 2.83 (d, 2H, 3-CH_2), 3.72 (s, 3H, OCH_3); 3.91 (kv, 1H, 4-CH), 4.50-4.62 (m, 2H, 5-CH_2), 6.67–6.74 (m, 3H, Ar-CH), 7.17 (t, 1H, Ar-CH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 30.6, 39.3, 46.3, 55.4, 79.6, 113.1, 113.8, 119.7, 130.3, 140.6, 160.2, 205.5; HRMS calcd for $C_{12}H_{15}NO_4$ (M^+) 237.1001, found 237.1004.

4-(3,4-Dimethoxyphenyl)-5-nitro-pentane-2-one (6b)

Yield: 49%; $[\alpha]_D^{20}$: −1.2° (c = 1, $CHCl_3$), 82% ee. The enantiomer excess was determined by HPLC analysis with Chiralcel OD (Daicel Chemical Industries); eluent: hexane:isopropanol = 8:2; flow rate: 1 ml/min; detection: UV 286 nm; temperature: 5°C, mp. 76–78°C, *Reichert* and *Posemann* gave 90–91°C (from methanol) for the pure racemic **6b**.[70,71] ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.05 (s, 3H, 1-CH_3), 2.82 (d, 2H, 3-CH_2), 3.78 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.88 (kv, 1H, 4-CH), 4.51–4.59 (m, 2H, 5-CH_2), 6.65-6.75 (m, 3H, Ar-CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.6, 39.0, 46.5, 56.1, 56.2, 79.9, 111.1, 111.7, 119.4, 131.5, 148.8, 149.4, 205.7; HRMS calcd for $C_{13}H_{17}NO_5$ (M^+) 267.1107, found 267.1113.

4-(3,4,5-Trimethoxyphenyl)-5-nitro-pentane-2-one (6c)

Yield: 72%; $[\alpha]_D^{20}$: −1.3° (*c* = 1, $CHCl_3$), 80% ee. The enantiomer excess was determined by HPLC analysis with Chiralcel OD (Daicel Chemical Industries); eluent: hexane:isopropanol = 8:2; flow rate: 1 ml/min; detection: UV 210 nm; temperature: 20°C, mp. 70–72°C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.07 (s, 3H, 1-CH_3), 2.82 (d, 2H, 3-CH_2), 3.74 (s, 3H, OCH_3), 3.77 (s, 6H, 2xOCH_3), 3.87 (kv, 1H, 4-CH), 4.50–4.63 (m, 2H, 5-CH_2), 6.34 (s, 2H, Ar-CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.6, 39.5, 46.5, 56.4, 61.0, 79.6, 104.7, 134.7, 137.8, 153.7, 205.5; HRMS calcd for $C_{14}H_{19}NO_6$ (M^+) 297.1212, found 297.1206.

4-(3,4-Methylenedioxy-phenyl)-5-nitro-pentane-2-one (6d)

Yield: 52%; $[\alpha]_D^{20}$: −2.1° (*c* = 1, $CHCl_3$), 100% ee. The enantiomer excess was determined by HPLC analysis with Chiralcel OD (Daicel Chemical Industries); eluent: hexane:isopropanol = 8:2; flow rate: 1 ml/min; detection: UV 286 nm; temperature: 5°C, mp. 100–102°C, *Walker* gave 96.5–98.5°C (from methanol) for the pure racemic **6d.**[61–69] ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.05 (s, 3H, 1-CH_3), 2.79 (d, 2H, 3-CH_2), 3.85 (kv, 1H, 4-CH), 4.43–4.60 (m, 2H, 5-CH_2), 5.87 (s, 2H, O—CH_2—O), 6.59–6.69 (m, 3H, Ar-CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.6, 39.1, 46.5, 79.9, 101.5, 107.9, 108.9, 120.9, 132.7, 147.4, 148.4, 205.5; HRMS calcd for $C_{12}H_{13}NO_5$ (M^+) 251.0794, found 251.0801.

4-(4-Hidroxy-3-methoxyphenyl)-5-nitro-pentane-2-one (6e)

Yield: 55%; $[\alpha]_D^{20}$: −0.5° (*c* = 1, $CHCl_3$), 67% ee. The enantiomer excess was determined by HPLC analysis with Chiralpak AD (Daicel Chemical Industries); eluent: hexane:isopropanol = 9:1; flow rate: 1 ml/min; detection: UV 224 nm; temperature: 5°C, mp. 66–68°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.13 (s, 3H, 1-CH_3), 2.89 (d, 2H, 3-CH_2), 3.89 (s, 3H, OCH_3), 3.94 (kv, 1H, 4-CH), 4.53–4.69 (m, 2H, 5-CH_2), 5.59 (s, 1H, OH), 6.69-6.88 (m, 3H, Ar-CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.7, 39.1, 46.6, 56.2, 80.0, 110.7, 115.0, 119.8, 130.9, 145.5, 146.9, 205.7; HRMS calcd for $C_{12}H_{15}NO_5$ (M^+) 253.0950, found 253.0955.

4-(4-Benzyloxy-3-methoxyphenyl)-5-nitro-pentane-2-one (6f)

Yield: 55%; $[\alpha]_D^{20}$: +1.5° (*c* = 1, $CHCl_3$), 71% ee. The enantiomer excess was determined by HPLC analysis with Chiralcel OD (Daicel Chemical Industries); eluent: hexane:isopropanol = 8:2; flow rate: 1 ml/min; detection: UV 210 nm; temperature: 30°C, 91–93°C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.03 (s, 3H, 1-CH_3), 2.79 (d, 2H, 3-CH_2), 3.80 (s, 3H, OCH_3), 3.85 (kv, 1H, 4-CH), 4.45-4.60 (m, 2H, 5-CH_2), 5.03 (s, 2H, O—CH_2—Ph), 6.58-6.76 (m, 3H, Ar-CH), 7.18–7.35 (m, 5H, Ar-CH); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 30.5, 38.8, 46.4, 56.2, 71.1, 79.7, 111.6, 114.3, 119.2, 127.3, 127.9, 128.6, 131.9, 137.0, 147.9, 150.0, 205.5; HRMS calcd for $C_{19}H_{21}NO_5$ (M^+) 343.1420, found 343.1427.

Single Crystal X-Ray Diffraction

The crystals of 3,4-methylenedioxy-phenyl-5-nitro-pentan-2-one are colorless platelets. The size of the crystal selected for single crystal X-ray diffraction measurement is 0.40 × 0.35 × 0.10 mm. Formula is $C_{12}H_{13}NO_5$, formula weight is 251.23, F(000) = 528. It crystallizes in the orthorhombic crystal system, space group $P2_12_12_1$. The cell dimensions are a = 5.6021(11) Å, b = 7.7172(13) Å, c = 27.479(6) Å, α = β = γ = 90°, V = 1188.0(4)A^3, Z = 4, D_x = 1.405 mgm^{-3}. A crystal was mounted on a loop in oil. The diffraction measurement was performed at T = 101(1) K. Intensity data were collected on a Rigaku R-Axis Rapid diffractometer (graphite monochromator; Mo-Kα radiation, λ = 0.71073 Å) in the range 3.0 ≤ θ ≤ 27.4°. Cell parameters were determined by least-squares of the setting angles of all collected reflections. A total of 45124 reflections were collected of which 2704 were unique [R(int) = 0.094, R(σ) = 0.0409]; 2576 reflections were >2σ(I). Completeness to 2θ = 0.998. An empirical absorption correction was applied to the data, μ = 0.111 mm^{-1}, the minimum and maximum transmission factors were 0.9571 and 0.9890. The structure was solved by direct methods with SHELXS97.[81] Neutral atomic scattering factors and anomalous scattering factors are taken from International Tables for X-ray Crystallography.[82] Anisotropic full-matrix least-squares refinement with SHELXL97[83,84] on F^2 for all nonhydrogen atoms yielded R1 = 0.0344 and wR2 = 0.0891 for 2576 [I > 2σ(I)], R1 = 0.0364 and wR2 = 0.0906 for all (2704) intensity data (goodness-of-fit = 1.032; the maximum and mean shift/esd 0.000 and 0.000).

TABLE 1. The yield, optical properties and melting point of the substituted phenyl-nitropentanones (6a–f) synthesized by asymmetric Michael addition of nitromethane to 4-aryl-but-3-en-2-ones 5a–f

Compound	R^1	R^2	R^3	Yield[a] (%)	ee[b] (%)	Optical rotation[c]	Mp (°C)
6a	CH_3O	H	H	68	74	−1.2°	– (oil)
6b	CH_3O	CH_3O	H	49	82	−1.2°	76–78
6c	CH_3O	CH_3O	CH_3O	72	80	−1.3°	70–72
6d	—OCH_2O—		H	52	100	−2.1°	100–102
6e	CH_3O	OH	H	55	67	−0.5°	66–68
6f	CH_3O	$PhCH_2O$	H	55	71	+1.5°	91–93

[a]Yields were determined after isolated by FC on silica gel.
[b]Enantiomer excess were determined with chiral HPLC on Chiracel OD.
[c]Conditions: 20°C, solvent: $CHCl_3$, $c = 1$.

The Flack x parameter[87] is −0.7(9), what is poorly reliable because of the lack of atoms with substantial anomalous scattering.

Number of parameters = 164. The maximum and minimum residual electron density in the final difference map was 0.274 and −0.207 e A^{-3}. The weighting scheme applied was

$$w = 1/\left[\sigma^2(F_0^2) + (0.0472P)^2 + 0.2884P\right], \quad \text{where} \quad P = (F_o^2 + 2F_c^2)/3$$

Hydrogen atomic positions were located in difference maps. 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.

Crystallographic data (excluding structure factors) for the above crystal structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 642785

RESULTS AND DISCUSSION

The synthesis of six new active 4-aryl-5-nitro-pentan-2-ones (**6a–f**) is reported by asymmetric Michael addition of nitromethane to the appropriate 4-aryl-butenones **5a–f** using Jørgensen's enantioselective organocatalyst **4**. The organocatalyst was carefully chosen based on the reported high enantioselectivity achieved with the unsubstituted phenyl-nitropentanone.

Organocatalyst **4** proved to be highly effective in our experiments: synthesis of all substituted phenyl-nitropentanones **6a–f** gave similar or better ee-ratio than the unsubstituted reactant.

The yield of the syntheses, enantiomer excess, optical rotation and melting point of the substituted phenyl-nitropentanones (**6a–f**) synthesized by asymmetric Michael addition of nitromethane to 4-aryl-but-3-en-2-ones **5a–f** are listed in Table 1. Considering the ee ratio of the products with increasing number of methoxy substituents higher enantioselectivity can be observed. Practically enantiopure product was obtained in case of the 3,4-methylenedioxy substituted derivative (**6d**). Presence of the free phenolic hydroxy or benzyloxy groups yielded lower ee ratio.

The asymmetric Michael addition reactions were carried out in nitromethane as solvent at ambient temperature using 20 mol % of catalyst **4**. The reaction time was 168 h in each case. After evaporation of the nitromethane in reduced pressure, the crude reaction mixture was purified

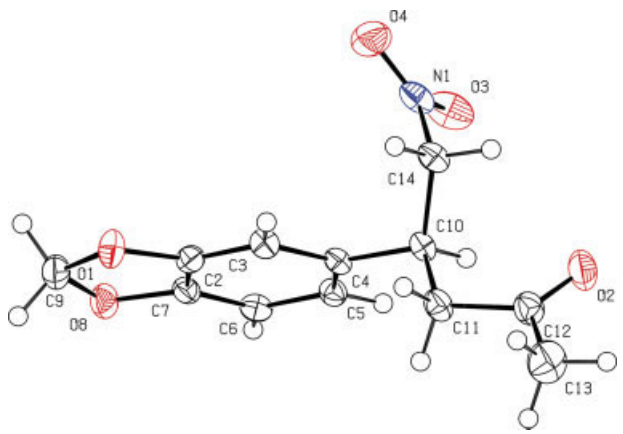


Fig. 1. The molecular structure[85] of **6d**. The displacement parameters are shown on 50% probability level. The chiral center is C10. Heteroatoms are shaded. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

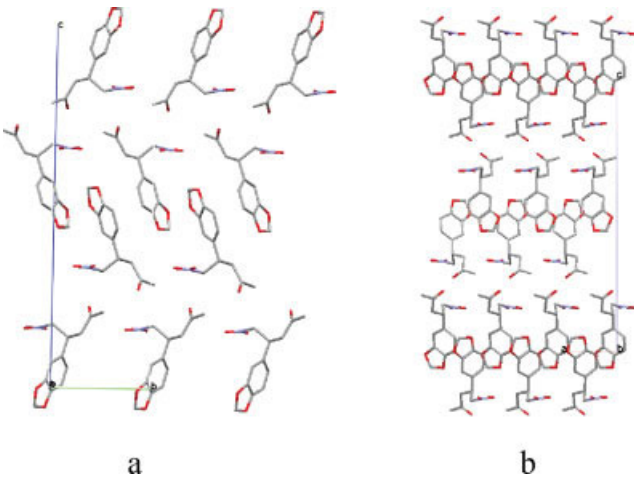


Fig. 2. The packing arrangement[86] in the crystal of **6d**. Hydrogen atoms are omitted for clarity. (**a**), View from the crystallographic axis *a* (**b**), View from the crystallographic axis *b*. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE 2. Hydrogen bonds in the crystal structure

Atoms	D-H	H···A	D···A	D-H···A	Symmetry operation
Intermolecular week H-bonds					
C9 – H9A .. O4	0.990	2.550	3.209(2)	124.00	$1/2 + x, -1/2 - y, -z$
C14 – H14A .. O3	0.990	2.510	3.450(2)	159.00	$1 + x, y, z$
C14 – H14B .. O2	0.990	2.520	3.143(2)	121.00	$-x, -1/2 + y, 1/2 - z$
Weak intramolecular H-bond stabilising the molecular conformation					
C14 – H14B .. O2	0.990	2.460	3.071(2)	119.00	–

by FC on silica gel. The residue was used directly for ee determination by HPLC on Chiracel OD. The products crystallized slowly in most cases. It was used for determination of optical rotation and melting point, and for analytical measurements, NMR and MS spectroscopy. Synthesis of **6d** resulted in practically enantiopure product.

Single crystal X-ray diffraction measurement was performed with 3,4-methylenedioxy-phenyl-5-nitro-pentan-2-one **6d**. There is one molecule in the asymmetric unit of the crystal structure (see Fig. 1).

6d crystallizes in the orthorhombic chiral space group $P2_12_12_1$ (No. 19). The quality of the crystal was good, the measurement was performed at low temperature (101 K), the structure is ordered, it was possible to locate all hydrogen atoms in the difference Fourier maps, and to refine the structure to $R = 0.0344$ for $I > 2\sigma$. The molecules are arranged by alternating layers of the constituents (see Fig. 2), the ring and the alkyl substituent moieties, respectively, along the crystallographic axis *c*, in the crystallographic *ab* plane.

There are no strong intermolecular interactions in the crystal structure owing to the lack of donors, although several potential acceptors are present. There are three weak C—H···O type intermolecular interactions among the molecules (Table 2). One intramolecular weak C—H···O hydrogen bond contributes to the stability of the molecular conformation, its graph set descriptor[87] is S6. There are no attractive π···π interactions, but two C—H···π interactions are found to the aromatic ring: C6-H6···π (2.63 Å, 3.3592(17) Å, 134°) and C9-H9B···π (2.81 Å, 3.4993(18) Å, 127°). The unit cell contains no residual solvent accessible void. The determined (S) absolute configuration[88] by single crystal X-ray diffraction is hardly reliable because of the lack of strong anomalous scattering centers.

CONCLUSION

The imidazolidine-type enantioselective organocatalyst **4** was utilized for synthesizing six new active 4-aryl-5-nitropentan-2-ones. According to the results, the catalyst proved to be very effective: the ee ratios of the products were between 67 and 100%. Single crystal X-ray diffraction was applied to determine the molecular and crystal structure having weak CH···π interactions only.

In summary, the application of the catalyst **4** can be highly utilized towards the synthesis of phenantridine alkaloids.

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