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Chlorodinitrophenylhydrazine, a useful crystalline agent for absolute configuration determination of various chiral ketones

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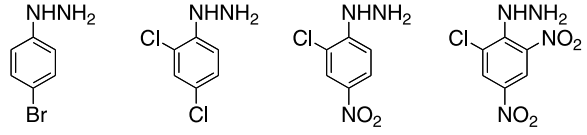
Abstract—For the determination of absolute configuration of various chiral ketones, we examined some hydrazines having a heavy atom as crystalline auxiliaries, and found that 2-chloro-4,6-dinitrophenylhydrazine is a useful crystalline agent for carbonyl compounds. Chiral hydrazones prepared from the hydrazine and various chiral ketones gave suitable single crystals for X-ray crystallographic analysis. The absolute configurations of the hydrazones were determined by X-ray crystallographic analysis using anomalous dispersion effect of the chlorine atom. The hydrazine is a useful crystalline agent for absolute configuration determination of various chiral ketones.

1. Introduction

Optically active α-substituted ketones (α-chiral ketones) are versatile intermediates for the synthesis of natural products, especially in pheromone synthesis.[1] A number of methods for the synthesis of α-chiral ketones have been reported, for example, stereoselective α-alkylation[2] and enantioselective protonation of enolates and enols.[3] Enzymatic transformations to obtain α-chiral ketones have also been reported, for example, hydrolysis of enol esters[4] and reduction of α,β-unsaturated carbonyl compounds (enones).[5] The enantioselective protonation of enol esters[6] and enol ethers[7] using a catalytic antibody has also been reported. We have developed the method for the asymmetric synthesis of α-chiral ketones by the reduction of enones with baker's yeast[8] or a carbon–carbon double bond reductase purified from baker's yeast.[9] However, few studies are found in the literature for the direct method to determine the absolute configurations of these chiral ketones. They have been determined by derivation to the known compounds[2g,6] or assumed from empirical rules.[2f,4c,10]

X-ray crystallographic analysis is the only method to determine the absolute configuration of a molecule. The anomalous dispersion effect of a heavy atom must be used for the determination of the absolute configuration. However, in most cases, the chiral ketones reduced from the corresponding enones are oily substances and contain no heavy atom, so that single crystals must be prepared with a certain crystalline auxiliary having a heavy atom. Hydrazines are well-known to be good crystalline agents for ketones. It is easy that a halogen atom as a heavy atom is introduced into a phenyl ring in the phenylhydrazine. Thus, a phenylhydrazine derivative having (a) halogen atom(s) is employed as a crystalline agent (Scheme 1). Recently, we reported some preliminary results on the determination of absolute configuration of chiral ketones.[11] This paper will describe the details and application of this method.



1 **2** **6** **8**

Scheme 1.

2. Results and discussion

2.1. Design and synthesis of crystalline agents

At first, commercial 4-bromophenylhydrazine (**1**) and 2,4-dichlorophenylhydrazine (**2**) were used as crystalline agents, and hydrazones of chiral ketones were prepared with them under acidic conditions. All chiral ketones here studied (**3a–e**) were obtained by baker's yeast reduction of enones (Scheme 2).[8c] The yields of hydrazone (**4**, **5c**,**e**) are

Keywords: Phenylhydrazine; Chiral ketone; X-ray crystallography; Absolute configuration.
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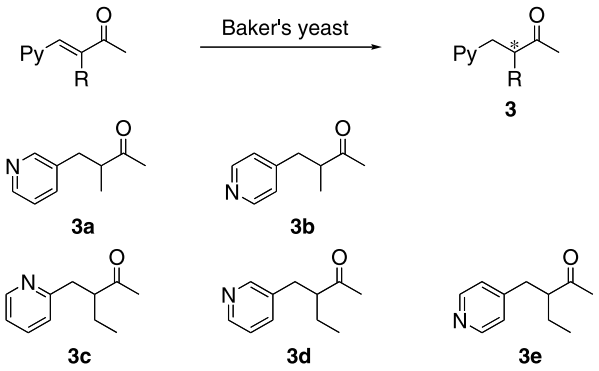


Scheme 2.

listed in Table 1. Unfortunately, these hydrazones did not give suitable single crystals for X-ray crystallographic analysis.

Table 1. Yields (%) of hydrazone

Ketone	Hydrazine			
	1	**2**	**6**	**8**
3a	**4** (70)			**10a** (64)
3b				**10b** (75)
3c		**5c** (63)	**7c** (40)	**10c** (31)
3d			**7d** (61)	**10d** (80)
3e		**5e** (35)	**7e** (24)	**10e** (86)
11				**14** (91)
12				**15** (59)
13				**16** (80)

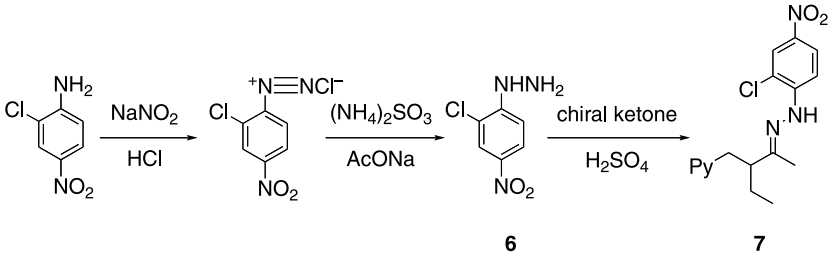
Since, a nitro group is also known to have a good crystallinity, introduction of a nitro group into the hydrazone is expected for more crystallinity. Therefore, 2-chloro-4-nitrophenylhydrazine (**6**) was designed and synthesized. It has a chlorine atom as a heavy atom and a nitro group for a crystallinity. Its synthesis was carried out in the conventional method (Scheme 3). 2-Chloro-4-nitrophenylhydrazones (**7**) were prepared from the corresponding hydrazine **6** and various chiral ketones (Table 1), but they did not give good single crystals as in the cases of **4** and **5**.

2-Chloro-4,6-dinitrophenylhydrazine (**8**) having two nitro groups was designed with the hope of more crystallinity.[12] 2-Chloro-4,6-dinitroaniline is a weak base because of two nitro groups and a chlorine atom, so that diazotization does not occur with a conventional way. Therefore, the aniline dissolved in hot acetic acid was diazotized with nitrosyl sulfate prepared from sodium nitrite and sulfuric acid,[13] and iodinated with potassium iodide to afford 1-chloro-2-iodo-3,5-dinitrobenzene (**9**). It was stirred with hydrazine monohydrate in methanol at room temperature to give the desired hydrazine **8** (Scheme 4).[14]

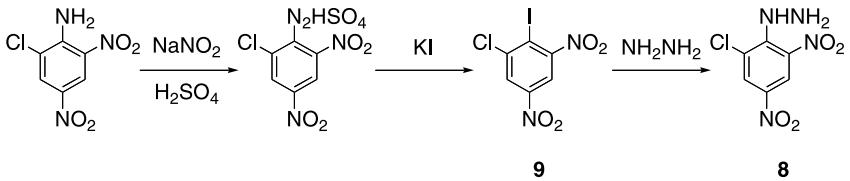
2.2. Determination of the absolute configuration of chiral ketones

The reaction of hydrazine **8** with chiral ketones in the presence of an acid catalyst gave chiral hydrazones **10** in good yields as shown in Table 1. The ketone **3a** and **3b** having a methyl group at the α-position of carbonyl group were racemized slowly under a strong acidic condition. The conditions to prevent the racemization were studied and found that ee of the chiral ketone kept with a catalytic amount of sulfuric acid. Therefore, syntheses of hydrazone with chiral ketones **3a** and **3b** having a methyl group at the α-position of carbonyl group were carried out under that condition (condition A). Syntheses with other ketones were done under a strong acid condition (condition B). Synthesized 2-chloro-4,6-dinitrophenylhydrazone derivatives (**10a–e**) were recrystallized from various solvents to obtain single crystals. Single crystals of the hydrazone were subjected to X-ray crystallographic analysis in order to elucidate their absolute configurations using the anomalous dispersion effect of a chlorine atom. The ORTEP drawings of **10a–e** are shown in Figures 1–5, respectively. Crystallographic data of the above analysis are listed in Table 2.

Except for **10c**, the structures of hydrazones exhibit (*E*)-forms at the carbon–nitrogen double bond, and the production of single isomer was confirmed by ^{1}H NMR experiments. As judged by ^{1}H NMR experiment, hydrazone **10c** consisted of two isomers, which should be (*E*)- and (*Z*)-forms. The ratio of isomers was about 1/1 estimated by



Scheme 3.



Scheme 4.

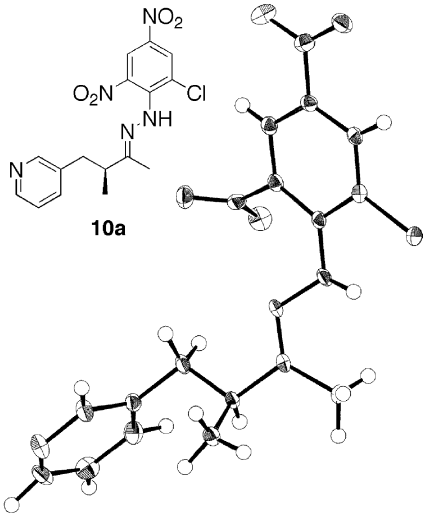


Figure 1. The ORTEP drawing of **10a** with displacement ellipsoids at 50% probability level. The asymmetric unit contains two independent molecules (only one molecule is shown).

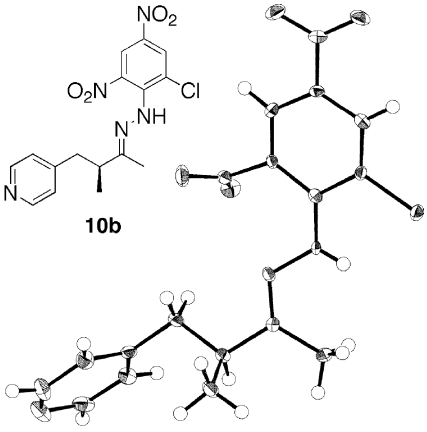


Figure 2. The ORTEP drawing of **10b** with displacement ellipsoids at 50% probability level. The asymmetric unit contains two independent molecules (only one molecule is shown).

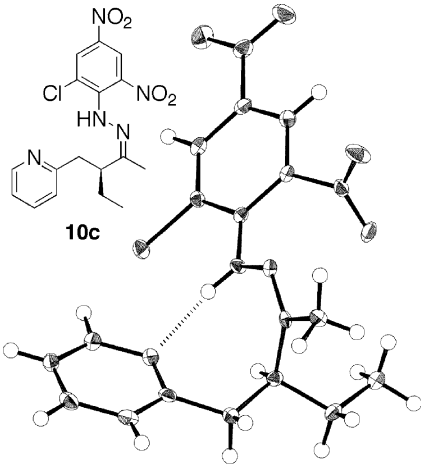


Figure 3. The ORTEP drawing of **10c** with displacement ellipsoids at 50% probability level.

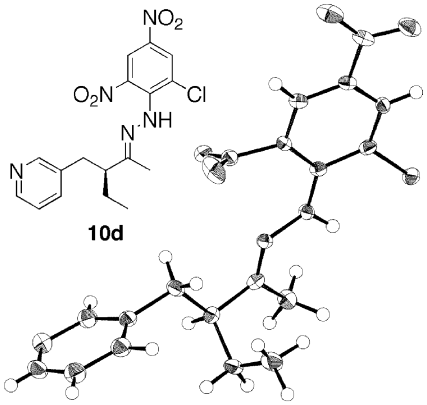


Figure 4. The ORTEP drawing of **10d** with displacement ellipsoids at 50% probability level.

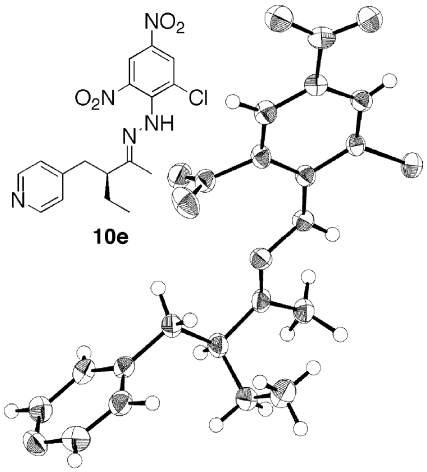


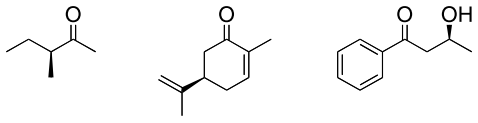
Figure 5. The ORTEP drawing of **10e** with displacement ellipsoids at 50% probability level.

integral curves in a ^{1}H NMR spectrum, but all the single crystals which subjected to X-ray crystallographic analysis were exhibited to be (*Z*)-form. The ORTEP drawing of (*Z*)-**10c** illustrated in Figure 3 shows that there exists a hydrogen bond between N in the pyridine ring and NH in the hydrazone moiety, the length of which is 2.91 Å. Because of the hydrogen bond, the (*Z*)-form should be stabilized and exhibit a good crystallinity. The absolute configurations of these hydrazones **10a–e** were determined to be *S* by Flack parameters[16] and intensities comparisons of Bijvoet pairs.[17] These configurations were determined by the anomalous dispersion effect of a chlorine atom in the crystalline auxiliary, 2-chloro-4,6-dinitrophenylhydrazine. Therefore, the absolute configurations of the chiral ketone obtained by baker's yeast reduction **3a–e** were determined to be *S*.

In order to apply this method to other types of chiral ketone, hydrazones were synthesized from a chiral alkyl ketone **11**, commercially available (*R*)-carvone **12**, and a chiral hydroxy ketone **13** (Scheme 5). The alkyl ketone **11** was supplied by Daicel Chemical Industries, Ltd and the hydroxy ketone **13** was obtained by baker's yeast reduction of the corresponding β-diketone.[15] The hydrazones **14–16** also gave single crystals which were subjected to X-ray crystallographic analysis in order to elucidate their absolute

Table 2. Crystallographic data of hydrazone **10a–e**

	10a	**10b**	**10c**	**10d**	**10e**
Formula	$C_{16}H_{16}ClN_5O_4$	$C_{16}H_{16}ClN_5O_4$	$C_{17}H_{18}ClN_5O_4$	$C_{17}H_{18}ClN_5O_4$	$C_{17}H_{18}ClN_5O_4$
Formula weight	377.79	377.79	391.81	391.81	391.81
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Monoclinic	Monoclinic
Space group	*C*2 (#5)	$P2_12_12$ (#18)	$P2_12_12_1$ (#19)	$P2_1$ (#4)	$P2_1$ (#4)
a (Å)	18.456 (10)	17.500 (2)	7.508 (4)	7.013 (7)	7.010 (4)
b (Å)	9.039 (5)	21.236 (2)	14.258 (7)	5.527 (5)	5.514 (2)
c (Å)	21.007 (11)	9.1634 (9)	16.590 (9)	23.38 (2)	23.89 (1)
β (°)	104.183 (6)			93.40 (2)	103.031 (5)
V (Å^3)	3397.6 (27)	3405.4 (5)	1776.0 (14)	904.6 (13)	899.7 (7)
Z value	8	8	4	2	2
No. observations	7616	7788	4045	3124	3899
No. variables	593	597	316	316	315
R_1 ($F^2>2.0\sigma(F^2)$)	0.050	0.050	0.038	0.049	0.060
wR_2 (all data)	0.128	0.085	0.066	0.133	0.168
S (all data)	1.04	1.01	1.00	1.08	1.10
Flack parameter	−0.03 (7) (*S*)	0.05 (5) (*S*)	0.03 (5) (*S*)	0.0 (1) (*S*)	0.0 (1) (*S*)



11 **12** **13**

Scheme 5.

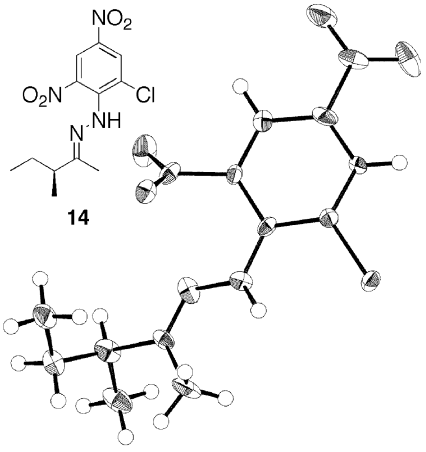
configurations using the anomalous dispersion effect of a chlorine atom. The ORTEP drawings of **14–16** are illustrated in Figures 6–8. The crystallographic data of **14–16** are listed in Table 3. The absolute configurations were successfully determined by Flack parameter[16] and intensities comparison of Bijvoet pairs.[17] To improve the practical usefulness of this method, Cu Kα ($\lambda=1.5418$ Å) radiation was tested as an alternative X-ray source. Structure determination of hydrazone **15** using Cu Kα radiation at room temperature also gave satisfactory results (Flack parameter[16] = 0.05 (2)).

In conclusion, we have developed a new method for the determination of the absolute configuration of chiral ketones. This is the simple and direct method and the potential of this methodology was clearly demonstrated. It should be noted that 2-chloro-4,6-dinitrophenylhydrazine (**8**) is a useful crystalline agent for this purpose. This method can be applied to both of aromatic and aliphatic chiral ketones, and is helpful for the determination of the absolute configuration of various chiral ketones.

3. Experimental

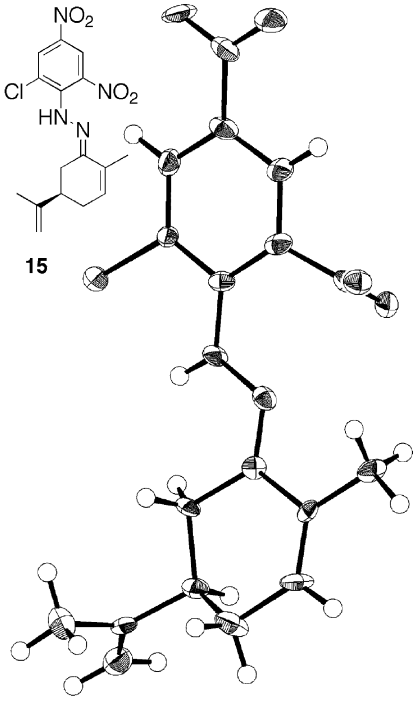
3.1. General

Organic reagents and solvents were purchased from Nacalai Tesque, Inc., Wako Pure Chemical Ind., Ltd, Tokyo Kasei Kogyo Co., Ltd, and Aldrich Chemical Co. Optically active 3-methyl-2-pentanone (**11**) was supplied by Daicel Chemical Industries, Ltd. ^{1}H NMR spectra (300 MHz) were recorded on a JEOL AL-300 spectrometer on $CDCl_3$



14

Figure 6. The ORTEP drawing of **14** with displacement ellipsoids at 50% probability level. The asymmetric unit contains two independent molecules (only one molecule is shown).



15

Figure 7. The ORTEP drawing of **15** with displacement ellipsoids at 50% probability level. The asymmetric unit contains two independent molecules (only one molecule is shown).

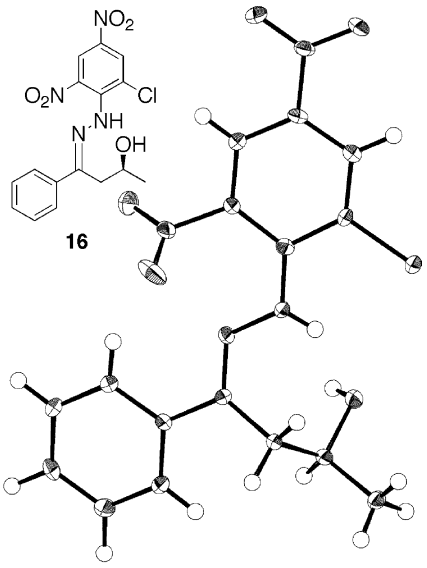


Figure 8. The ORTEP drawing of **16** with displacement ellipsoids at 50% probability level.

Table 3. Crystallographic data of hydrazone **14–16**

	14	**15**	**16**
Formula	$C_{12}H_{15}ClN_4O_4$	$C_{16}H_{17}ClN_4O_4$	$C_{16}H_{15}ClN_4O_5$
Formula weight	314.73	364.79	378.77
Crystal system	Monoclinic	Triclinic	Orthorhombic
Space group	$P2_1$ (#4)	$P1$ (#1)	$P2_12_12_1$ (#19)
a (Å)	7.090 (6)	8.146 (9)	7.0719 (5)
b (Å)	16.003 (12)	8.748 (10)	13.1074 (11)
c (Å)	12.855 (10)	12.388 (14)	17.718 (2)
α (°)		97.347 (13)	
β (°)	96.229 (11)	91.298 (10)	
γ (°)		108644 (14)	
V (Å^3)	1449.9 (17)	827.7 (16)	1642.3 (2)
Z value	4	2	4
No. observations	2813[a]	5013	3736
No. variables	379	456	295
R_1 ($F^2>2.0\sigma(F^2)$)	0.074[a]	0.074	0.028
wR_2 (all data)	0.184[a]	0.222	0.066
S (all data)	1.01[a]	1.24	1.00
Flack parameter	−0.1 (2) (*S*)	0.00 (11) (*R*)	−0.02 (5) (*S*)

[a] $F^2>3.0\sigma(F^2)$

with TMS as an internal reference. IR spectra were obtained on a HORIBA FT-720 spectrophotometer. Elemental analysis was performed with a Yanaco MT-5 elemental analyzer.

3.2. Preparation of hydrazine 8

3.2.1. 1-Chloro-2-iodo-3,5-dinitrobenzene (9). A slight modification of the reported method was adopted for the synthesis of this compound.[13,18] 2-Chloro-4,6-dinitroaniline (2.18 g, 10 mmol) in 27 mL of acetic acid was stirred at 70 °C until the aniline was dissolved. The solution was rapidly cooled below 20 °C. In another flask, 5.6 mL of sulfuric acid was cooled and vigorously stirred on an ice bath, sodium nitrite (0.80 g, 12 mmol) was added slowly. The mixture was heated at 70 °C until the solution was became clear, then the solution was cooled below 20 °C. With aniline solution stirring, nitrite solution was added dropwise to it keeping the temperature below 20 °C. The solution was stirred at 15–20 °C for 1 h. To the solution, potassium iodide (2.32 g, 14 mmol) dissolved in 20 mL of water was added slowly, then heated at 50 °C for 15 min. The solution was neutralized with aqueous sodium carbonate and the aqueous solution was extracted with ethyl acetate. The combined extracts were washed with aqueous sodium hydrogensulfite and brine, and dried over anhydrous magnesium sulfate. Removal of the solvent gave 1-chloro-2-iodo-3,5-dinitrobenzene quantitatively. ^{1}H NMR ($CDCl_3$, TMS) δ=8.35 (1H, d, J=2.4 Hz), 8.49 (1H, d, J=2.4 Hz). IR (KBr) 3082, 1554, 1534, 1364, 1342 cm^{-1}.

3.2.2. 2-Chloro-4,6-dinitrophenylhydrazine (8). A slight modification of the reported method was adopted for the synthesis of this compound.[14] 1-Chloro-2-iodo-3,5-dinitrobenzene (**9**, 3.28 g, 10 mmol) was dissolved in 30 mL of methanol. To the solution, hydrazine hydrate (1.03 g, 20.6 mmol) in 6 mL of methanol was added dropwise and stirred at room temperature, yellow precipitate was generated. After 28 h, the solvent and excess hydrazine were removed by suction filtration, and the residue was washed with methanol. The solid was recrystallized from ethyl acetate, 2-chloro-4,6-dinitrophenylhydrazine was obtained as yellow needles (1.36 g, 58.4%). ^{1}H NMR ($CDCl_3$, TMS) δ 4.08 (2H, br), 6.91 (1H, br), 8.32 (1H, d, J=2.4 Hz), 8.47 (1H, d, J=2.4 Hz). IR (KBr) 3353, 1654, 1540, 1508, 1324 cm^{-1}. Found: C, 30.76; H, 2.23; N, 23.86%. Calcd for $C_6H_5ClN_4O_4$: C, 30.98; H, 2.17; N, 24.09%.

3.3. Preparation of hydrazones

Method A. Phenylhydrazine derivative (0.43 mmol) was in 5 drops of sulfuric acid and 15 mL of ethanol, and heated on a boiling water bath until hydrazine was dissolved. After cooling, chiral ketone (0.43 mmol) in 2 mL of ethanol and 1 mL of water was added to the solution. After appropriate time, the solution was basified with saturated aqueous sodium carbonate and the aqueous solution was extracted with dichloromethane. The combine extracts were dried

over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate as an eluent to obtain phenylhydrazone derivative. The hydrazone was recrystallized to generate single crystals for X-ray crystallographic analysis. The yields of the isolated products, recrystallization solvents, and their spectra as well as physical data are listed below.

3.3.1. (*E*)-3-Methyl-4-(3-pyridyl)-2-butanone 2-chloro-4,6-dinitrophenylhydrazone (10a). Recrystallized from dichloromethane/ethyl acetate. Mp 146.5–147.8 °C; 64% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 1.11 (3H, d, J=6.5 Hz), 1.96 (3H, s), 2.58–2.71 (2H, m), 2.95 (1H, dd, J=5.6, 13.1 Hz), 7.20–7.25 (1H, m), 7.49–7.51 (1H, m), 8.36–8.47 (4H, m); IR (KBr) 3333, 1598, 1545, 1518, 1327 cm^{-1}. Found: C, 50.71; H, 4.29; N, 18.46%. Calcd for $C_{16}H_{16}ClN_5O_4$: C, 50.87; H, 4.27; N, 18.54%.

3.3.2. (*E*)-3-Methyl-4-(4-pyridyl)-2-butanone 2-chloro-4,6-dinitrophenylhydrazone (10b). Recrystallized from dichloromethane/ethyl acetate. Mp 182.3–183.9 C; 75% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 1.11 (3H, d, J=6.9 Hz), 1.96 (3H, s), 2.60 (1H, dd, J=8.4, 13.7 Hz), 2.67–2.79 (1H, m), 2.95 (1H, dd, J=6.0, 13.7 Hz), 7.10 7.12 (2H, m), 8.36–8.38 (2H, m), 8.46–8.51 (2H, m); IR (KBr) 3350, 1601, 1543, 1521, 1328 cm^{-1}. Found: C, 50.88; H, 4.40; N, 18.50%. Calcd for $C_{16}H_{16}ClN_5O_4$: C, 50.87; H, 4.27; N, 18.54%.

3.3.3. (*E*)-3-Methyl-2-pentanone 2-chloro-4,6-dinitrophenylhydrazone (14). Recrystallized from anisole/hexane. mp 61.2–63.3 °C; 91% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 0.88 (3H, t, J=7.4 Hz), 1.08 (3H, d, J=6.8 Hz), 1.33–1.48 (1H, m), 1.52–1.66 (1H, m), 1.95 (3H, s), 2.34 (1H, sextet, J=6.8 Hz), 8.36 (1H, d, J=2.5 Hz), 8.40 (1H, br), 8.47 (1H, d, J=2.5 Hz); IR (KBr) 3347, 1602, 1542, 1521, 1333 cm^{-1}; HRMS m/z found: 314.0782. Calcd for $C_{12}H_{15}ClN_4O_4$: 314.0782.

3.3.4. (*R*)-Carvone 2-chloro-4,6-dinitrophenylhydrazone (15). Recrystallized from dichlorometane/ethanol. Mp 189.5–190.2 °C; 59% yield; ^{1}H NMR ($CDCl_3$, TMS) δ; 1.56 (3H, s), 1.81 (3H, s), 2.14–2.26 (2H, m), 2.33–2.39 (1H, m), 2.50–2.57 (1H, m), 2.75 (1H, dd, J=3.9, 15.3 Hz), 4.83 (1H, br), 4.88 (1H, br), 6.19 (1H, br), 8.37 (1H, d, J=2.5 Hz), 8.47 (1H, d, J=2.5 Hz), 8.69 (1H, br); IR (KBr) 3348, 1600, 1550, 1517, 1323 cm^{-1}. Found: C, 52.41; H, 4.70; N, 15.20%. Calcd for $C_{16}H_{17}ClN_4O_4$: C, 52.68; H, 4.70; N, 15.36%.

3.3.5. (*S*)-3-Hydroxy-1-phenylbutan-1-one 2-chloro-4,6-dinitrophenylhydrazone (16). Recrystallized from dichlorometane/ethanol. Mp 204.5–205.8 °C; 80% yield; ^{1}H NMR ($CDCl_3$, TMS) δ; 1.47 (3H, d, J=6.1 Hz), 2.30 (1H, br), 3.00 (1H, d, J=14.5 Hz), 3.09 (1H, dd, J=9.2, 14.5 Hz), 4.41–4.45 (1H, m), 7.39–7.42 (3H, m), 7.64–7.66 (2H, m), 8.34 (1H, d, J=2.4 Hz), 8.44 (1H, d, J=2.4 Hz), 10.59 (1H, br); IR (KBr) 3519, 1598, 1539, 1507, 1319 cm^{-1}. Found: C, 50.51; H, 3.70; N, 14.60%. Calcd for $C_{16}H_{15}ClN_4O_5$: C, 50.74; H, 3.99; N, 14.79%.

Method B. Phenylhydrazine derivative (0.23 mmol) was dissolved in 0.25 mL of sulfuric acid and 0.37 mL of water, then 1 mL of ethanol were added. To the solution, chiral ketone (0.23 mmol) in 1 mL of ethanol was added, and heated on boiling water for 3 min. After appropriate time, the solution was basified with 2 M sodium hydroxide and the aqueous solution was extracted with dichloromethane. The combined extracts were dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel with ethyl acetate as an eluent to obtain six chloro-2.4-dinitrophenylhydrazone derivatives. The hydrazone was recrystallized to generate single crystals for X-ray crystallographic analysis. The yields of the isolated products, recrystallization solvents, and their spectra as well as physical data are listed below.

3.3.6. 3-(2-Pyridylmethyl)-2-pentanone 2-chloro-4,6-dinitrophenylhydrazone (10c)

Recrystallized from ethyl acetate. Mp 149.8–155.9 °C (dec); 31% yield; ^{1}H NMR of (*E*)- and (*Z*)-forms mixture ($CDCl_3$, TMS) δ 0.89 (3H, t, J=7.4 Hz), 1.03 (3H, t, J=7.4 Hz), 1.56–1.73 (2H×2, m), 1.81 (3H, s), 1.93 (3H, s), 2.90–3.02 (2H×2, m), 3.28 (1H, dd, J=4.2, 17.1 Hz), 3.76–3.88 (1H, m), 7.07–7.17 (2H×2, m), 7.55–7.64 (1H×2, m), 8.33–8.57 (3H×2+1H, m), 10.81 (1H, br); IR (KBr) 2959, 1601, 1534, 1517, 1324 cm^{-1}. Found: C, 52.13; H, 4.64; N, 17.75%. Calcd for $C_{17}H_{18}ClN_5O_4$: C, 52.11; H, 4.63; N, 17.83%.

3.3.7. (*E*)-3-(3-Pyridylmethyl)-2-pentanone 2-chloro-4,6-dinitrophenylhydrazone (10d)

Recrystallized from hexane/ethyl acetate. Mp 108.5–110.0 °C; 80% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 0.89 (3H, t, J=7.5 Hz), 1.54–1.63 (2H, m), 1.88 (3H, s), 2.54–2.63 (1H, m), 2.77–2.82 (2H, m), 7.19–7.24 (1H, m), 7.48–7.52 (1H, m), 8.35–8.47 (5H, m); IR (KBr) 3342, 1603, 1539, 1517, 1341 cm^{-1}. Found: C, 52.05; H, 4.57; N, 17.96%. Calcd for $C_{17}H_{18}ClN_5O_4$: C, 52.11; H, 4.63; N, 17.83%.

3.3.8. (*E*)-3-(4-Pyridylmethyl)-2-pentanone 2-chloro-4,6-dinitrophenylhydrazone (10e)

Recrystallized from methanol/chloroform/ethyl acetate. Mp 129.7–129.9 °C; 86% yield; ^{1}H NMR ($CDCl_3$, TMS) δ 0.89 (3H, t, J=7.4 Hz), 1.53–1.60 (2H, m), 1.88 (3H, s), 2.60–2.67 (1H, m), 2.72–2.86 (2H, m), 7.09–7.12 (2H, m), 8.35–8.47 (5H, m); IR (KBr) 3342, 1603, 1539, 1517, 1340 cm^{-1}; HRMS m/z found: 391.1035. Calcd for $C_{17}H_{18}ClN_5O_4$: 391.1047.

3.4. Crystallographic studies

A prismatic single crystal was mounted on a glass fiber. The lattice parameters and intensity data were measured on a Rigaku R-CCD/III diffractometer and radiation was Mo Kα (λ=0.71070 Å). The data were collected at a temperature of −180 °C using the ω scan technique to a maximum 2θ value of 55.0 degree. A total of 1200 oscillation images were collected. All the structures were solved by direct method SIR97[19] and expanded Fourier techniques.[20] All

non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically by full-matrix least square method. All calculations were performed using CrystalClear software package of Rigaku Corporation.[21,22] The ORTEP drawings are presented in Figures 1–8, and the crystallographic parameters are listed in Tables 2 and 3.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposit with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 172429 for **10a**, CCDC 172430 for **10b**, CCDC 172427 for **10c**, CCDC 172428 for **10d**, CCDC 172432 for **10e**, CCDC 172431 for **14**, CCDC 262899 for **15**, CCDC 262900 for **16**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

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