Studies on Direct Stereoselective Aldol Reactions in Aqueous Media

by **Yin-Su Wu**[a]), **Wei-Yan Shao**[b]), **Chuan-Qi Zheng**[b]), **Zhong-Li Huang**[b]), **Jiwen Cai***[a]), and **Qin-Ying Deng**[a])

[a]) School of Chemistry & Chemical Engineering, Sun Yat-Sen University, Guangzhou 510275, P. R. China (phone: +86-20-84114215; fax +86-20-84112245; e-mail: puscjw@zsu.edu.cn)

[b]) Instrumentation Analysis & Research Center, Sun Yat-Sen University, Guangzhou 510275, P. R. China

The direct aldol reaction of 4-nitrobenzaldehyde catalyzed by $NaHCO_3$, with three different ketones, Zn–proline, $NaHCO_3$/Zn–proline, and L-proline/Zn–proline in aqueous media, was studied to explore the selectivity of this environmentally benign type of reaction. Amazingly, $NaHCO_3$ proper was found to be an efficient catalyst for the selective synthesis of β-hydroxy ketones, showing good regio- and diastereoselectivity, with all reactions being completed within 9 h. Cyclopentanone and cyclohexanone were found to give rise to reversed diastereoisomer ratios, the *syn* and *anti* isomers being the major products, respectively – an unprecedented result. Also, the observed *syn* diastereoselectivity of aldol reactions catalyzed by L-proline and Zn–proline is remarkable. The corresponding condensation products **7** and **8** were characterized by ^{1}H-NMR and single-crystal X-ray analyses. Finally, a chelate- *vs.* nonchelate-type transition state is proposed to account for the differential diastereoselectivities.

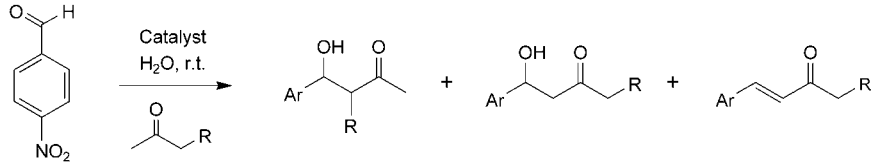
1. Introduction. – The *Mukaiyama* variant of the aldol reaction [1], in which acetone (or a similar substrate) is first converted to an active silyl enol ether, has been a popular tool in organic synthesis for the formation of C–C bonds. However, with increasing interest in environmentally safe and atom-economic reactions, *direct* aldol reactions, carried out in aqueous media, have attracted much attention [2–6]. The first example of a direct aldol reaction in aqueous medium, catalyzed by a metal-containing chiral *Lewis* acid, was reported just recently and proceeded only with moderate enantioselectivity [3]. Proline-catalyzed aldol reactions in phosphate buffer [4] and in aqueous micelles [5] showed no or only moderate diastereo- and enantioselectivities. However, even though tremendous progress has been made on stereoselective direct aldol reactions in *organic* solvents [7], the diastereoselectivity in *aqueous* media was found to be even higher in some cases [5][6]. Nevertheless, further systematic investigations are required to understand and gain control over the stereoselectivity of direct aldol reactions carried out in aqueous media.

An ideal catalyst for aldol reactions should be acidic enough to activate the aldehyde (to get high stereoselectivities), but also basic enough to abstract the α-H-atom of the ketone to generate a nucleophilic enolate [8]. Inspired by the successful design of asymmetric two-center catalysts for direct aldol reactions in organic solvents [8], we carried out a detailed investigation of the catalytic effect of $NaHCO_3$ (a *Brønsted* base), Zn–proline (a *Lewis* acid), and a combination of both. As a model reaction, 4-nitrobenzaldehyde was reacted, with three different ketones (butan-2-one, cyclopentanone and cyclohexanone) in aqueous medium. For comparison, the chiral

base L-proline in combination with Zn–proline was also examined to evaluate the influence of chiral or nonchiral co-catalysts on the stereoselectivity of the reaction.

2. Results and Discussion. – Conventionally, strong bases such as NaOH, KOH, EtONa, or Na_2CO_3 are being used as catalysts for aldol condensations of a ketone and an aldehyde, which typically produces a mixture of β-hydroxy and α,β-unsaturated ketones. We have screened the catalytic results of a variety of inorganic bases in a pH range of 8–11, using either acetone (**1**) or butan-2-one (**2**) in combination with 4-nitrobenzaldehyde (**3**) as the model reaction. We found that the use of $NaHCO_3$ and $KHCO_3$ as catalysts at pH 8.5–9.0 gave rise to β-hydroxy ketones exclusively (no elimination products), in contrast to stronger bases (*Table 1*). As a matter of fact, the reaction proceeded best with $NaHCO_3$, both in terms of yield and regioselectivity. Therefore, $NaHCO_3$ was chosen for further experiments.

Table 1. *Effect of Catalyst on the Direct Aldol Condensation between Acetone* (**1**) *or Butan-2-one* (**2**) *and 4-Nitrobenzaldehyde* (**3**) *in H_2O.* Overall yields were close to 100%.



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Ketone	Catalyst	pH	Time [h]	Product ratio
1	$KHCO_3$	8.5	8	**4c**/**4d** 100 : 0
1	$NaHCO_3$	9	7	**4c**/**4d** 100 : 0
1	Na_2CO_3	10	5	**4c**/**4d** 85 : 15
1	NaOH	11	5	**4c**/**4d** 3 : 97
2	$KHCO_3$	8.5	10	**4a**/**4b** 75 : 25
2	$NaHCO_3$	8.5	8	**4a**/**4b** 84 : 16
2	$Na_2B_4O_7$	8.5	8	**4a**/**4b** 78 : 22

As shown in *Scheme 1* and *Table 2*, in the model reaction of 4-nitrobenzaldehyde (**3**) with different ketones, the electrophile was completely converted to β-hydroxy ketones within a time period of 1 h–2 d. With butan-2-one (**2**) as the nucleophile, the isomer **4a** was obtained as the major product (*Entry 1* in *Table 2*). With cyclopentanone (**5**) or cyclohexanone (**6**), moderate to high diastereoselectivities were observed in the presence of different catalysts.

It is remarkable to observe that $NaHCO_3$ proper is an effective and efficient catalyst in the case of the reaction of **3** with butan-2-one (**2**) (high regioselectivity; *Entry 1* in *Table 2*), whereas only moderate diastereoselectivities were observed in the case of cyclopentanone (**5**) or cyclohexanone (**6**) (*Entries 5* and *9*, resp.), all reactions being completed within 9 h. Notably, the regioselectivity (**4a**/**4b** 84 : 16; *Entry 1*) with $NaHCO_3$ alone was higher than that observed with proline as catalyst in aqueous micelles (**4a**/**4b** 66 : 23) [5], where the reaction time was 96 h. The rate of conversion was even more slowed down, when the reaction was catalyzed by Zn–proline alone,

with a slightly decreased regioselectivity. However, when $NaHCO_3$ and Zn–proline were used as co-catalysts, the reaction rate was increased to a great extent, and the condensation was completed within 1 h, the regioselectivity being only marginally reduced (*Entry 3*). Similar results were obtained for a combination of $NaHCO_3$, Zn–proline, L-proline (*Entries 7* and *11*). These observations strongly suggest that $NaHCO_3$ can be used as a co-catalyst to increase the rate of the aldol reaction.

Scheme 1

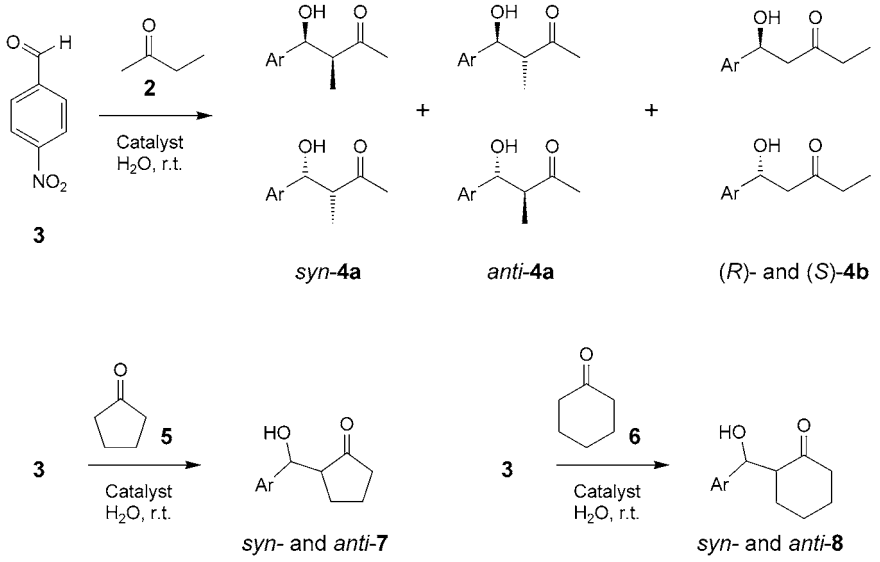


Table 2. *Results of Base-Catalyzed Direct Aldol Reactions of 4-Nitrobenzaldehyde* (**3**) *with Butan-2-one* (**2**), *Cylcopentanone* (**5**), *or Cyclohexanone* (**6**) *at Ambient Temperature in H_2O.* All conversions proceeded in basically quantitative yield, as judged by TLC, anal. HPLC, and ^{1}H-NMR. The literature yields [6] for **7** (*Entry 8*) and **8** (*Entry 12*) were 81 and 78%, resp. Asterisks (*) mark reversed diastereoselectivities (de). The term 'Pro' denotes 'proline'.

Entry	Ketone	Catalyst	Time[a]) [h]	Products[a])	*syn*/*anti*[a])	de [%][a])
1	**2**	$NaHCO_3$	8	**4a**/**4b** 84 : 16	48 : 52	4
2	**2**	Zn–Pro	43.5	**4a**/**4b** 71 : 29	44 : 56	12
3	**2**	$NaHCO_3$/Zn–Pro	1	**4a**/**4b** 71 : 29	32 : 68	34
4	**2**	L-Pro/Zn–Pro	29 (96)	**4a**/**4b** 79 : 21 (74 : 26)	48 : 52 (41 : 59)	4 (18)
5	**5**	$NaHCO_3$	5.5	**7**	74 : 26	48*
6	**5**	Zn–Pro	2	**7**	81 : 19	62*
7	**5**	$NaHCO_3$/Zn–Pro	1.5	**7**	78 : 22	56*
8	**5**	L-Pro/Zn–Pro	2 (120)	**7**	86 : 14[b]) (20 : 80)	72* (60)
9	**6**	$NaHCO_3$	9	**8**	33 : 67	34
10	**6**	Zn–Pro	43	**8**	15:85	70
11	**6**	$NaHCO_3$/Zn–Pro	4	**8**	22 : 78	56
12	**6**	L-Pro Zn–Pro	40 (96)	**8**	17:83 (26 : 74)	66

[a]) Values in parentheses according to [6]. [b]) At 0°, a *syn*/*anti* ratio of 97 : 3 (94% de) was observed.

Reversed diastereoselectivities were observed for the condensation of cyclopentanone (**5**) and cyclohexanone (**6**) in their reaction with 4-nitrobenzaldehyde (**3**), the *syn* and *anti* isomers being the major products, respectively. The isomer assignment was confirmed by single-crystal X-ray structure analyses of the products **7** and **8** (see the *Figure*). In the crystals, both isomers of **7** and **8** formed racemic dimers *via* pairs of strong intermolecular H-bonds formed between the C=O and OH groups.

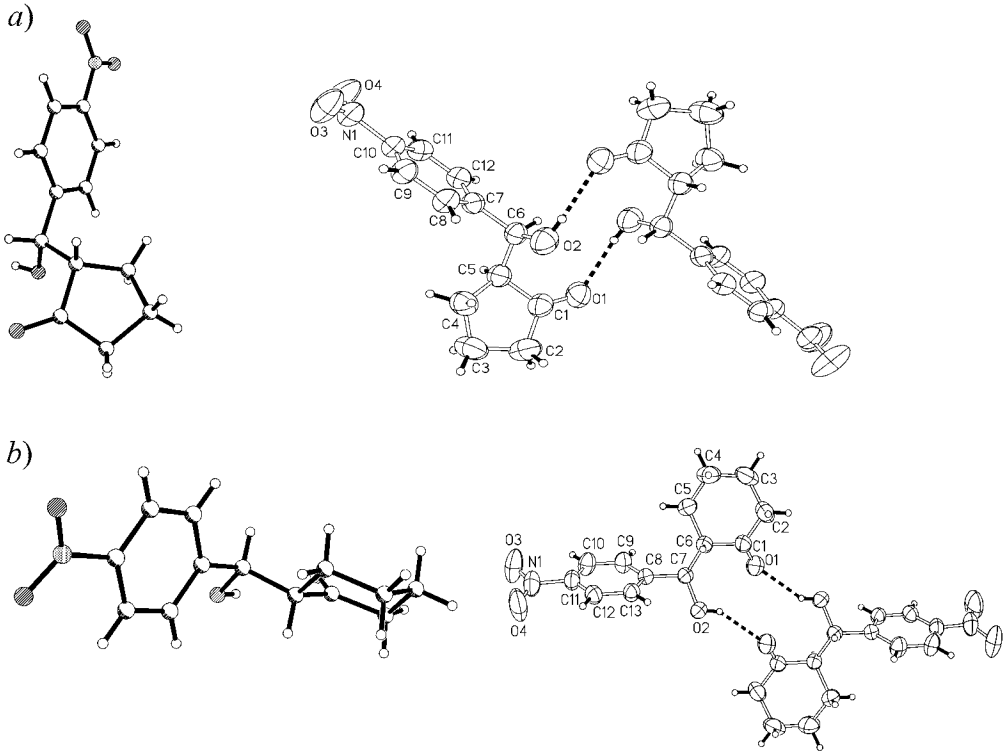
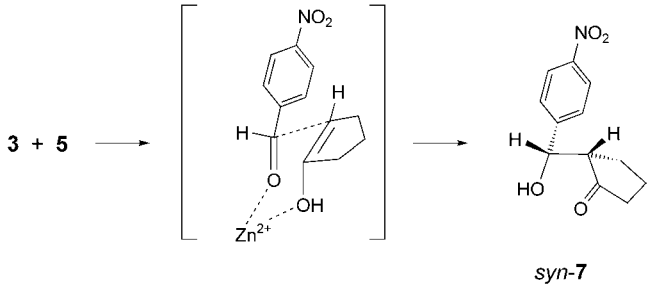


Figure. *Crystal structures of* a) *compound* **7** *and* b) *compound* **8**. Intermolecular H-bonds are indicated: O(1)···O(2) = 2.865(3) and 2.9740(15) Å, [O(1)–H···O(2)] = 161.4 and 150.1° for **7** and **8**, resp.

In the case of the model reaction of cyclopentanone (**5**), the diastereoselectivity was reversed relative to that observed in the proline-catalyzed aldol reaction carried out in aqueous micelles (*syn*/*anti* 20:80) [5], as well as that catalyzed by proline in organic solvent (*syn*/*anti* 27:46) [7e]. It was reported that, when chelates appear to be involved, H_2O (as a solvent) gives rise to better selectivities than organic solvents, with a *syn* preference being observed [6], which is in agreement with our results. This behavior can be rationalized by a chelate-type transition state, as proposed in *Scheme 2* for the reaction between **3** and **5**.

Scheme 2. *Proposed Chelate-Type Transition State Leading to the* syn-*Configured Product* **7**



By lowering the temperature, the *syn*/*anti* ratio of our model reaction could be increased from 86:14 (de 72%)[1]) at room temperature to 97:3 (de 94%) at 0°, indicating that the reaction might be kinetically controlled [9]. When the chiral auxiliary base L-proline was used as a co-catalyst, the reaction showed moderate diastereoselectivity (de 72%; *Entry 8* in *Table 2*). With Zn–proline only, a de value of 70% was achieved (*Entry 10*).

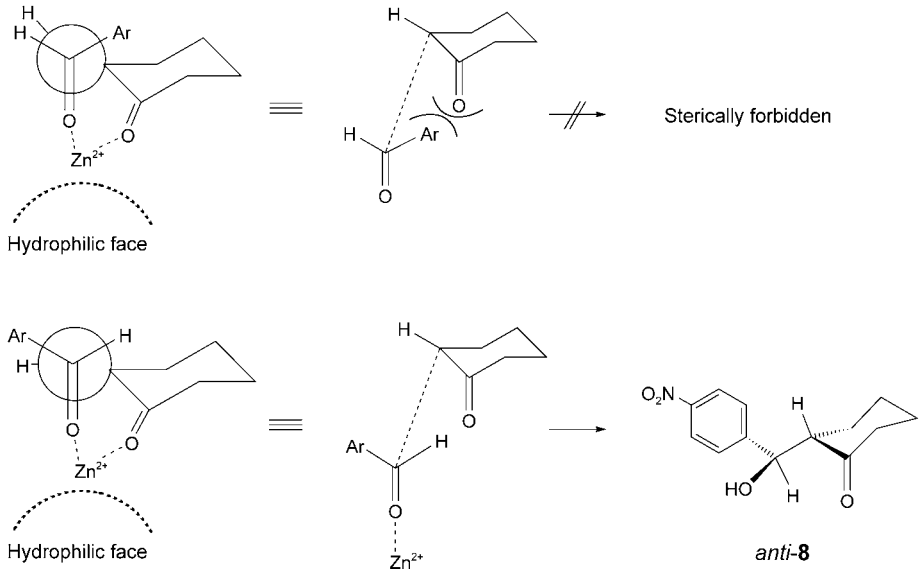
It is known that, in aqueous media, the concentration of the enol conjugate of cyclohexanone (**6**) is *ca.* 32-times lower (*ca.* 4 *vs.* 130 ppm) than that of the enol form of cyclopentanone (**5**) [10]. Therefore, a nonchelated, sterically controlled transition state is more likely to be involved in the case of **6**, with a preference of the thermally stable *anti* isomer similar to that in proline-catalyzed aqueous micelles [5], as well as in organic media [7e]. With cyclohexanone (**6**), the reaction is also much slower than with cyclopentanone (**5**).

Lubineau [11] first reported that the reaction of the Me_3Si enol ether of **6** with benzaldehyde in aqueous solution at room temperature gives good yields of β-hydroxy ketone even in the absence of catalyst, with a *syn* preference, which is the reverse compared to the *Lewis* acid catalyzed *Mukaiyama* reaction under anhydrous conditions [1]. However, *Yamamoto* and *Maruyama* [12] re-investigated this reaction under high-pressure conditions (without a catalyst), and found that the *syn* isomers predominate. *Lubineau* concluded that organic reactions in aqueous media are similar to reactions under high-pressure conditions: nonpolar substrates in H_2O aggregate due to hydrophobic interactions, thereby creating an interior cavity similar as that generated by high pressure [11]. Therefore, H_2O molecules, together with metal ions, can alter the stereoselectivity observed in organic media, most probably *via* variant transition states. A possible reaction mechanism that takes these aspects into account is proposed in *Scheme 3* for the aldol reaction of cyclohexanone (**6**).

3. Conclusions. – We have identified a simple inorganic *Brønsted* base, $NaHCO_3$, as an effective and efficient catalyst for direct aldol condensation reactions in aqueous media. This catalyst gives rise to β-hydroxy ketones only, with high regioselectivities and moderate diastereoselectivities. $NaHCO_3$ can also be used as a co-catalyst to speed up aldol condensations, basically without affecting the stereochemical outcome of the

[1]) Diastereoisomeric excess (de).

Scheme 3. *Proposed Chelate-Free, but Hydrophilically Controlled Transition State Leading to the* anti-*Configured Product* **8**



reaction. For the first time, a differential preference in terms of diastereoselectivity was observed in the direct aldol reaction of cyclopentanone *vs.* cyclohexanone under identical conditions. The observed *syn* or *anti* preferences might be controlled by different transition states, depending on the concentration of the nucleophilic enol forms of the ketones. Finally, the *syn* diastereoselectivity observed for condensations catalyzed by L-proline and Zn–Proline is remarkable and unprecedented in direct aldol reactions.

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Experimental Part

General. All reagents were commercially available and used as received. ^{1}H-NMR Spectra were recorded at ambient temp. on a *Varian UNITY/NOVA-500* spectrometer, using $CDCl_3$ as solvent. Chemical shifts δ are expressed in ppm rel. to $SiMe_4$ (=0 ppm), coupling constants J are given in Hz.

General Procedure for Direct Aldol Condensation in H_2O. To a mixture of the ketone (20 mmol) and 4-nitrobenzaldehyde (1 mmol), a soln. of the corresponding catalysts (0.2 mmol) in H_2O (4 ml) was added. The resulting mixture was stirred at r.t., and the reaction was followed by TLC until no 4-nitrobenzaldehyde was detected. The mixture was then extracted with AcOEt, the org. phase was dried ($MgSO_4$) and evaporated to give the basically pure products, which were identified by ^{1}H-NMR and/or X-ray crystallography.

4-Hydroxy-3-methyl-4-(4-nitrophenyl)butan-2-one (**4a**). ^{1}H-NMR ($CDCl_3$; *syn*-isomers): 7.51–8.20 (*m*, 4 arom H); 5.26 (*d*, *J* = 3.0, H–C(4)); 2.86 (*m*, H–C(3)); 2.23 (*s*, Me(1)); 1.05 (*d*, *J* = 4.5, Me–C(3)). ^{1}H-NMR ($CDCl_3$; *anti*-isomers): 7.51–8.92 (*m*, 4 arom. H); 4.88 (*d*, *J* = 8.0, H–C(4)); 2.91 (*q*, H–C(3)); 2.23 (*s*, Me(1)); 0.98 (*d*, *J* = 7.5, Me–C(3)).

5-Hydroxy-5-(4-nitrophenyl)pentan-3-one (**4b**). ^{1}H-NMR ($CDCl_3$): 7.51–8.92 (*m*, 4 arom. H); 5.63 (*m*, H–C(5)); 2.86 (*m*, CH_2(4)); 2.49 (*q*, *J* = 7.5, CH_2(2)); 1.07 (*t*, Me(1)).

2-[Hydroxy(4-nitrophenyl)methyl]cyclopentanone (**7**). ^{1}H-NMR ($CDCl_3$; *syn*-isomers): 7.53–8.23 (*m*, 4 arom. H); 5.42 (*d*, *J* = 2.5, O–CH); 1.53–2.51 (br. *m*, 7 H). ^{1}H-NMR ($CDCl_3$; *anti*-isomers): 7.53–8.23 (*m*, 4 arom. H), 4.84 (*d*, *J* = 9.5, O–CH); 1.53–2.51 (br. *m*, 7 H).

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone (**8**). ^{1}H-NMR ($CDCl_3$; *syn*-isomers): 7.48–8.22 (*m*, 4 arom. H); 5.48 (*d*, *J* = 2.5, O–CH); 1.34–2.64 (br. *m*, 9 H). ^{1}H-NMR ($CDCl_3$; *anti*-isomers): 7.48–8.22 (*m*, 4 arom. H); 4.90 (*d*, *J* = 8.5, O–CH); 1.34–2.51 (br. *m*, 9 H).

X-Ray Crystallography. Single crystals of both **7** (*syn*-isomers from *Entry 8* of *Table 2*) and **8** (*anti*-isomers from *Entry 10* of *Table 2*), were obtained by slow evaporation of the corresponding AcOEt soln. X-Ray data were collected on a *Bruker SMART 1000 CCD* diffractometer at ambient temp. Absorption corrections were applied. The structures were solved by direct methods, and all non-H-atoms were refined with anisotropic displacement parameters. All H-atoms were placed at idealized positions and refined as riding atoms. The crystallographic data are listed in *Table 3*. Crystallographic data (excluding structure factors) have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication numbers CCDC-225073 and -225074, respectively. 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 *via* e-mail at deposit@ccdc.cam.ac.uk.

Table 3. *Crystallographic Data*

	7	**8**
Empirical formula	$C_{12}H_{13}NO_4$	$C_{13}H_{15}NO_4$
Formula weight [g mol^{-1}]	235.23	249.26
Temperature [K]	293(2)	293(2)
Wavelength [Å]	0.71073	0.71073
Crystal size [mm]	0.50 × 0.50 × 0.37	0.44 × 0.33 × 0.29
Crystal system (space group)	Monoclinic ($P2_1/a$)	Monoclinic ($P2_1/c$)
a [Å]	7.5141(10)	5.4517(6)
b [Å]	12.2194/17)	25.590(3)
c [Å]	12.4822(16)	8.9124(10)
β [°]	96.174(2)	91.543(2)
Volume [Å^3]	1139.4(3)	1242.9(2)
Z	4	4
Calc. density [g cm^{-3}]	1.371	1.332
Absorption coefficient [mm^{-1}]	0.104	0.099
F(000)	496	528
Theta range (°)	2.34–25.00	2.42–30.03
Limiting indices	$-8 \le h \ge 8$	$-6 \le h \ge 7$
	$14 \le k \ge 9$	$-35 < k \ge 26$
	$-14 \le l \ge 14$	$-12 \le l \ge 11$
Reflections collected	5604	8374
Unique	2001 [R(int) = 0.0194]	3303 [R(int) = 0.0158]
Completeness	100.0%	90.7%
Data / restraints / parameters	2001 / 0 / 155	3303 / 0 / 164
Goodness-of-fit on F^2	1.093	1.038
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0648$	$R1 = 0.0515$
	w$R2 = 0.2025$	w$R2 = 0.1411$

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