Tetrahedron 64 (2008) 7729–7740

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Racemic and asymmetric cobalt-catalysed reductive aldol couplings of α,β-unsaturated amides with ketones

Ralph J.R. Lumby, Pekka M. Joensuu, Hon Wai Lam *

School of Chemistry, University of Edinburgh, Joseph Black Building, The King's Buildings, West Mains Road, Edinburgh EH9 3JJ, United Kingdom

ARTICLE INFO

Article history:
Received 27 March 2008
Received in revised form 15 May 2008
Accepted 5 June 2008
Available online 10 June 2008

ABSTRACT

In the presence of diethylzinc as a stoichiometric reductant, substoichiometric quantities of an appropriate cobalt source catalyse diastereoselective reductive aldol coupling reactions of α,β-unsaturated amides with ketones. The use of a readily available oxazolidine as a chiral auxiliary imparts high levels of asymmetric induction in these reactions.

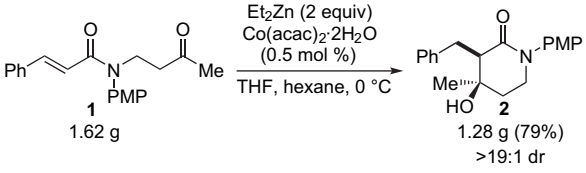
1. Introduction

The reductive aldol reaction, in which an aldehyde or ketone undergoes reaction with an enolate generated in situ by the conjugate reduction of an α,β-unsaturated carbonyl compound, is a powerful and well-established method of carbon–carbon bond formation.[1,2] Using various metal precatalysts and stoichiometric reductants that include silanes, triethylborane and molecular hydrogen, a wide variety of inter- and intramolecular reductive aldol reactions have been described.[1,2] A recent major development in this area is the ability to control the absolute stereochemistry of the products through the use of substoichiometric quantities of chiral metal–ligand complexes.[2]

One contribution to this field from our research group has been the development of both inter- and intramolecular reductive aldol reactions that employ diethylzinc as the stoichiometric reductant, in conjunction with cobalt[3] or nickel[4] precatalysts. An advantageous feature of these conditions is the ability to promote high-yielding reactions between β-substituted α,β-unsaturated carboxylic acid derivatives and ketones, reaction partners that are situated on the lower end of the reactivity scale in reductive aldol reactions. In this article, we provide a full account of the intermolecular reactions[3b] promoted by Et_2Zn in combination with a cobalt source,[5] along with extension to an asymmetric variant using a chiral oxazolidine auxiliary.

2. Results and discussion

During ongoing efforts to develop new catalyst systems for the diastereoselective synthesis of β-hydroxylactones[4,6a] and lactams[3a,4,6b] using reductive aldol cyclisations, we recently established the exceptional ability of $Co(acac)_2{\cdot}2H_2O/Et_2Zn$[3a] in promoting reactions of substrates that were problematic under previously reported conditions using copper catalysis[6] (representative example in Eq. 1).



(1)

Whether the $Co(acac)_2{\cdot}2H_2O/Et_2Zn$ combination could also be applied to the corresponding *intermolecular* reductive aldol reactions was an important issue to address, and with this consideration in mind, the reaction of *N*,*N*-dimethylacrylamide (**3**) with acetophenone was conducted. This experiment was successful, and provided the aldol product **4a**[7] in 75% yield, accompanied by the diastereomeric product (not shown), in a 5:1 ratio (Table 1, entry 1). The use of 4-acryloylmorpholine (**6**) as the pronucleophilic component provided very similar results (Table 2, entry 1).

Further examination of substrate scope revealed that acetophenone derivatives containing alkyl, methoxy or bromo substituents were competent electrophiles in these reactions, providing tertiary alcohol-containing aldol products with up to 9:1 diastereomeric ratio and 85% isolated yield of the major diastereomer (Table 1, entries 2–6 and Table 2, entries 1–3). *ortho*-Substitution in the acetophenone was found to result in enhanced levels of diastereoselection (Table 1, entries 2 and 5 and Table 2, entry 2). However, the reaction of 4-nitroacetophenone with **3** provided none of the desired product **4g**, with a complex mixture being obtained instead (Table 1, entry 7). Presumably, the highly electron-deficient nature of this particular ketone leads to deleterious side reactions under these conditions. Other aromatic

* Corresponding author. Tel.: +44 131 650 4831; fax: +44 131 650 6453.
E-mail address: h.lam@ed.ac.uk (H.W. Lam).

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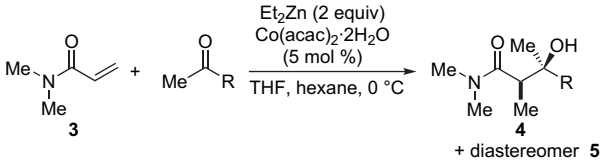
doi:10.1016/j.tet.2008.06.022

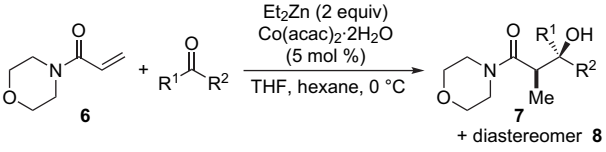
Table 1
Cobalt-catalysed reductive aldol reactions of *N*,*N*-dimethylacrylamide (**3**) with representative ketones[a]



Entry	R	Product(s)	dr[b]	Yield(s)[c] (%)
1	Ph	**4a**	5:1	75
2	2-MePh	**4b**	9:1	68
3	4-MePh	**4c**	5.5:1	79
4	4-MeOPh	**4d**	6:1	84
5	2-BrPh	**4e**	7:1	56
6	4-BrPh	**4f**, **5f**	3.5:1	73 (15)
7	4-NO_2Ph	**4g**	n/a	0[d]
8	2-Naphthyl	**4h**	5:1	78
9	2-Furyl	**4i**, **5i**	2.5:1	66 (25)
10	CO_2Et	**4j**	n/a	0[d]

[a] Reactions were conducted using 1.0 mmol of **3** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 1–29 h.
[b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures.
[c] Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.
[d] A complex mixture of unidentified products was obtained.

Table 2
Cobalt-catalysed reductive aldol reactions of 4-acryloylmorpholine (**6**) with representative ketones[a]



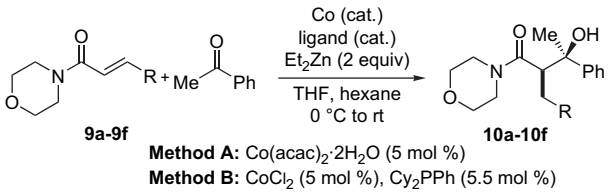
Entry	R^1	R^2	Product(s)	dr[b]	Yield(s)[c] (%)
1	Me	Ph	**7a**	5.5:1	80
2	Me	2-MePh	**7b**	9:1	84
3	Me	4-MeOPh	**7c**	6.5:1	85
4	Me	2-Naphthyl	**7d**, **8d**	4.5:1	82 (17)
5	Me	2-Furyl	**7e**, **8e**	3:1	72 (22)
6	Me	*i*-Pr	**7f**, **8f**	1:1	33 (31)
7	Me	*i*-Bu	**7g**, **8g**	1:1	35 (36)
8	Et	Ph	**7h**	6:1	75
9	Ph	Ph	**7i**	n/a	62

[a] Reactions were conducted using 1.0 mmol of **6** and 1.1 mmol of ketone in THF (10 mL) and hexane (2 mL) for 3–7 h.
[b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures.
[c] Isolated yield of major diastereomer; numbers in parentheses refer to yields of minor diastereomers if isolated.

ketones, such as those containing naphthyl or furyl substituents (Table 1, entries 8 and 9 and Table 2, entries 4 and 5), propiophenone (Table 2, entry 8) and benzophenone (Table 2, entry 9), were also tolerated. Aliphatic ketones also proved to be viable substrates in these reactions (Table 2, entries 6 and 7). However, no diastereoselection was observed in these cases, and both diastereomeric products were isolated in comparable yields. The reaction of ethyl pyruvate with **3** provided only a complex mixture (Table 1, entry 10).

Next, using acetophenone as the electrophile, a study of the effect of substitution at the β-carbon of the α,β-unsaturated amide component was carried out (Table 3). These reactions proceeded to give aldol products **10a**–**10f** with ≥9:1 dr, demonstrating the beneficial effect of a β-substituent on diastereoselectivity. Amides containing linear or branched alkyl groups at the β-position were tolerated (entries 1–3), but the use of an alternative precatalyst combination of $CoCl_2$ with the electron-rich monophosphine Cy_2PPh was required for complete conversions.[3a] Under standard

Table 3
Cobalt-catalysed reductive aldol reactions of acetophenone with representative α,β-unsaturated morpholine amides[a]

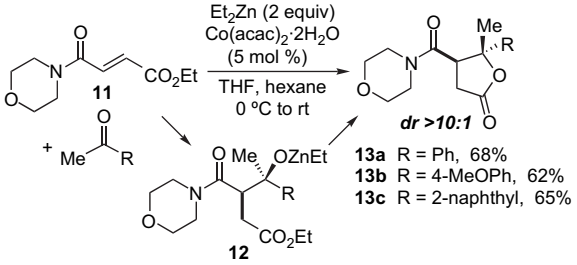


Entry	Method	R	Substrate	Product	dr[b]	Yield[c] (%)
1	B	Me	**9a**	**10a**	>19:1	76
2	B	*i*-Bu	**9b**	**10b**	>19:1	85
3	B	CH_2CH_2Ph	**9c**	**10c**	16:1	81[d]
4	A	Ph	**9d**	**10d**	>19:1	71
5	A	2-Naphthyl	**9e**	**10e**	10:1	74
6	A	2-Furyl	**9f**	**10f**	9:1	84

[a] Reactions were conducted using 1.0 mmol of **9a**–**9f** and 1.1 mmol of acetophenone in THF (10 mL) and hexane (2 mL) for 2–6 h.
[b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures.
[c] Isolated yield of major diastereomer.
[d] Yield of a 16:1 inseparable mixture of diastereomers.

conditions, substrates containing aromatic (entries 4 and 5) or heteroaromatic (entry 6) groups also provided good results.

Although α,β-unsaturated esters such as *tert*-butyl acrylate and methyl cinnamate also underwent successful reaction with acetophenone under these conditions, they provided the products as ca. 1:1 mixtures of diastereoisomers. Therefore, the reaction of substrate **11** was of interest, since there is the potential to generate products of reductive aldol coupling α- to the ester, as well as α- to the amide. In the event, reaction of **11** with a range of methyl ketones provided only lactones **13a**–**13c**, formed through cyclisation of the intermediate zinc alkoxides **12** onto the pendant ethyl ester, in 62–68% yield (Scheme 1). These experiments demonstrate the high chemoselectivity for generation of amide enolates rather than ester enolates under these conditions.



Scheme 1. Formation of lactones **13a**–**13c** via reductive aldol coupling of **11**.

Attempts to extend the scope of these reactions by using α-substituted α,β-unsaturated amides such as 4-methacryloyl morpholine were unsuccessful, providing only complex mixtures.

X-ray crystal structures of aldol products **4d**, **7f** and **7g** allowed determination of their relative stereochemistry[8] (Fig. 1), and the relative configurations of the remaining products in Tables 1–3 and Scheme 1 were assigned by analogy.

Our current working model for the mechanism of these reactions[9] is presented in Scheme 2, and involves the participation of π-allylcobalt species. Seminal work by MacKenzie and co-workers[10] along with important contributions by Ogoshi, Kurosawa and co-workers[11] have described the oxidative addition of low-valent transition metals to α,β-unsaturated carbonyl compounds in the presence of a suitable Lewis acid to form π-allylmetal complexes. In addition, strong evidence has been provided that such π-allylmetal species are intermediates in Pd-catalysed conjugate addition reactions of organometallic reagents[11a] and disilanes.[11b]

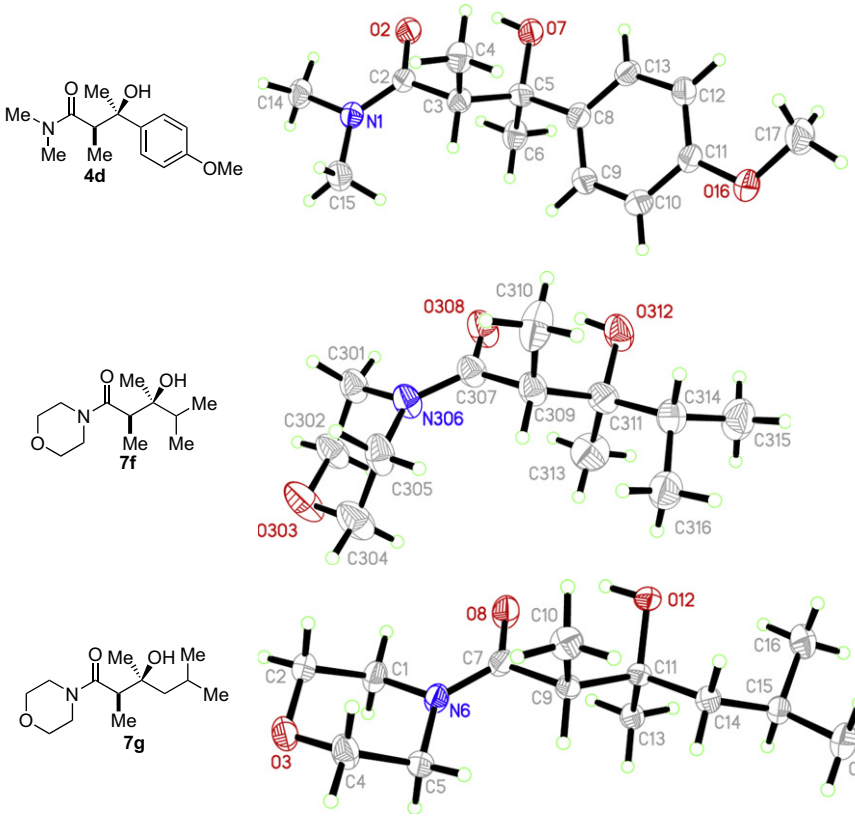
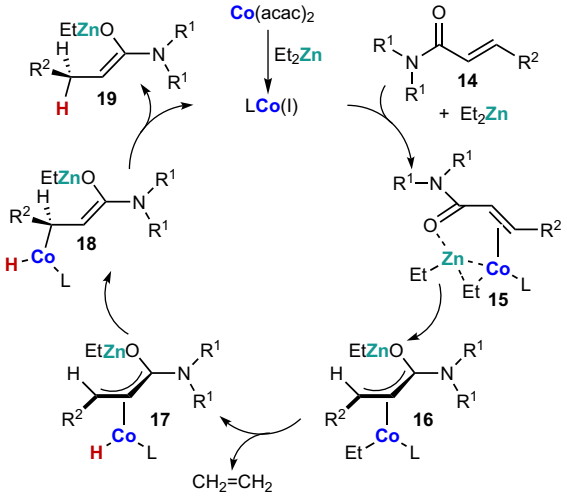


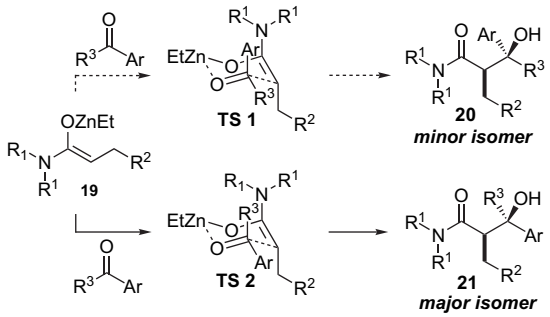
Figure 1. X-ray structures of **4d**, **7f** and **7g**.

Given this precedent, we believe that treatment of $Co(acac)_2$ with Et_2Zn leads to the formation of a cobalt(I) species that, with the assistance of additional Et_2Zn, binds to the substrate **14**, as in **15**. The presence of a three-centre–two-electron bridging interaction between cobalt, zinc and an ethyl ligand in **15** has precedent in a detailed study by Schleger, Montgomery and co-workers in related nickel-catalysed reactions,[12] and has been observed crystallographically for cobalt[13] and nickel[14] complexes involving Grignard[13,14a] and organoaluminium[14b] reagents. From **15**, oxidative addition of Co(I) into the α,β-unsaturated amide along with transmetalation of an ethyl group from zinc to cobalt would then generate π-allylcobalt(III) species **16**, that can then undergo β-hydride elimination to give cobalt hydride **17**. η^3–η^1 Isomerisation would then provide **18**, which upon reductive elimination would give *Z*-zinc enolate **19** that undergoes aldol reaction with the ketone, along with regeneration of Co(I). In this model, the regiochemical outcome of conjugate reduction of **11** (Scheme 1) may be explained by preferential binding of Et_2Zn/Co at the amide carbonyl rather than the ester carbonyl, due to the greater Lewis basicity of the amide.

The diastereochemical outcomes of these reactions[7,8] may be explained via the intervention of a chelated chair-like Zimmerman–Traxler transition state[15] in which the larger aromatic substituent of the ketone prefers to reside in a less sterically hindered pseudoequatorial position (as in **TS 2**) (Scheme 3), rather than in a pseudoaxial position (as in **TS 1**). The absence of diastereoselectivity with aliphatic ketones (Table 1, entries 6 and 7) is due presumably to reduced differences in size between the two substituents attached to the carbonyl group.



Scheme 2. Possible catalytic cycle.



Scheme 3. Model for stereochemical outcome.

Having demonstrated the general scope of these intermolecular reductive aldol reactions, we sought to develop an asymmetric variant of the process. Examination of the literature reveals that

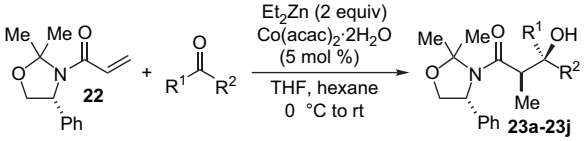
compared with the large body of work pertaining to asymmetric aldol reactions using aldehydes as the electrophiles,[16] there are far fewer examples using ketones.[17–19] Factors responsible for this paucity include the attenuated reactivity of ketones compared with aldehydes, problems with retroaldolisation and smaller differences in steric properties between the two substituents attached to the ketone carbonyl. The latter feature is often manifested in low levels of diastereoselectivity (such as in Table 1, entries 6 and 7) and enantiofacial discrimination. Although a number of approaches to address these challenges have been documented,[17–19] there remains room for improvement, since existing procedures often display suboptimal selectivities or narrow substrate scope. Therefore, the development of new, complementary methods for conducting asymmetric ketone aldol reactions continues to be a valuable endeavour.

The prospects of developing a catalytic asymmetric variant of the reactions described herein through the use of a suitable chiral cobalt–ligand complex were deemed unpromising, since according to our mechanistic hypotheses (Schemes 2 and 3), cobalt is not a participant in the aldol reaction. Indeed, initial trials using substoichiometric quantities of various chiral ligands did not give rise to any enantioselection.[20] Therefore, we turned to a chiral auxiliary strategy, and a number of potential candidates were screened for their ability to give both high reaction efficiencies and high levels of enolate diastereofacial selectivity. Although *N*-alkenoyloxazolidinones seemed an obvious first choice,[16a] these substrates did not provide aldol products under our conditions. Fortunately, *N*-acryloyloxazolidine **22**[21] was found to meet our desired criteria, reacting with acetophenone to afford aldol product **23a** in 73% yield and with 11:1 diastereoselectivity [major isomer/Σ(other isomers)][22] (Table 4, entry 1). Further exploration of ketone scope revealed that acetophenone derivatives containing substituents of varying electronic properties were tolerated, giving aldol products in 58–76% yield and with up to 12:1 diastereoselectivity (entries 2–6).[22] Acryloyloxazolidine **22** also underwent reaction with ketones bearing naphthyl (entries 7 and 9), heteroaromatic (entry 8) and ethyl substituents (entry 10). Aliphatic ketones proved to be less suitable substrates in this reaction, providing what appeared to be mixtures of all four possible diastereoisomers (entry 9).

Table 5 presents the results of reaction of a range of *N*-alkenoyloxazolidines **24a**–**24h** with acetophenone. As seen previously in Table 3, these examples illustrate that substitution at the acrylamide has a beneficial effect on reaction diastereoselectivity (≥15:1). In addition, the reactions of **24a**–**24h** were cleaner than those of *N*-acryloyloxazolidine **22**, which resulted in higher isolated yields of products. Once again, the combination of $CoCl_2$ and Cy_2PPh[3a] was required for complete conversions when acrylamides **24a**–**24c** containing alkyl substitution were employed (entries 1–3). Aromatic- and heteroaromatic-substituted *N*-alkenoyloxazolidines **24d**–**24h** were the best substrates in these reactions, affording aldol products in 83–90% yield as one observable diastereomer (>19:1 by ^{1}H NMR analysis) (entries 4–8).

The yields and diastereoselectivities of these reactions are maintained on increasing the scale. For example, reaction of cinnamoyl-substituted oxazolidine **24d** with 2-acetonaphthone to give **26** on 0.5 mmol and 5 mmol scales gave comparable results (Eq. 2).

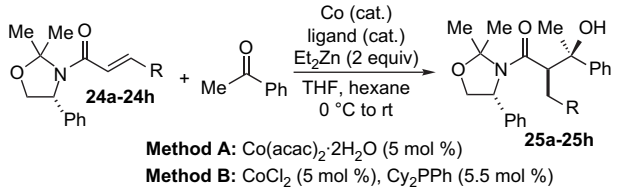
Table 4
Cobalt-catalysed reductive aldol reactions of *N*-acryloyloxazolidine **22** with representative ketones[a]



Entry	R^1	R^2	Product	dr[b,c]	Yield[d] (%)
1	Me	Ph	**23a**	11:1	73
2	Me	4-MePh	**23b**	9:1	76
3	Me	3-MePh	**23c**	12:1	72
4	Me	4-MeOPh	**23d**	8.5:1	72
5	Me	4-BrPh	**23e**	12:1	63
6	Me	3-ClPh	**23f**	7:1	58
7	Me	2-Naphthyl	**23g**	13:1	75
8	Me	2-Thienyl	**23h**	6:1	61
9	Me	*t*-Bu	**23i**	n/a	0[e]
10	Et	6′-MeO-2-naphthyl	**23j**	6:1	59

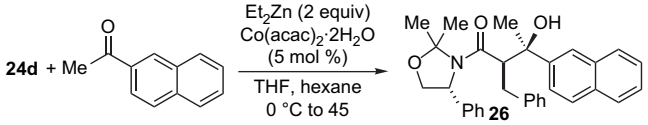
[a] Reactions were conducted using 1.0 mmol of **22** and 1.1 mmol of ketone in THF (5 mL) and hexane (2 mL) for 3–17 h.
[b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures.
[c] dr=(major isomer)/Σ(other isomers).
[d] Isolated yield of major diastereomer.
[e] A complex mixture was obtained.

Table 5
Cobalt-catalysed reductive aldol reactions of acetophenone with representative *N*-alkenoyloxazolidines[a]



Entry	Method	R	Substrate	Product	dr[b,c]	Yield[d] (%)
1	B	Me	**24a**	**25a**	16:1	82
2	B	*i*-Pr	**24b**	**25b**	15:1	79
3	B	CH_2CH_2Ph	**24c**	**25c**	15:1	80
4	A	Ph	**24d**	**25d**	>19:1	86
5	A	4-MeOPh	**24e**	**25e**	>19:1	86
6	A	4-ClPh	**24f**	**25f**	>19:1	84
7	A	2-Naphthyl	**24g**	**25g**	>19:1	90
8	A	2-Furyl	**24h**	**25h**	>19:1	83

[a] Reactions were conducted using 0.5 mmol of **24a**–**24h** and 0.55 mmol of acetophenone in THF (2.5 mL) and hexane (1 mL) for 4–6 h.
[b] Determined by ^{1}H NMR analysis of the unpurified reaction mixtures.
[c] dr=(major isomer)/Σ(other isomers).
[d] Isolated yield of major diastereomer.



(2)

The stereochemistries of **23a**, **23d** and **25f** were determined by X-ray crystallography (Fig. 2),[23] and the stereochemistries of the remaining aldol products in Tables 4 and 5, and of **26** were assigned by analogy.

To explain the sense of asymmetric induction observed in these reactions, we suggest that in the Zimmerman–Traxler transition state,[15] the geminal dimethyl groups of the oxazolidine are oriented *anti* to the enolate oxygen to minimise unfavourable nonbonding interactions (Scheme 4). Inspection of alternative transition states **TS 3** and **TS 4** reveals that the oxazolidine phenyl substituent suffers fewer nonbonding interactions in **TS 4**, which lead to the observed stereochemistry of the major isomer **29**.

Obviously, the utility of this chiral auxiliary methodology is apparent only if the oxazolidine may be cleaved cleanly from the aldol products in high yield. On the basis of literature precedent,[21b]

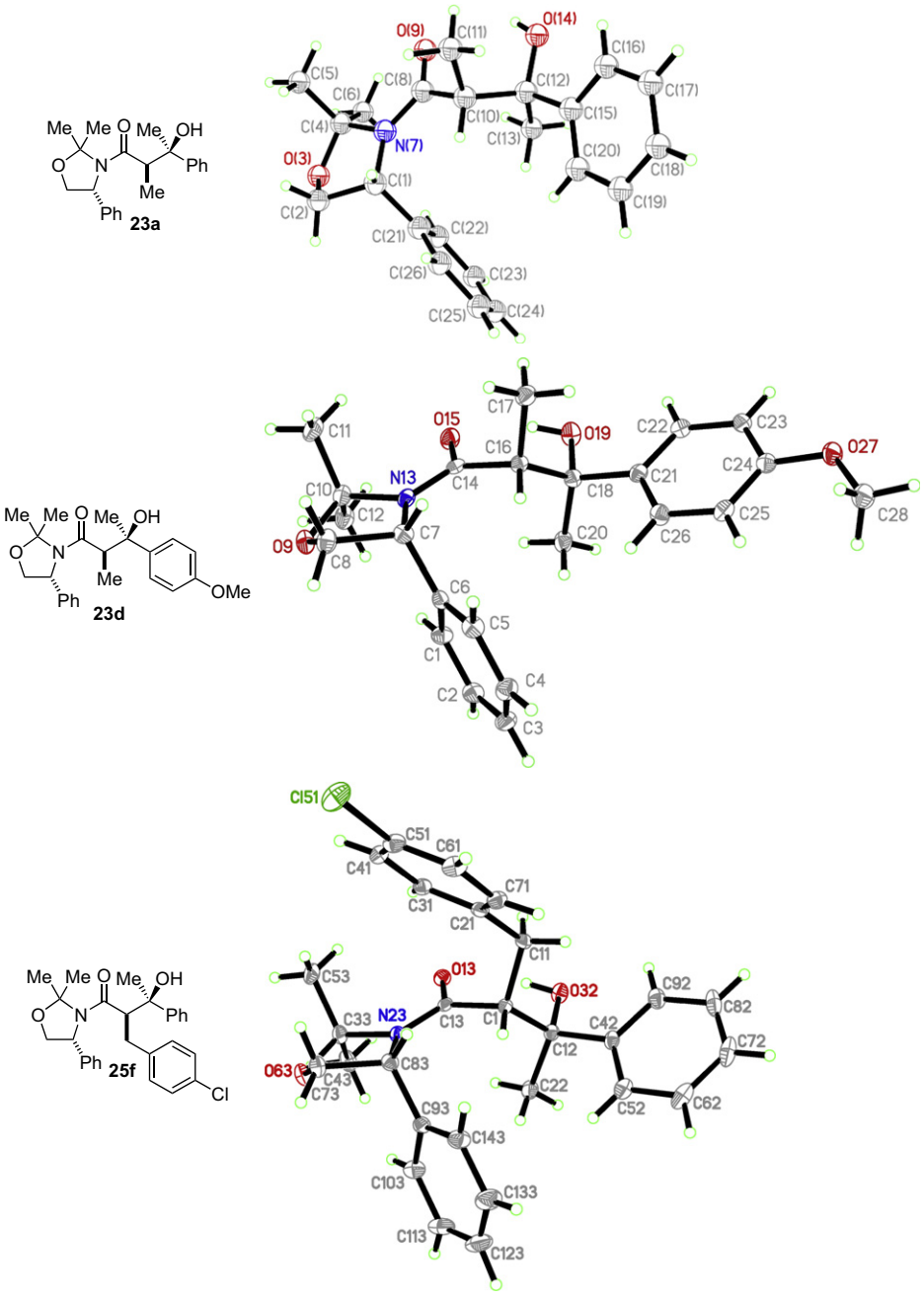
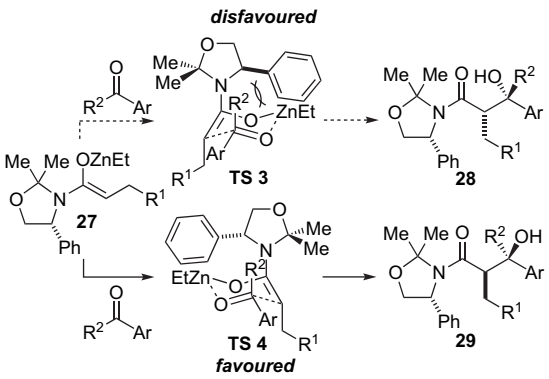


Figure 2. X-ray structures of **23a**, **23d** and **25f**.



Scheme 4. Model for asymmetric induction.

we expected this task to be straightforward. However, all of our efforts have been frustrated by the low reactivity of the amide carbonyl of these compounds, presumably due to high steric shielding. For example, attempted reductive cleavage of the oxazolidine from **23a** using hydride reagents such as $LiBEt_3H$,[21b] LAB,[24] $LiAlH_4$ or DIBAL resulted in no reaction at low-to-moderate temperatures, or retroaldol fragmentation at elevated temperatures. The TBS ether of **23a** was also inert to these reagents, even under forcing conditions. Various efforts to protect the tertiary alcohol of the aldol products with other protecting groups such as MEM or benzyl ethers were unsuccessful, again presumably due to high steric hindrance. Finally, attempts at acidic hydrolysis[25] of the oxazolidine of **23a**, or efforts to remove the isopropylidine group[21b] under various Brønsted or Lewis acidic conditions, were complicated by elimination of the tertiary alcohol to provide β,γ-unsaturated compounds.

3. Conclusion

Cobalt-catalysed conjugate reduction of α,β-unsaturated amides using diethylzinc as the stoichiometric reductant generates zinc enolates that participate in efficient aldol couplings with ketones, providing tertiary β-hydroxycarbonyl products. A wide range of substitution at the β-carbon of the α,β-unsaturated amide is tolerated, and best results in terms of diastereoselectivity are obtained with aromatic ketones such as acetophenone derivatives. Although aliphatic ketones were found to undergo the reductive aldol reaction, their reactions exhibit no diastereoselectivity.

Although a readily accessible *N*-phenylglycinol-derived chiral auxiliary was found to impart high levels of asymmetric induction in these reactions, all attempts to cleave the oxazolidine from the products have been unsuccessful due to the sterically hindered nature of the products, coupled with the presence of relatively sensitive tertiary benzylic alcohols. However, this study has defined structural features for an auxiliary that gives high levels of asymmetric induction, and provides useful information that might aid in the design of improved auxiliaries in future.

4. Experimental section

4.1. General

All nonaqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 and THF were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontoursolventsystems.com. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40–60 °C. Commercially available $CoCl_2$ was dried by heating under vacuum until it turned from purple to blue. All other commercially available reagents were used as-received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien $60F_{254}$ 0.2 mm precoated plates. Product spots were visualised by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35–70 μm) employing the method of Still and co-workers. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in $CHCl_3$. ^{1}H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer or a Bruker ARX250 (250 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), app (apparent), br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard ($CDCl_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. ^{31}P NMR spectra were recorded on a Bruker ARX250 (101.2 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of H_3PO_4. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer or a Kratos MS50TC spectrometer at the School of Chemistry, University of Edinburgh. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

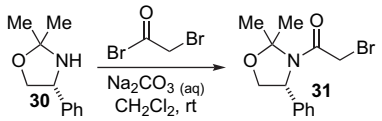
Products **4**–**13c** in Tables 1–3 and Scheme 1 have been reported previously.[3b]

4.2. Preparation of *N*-alkenoyloxazolidines 22 and 24a–24h

*4.2.1. (4R)-2,2-Dimethyl-4-phenyl-3-[(E)-propenoyl]-oxazolidine (**22**)*

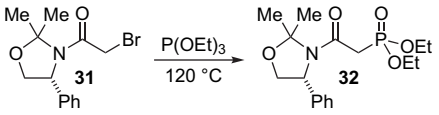
Prepared according to a previously reported procedure.[21a]

*4.2.2. (4R)-3-Bromoacetyl-2,2-dimethyl-4-phenyloxazolidine (**31**)*



Bromoacetyl bromide (7.2 mL, 82.5 mmol) was added in one portion to a vigorously stirred mixture of oxazolidine **30**[21a] (9.75 g, 55.0 mmol) in CH_2Cl_2 (55 mL) and saturated aqueous Na_2CO_3 solution (220 mL), and the mixture was stirred at room temperature for 4 h. The reaction was partitioned between saturated aqueous $NaHCO_3$ solution (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3×100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (15% EtOAc/hexane) gave the *bromoamide* **31** (10.14 g, 62%) as a light brown solid. Mp 90–92 °C; $[\alpha]_D^{21}$ −190 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2985, 1660 (C=O), 1400, 1379, 1255, 1237, 1137, 1066, 844, 702 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.40–7.36 (2H, m, Ar*H*), 7.34–7.29 (3H, m, Ar*H*), 5.07 (1H, dd, *J*=6.6, 2.7 Hz, C*H*$_2$O), 4.39 (1H, dd, *J*=9.0, 6.6 Hz, C*H*N), 3.91 (1H, dd, *J*=9.0, 2.7 Hz, C*H*$_2$O), 3.55 (1H, d, *J*=11.0 Hz, C*H*$_2$Br), 3.44 (1H, d, *J*=11.0 Hz, C*H*$_2$Br), 1.86 (3H, s, C(C*H*$_3$)$_2$), 1.63 (3H, s, C(C*H*$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.7 (C), 140.3 (C), 129.0 (2×CH), 128.1 (CH), 125.6 (2×CH), 96.4 (C), 71.2 (CH_2), 61.0 (CH), 29.2 (CH_2), 25.0 (CH_3), 22.2 (CH_3); HRMS (FAB) exact mass calcd for $C_{13}H_{17}^{79}BrNO_2$ $[M+H]^+$: 298.0438, found: 298.0444.

*4.2.3. (4R)-3-Diethylphosphonacetyl-2,2-dimethyl-4-phenyl-oxazolidine (**32**)*



A stirred solution of the bromoamide **31** (10.40 g, 35.0 mmol) in triethyl phosphite (70 mL) was heated at 120 °C for 2 h. Excess triethyl phosphite was removed by distillation to leave *phosphonate* **32** (11.82 g, 95%) as a yellow oil. $[\alpha]_D^{21}$ −114 (*c* 1.00, $CHCl_3$); IR (film) 2985, 1654 (C=O), 1419, 1392, 1365, 1254, 1052, 1025, 974, 704 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.41–7.36 (2H, m, Ar*H*), 7.34–7.29 (3H, m, Ar*H*), 5.39 (1H, dd, *J*=6.5, 1.9 Hz, OC*H*$_2$CHN), 4.40 (1H, dd, *J*=8.9, 6.5 Hz, C*H*N), 4.22–4.05 (4H, m, P(OC*H*$_2$CH$_3$)$_2$), 3.91 (1H, dd, *J*=8.9, 1.9 Hz, OC*H*$_2$CHN), 2.83 (1H, dd, *J*=20.3, 14.2 Hz, C*H*$_2$P), 2.61 (1H, dd, *J*=23.5, 14.2 Hz, C*H*$_2$P), 1.86 (3H, s, C(C*H*$_3$)$_2$), 1.65 (3H, s, C(C*H*$_3$)$_2$), 1.37–1.33 (3H, m, CH$_2$C*H*$_3$), 1.32–1.28 (3H, m, CH$_2$C*H*$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 162.2 (C, d, J_P=5.3 Hz), 140.8 (C), 128.7 (2×CH), 127.6 (CH), 125.8 (2×CH), 95.9 (C), 70.8 (CH_2), 62.5 (CH_2, d, J_P=6.4 Hz), 61.8 (CH_2, d, J_P=6.4 Hz), 60.9 (CH), 35.9 (CH_2, d, J_P=130.8 Hz), 25.0 (CH_3), 22.3 (CH_3), 16.0 (CH_3, d, J_P=5.8 Hz), 15.9 (CH_3, d, J_P=5.7 Hz); ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 21.7; HRMS (FAB) exact mass calcd for $C_{17}H_{27}NO_5P$ $[M+H]^+$: 356.1622, found: 356.1627.

4.2.4. Wadsworth–Emmons reactions: general procedure A

A solution of phosphonate **32** (1.42 g, 4.00 mmol) in THF (15 mL) was added via cannula to a suspension of NaH (60% dispersion in mineral oil, 160 mg, 4.00 mmol) in THF (15 mL) over 3 min at 0 °C. The mixture was then stirred at room temperature for 30 min before being cooled to 0 °C. The appropriate aldehyde (1 equiv) was added dropwise or portionwise over 5 min, and the mixture was then stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (20 mL), followed by the addition of Et_2O (20 mL). The organic layer was separated and washed with NH_4Cl solution (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography (EtOAc/hexane) afforded the *N*-alkenoyloxazolidine.

*4.2.5. (4R)-3-[(E)-But-2-enoyl]-2,2-dimethyl-4-phenyl-oxazolidine (**24a**)*

Prepared according to a previously reported procedure.[25]

*4.2.6. (4R)-2,2-Dimethyl-3-[(E)-4-methylpent-2-enoyl]-4-phenyloxazolidine (**24b**)*

The title compound was prepared according to general procedure A from isobutyraldehyde (363 μL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a yellow solid (910 mg, 83%). Mp 90–92 °C; $[\alpha]_D^{21}$ −120 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2961, 1660 (C=O), 1455, 1396, 1361, 1256, 1068, 980, 846, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30–7.18 (5H, m, Ar*H*), 6.72 (1H, dd, *J*=15.1, 6.6 Hz, C*H*=CHC=O), 5.66 (1H, dd, *J*=15.1, 1.2 Hz, CH=C*H*C=O), 4.95 (1H, dd, *J*=6.6, 2.8 Hz, CH_2O), 4.31 (1H, dd, *J*=8.9, 6.6 Hz, C*H*N), 3.84 (1H, dd, *J*=8.9, 2.8 Hz, CH_2O), 2.21–2.11 (1H, m, C*H*$(CH_3)_2$), 1.82 (3H, s, C$(CH_3)_2$), 1.63 (3H, s, C$(CH_3)_2$), 0.79 (3H, d, *J*=6.8 Hz, CH$(CH_3)_2$), 0.76 (3H, d, *J*=6.8 Hz, CH$(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 151.7 (CH), 141.4 (C), 128.5 (2×CH), 127.3 (CH), 125.7 (2×CH), 120.1 (CH), 95.7 (C), 71.0 (CH_2), 61.0 (CH), 30.3 (CH), 25.0 (CH_3), 23.2 (CH_3), 20.9 (2×CH_3); HRMS (FAB) exact mass calcd for $C_{17}H_{24}NO_2$ $[M+H]^+$: 274.1802, found: 274.1807.

*4.2.7. (4R)-2,2-Dimethyl-3-[(E)-5-phenylpent-2-enoyl]-4-phenyloxazolidine (**24c**)*

The title compound was prepared according to general procedure A from hydrocinnamaldehyde (527 μL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a yellow oil (1.12 g, 83%). $[\alpha]_D^{21}$ −98.0 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2983, 1660 (C=O), 1495, 1375, 1252, 1141, 1068, 848, 735, 700 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40–7.16 (8H, m, Ar*H*), 7.08 (2H, d, *J*=7.1 Hz, Ar*H*), 6.88 (1H, dt, *J*=14.9, 6.9 Hz, C*H*=CHC=O), 5.79 (1H, d, *J*=14.9 Hz, CH=C*H*C=O), 4.93 (1H, dd, *J*=6.5, 2.4 Hz, CH_2O), 4.38 (1H, dd, *J*=8.9, 6.5 Hz, C*H*N), 3.93 (1H, dd, *J*=8.9, 2.4 Hz, CH_2O), 2.65–2.51 (2H, m, CH_2Ph), 2.39–2.28 (2H, m, CH_2CH_2Ph), 1.90 (3H, s, C$(CH_3)_2$), 1.71 (3H, s, C$(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 144.8 (CH), 141.5 (C), 140.9 (C), 128.8 (2×CH), 128.3 (2×CH), 128.2 (2×CH), 127.7 (CH), 125.9 (3×CH), 123.5 (CH), 96.1 (C), 71.3 (CH_2), 61.2 (CH), 34.2 (CH_2), 33.6 (CH_2), 25.3 (CH_3), 23.4 (CH_3); HRMS (FAB) exact mass calcd for $C_{22}H_{26}NO_2$ $[M+H]^+$: 336.1959, found: 336.1966.

*4.2.8. (4R)-2,2-Dimethyl-4-phenyl-3-[(E)-3-phenyl-propenoyl]oxazolidine (**24d**)*

Prepared according to a previously reported procedure.[25]

*4.2.9. (4R)-3-[(E)-3-(4-Methoxyphenyl)propenoyl]-2,2-dimethyl-4-phenyloxazolidine (**24e**)*

The title compound was prepared according to general procedure A from *p*-anisaldehyde (489 μL, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.09 g, 76%). Mp 125–127 °C; $[\alpha]_D^{21}$ −382 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2983, 1649 (C=O), 1511, 1422, 1395, 1304, 1242, 1173, 826, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.55 (1H, d, *J*=15.3 Hz, ArC*H*=), 7.42–7.28 (5H, m, Ar*H*), 7.19 (2H, d, *J*=8.7 Hz, Ar*H*), 6.80 (2H, d, *J*=8.7 Hz, Ar*H*), 6.27 (1H, d, *J*=15.3 Hz, ArCH=C*H*), 5.10 (1H, dd, *J*=6.6, 2.6 Hz, CH_2O), 4.43 (1H, dd, *J*=8.9, 6.6 Hz, C*H*N), 3.97 (1H, dd, *J*=8.9, 2.6 Hz, CH_2O), 3.79 (3H, s, OCH_3), 1.94 (3H, s, C$(CH_3)_2$), 1.75 (3H, s, C$(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 164.2 (C), 160.8 (C), 141.8 (C), 141.7 (CH), 129.3 (2×CH), 129.0 (2×CH), 127.9 (CH), 127.7 (C), 126.0 (2×CH), 117.8 (CH), 114.1 (2×CH), 96.3 (C), 71.4 (CH_2), 61.4 (CH), 55.3 (CH_3), 25.4 (CH_3), 23.5 (CH_3); HRMS (FAB) exact mass calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$: 338.1751, found: 338.1751.

*4.2.10. (4R)-3-[(E)-3-(4-Chlorophenyl)propenoyl]-2,2-dimethyl-4-phenyloxazolidine (**24f**)*

The title compound was prepared according to general procedure A from 4-chlorobenzaldehyde (562 mg, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.15 g, 84%). Mp 117–119 °C; $[\alpha]_D^{21}$ −342 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2984, 1651 (C=O), 1568, 1492, 1393, 1301, 1245, 971, 819, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53 (1H, d, *J*=15.4 Hz, ArC*H*=), 7.42–7.28 (5H, m, Ar*H*), 7.20 (2H, d, *J*=8.4 Hz, Ar*H*), 7.12 (2H, d, *J*=8.4 Hz, Ar*H*), 6.39 (1H, d, *J*=15.4 Hz, ArCH=C*H*), 5.11 (1H, dd, *J*=6.5, 2.6 Hz, CH_2O), 4.42 (1H, dd, *J*=8.9, 6.5 Hz, C*H*N), 3.96 (1H, dd, *J*=8.9, 2.6 Hz, CH_2O), 1.95 (3H, s, C$(CH_3)_2$), 1.75 (3H, s, C$(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.2 (C), 141.4 (C), 140.2 (CH), 135.1 (C), 133.3 (C), 128.9 (2×CH), 128.6 (4×CH), 127.8 (CH), 125.7 (2×CH), 120.6 (CH), 96.1 (C), 71.2 (CH_2), 61.2 (CH), 25.1 (CH_3), 23.3 (CH_3); HRMS (FAB) exact mass calcd for $C_{20}H_{21}^{35}ClNO_2$ $[M+H]^+$: 342.1256, found: 342.1261.

*4.2.11. (4R)-2,2-Dimethyl-3-[(E)-3-(naphthalen-2-yl)propenoyl]-4-phenyloxazolidine (**24g**)*

The title compound was prepared according to general procedure A from 2-naphthaldehyde (625 mg, 4.00 mmol) for a reaction time of 16 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow solid (1.09 g, 76%). Mp 131–133 °C; $[\alpha]_D^{21}$ −402 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2984, 1651 (C=O), 1401, 1362, 1255, 1239, 1068, 848, 749, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.83–7.79 (3H, m, Ar*H*), 7.75–7.73 (2H, m, Ar*H*), 7.51–7.43 (6H, m, ArC*H*= and Ar*H*), 7.39–7.31 (2H, m, Ar*H*), 6.56 (1H, d, *J*=15.3 Hz, ArCH=C*H*), 5.16 (1H, dd, *J*=6.6, 2.8 Hz, CH_2O), 4.48 (1H, dd, *J*=8.9, 6.6 Hz, C*H*N), 4.03 (1H, dd, *J*=8.9, 2.8 Hz, CH_2O), 2.03 (3H, s, C$(CH_3)_2$), 1.84 (3H, s, C$(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.8 (C), 141.8 (CH), 141.7 (C), 133.7 (C), 133.1 (C), 132.4 (C), 129.2 (CH), 129.0 (2×CH), 128.3 (3×CH), 127.9 (CH), 127.5 (CH), 126.8 (CH), 126.4 (CH), 125.9 (2×CH), 123.3 (CH), 120.4 (CH), 96.3 (C), 71.3 (CH_2), 61.4 (CH), 25.3 (CH_3), 23.5 (CH_3); HRMS (FAB) exact mass calcd for $C_{24}H_{24}NO_2$ $[M+H]^+$: 358.1802, found: 358.1807.

*4.2.12. (4R)-3-[(E)-3-(Furan-2-yl)propenoyl]-2,2-dimethyl-4-phenyloxazolidine (**24h**)*

The title compound was prepared according to general procedure A from 2-furaldehyde (331 μL, 4.00 mmol) for a reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane) to give a light yellow solid (1.02 g, 84%). Mp 94–96 °C; $[\alpha]_D^{21}$ −384 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2985, 1651 (C=O), 1557, 1484, 1392, 1246, 1067, 974, 746, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40–7.33 (5H, m), 7.30–7.23 (2H, m, Ar*H*, C*H*=CHC=O and C*H*), 6.41 (1H, d, *J*=3.3 Hz, C*H*), 6.36–6.30 (2H, m, CH=C*H*C=O and C*H*), 5.09 (1H, dd, *J*=6.4, 2.1 Hz, CH_2O), 4.38 (1H, dd, *J*=8.9, 6.4 Hz, C*H*N), 3.94 (1H, dd, *J*=8.9, 2.1 Hz, CH_2O), 1.93 (3H, s, C$(CH_3)_2$), 1.73 (3H, s, C$(CH_3)_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 163.4 (C), 151.1 (C), 143.8 (CH), 141.5 (C), 128.7 (2×CH), 128.5 (CH), 127.5 (CH), 125.7 (2×CH),

117.4 (CH), 113.7 (CH), 111.8 (CH), 96.0 (C), 71.1 (CH_2), 60.9 (CH), 25.2 (CH_3), 23.1 (CH_3); HRMS (FAB) exact mass calcd for $C_{18}H_{20}NO_3$ $[M+H]^+$: 298.1438, found: 298.1443.

4.3. Cobalt-catalysed reductive aldol reactions of *N*-acryloyloxazolidine 22 with various ketones: general procedure B

A solution of *N*-alkenoyloxazolidine **22** (231 mg, 1.00 mmol), the appropriate ketone (1.10 mmol) and $Co(acac)_2 \cdot 2H_2O$ (12.9 mg, 0.05 mmol) in THF (5.0 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 2.00 mL, 2.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (30 mL) and the mixture was then extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatography afforded the aldol product.

*4.3.1. (4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23a**)*

The title compound was prepared according to general procedure B from acetophenone (130 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (257 mg, 73%). Recrystallisation of a CH_2Cl_2/hexane solution of **23a** at −20 °C was found to give colourless crystals suitable for X-ray diffraction. Mp 215–217 °C; $[\alpha]_D^{21}$ −231 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3388 (OH), 2980, 2933, 2878, 1624 (C=O), 1458, 1420, 1065, 765, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53–7.48 (2H, m, Ar*H*), 7.47–7.42 (3H, m, Ar*H*); 7.23–7.12 (3H, m, Ar*H*), 6.94 (2H, app d, *J*=7.2 Hz, Ar*H*), 5.48 (1H, br s, O*H*), 4.77 (1H, dd, *J*=6.6, 2.2 Hz, CH_2O), 4.41 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 3.99 (1H, dd, *J*=9.1, 2.2 Hz, CH_2O), 2.60 (1H, q, *J*=7.1 Hz, CH_3CH), 1.98 (3H, s, $C(CH_3)_2$), 1.67 (3H, s, $C(CH_3)_2$), 0.99 (3H, s, CH_3COH), 0.90 (3H, d, *J*=7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 145.8 (C), 142.0 (C), 129.2 (2×CH), 128.5 (CH), 127.8 (2×CH), 126.7 (2×CH), 126.1 (CH), 124.5 (2×CH), 96.3 (C), 74.6 (C), 71.0 (CH_2), 61.6 (CH), 46.7 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) exact mass calcd for $C_{22}H_{28}NO_3$ $[M+H]^+$: 354.2064, found: 354.2064.

*4.3.2. (4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(4-methylphenyl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23b**)*

The title compound was prepared according to general procedure B from 4′-methylacetophenone (155 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (280 mg, 76%). Mp 171–173 °C; $[\alpha]_D^{21}$ −249 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 2985, 2932, 1621 (C=O), 1458, 1423, 1377, 1303, 1205, 1065 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52–7.48 (2H, m, Ar*H*), 7.46–7.41 (3H, m, Ar*H*), 7.03–7.01 (2H, m, Ar*H*), 6.82 (2H, d, *J*=7.9 Hz, Ar*H*), 5.43 (1H, s, O*H*), 4.77 (1H, dd, *J*=6.6, 2.2 Hz, CH_2O), 4.40 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 3.98 (1H, dd, *J*=9.1, 2.2 Hz, CH_2O), 2.58 (1H, q, *J*=7.1 Hz, CH_3CH), 2.29 (3H, s, ArCH_3), 1.98 (3H, s, $C(CH_3)_2$), 1.67 (3H, s, $C(CH_3)_2$), 0.98 (3H, s, CH_3COH), 0.90 (3H, d, *J*=7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 142.9 (C), 142.0 (C), 135.6 (C), 129.1 (2×CH), 128.5 (3×CH), 126.7 (2×CH), 124.4 (2×CH), 96.2 (C), 74.6 (C), 71.0 (CH_2), 61.6 (CH), 46.7 (CH), 29.7 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 20.9 (CH_3), 12.2 (CH_3); HRMS (ES) exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2220, found: 368.2218.

*4.3.3. (4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(3-methylphenyl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23c**)*

The title compound was prepared according to general procedure B from 3′-methylacetophenone (150 μL, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (278 mg, 72%). Mp 95–97 °C; $[\alpha]_D^{21}$ −199 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 2980, 2933, 2878, 1624 (C=O), 1419, 1302, 1066, 845, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54–7.49 (2H, m, Ar*H*), 7.47–7.43 (3H, m, Ar*H*), 7.09 (1H, t, *J*=7.7 Hz, Ar*H*), 6.96 (1H, d, *J*=7.7 Hz, Ar*H*), 6.75–6.73 (2H, m, Ar*H*), 5.41 (1H, s, O*H*), 4.78 (1H, dd, *J*=6.6, 2.2 Hz, CH_2O), 4.41 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 3.98 (1H, dd, *J*=9.1, 2.2 Hz, CH_2O), 2.61 (1H, q, *J*=7.1 Hz, CH_3CH), 2.28 (3H, s, ArCH_3), 1.99 (3H, s, $C(CH_3)_2$), 1.67 (3H, s, $C(CH_3)_2$), 0.99 (3H, s, CH_3COH), 0.91 (3H, d, *J*=7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.2 (C), 145.7 (C), 142.0 (C), 137.2 (C), 129.1 (2×CH), 128.4 (CH), 127.6 (CH), 126.8 (CH), 126.7 (2×CH), 125.2 (CH), 121.5 (CH), 96.1 (C), 74.6 (C), 70.9 (CH_2), 61.6 (CH), 46.6 (CH), 29.6 (CH_3), 25.5 (CH_3), 22.6 (CH_3), 21.5 (CH_3), 12.1 (CH_3); HRMS (ES) exact mass calcd for $C_{23}H_{30}NO_3$ $[M+H]^+$: 368.2221, found: 368.2230.

*4.3.4. (4R)-3-[(2R,3R)-3-Hydroxy-3-(4-methoxyphenyl)-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23d**)*

The title compound was prepared according to general procedure B from 4′-methoxyacetophenone (165 mg, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (274 mg, 72%). Recrystallisation of an EtOAc/hexane solution of **23d** at −20 °C was found to give colourless crystals suitable for X-ray diffraction. Mp 183–185 °C; $[\alpha]_D^{21}$ −222 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3366 (OH), 2984, 2971, 2928, 1617 (C=O), 1510, 1250, 1177, 1065, 841 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52–7.47 (2H, m, Ar*H*), 7.46–7.42 (3H, m, Ar*H*), 6.85 (2H, d, *J*=8.7 Hz, Ar*H*), 6.75–6.73 (2H, m, Ar*H*), 5.44 (1H, br s, O*H*), 4.77 (1H, dd, *J*=6.6, 2.1 Hz, CH_2O), 4.40 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 3.98 (1H, dd, *J*=9.1, 2.1 Hz, CH_2O), 3.76 (3H, s, OCH_3), 2.54 (1H, q, *J*=7.1 Hz, CH_3CH), 1.98 (3H, s, $C(CH_3)_2$), 1.66 (3H, s, $C(CH_3)_2$), 0.97 (3H, s, CH_3COH), 0.90 (3H, d, *J*=7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 157.9 (C), 142.0 (C), 138.0 (C), 129.1 (2×CH), 128.5 (CH), 126.7 (2×CH), 125.6 (2×CH), 113.1 (2×CH), 96.2 (C), 74.4 (C), 71.0 (CH_2), 61.6 (CH), 55.1 (CH_3), 46.8 (CH), 29.6 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.2 (CH_3); HRMS (ES) exact mass calcd for $C_{23}H_{30}NO_4$ $[M+H]^+$: 384.2169, found: 384.2167.

*4.3.5. (4R)-3-[(2R,3R)-3-(4-Bromophenyl)-3-hydroxy-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23e**)*

The title compound was prepared according to general procedure B from 4′-bromoacetophenone (219 mg, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (273 mg, 63%). Mp 132–134 °C; $[\alpha]_D^{21}$ −236 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3418 (OH), 2981, 2933, 2878, 1625 (C=O), 1457, 1411, 1066, 840, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52–7.40 (5H, m, Ar*H*), 7.33–7.31 (2H, m, Ar*H*), 6.79 (2H, d, *J*=8.3 Hz, Ar*H*), 5.48 (1H, s, O*H*), 4.75 (1H, dd, *J*=6.6, 2.2 Hz,), 4.40 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 3.98 (1H, dd, *J*=9.1, 2.2 Hz, CH_2O), 2.53 (1H, q, *J*=7.1 Hz, CH_3CH), 1.97 (3H, s, $C(CH_3)_2$), 1.66 (3H, s, $C(CH_3)_2$), 0.96 (3H, s, CH_3COH), 0.88 (3H, d, *J*=7.1 Hz, CH_3CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.9 (C), 144.9 (C), 141.9 (C), 130.8 (2×CH), 129.2 (2×CH), 128.6 (CH), 126.7 (2×CH), 126.5 (2×CH), 120.1 (C), 96.3 (C), 74.4 (C), 71.0 (CH_2), 61.6 (CH), 46.5 (CH), 29.4 (CH_3), 25.6 (CH_3), 22.7 (CH_3), 12.1 (CH_3); HRMS (ES) exact mass calcd for $C_{22}H_{27}^{79}BrNO_3$ $[M+H]^+$: 432.1169, found: 432.1168.

*4.3.6. (4R)-3-[(2R,3R)-3-(4-Bromophenyl)-3-hydroxy-2-methylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23f**)*

The title compound was prepared according to general procedure B from 3′-chloroacetophenone (143 μL, 1.10 mmol) for a reaction time of 17 h and purified by column chromatography (5% EtOAc/petrol) to give a colourless oil (225 mg, 58%). $[\alpha]_D^{21}$ −162 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3418 (OH), 2981, 2934, 2877, 1627 (C=O), 1419, 1205, 1066, 842, 701 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$)

δ 7.54–7.49 (2H, m, Ar*H*), 7.48–7.42 (3H, m, Ar*H*), 7.15–7.10 (2H, m, Ar*H*), 6.89–6.83 (2H, m, Ar*H*), 5.45 (1H, s, O*H*), 4.75 (1H, dd, *J*=6.7, 2.2 Hz, C*H*$_2$O), 4.40 (1H, dd, *J*=9.1, 6.7 Hz, C*H*N), 3.99 (1H, dd, *J*=9.1, 2.2 Hz, C*H*$_2$O), 2.58 (1H, q, *J*=7.1 Hz, CH$_3$C*H*), 1.97 (3H, s, C(C*H*$_3$)$_2$), 1.66 (3H, s, C(C*H*$_3$)$_2$), 0.93 (3H, s, C*H*$_3$COH), 0.89 (3H, d, *J*=7.1 Hz, C*H*$_3$CH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 175.8 (C), 148.0 (C), 141.9 (C), 133.9 (C), 129.3 (2×CH), 129.1 (CH), 128.6 (CH), 126.7 (2×CH), 126.3 (CH), 1245.0 (CH), 122.7 (CH), 96.2 (C), 74.4 (C), 70.9 (CH$_2$), 61.7 (CH), 46.5 (CH), 29.4 (CH$_3$), 25.5 (CH$_3$), 22.7 (CH$_3$), 12.1 (CH$_3$); HRMS (ES) exact mass calcd for $C_{22}H_{27}^{35}ClNO_3$ [M+H]$^+$: 388.1675, found: 388.1675.

4.3.7. (4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(naphthalen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23g**)

The title compound was prepared according to general procedure B from 2′-acetonaphthone (187 mg, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (5% EtOAc/petrol) to give a white solid (302 mg, 75%). Mp 215–217 °C; $[\alpha]_D^{21}$ −11.2 (*c* 1.00, CHCl$_3$); IR (CHCl$_3$) 3410 (OH), 2980, 2933, 2878, 1624 (C=O), 1456, 1418, 1377, 1299, 1065 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.78–7.76 (2H, m, Ar*H*), 7.67 (1H, d, *J*=8.7 Hz, Ar*H*), 7.61–7.40 (8H, m, Ar*H*), 6.86–6.84 (1H, m, Ar*H*), 5.59 (1H, br s, O*H*), 4.80 (1H, dd, *J*=6.6, 2.2 Hz, C*H*$_2$O), 4.42 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 4.01 (1H, dd, *J*=9.1, 2.2 Hz, C*H*$_2$O), 2.74 (1H, q, *J*=7.1 Hz, CH$_3$C*H*), 2.02 (3H, s, C(C*H*$_3$)$_2$), 1.69 (3H, s, C(C*H*$_3$)$_2$), 1.09 (3H, s, C*H*$_3$COH), 0.91 (3H, d, *J*=7.1 Hz, C*H*$_3$CH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 176.2 (C), 143.2 (C), 142.1 (C), 133.1 (C), 132.0 (C), 129.3 (2×CH), 128.6 (CH), 128.1 (CH), 127.4 (CH), 127.3 (CH), 126.8 (2×CH), 125.8 (CH), 125.4 (CH), 123.5 (CH), 122.8 (CH), 96.3 (C), 74.9 (C), 71.0 (CH$_2$), 61.7 (CH), 46.6 (CH), 29.6 (CH$_3$), 25.6 (CH$_3$), 22.7 (CH$_3$), 12.2 (CH$_3$); HRMS (ES) exact mass calcd for $C_{26}H_{30}NO_3$ [M+H]$^+$: 404.2220, found: 404.2221.

4.3.8. (4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(thiophen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**23h**)

The title compound was prepared according to general procedure B from 2-acetylthiophene (119 μL, 1.10 mmol) for a reaction time of 16 h and purified by column chromatography (20% EtOAc/petrol) followed by recrystallisation from CH$_2$Cl$_2$/hexane to give a white solid (220 mg, 61%). Mp 143–145 °C; $[\alpha]_D^{21}$ −11.8 (*c* 1.00, CHCl$_3$); IR (CHCl$_3$) 3399 (OH), 2983, 2933, 2878, 1625 (C=O), 1422, 1237, 1066, 844, 702 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.50–7.39 (5H, m, Ar*H*), 7.09 (1H, dd, *J*=5.1, 1.2 Hz, C*H*), 6.86 (1H, dd, *J*=5.1, 3.5 Hz, C*H*), 6.35 (1H, dd, *J*=3.5, 1.2 Hz, C*H*), 5.57 (1H, s, O*H*), 4.76 (1H, dd, *J*=6.6, 2.1 Hz, C*H*$_2$O), 4.40 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 3.99 (1H, dd, *J*=9.1, 2.1 Hz, C*H*$_2$O), 2.60 (1H, q, *J*=7.1 Hz, CH$_3$C*H*), 1.96 (3H, s, C(C*H*$_3$)$_2$), 1.65 (3H, s, C(C*H*$_3$)$_2$), 1.04 (3H, d, *J*=7.1 Hz, C*H*$_3$CH), 1.00 (3H, s, C*H*$_3$COH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 175.8 (C), 151.0 (C), 141.8 (C), 129.1 (2×CH), 128.4 (CH), 126.6 (2×CH), 126.5 (CH), 123.1 (CH), 121.0 (CH), 96.2 (C), 74.7 (C), 70.9 (CH$_2$), 61.5 (CH), 47.7 (CH), 30.6 (CH$_3$), 25.5 (CH$_3$), 22.6 (CH$_3$), 12.4 (CH$_3$); HRMS (ES) exact mass calcd for $C_{20}H_{26}NO_3S$ [M+H]$^+$: 360.1628, found: 360.1637.

4.3.9. (4R)-3-[(2R,3R)-3-Hydroxy-2-methyl-3-(6-methoxy-naphthalen-2-yl)pentanoyl]-2,2-dimethyl-4-phenyl-oxazolidine (**23j**)

The title compound was prepared according to general procedure B from 6′-methoxy-2′-propiononaphthone (236 mg, 1.10 mmol) for a reaction time of 3 h and purified by column chromatography (20% EtOAc/petrol) followed by recrystallisation from CH$_2$Cl$_2$/hexane to give a white solid (265 mg, 59%). Mp 164–166 °C; $[\alpha]_D^{21}$ −3.9 (*c* 1.00, CHCl$_3$); IR (CHCl$_3$) 3388 (OH), 2975, 2935, 2877, 1623 (C=O), 1417, 1266, 1173, 1067, 703 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.66 (1H, d, *J*=8.8 Hz, Ar*H*), 7.58–7.45 (7H, m, Ar*H*), 7.12 (1H, dd, *J*=8.9, 5.6 Hz, Ar*H*), 7.08 (1H, d, *J*=2.5 Hz, Ar*H*), 5.21 (1H, s, O*H*), 4.79 (1H, dd, *J*=6.6, 2.1 Hz, C*H*$_2$O), 4.41 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 3.99 (1H, dd, *J*=9.1, 2.1 Hz, C*H*$_2$O), 3.91 (3H, s, OC*H*$_3$), 2.67 (1H, q, *J*=7.1 Hz, CH$_3$C*H*), 2.00 (3H, s, C(C*H*$_3$)$_2$), 1.67 (3H, s, C(C*H*$_3$)$_2$), 1.65–1.55 (1H, m, C*H*$_2$CH$_3$), 0.96–0.85 (1H, m, C*H*$_2$CH$_3$), 0.90 (3H, d, *J*=7.1 Hz, C*H*$_3$CH), 0.43 (3H, t, *J*=7.3 Hz, CH$_2$C*H*$_3$); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 176.5 (C), 157.3 (C), 142.1 (C), 138.6 (C), 132.9 (C), 129.5 (CH), 129.2 (2×CH), 128.5 (CH and C), 126.7 (2×CH), 126.2 (CH), 124.5 (CH), 123.7 (CH), 118.5 (CH), 105.3 (CH), 96.2 (C), 77.9 (C), 71.0 (CH$_2$), 61.6 (CH), 55.2 (CH$_3$), 46.8 (CH), 33.3 (CH$_2$), 25.7 (CH$_3$), 22.6 (CH$_3$), 12.3 (CH$_3$), 7.7 (CH$_3$); HRMS (ES) exact mass calcd for $C_{28}H_{34}NO_4$ [M+H]$^+$: 448.2483, found: 448.2490.

4.4. Cobalt-catalysed reductive aldol reactions of *N*-alkenoyloxazolidines 24a–24h with acetophenone

4.4.1. Using Co(acac)$_2$·2H$_2$O/Et$_2$Zn: general procedure C

A solution of the appropriate *N*-alkenoyloxazolidine (0.50 mmol), acetophenone (65 μL, 0.55 mmol) and Co(acac)$_2$·2H$_2$O (6.4 mg, 0.025 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et$_2$Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction mixture was filtered through a short plug of SiO$_2$ using EtOAc as eluent (ca. 50 mL) and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography afforded the aldol product.

4.4.2. Using CoCl$_2$/Cy$_2$PPh/Et$_2$Zn: general procedure D

A solution of the appropriate *N*-alkenoyloxazolidine (0.50 mmol), the acetophenone (65 μL, 0.55 mmol), CoCl$_2$ (3.2 mg, 0.025 mmol) and Cy$_2$PPh (7.5 mg, 0.0275 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et$_2$Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature until complete consumption of the *N*-alkenoyloxazolidine as observed by TLC analysis. The reaction mixture was filtered through a short plug of SiO$_2$ using EtOAc as eluent (ca. 50 mL) and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography afforded the aldol product.

4.4.3. (4R)-3-[(2R,3R)-2-Ethyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25a**)

The title compound was prepared according to general procedure D from *N*-alkenoyloxazolidine **24a** (123 mg, 0.50 mmol) for a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (150 mg, 82%). Mp 131–133 °C; $[\alpha]_D^{21}$ −226 (*c* 1.00, CHCl$_3$); IR (CHCl$_3$) 3387 (OH), 2973, 1620 (C=O), 1457, 1408, 1308, 1133, 1067, 766, 703 cm^{-1}; ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.54–7.42 (5H, m, Ar*H*), 7.24–7.13 (3H, m, Ar*H*), 6.98 (2H, d, *J*=7.3 Hz, Ar*H*), 5.33 (1H, s, O*H*), 4.94 (1H, dd, *J*=6.6, 1.6 Hz, C*H*$_2$O), 4.41 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 4.00 (1H, dd, *J*=9.1, 1.6 Hz, C*H*$_2$O), 2.67 (1H, dd, *J*=10.8, 4.0 Hz, C*H*C=O), 2.01 (3H, s, C(C*H*$_3$)$_2$), 1.87–1.74 (1H, m, C*H*$_2$CH$_3$), 1.72 (3H, s, C(C*H*$_3$)$_2$), 1.21–1.10 (1H, m, C*H*$_2$CH$_3$), 0.87 (3H, t, *J*=6.6 Hz, CH$_2$C*H*$_3$), 0.78 (3H, s, C*H*$_3$COH); ^{13}C NMR (62.9 MHz, CDCl$_3$) δ 175.7 (C), 146.1 (C), 142.0 (C), 129.1 (2×CH), 128.6 (CH), 127.7 (2×CH), 127.4 (2×CH), 126.1 (CH), 124.6 (2×CH), 96.6 (C), 74.9 (C), 70.8 (CH$_2$), 61.9 (CH), 53.6 (CH), 29.8 (CH$_3$), 25.7 (CH$_3$), 22.6 (CH$_3$), 21.7 (CH$_2$), 12.1 (CH$_3$); HRMS (ES) exact mass calcd for $C_{23}H_{30}NO_3$ [M+H]$^+$: 368.2220, found: 368.2221.

4.4.4. (4R)-3-[(2R,3R)-2-iso-Butyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25b**)

The title compound was prepared according to general procedure D from *N*-alkenoyloxazolidine **24b** (137 mg, 0.50 mmol) for

a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (156 mg, 79%). Mp 195–197 °C; $[\alpha]_D^{21}$ −182 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3346 (OH), 2954, 1612 (C=O), 1456, 1409, 1303, 1130, 1067, 768, 705 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.54–7.41 (5H, m, Ar*H*), 7.23–7.11 (3H, m, Ar*H*), 6.97 (2H, d, *J*=7.3 Hz, Ar*H*), 5.25 (1H, s, O*H*), 4.90 (1H, dd, *J*=6.6, 1.6 Hz, CH_2O), 4.41 (1H, dd, *J*=9.1, 6.6 Hz, C*H*N), 4.00 (1H, dd, *J*=9.1, 1.6 Hz, CH_2O), 2.74 (1H, dd, *J*=10.1, 3.2 Hz, C*H*C=O), 2.01 (3H, s, C(CH_3)$_2$), 1.76–1.67 (1H, m, CH_2CH(CH$_3$)$_2$), 1.61 (3H, s, C(CH_3)$_2$), 1.32–1.20 (1H, m, C*H*(CH$_3$)$_2$), 1.04 (1H, ddd, *J*=14.1, 9.5, 3.2 Hz, CH_2CH(CH$_3$)$_2$), 0.82 (3H, d, *J*=6.5 Hz, CH(CH_3)$_2$), 0.77 (3H, s, CH_3COH), 0.75 (3H, d, *J*=6.5 Hz, CH(CH_3)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 176.3 (C), 146.1 (C), 141.9 (C), 129.2 (2×CH), 128.6 (CH), 127.7 (2×CH), 127.2 (2×CH), 126.1 (CH), 124.5 (2×CH), 96.6 (C), 75.3 (C), 70.9 (CH_2), 61.6 (CH), 50.6 (CH), 38.5 (CH_2), 30.2 (CH_3), 26.0 (CH), 25.6 (CH_3), 23.9 (CH_3), 22.7 (CH_3), 22.6 (CH_3); HRMS (ES) exact mass calcd for $C_{25}H_{34}NO_3$ $[M+H]^+$: 396.2533, found: 396.2534.

4.4.5. (4R)-3-[(2R,3R)-3-Hydroxy-3-phenylbutanoyl-2-(3-phenylpropyl)]-2,2-dimethyl-4-phenyloxazolidine (**25c**)

The title compound was prepared according to general procedure D from *N*-alkenoyloxazolidine **24c** (168 mg, 0.50 mmol) for a reaction time of 14 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (182 mg, 80%). Mp 130–132 °C; $[\alpha]_D^{21}$ −190 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 3028, 1619 (C=O), 1427, 1397, 1066, 1053, 837, 740, 706 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.59–7.48 (5H, m, Ar*H*), 7.34–7.22 (6H, m, Ar*H*), 7.11 (2H, d, *J*=7.2 Hz, Ar*H*), 7.06 (2H, d, *J*=7.2 Hz, Ar*H*), 5.41 (1H, s, O*H*), 4.86 (1H, dd, *J*=6.5, 1.5 Hz, CH_2O), 4.37 (1H, dd, *J*=9.1, 6.5 Hz, C*H*N), 4.01 (1H, dd, *J*=9.1, 1.5 Hz, CH_2O), 2.77 (1H, dd, *J*=9.9, 4.0 Hz, C*H*C=O), 2.52 (2H, t, *J*=7.2 Hz, CH_2Ar), 2.07 (3H, s, C(CH_3)$_2$), 1.94–1.82 (1H, m, CHCH_2CH$_2$), 1.76 (3H, s, C(CH_3)$_2$), 1.69–1.56 (1H, m, CHCH_2CH$_2$), 1.50–1.31 (2H, m, CH$_2$CH_2CH$_2$), 0.89 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 175.6 (C), 146.0 (C), 141.9 (C), 141.8 (C), 129.1 (2×CH), 128.5 (CH), 128.3 (2×CH), 128.1 (2×CH), 127.7 (2×CH), 127.2 (2×CH), 126.1 (CH), 125.7 (CH), 124.6 (2×CH), 96.5 (C), 74.8 (C), 70.8 (CH_2), 61.7 (CH), 52.3 (CH), 36.2 (CH_2), 29.8 (CH_3 and CH_2), 28.4 (CH_2), 25.6 (CH_3), 22.5 (CH_3); HRMS (FAB) exact mass calcd for $C_{30}H_{36}NO_3$ $[M+H]^+$: 458.2690, found: 458.2687.

4.4.6. (4R)-3-[(2R,3R)-2-Benzyl-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25d**)

The title compound was prepared according to general procedure C from *N*-alkenoyloxazolidine **24d** (154 mg, 0.50 mmol) for a reaction time of 4 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (184 mg, 86%). Mp 139–141 °C; $[\alpha]_D^{21}$ −286 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3387 (OH), 3026, 1620 (C=O), 1455, 1421, 1301, 1249, 1065, 843, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52–7.41 (3H, m, Ar*H*), 7.39–7.24 (8H, m, Ar*H*), 7.14–7.09 (4H, m, Ar*H*), 5.56 (1H, s, O*H*), 3.68 (1H, dd, *J*=9.0, 6.4 Hz, C*H*N), 3.62 (1H, dd, *J*=9.0, 1.3 Hz, CH_2O), 3.35 (1H, app d, *J*=5.4 Hz, CH_2O), 3.05 (1H, app t, *J*=12.5 Hz, C*H*C=O), 2.90 (1H, dd, *J*=11.9, 2.6 Hz, CH_2Ph), 2.43 (1H, dd, *J*=13.0, 2.6 Hz, CH_2Ph), 1.98 (3H, s, C(CH_3)$_2$), 1.65 (3H, s, C(CH_3)$_2$), 0.92 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 146.0 (C), 142.1 (C), 140.0 (C), 129.1 (2×CH), 128.9 (2×CH), 128.5 (2×CH), 128.3 (CH), 127.9 (2×CH), 127.0 (2×CH), 126.7 (CH), 126.3 (CH), 124.5 (2×CH), 96.3 (C), 75.3 (C), 70.4 (CH_2), 60.5 (CH), 55.7 (CH), 34.9 (CH_2), 29.7 (CH_3), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) exact mass calcd for $C_{28}H_{32}NO_3$ $[M+H]^+$: 430.2377, found: 430.2382.

4.4.7. (4R)-3-[(2R,3R)-3-Hydroxy-2-(4-methoxybenzyl)-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25e**)

The title compound was prepared according to general procedure C from *N*-alkenoyloxazolidine **24e** (169 mg, 0.50 mmol) for a reaction time of 6 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (198 mg, 86%). Mp 115–117 °C; $[\alpha]_D^{21}$ −304 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3386 (OH), 3027, 1618 (C=O), 1511, 1456, 1418, 1109, 1066, 768, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.52–7.41 (3H, m, Ar*H*), 7.36–7.22 (5H, m, Ar*H*), 7.07–7.05 (2H, m, Ar*H*), 7.02 (2H, d, *J*=8.6 Hz, Ar*H*), 6.90 (2H, d, *J*=8.6 Hz, Ar*H*), 5.56 (1H, s, O*H*), 3.83 (3H, s, OCH_3), 3.75 (1H, dd, *J*=9.0, 6.5 Hz, C*H*N), 3.65 (1H, dd, *J*=9.0, 1.1 Hz, CH_2O), 3.47 (1H, app d, *J*=5.8 Hz, CH_2O), 3.00 (1H, dd, *J*=13.1, 11.9 Hz, C*H*C=O), 2.88 (1H, dd, *J*=11.9, 2.4 Hz, CH_2Ar), 2.36 (1H, dd, *J*=13.1, 2.4 Hz, CH_2Ar), 1.98 (3H, s, C(CH_3)$_2$), 1.66 (3H, s, C(CH_3)$_2$), 0.91 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.0 (C), 158.4 (C), 146.0 (C), 142.1 (C), 131.9 (C), 130.0 (2×CH), 128.9 (2×CH), 128.3 (CH), 127.9 (2×CH), 127.0 (2×CH), 126.2 (CH), 124.4 (2×CH), 113.8 (2×CH), 96.2 (C), 75.2 (C), 70.4 (CH_2), 60.6 (CH), 55.7 (CH), 55.2 (CH_3), 34.0 (CH_2), 29.7 (CH_3), 25.4 (CH_3), 22.2 (CH_3); HRMS (ES) exact mass calcd for $C_{29}H_{34}NO_4$ $[M+H]^+$: 460.2482, found: 460.2482.

4.4.8. (4R)-3-[(2R,3R)-2-(4-Chlorobenzyl)-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25f**)

The title compound was prepared according to general procedure C from *N*-alkenoyloxazolidine **24f** (171 mg, 0.50 mmol) for a reaction time of 6 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (194 mg, 84%). Slow evaporation of a $CDCl_3$ solution of **25f** was found to give colourless crystals suitable for X-ray diffraction. Mp 139–140 °C; $[\alpha]_D^{21}$ −304 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3398 (OH), 3027, 1627 (C=O), 1493, 1423, 1313, 1296, 910, 767, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.53–7.43 (3H, m, Ar*H*), 7.36–7.23 (7H, m, Ar*H*), 7.04 (4H, dm, *J*=8.4 Hz, Ar*H*), 5.46 (1H, s, O*H*), 3.76 (1H, dd, *J*=9.1, 6.5 Hz, C*H*N), 3.68 (1H, dd, *J*=9.1, 1.3 Hz, CH_2O), 3.48 (1H, dd, *J*=6.5, 1.3 Hz, CH_2O), 3.00 (1H, dd, *J*=13.1, 11.9 Hz, C*H*C=O), 2.88 (1H, dd, *J*=11.9, 2.7 Hz, CH_2Ar), 2.37 (1H, dd, *J*=13.1, 2.7 Hz, CH_2Ar), 1.98 (3H, s, C(CH_3)$_2$), 1.62 (3H, s, C(CH_3)$_2$), 0.89 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 145.8 (C), 141.9 (C), 138.5 (C), 132.5 (C), 130.5 (2×CH), 129.0 (2×CH), 128.5 (4×CH), 128.0 (2×CH), 127.1 (2×CH), 126.4 (CH), 124.5 (CH), 96.4 (C), 75.2 (C), 70.4 (CH_2), 60.8 (CH), 55.4 (CH), 34.2 (CH_2), 29.6 (CH_3), 25.5 (CH_3), 22.2 (CH_3); HRMS (ES) exact mass calcd for $C_{28}H_{31}^{35}ClNO_3$ $[M+H]^+$: 464.1987, found: 464.1990.

4.4.9. (4R)-3-[(2R,3R)-3-Hydroxy-2-(naphthalen-2-ylmethyl)-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25g**)

The title compound was prepared according to general procedure C from *N*-alkenoyloxazolidine **24g** (179 mg, 0.50 mmol) for a reaction time of 16 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (216 mg, 90%). Mp 136–138 °C; $[\alpha]_D^{21}$ −358 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3389 (OH), 3026, 1620 (C=O), 1420, 1302, 1249, 1067, 908, 733, 703 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.94–7.88 (2H, m, Ar*H*), 7.85 (2H, d, *J*=8.6 Hz, Ar*H*), 7.61–7.51 (5H, m, Ar*H*), 7.38–7.29 (5H, m, Ar*H*), 7.14–7.11 (2H, m, Ar*H*), 6.99 (1H, br s, Ar*H*), 5.72 (1H, s, O*H*), 3.73 (1H, dd, *J*=9.0, 6.4 Hz, C*H*N), 3.66 (1H, dd, *J*=9.0, 1.1 Hz, CH_2O), 3.38 (1H, app d, *J*=5.9 Hz, CH_2O), 3.15 (1H, dd, *J*=12.6, 12.0 Hz, C*H*C=O), 3.06 (1H, dd, *J*=12.0, 1.8 Hz, CH_2Ar), 2.48 (1H, dd, *J*=12.6, 1.8 Hz, CH_2Ar), 2.05 (3H, s, C(CH_3)$_2$), 1.71 (3H, s, C(CH_3)$_2$), 1.07 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 143.2 (C), 142.2 (C), 139.9 (C), 133.1 (C), 132.1 (C), 129.1 (2×CH), 129.0 (2×CH), 128.4 (3×CH), 128.1 (CH), 127.6 (CH), 127.3 (CH), 127.1 (2×CH), 126.7 (CH), 125.9 (CH), 125.5 (CH), 123.6 (CH), 122.7 (CH), 96.3 (C), 75.5 (C), 70.4 (CH_2), 60.5 (CH), 55.5 (CH), 35.0 (CH_2), 29.7 (CH_3), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) Exact mass calcd for $C_{32}H_{34}NO_3$ $[M+H]^+$: 480.2533, found: 480.2539.

4.4.10. (4R)-3-[(2R,3R)-2-(Furan-2-ylmethyl)-3-hydroxy-3-phenylbutanoyl]-2,2-dimethyl-4-phenyloxazolidine (**25h**)

The title compound was prepared according to general procedure C from *N*-alkenoyloxazolidine **24h** (149 mg, 0.50 mmol) for

a reaction time of 4 h and purified by column chromatography (10% EtOAc/hexane) to give a white solid (174 mg, 83%). Mp 96–98 °C; $[\alpha]_D^{21}$ −298 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3378 (OH), 3028, 1622 (C=O), 1456, 1378, 1066, 1013, 914, 767, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.55–7.51 (2H, m, Ar*H*), 7.47–7.43 (4H, m, Ar*H*), 7.33–7.29 (2H, m, Ar*H*), 7.25–7.21 (1H, m, Ar*H*) 7.09–7.07 (2H, m, Ar*H*, C*H*), 6.38 (1H, dd, *J*=3.2, 1.9 Hz, C*H*), 6.03 (1H, d, *J*=3.2 Hz, C*H*), 5.56 (1H, s, O*H*), 4.00 (1H, dd, *J*=8.8, 6.5 Hz, CH_2N), 3.87 (1H, dd, *J*=6.5, 1.2 Hz, CH_2O), 3.82 (1H, dd, *J*=8.8, 1.2 Hz, CH_2O), 3.13 (1H, dd, *J*=13.1, 11.8 Hz, C*H*C=O), 3.07 (1H, dd, *J*=11.8, 1.7 Hz, CH_2CHC=O), 2.39 (1H, dd, *J*=13.1, 1.7 Hz, CH_2CH), 1.99 (3H, s, C(CH_3)$_2$), 1.61 (3H, s, C(CH_3)$_2$), 0.89 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.6 (C), 153.7 (C), 145.4 (C), 142.3 (C), 141.0 (CH), 129.0 (2×CH), 128.4 (CH), 127.9 (2×CH), 127.2 (2×CH), 126.4 (CH), 124.5 (2×CH), 110.9 (CH), 107.1 (CH), 96.3 (C), 74.8 (C), 70.6 (CH_2), 60.7 (CH), 52.4 (CH), 29.7 (CH_3), 26.8 (CH_2), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) exact mass calcd for $C_{26}H_{30}NO_4$ $[M+H]^+$: 420.2169, found: 420.2171.

*4.4.11. (4R)-3-[(2R,3R)-2-Benzyl-3-hydroxy-3-(naphthalen-2-yl)butanoyl]-2,2-dimethyl-4-phenyloxazolidine (**26**)*

On a 0.50 mmol scale: a solution of *N*-alkenoyloxazolidine **24d** (154 mg, 0.50 mmol), 2′-acetonaphthone (94 mg, 0.55 mmol) and $Co(acac)_2 \cdot 2H_2O$ (6.4 mg, 0.025 mmol) in THF (2.5 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 1.00 mL, 1.00 mmol) was then added dropwise over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 6 h. The reaction mixture was filtered through a short plug of SiO_2 using EtOAc as eluent (ca. 50 mL) and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *aldol product* **26** (218 mg, 91%) as a white solid.

On a 5.00 mmol scale: a solution of *N*-alkenoyloxazolidine **24d** (1.54 g, 5.00 mmol), 2′-acetonaphthone (936 mg, 5.50 mmol) and $Co(acac)_2 \cdot 2H_2O$ (64 mg, 0.25 mmol) in THF (25 mL) was stirred at room temperature for 10 min. The mixture was cooled to 0 °C and Et_2Zn (1 M solution in hexane, 10.0 mL, 10.0 mmol) was then added over 1 min. The reaction was stirred at 0 °C for 15 min and then at room temperature for 16 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (20 mL), and the mixture was extracted with CH_2Cl_2 (3×15 mL). Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *aldol product* **26** (2.16 g, 90%) as a white solid. Mp 139–141 °C; $[\alpha]_D^{21}$ −374 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3389 (OH), 3026, 1622 (C=O), 1455, 1417, 1377, 1066, 909, 768, 702 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.82–7.76 (2H, m, Ar*H*), 7.82–7.79 (1H, m, Ar*H*) 7.55–7.13 (12H, m, Ar*H*), 7.07 (2H, br s, Ar*H*), 5.53 (1H, s, O*H*), 3.35 (1H, app d, *J*=8.7 Hz, CH_2O), 3.22–3.09 (2H, m, CH_2O and C*H*C=O), 3.17 (1H, dd, *J*=8.7, 6.6 Hz, CH_2N), 2.93 (1H, dd, *J*=11.9, 2.8 Hz, CH_2Ph), 2.52 (1H, dd, *J*=13.2, 2.8 Hz, CH_2Ph), 1.91 (3H, s, C(CH_3)$_2$), 1.53 (3H, s, C(CH_3)$_2$), 0.87 (3H, s, CH_3COH); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 174.9 (C), 145.0 (C), 142.0 (C), 137.3 (C), 133.2 (C), 132.0 (C), 128.9 (2×CH), 128.3 (CH), 128.2 (CH), 128.0 (2×CH), 127.7 (CH), 127.5 (CH), 127.3 (CH), 127.1 (2×CH), 127.0 (CH), 126.5 (CH), 126.4 (CH), 125.6 (CH), 124.5 (2×CH), 96.1 (C), 75.3 (C), 70.1 (CH_2), 60.5 (CH), 55.6 (CH), 35.1 (CH_2), 29.7 (CH_3), 25.5 (CH_3), 22.1 (CH_3); HRMS (ES) exact mass calcd for $C_{32}H_{34}NO_3$ $[M+H]^+$: 480.2533, found: 480.2532.

Acknowledgements

This work was supported by the EPSRC, Merck Sharp & Dohme and the University of Edinburgh. We thank Professor Simon Parsons, Dr. Anna Collins, Laura E. Budd, Fraser J. White and Peter A. Wood at the University of Edinburgh for assistance with X-ray crystallography. We also thank the EPSRC National Mass Spectrometry Service Centre at the University of Wales, Swansea for providing high resolution mass spectra.

Supplementary data

Copies of ^1H and ^{13}C NMR spectra for new compounds in Tables 4 and 5 and Eq. 2. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.06.022.

References and notes

1. For a seminal reference, see: (a) Revis, A.; Hilty, T.K. *Tetrahedron Lett.* **1987**, *28*, 4809–4812; For an extensive collection of reports of catalytic reductive aldol reactions, see references cited within: (b) Ngai, M.-Y.; Kong, J.-R.; Krische, M.J. *J. Org. Chem.* **2006**, *72*, 1063–1072; For relevant reviews, see: (c) Nishiyama, H.; Shiomi, T. *Top. Curr. Chem.* **2007**, *279*, 105–137; (d) Jang, H.-Y.; Krische, M. J. *Eur. J. Org. Chem.* **2004**, 3953–3958; (e) Jang, H.-Y.; Krische, M. J. *Acc. Chem. Res.* **2004**, *37*, 653–661; (f) Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12–21; (g) Chiu, P. *Synthesis* **2004**, 2210–2215; (h) Motherwell, W. B. *Pure Appl. Chem.* **2002**, *74*, 135–142.
2. (a) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2746–2747; (b) Shiomi, T.; Nishiyama, H. *Org. Lett.* **2007**, *9*, 1651–1654; (c) Deschamp, J.; Chuzel, O.; Hannedouche, J.; Riant, O. *Angew. Chem., Int. Ed.* **2006**, *45*, 1292–1297; (d) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 14440–14441; (e) Zhao, D.; Oisaki, K.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2006**, *46*, 1403–1407; (f) Nishiyama, H.; Shiomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972–6973; (g) Russell, A. E.; Fuller, N. O.; Taylor, S. J.; Aurriset, S.; Morken, J. P. *Org. Lett.* **2004**, *6*, 2309–2312; (h) Zhao, C.-X.; Duffey, M. O.; Taylor, S. O.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829–1831; (i) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528–4529.
3. (a) Lam, H. W.; Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Prieto, O.; Luebbers, T. *Org. Lett.* **2006**, *8*, 3729–3732; (b) Lumby, R. J. R.; Joensuu, P. M.; Lam, H. W. *Org. Lett.* **2007**, *9*, 4367–4370.
4. Joensuu, P. M.; Murray, G. J.; Fordyce, E. A. F.; Luebbers, T; Lam, H. W. *J. Am. Chem. Soc.* **2008**, *130*, 7328–7338.
5. For cobalt-catalysed reductive aldol reactions, see: (a) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005–2008; (b) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448–9453.
6. (a) Lam, H. W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225–4228; (b) Lam, H. W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743–5746.
7. The relative stereochemistry of the known compound **4a** was assigned by comparison with literature spectral data. See: Taniguchi, M.; Hideaki, F.; Koichiro, O.; Kiitiro, U. *Tetrahedron Lett.* **1992**, *33*, 4353–4356.
8. Crystallographic data (excluding structure factors) for products **4c**, **7f** and **7g** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 666641–666643. 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).
9. For initial, speculative proposals about the mechanism of cobalt-catalysed conjugate reduction of α,β-unsaturated amides in the presence of diethylzinc, see Ref. 3a. Figure 1 presents a revised model.
10. (a) Johnson, J. R.; Tully, P. S.; MacKenzie, P. B.; Sabat, M. *J. Am. Chem. Soc.* **1991**, *113*, 6172–6177; (b) Grisso, B. A.; Johnson, J. R.; MacKenzie, P. B. *J. Am. Chem. Soc.* **1992**, *114*, 5160–5165.
11. (a) Ogoshi, S.; Yoshida, T.; Nishida, T.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2001**, *123*, 1944–1950; (b) Ogoshi, S.; Tomiyasu, S.; Morita, M.; Kurosawa, H. *J. Am. Chem. Soc.* **2002**, *124*, 11598–11599.
12. Hratchian, H. P.; Chowdhury, S. K.; Gutiérrez-García, V. M.; Amarasinghe, K. K. D.; Heeg, M. J.; Schlegel, H. B.; Montgomery, J. *Organometallics* **2004**, *23*, 4636–4646.
13. Jonas, K.; Koepe, G.; Krueger, C. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 923–925.
14. (a) Kaschube, W.; Pörschke, K.-R.; Angermund, K.; Krüger, C.; Wilke, G. *Chem. Ber.* **1988**, *121*, 1921–1929; (b) Ogoshi, S.; Ueta, M.; Arai, T.; Kurosawa, H. *J. Am. Chem. Soc.* **2005**, *127*, 12810–12811.
15. Zimmerman, H. E.; Traxler, M. D. *J. Am. Chem. Soc.* **1957**, *79*, 1920–1923.
16. (a) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23–32; (b) Heathcock, C. H. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 181; (c) Arya, P.; Qin, H. *Tetrahedron* **2000**, *56*, 917–947; (d) Palomo, C.; Oiarbide, M.; García, J. M. *Chem.—Eur. J.* **2002**, *8*, 36–44.
17. For chiral auxiliary-controlled asymmetric ketone aldol reactions, see: (a) Ojima, I.; Yoshida, K.; Inaba, S.-i. *Chem. Lett.* **1977**, 429–432; (b) Sakito, Y.; Asami, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 455–458; (c) Basavaiah, D.; Bharathi, T. K. *Tetrahedron Lett.* **1991**, *28*, 3417–3420; (d) Akiyama, T.; Ishikawa, K.; Ozaki, S. *Synlett* **1994**, 275–276; (e) Bartroli, J.; Turmo, E.; Belloc, J.; Forn, J. *J. Org. Chem.* **1995**, *60*, 3000–3012; (f) Jacobson, I. C.; Reddy, G. P. *Tetrahedron Lett.* **1996**, *37*, 8263–8266; (g) Soloshonok, V. A.; Avilov, D. V.; Kukhar, V. P. *Tetrahedron* **1996**, *38*, 12433–12442; (h) Judge, T. M.; Phillips, G.; Morris, J. K.; Lovasz, K. D.; Romines, K. R.; Luke, G. P.; Tulinsky, J.; Tustin, J. M.; Chrusciel, R. A.; Dolak, L. A.; Mizsak, S. A.; Watt, W.; Morris, J.; Vander Velde, S. L.; Strohbach, J. W.; Gammill, R. B. *J. Am. Chem. Soc.* **1997**, *119*, 3627–3628; (i) García Ruano, J. L.; Barros, D.; Carmen Maestro, M.; Slawin, A. M. Z.; Bulman Page, P. C. *J. Org. Chem.* **2000**, *65*, 6027–6034.
18. For catalytic enantioselective aldol reactions of preformed enolates with ketones, see: (a) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893–7894; (b) Evans, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 10859–10860; (c) Evans, D. A.; Burgey, C. S.;

Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686–699; (d) Le, J. C.-D.; Pagenkopf, B. L. *Org. Lett.* **2004**, *6*, 4097–4099; (e) Denmark, S. E.; Fan, Y.; Eastgate, M. D. *J. Org. Chem.* **2005**, *70*, 5235–5248; (f) Moreau, X.; Bazán-Tejeda, B.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 7288–7289; (g) Oisaki, K.; Zhao, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7164–7165; For a catalytic enantioselective Reformatsky reaction with ketones, see: (h) Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951–2954.

19. For catalytic enantioselective reductive aldol reactions with ketones, see Refs. 2b–e and 6a.
20. For similar observations in related reactions, see Ref. 3a, and: Chrovian, C. C.; Montgomery, J. *Org. Lett.* **2007**, *9*, 537–540.
21. (a) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631–8644; (b) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8645–8658; For the use of chiral oxazolidines in related reactions, see: (c) Lettan, R. B., II; Reynolds, T. E.; Galliford, C. V.; Scheidt, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 15566–15567; (d) Lettan, R. B., II; Woodward, C. C.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2294–2297.
22. The stereochemistries of the minor diastereomers produced in the reactions in Tables 4 and 5 were not determined.
23. Crystallographic data (excluding structure factors) for products **23a**, **23d** and **25f** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 634191–634193. 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).
24. (a) Myers, A. G.; Yang, B. H.; Kopecky, D. J. *Tetrahedron Lett.* **1996**, *37*, 3623–3626; (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496–6511.
25. Kanemasa, S.; Suenaga, H.; Onimura, K. *J. Org. Chem.* **1994**, *59*, 6949–6954.