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β-Amidoaldehydes *via* oxazoline hydroformylation†‡

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Received (in College Park, MD, USA) 9th July 2009, Accepted 10th August 2009
First published as an Advance Article on the web 1st September 2009
DOI: 10.1039/b913698c

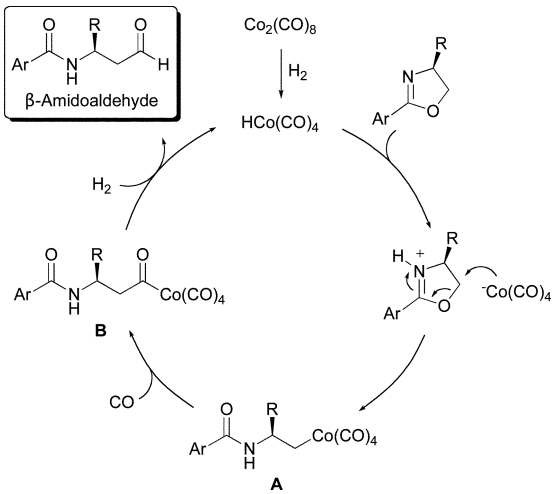
4-Substituted oxazolines, which are readily synthesized from naturally occurring α-amino acids, are converted efficiently and stereospecifically to β-amidoaldehydes in the presence of synthesis gas and catalytic dicobalt octacarbonyl.

Enantiomerically pure N-protected β-aminoaldehydes are useful building blocks for addition of β-amino functionality in a stereospecific fashion. This method has been utilized for the synthesis of β-peptide derivatives[1] as well as other bioactive molecules.[2] Maraviroc, a promising antiretroviral, uses a β-amidoaldehyde as a key intermediate in its synthesis.[3] Given the utility of enantiopure N-protected β-aminoaldehydes, there has been interest in their efficient synthesis. Two general strategies can be employed: enantioselective coupling of two prochiral substrates[4–9] or synthetic transformation of a naturally occurring chiral molecule.[10]

The Mannich reaction is frequently used for the enantioselective synthesis of N-protected β-aminoaldehydes, either through the coupling of imines with aldehydes[4] or indirectly through the coupling of imines with esters[5] or Weinreb amides[6] followed by reduction. Enantioenriched β-aminoaldehydes have also been synthesized by the organocatalytic conjugate addition of nitrogen nucleophiles to α,β-unsaturated aldehydes;[7] by the cyclization of *N*-acyl imines with chiral vinyl ethers followed by hydrolysis;[8] and by using an enantioselective aza-Petasis–Ferrier rearrangement of vinyl hemiaminals.[9]

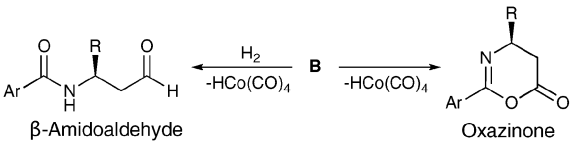
α-Amino acids are the most common chiral precursors for the synthesis of enantiomerically pure β-amidoaldehydes, and are first converted to β-amino acids using the Arndt–Eistert protocol followed by reduction.[10] This route uses the hazardous reagent diazomethane as well as stoichiometric amounts of silver salts, precluding its use on large scale.

For the past several years, our group has studied the carbonylation of heterocycles using cobalt catalysts.[11,12] Recently, inspired by work of Jia and co-workers,[13] we have developed an efficient method for the carbonylation of 4- and 5-substituted oxazolines to oxazinones using the catalyst $HCo(CO)_4$.[14] Given that $HCo(CO)_4$ is an effective olefin hydroformylation catalyst,[15] we hypothesized that the reaction conditions used for the carbonylation of oxazolines to oxazinones might be adapted to favor the formation of β-amidoaldehydes through addition of hydrogen. Herein, we report that 4-substituted oxazolines, prepared in one step from commercially available α-amino alcohols, are efficiently converted to β-amidoaldehydes using hydrogen, carbon monoxide and the inexpensive precatalyst dicobalt octacarbonyl.



Scheme 1 Proposed catalytic cycle for the hydroformylation of oxazolines to β-amidoaldehydes.

The reaction is presumed to proceed through a catalytic cycle similar to that of oxazoline carbonylation to oxazinones, where initial protonation of an oxazoline by $HCo(CO)_4$ is followed by ring opening to form a cobalt alkyl intermediate **A** (Scheme 1). Upon migratory insertion of CO, production of the desired β-amidoaldehyde would depend on a faster reaction of the resulting cobalt acyl complex **B** with hydrogen than intramolecular ring closure to form oxazinone [eqn (1)].



(1)

On the basis of this proposed mechanism, we hypothesized that it would be critical to find reaction conditions that provided selectivity for β-amidoaldehyde over oxazinone formation. We have previously shown that solvent choice is important for achieving optimal rates and product selectivities in epoxide carbonylation[16] and began by screening the hydroformylation of 4-methyl-2-phenyloxazoline in solvents of varying polarity and donicity (Table 1). The optimized reaction conditions for oxazoline carbonylation to oxazinones under a pressure of

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† Electronic supplementary information (ESI) available: Experimental procedures, characterization data for all new compounds, and X-ray tabular data for **3**. CCDC 739579. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b913698c

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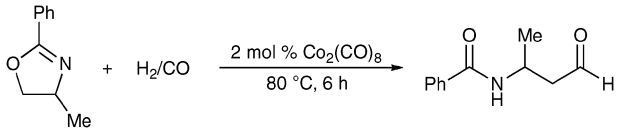
Table 1 Effect of solvent on oxazoline hydroformylation[a]



Entry	Solvent	[Oxazoline]/M	Conversion[b] (%)
1	DME	0.50	15
2	CH_3CN	0.50	0
3	THF	0.50	53
4	Et_2O	0.50	45
5	1,4-Dioxane	0.50	68
6	Toluene	0.50	80
7	Hexanes	0.50	11
8	Toluene	1.00	38
9	Toluene	0.25	95

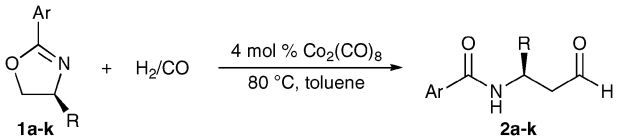
[a] H_2/CO (1 : 1, 82 atm). [b] Conversion determined by ^{1}H NMR spectroscopy relative to an internal standard.

hydrogen and carbon monoxide gave a complicated mixture of products and only a small amount of the desired β-amidoaldehyde was formed (entry 1). Other solvents of moderate donicity such as tetrahydrofuran (entry 3), diethyl ether (entry 4) and 1,4-dioxane (entry 5) also provided only modest yields of the desired product, while the strongly coordinating solvent acetonitrile (entry 2) completely inhibited the reaction. Of the solvents screened, toluene (entry 6) proved to be the highest yielding. The yield of 3-benzamidobutanal was also significantly impacted by reaction concentration (entries 6, 8 and 9), where reactions run under more dilute conditions resulted in higher yields. Under optimized conditions, 3-benzamidobutanal was formed in 95% conversion.

With optimized reaction conditions established, the hydroformylation of a wide range of 4-substituted oxazolines was attempted (Table 2). Variation at the 2-position with aryl groups containing both electron-donating and -withdrawing substituents was tolerated (entries 1–3). A number of oxazolines derived from naturally occurring α-amino acids including glycine (entry 1), alanine (entry 4), valine (entry 6), leucine (entry 7), isoleucine (entry 8), and phenylalanine (entry 10) were hydroformylated to their corresponding β-amidoaldehydes in good to excellent isolated yield. For oxazolines possessing 4-substituents with groups larger than methyl, higher catalyst loadings and longer reaction times were required to reach full conversion. The serine-derived oxazoline required protection of the alcohol group (entry 11) for clean hydroformylation to the corresponding β-amidoaldehyde. The reactions generally produced minimal byproducts, however for oxazolines that lacked substitution at the 4-position (entries 1–3) small amounts (5%) of the branched aldehyde isomer were formed.[17] In the case of phenyl-substituted oxazoline **1i** (entry 9), a significant amount of 1-phenylethylbenzamide (~15%) was detected in the crude reaction mixture by ^{1}H NMR spectroscopy.

In contrast to the carbonylation of oxazolines to oxazinones, optical purity was not always transferred from oxazolines to their β-amidoaldehyde products. Racemization was particularly problematic with the oxazoline bearing a phenyl substituent at the 4-position (Table 2, entry 9), and some racemization was observed with methyl and benzyl-substituted substrates (entries 4 and 10). We hypothesize that this racemization is the result of β-hydride elimination from cobalt

Table 2 Hydroformylation of oxazolines to β-amidoaldehydes[a]



	Oxazoline					
Entry	Cpd	Ar	R	t_{rxn}/h	Yield[b] (%)	ee[c] (%)
1[d]	**1a**	Ph	H	6	81[e]	na[f]
2[d]	**1b**	*p*-FC_6H_4	H	6	83[e]	na[f]
3[d]	**1c**	*p*-$MeOC_6H_4$	H	6	64[e]	na[f]
4[dg]	**1d**	Ph	Me	6	71	94
5	**1e**[h]	Ph	Et	6	85	99
6	**1f**	Ph	^{i}Pr	20	84	99
7	**1g**	Ph	^{i}Bu	20	88	99
8	**1h**	Ph	(*S*)-^{s}Bu	20	89	99
9	**1i**[h]	Ph	Ph	20	63	10
10	**1j**	Ph	CH_2Ph	6	82	96
11	**1k**[i]	*p*-^{t}BuC_6H_4	CH_2OTBS[j]	20	90	na[f]

[a] Conditions: [oxazoline] = 0.25 M; H_2/CO (1 : 1, 82 atm). [b] Isolated yield, average of two runs. [c] %ee determined by ^{1}H NMR spectroscopy using (+)-Eu(tfc)$_3$. [d] 2 mol% $Co_2(CO)_8$ used. [e] Yield determined by ^{1}H NMR spectroscopy relative to an internal standard. [f] na: not applicable. [g] Reaction run at 70 °C. [h] Enantiomeric compound used. [i] Racemic substrate used. [j] TBS = *tert*-butyldimethylsilyl.

alkyl intermediate **A** (Scheme 1) followed by hydroformylation of the resulting ene-amide (Fig. 1). Hydroformylation of optically pure 5-methyl-2-phenyloxazoline led to partially racemized β-amidoaldehyde product.†

Alkyl cobalt tetracarbonyl compounds were shown to undergo reversible β-hydrogen elimination more than 40 years ago by Heck and Breslow.[18] They found that the rate of elimination is more rapid at elevated temperatures and low pressures of carbon monoxide. The degree of racemization in oxazoline hydroformylation is also impacted by temperature and pressure (Table 3). As the reaction temperature is lowered,

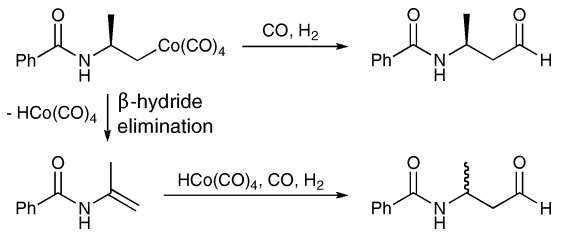
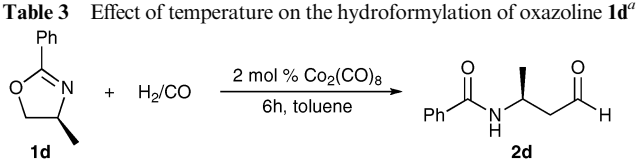


Fig. 1 Proposed racemization pathway.

Table 3 Effect of temperature on the hydroformylation of oxazoline **1d**[a]



Entry	Temperature/°C	H_2/CO Pressure/atm	ee[b] (%)
1	90	82	70
2	80	82	87
3	80	55	53
4	70	82	94

[a] Conditions: [oxazoline] = 0.25 M; 1 : 1 H_2/CO. [b] %ee determined by ^{1}H NMR spectroscopy using (+)-Eu(tfc)$_3$.

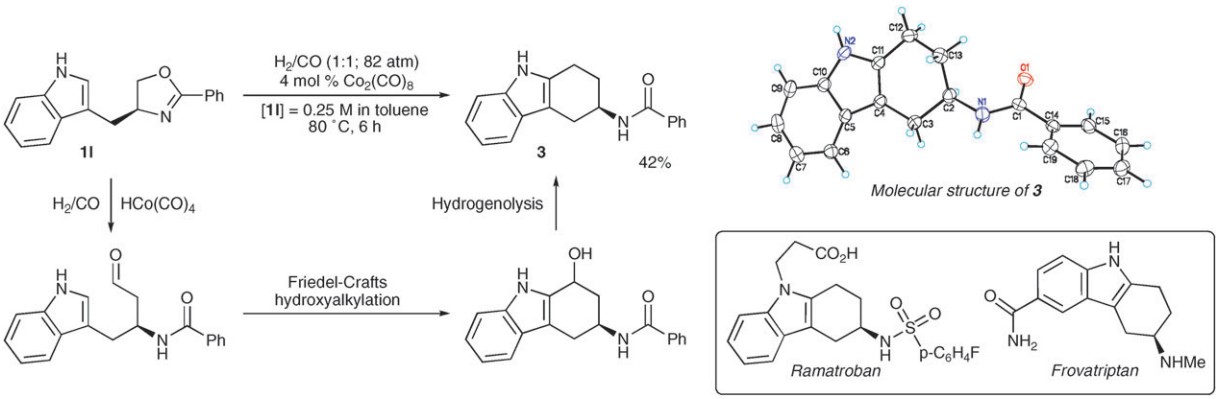


Fig. 2 Proposed formation of **3** (left), ORTEP of **3** drawn with 50% thermal ellipsoids (top right), and structurally-related pharmaceuticals (bottom right).

an increase in the enantiomeric excess of β-amidoaldehyde was observed (entries 1, 3 and 4). Also, an increase in %ee was observed when the total pressure of H_2/CO was increased (entry 2 and 3). Hydroformylation at temperatures below 70 °C led to formation of significant amounts of oxazinone.

While exploring the substrate scope of oxazolines derived from naturally occurring α-amino acids, hydroformylation of the tryptophan-derived oxazoline **1l** led to a product whose ^{1}H NMR spectrum was inconsistent with formation of a β-amidoaldehyde. Further spectroscopic studies supported the formation of the tetrahydrocarbazole product **3** (Fig. 2), which was confirmed by single-crystal X-ray crystallography.† We propose a reaction pathway where the expected β-amidoaldehyde product is initially formed, followed by intramolecular Friedel–Crafts hydroxyalkylation. The intramolecular reaction of the indole π system at the 2-position with electrophiles is well precedented,[19] including aldehydes.[20] The mechanism for hydrogenolysis of the alcohol-substituted intermediate to **3** has not been studied. In the homologation of benzyl alcohols using synthesis gas and catalytic $HCo(CO)_4$, the major products are frequently methyl benzenes[21] and an analogous reaction mechanism may be operative here. The tetrahydrocarbazole core found in **3** is present in a number of bioactive molecules including Ramatroban,[22] a drug used to treat coronary artery disease and asthma, and Frovatriptan,[23] a drug used to treat migraine headaches (Fig. 2).

In conclusion, we have developed an efficient route to β-amidoaldehydes from oxazolines using the inexpensive, commercially available precatalyst $Co_2(CO)_8$ with relatively high levels of stereochemical retention. Efforts to further optimize stereospecificity and substrate scope of oxazoline hydroformylation are underway.

We are grateful to the Department of Energy for funding (DE-FG02-05ER15687). We thank Dr Christopher M. Byrne for the preparation of oxazoline starting materials and Dr Sze-Sze Ng for helpful discussions.

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