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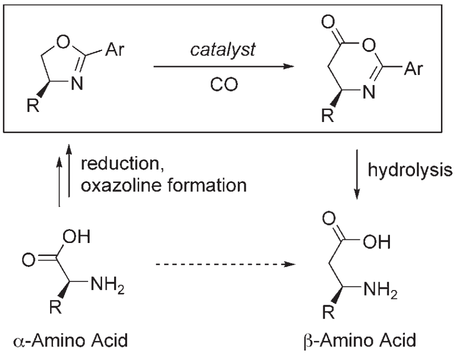
β-Amino Acids

Catalytic Synthesis of β^3-Amino Acid Derivatives from α-Amino Acids**

*Christopher M. Byrne, Tamara L. Church, John W. Kramer, and Geoffrey W. Coates**

The synthesis of β-amino acids and their derivatives has garnered considerable interest over the past decades.[1] These one-carbon homologues of α-amino acids are vital components of several pharmaceutics[1c,d,2] and have important roles in medicinal chemistry[2a] and biochemistry.[3] Pioneering work by Seebach et al.[4] and Gellman et al.[5] has revealed that incorporating β-amino acids into peptide chains induces new secondary and tertiary structures and leads to biological activity in select cases. Central to all of these applications is the use of stereochemically pure β-amino acids, and recently reported enantioselective routes include Mannich reactions,[6] Kowalsky rearrangements,[7] radical reactions,[8] isoxazoline intermediates,[9] organocatalysis,[10] and enzymatic hydrolysis of β-lactams.[11] The use of transition-metal catalysis shows promise for the generation of enantiomerically pure β-amino acid derivatives[12] and current research focuses on asymmetric hydrogenation reactions using Rh catalysts.[13] Classic synthetic methods such as the Arndt–Eistert protocol work well for the β^3-amino acids, but the hazardous nature of diazomethane and high cost of silver render it undesirable for large-scale synthesis.[1]

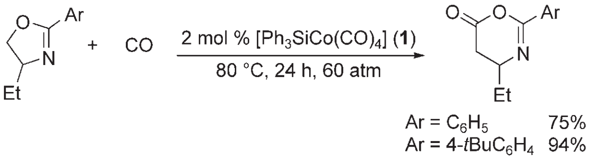
Given our previous work on the carbonylation of heterocycles,[14] we were interested in two reports from Jia and co-workers[15] on the catalytic carbonylation of 2-oxazolines to give 2-oxazin-6-ones, which are precursors to β-amino acids. The system featured benzyl tetracarbonylcobalt(I) as the catalyst, and although 2-phenyl-2-oxazoline was converted cleanly to oxazinone (19 turnovers in 48 h), 4- and 5-substituted oxazolines were quite challenging (< 10 turnovers in 48 h). We believed that our Lewis acid based carbonylation catalysts could effect this transformation quickly and efficiently. Though these catalysts may improve the carbonylation step, the benefit of this method is the ease and generality of substrate synthesis (Scheme 1). There are many synthetic pathways to oxazolines;[16] we focused on those using β-amino alcohols due to their commercial availability and accessibility by α-amino acid reduction. The overall synthetic pathway, shown in Scheme 1, begins with a biorenewable, stereochemically rich resource and yields enantiomerically pure β-amino acids.



Scheme 1. Synthetic pathway from α-amino acids to β-amino acids via oxazoline carbonylation.

We began investigating catalysts of the form [Lewis acid]$^+$[$Co(CO)_4$]$^-$, which demonstrate good activity for epoxide, aziridine, and β-lactone carbonylation.[14,17] Though these complexes showed poor activity for oxazoline carbonylation, we continued to pursue an active catalyst system for this transformation. Related work by Murai and co-workers on the carbonylation of epoxides,[18a] oxetanes,[18b] and benzylic esters[18c] using $HSiR_3$/[$Co_2(CO)_8$] systems led to the selection of [$Ph_3SiCo(CO)_4$] (**1**) as a candidate. The complex is readily synthesized by the addition of two equivalents of Ph_3SiH to a hexanes solution of [$Co_2(CO)_8$].[17,19]

Our initial experiments focused on the carbonylation of a representative substrate, 4-ethyl-2-phenyl-2-oxazoline, which proceeded smoothly in 75 % yield using **1** in tetrahydropyran (THP) [Eq. (1)]. We examined the effect of a *tert*-butyl group in the 4-position of the aromatic ring and found that the presence of this substituent increased the yield to 94 % using the same conditions. Although this change in reactivity is significant, we discovered that the reaction medium had a greater effect on the yield of oxazinone.



(1)

We surveyed a collection of solvents diverse in dielectric constant and donor ability, and the results are shown in Table 1. The highest conversions to oxazinone were obtained

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[*] Dr. C. M. Byrne, Dr. T. L. Church, J. W. Kramer, Prof. Dr. G. W. Coates
Department of Chemistry and Chemical Biology
Cornell University
Baker Laboratory, Ithaca, NY 14853-1301 (USA)
Fax: (+1) 607-255-4137
E-mail: gc39@cornell.edu

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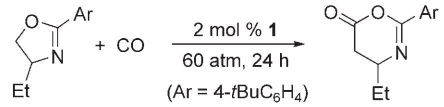
Table 1: Solvent effect on oxazoline carbonylation using **1**.[a]



Entry	Solvent	Yield[b] [%]
1	toluene	19
2	1,4-dioxane	38
3	tetrahydrofuran	95
4	1,2-dimethoxyethane	95
5	tetrahydropyran	94

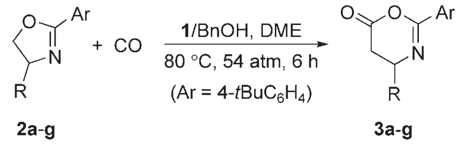
[a] All reactions were performed using 2 mol % **1**, 1 mmol substrate, 60 atm CO, 2 mL solvent, 80 °C, 24 h. [b] Yield of oxazinone determined by ^{1}H NMR spectroscopy.

for carbonylations using tetrahydrofuran (THF), 1,2-dimethoxyethane (DME), or THP, though reactions run in THF or DME displayed a lack of reproducibility. Intrigued by these results, we monitored a typical carbonylation reaction of 2-(4-*tert*-butylphenyl)-4-methyl-2-oxazoline (**2a**) in THP using in situ IR spectroscopy. We observed an initiation period before relatively clean consumption of oxazoline occurred.[17] Previous work by Murai demonstrated that HSiR$_3$/[Co$_2$(CO)$_8$] systems are capable of ring-opening THF[20] and, on the basis of his work, we hypothesized that a similar reaction between THP and **1** might be generating an alkylcobalt species. β-Hydride elimination from this species would produce [HCo(CO)$_4$], which could serve as the active catalyst. We pursued the alcoholysis of the silicon–cobalt bond as a reproducible route to [HCo(CO)$_4$] by adding a stoichiometric amount of methanol to a toluene solution of **1**. The carbonylation of **2a** using **1**/MeOH under standard reaction conditions was monitored by in situ IR spectroscopy and displayed a markedly higher reaction rate and no induction period.[17]

The indication from these in situ IR reactions is that [HCo(CO)$_4$] is generated by the reaction of methanol and **1**, and is acting as the catalyst. However, direct observation of the cobalt–hydride species was not possible by IR spectroscopy due to overlap of the [HCo(CO)$_4$] signals with those of the instrument window. To observe [HCo(CO)$_4$] directly, we examined the reaction between benzyl alcohol and **1** by ^{1}H NMR spectroscopy. In C$_6$D$_6$, the reaction between BnOH and **1** did yield [HCo(CO)$_4$] ($\delta = -11.6$ ppm),[21] albeit slowly and with significant decomposition to H$_2$ and a red cobalt species.[22] To more closely emulate reaction conditions, we performed the reaction in [D$_{10}$]Et$_2$O. The combination of **1** and BnOH immediately generated an equivalent of [HCo(CO)$_4$], which decomposed to H$_2$ and [Co$_2$(CO)$_8$] over the course of 16 h. Though the production of [HCo(CO)$_4$] in ether solvent is clean and efficient, instability is problematic. To further approximate carbonylation conditions, the reaction of BnOH and **1** was repeated in the presence of oxazoline **2h**, as this substrate is slower to react under typical carbonylation conditions (vide infra). The ^{1}H NMR spectrum of this combination is consistent with the formation of Ph$_3$SiOBn and a new oxazoline-derived product. The downfield shift of the oxazoline resonances and the presence of a broad singlet near $\delta = 12$ ppm indicate the presence of a protonated oxazoline species.[17] Moreover, the absence of peaks representing either [HCo(CO)$_4$] or H$_2$ indicates that there is no significant free [HCo(CO)$_4$] present under these conditions. Therefore, we conclude that the alcoholysis of **1** in the presence of oxazoline generates an oxazolinium cobaltate species (Scheme 2, **A**), which is similar to previously reported trialkylammonium cobaltate salts.[23]

On the basis of the IR and ^{1}H NMR data and the results from the solvent-screening reactions,[17,24] we established a standard set of conditions (54 atm CO, 80 °C, 6 h) and examined the use of **1** and BnOH (1:1) as a catalyst system for the carbonylation of oxazolines, which were derived from an assortment of α-amino acids (Table 2). In general, reactivity declined with increasing steric bulk at the 4-position. The 4-methyl- (**2a**, entry 1) and 4-ethyl-substituted oxazolines (**2b**, entry 2) required 1 and 3 mol % of the catalyst system, respectively. Attempted carbonylation of **2b** using lower CO pressure (6.8 atm) gave roughly an 80 % yield of oxazinone and about 11 % yield of an *E*/*Z* mixture of 4-*tert*-butyl-*N*-(1-methylpropenyl)benzamide.[17] Oxazolines derived from leucine (**2c**, entry 3), phenylalanine (**2d**, entry 4), and serine (**2e**, entry 5) were all carbonylated cleanly to the corresponding oxazinones using 3 mol % **1**/BnOH. Larger substituents at the 4-position, such as isopropyl (**2f**, entry 6) or phenyl groups (**2g**, entry 7) required more catalyst, but were still carbonylated in high yield.

Table 2: Carbonylation of 4-substituted oxazolines using **1**/BnOH.[a]

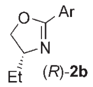
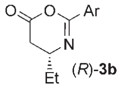
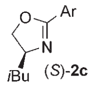
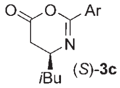
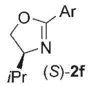
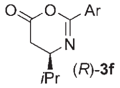
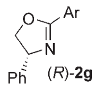
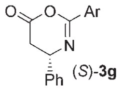


Entry	Oxazoline (R)	mol % **1**	Yield[b] [%]
1	**2a** (Me)	1	97
2	**2b** (Et)	3	99
3	**2c** (*i*Bu)	3	99
4	**2d** (CH$_2$Ph)	3	99
5	**2e** (CH$_2$OSiMe$_2$*t*Bu)	3	99
6	**2f** (*i*Pr)	5	99
7	**2g** (Ph)	10	86

[a] All reactions were performed using [**1**]/[BnOH] = 1, [**2**] = 0.5 M in DME, 54 atm CO, 80 °C, 6 h. [b] Yield of oxazinone determined by ^{1}H NMR spectroscopy; yields of isolated, analytically pure compounds are ca. 90 % of spectroscopic yields.

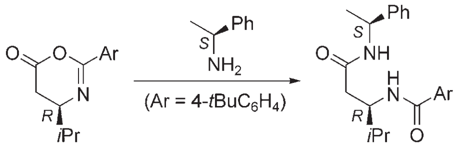
The catalytic carbonylation of oxazolines is applicable to the synthesis of a range of racemic 4-substituted oxazinones, which complements exciting recent work by Berkessel et al. on the kinetic resolution of oxazinones using thiourea-based organocatalysts.[25] However, we sought to establish this route as a direct approach to stereopure oxazinones and therefore enantiopure β-amino acids. To this end, we synthesized oxazolines bearing 4*R*-ethyl ((*R*)-**2b**), 4*S*-isobutyl ((*S*)-**2c**), 4*S*-isopropyl ((*S*)-**2f**), and 4*R*-phenyl ((*R*)-**2g**) substituents (Table 3). The retention of configuration at the 4-position was demonstrated by derivatization of the racemic and enantiopure oxazinones with (*S*)-(−)-α-methylbenzylamine

Table 3: Carbonylation of enantiopure oxazolines using **1**/BnOH.[a]

Entry	Oxazoline[b]	Oxazinone[c]	mol % **1**	*ee*[d] [%]
1			3	> 99
2			3	> 99
3			5	> 99
4			10	> 99

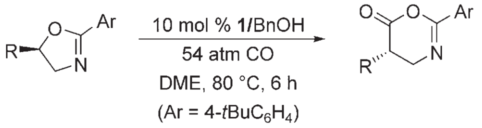
[a] All reactions were performed using [**1**]/[BnOH] = 1, [**2**] = 0.5 M in DME, 54 atm CO, 80 °C, 6 h. [b] Ar = 4-*t*BuC_6H_4; > 99% *ee*, determined by chiral HPLC. [c] Isolated and spectroscopic yields comparable to those of the racemic substrates (Table 2). [d] Determined by ^{1}H NMR spectroscopy of (*S*)-(−)-α-methylbenzylamine derivatives; see Supporting Information.

[Eq. (2)]. The difference in ^{1}H NMR chemical shifts of the diastereomers allowed for the determination of diastereomeric excess, and therefore, enantiomeric purity of the oxazinone.[17] In all cases, the oxazinones retained the absolute configuration of the oxazoline precursor.[26] The x-ray crystal structure of (*R*,*S*)-**4f** displays retention at the 4-position, as the *N*-(*S*)-α-methylbenzyl center allows the absolute configuration to be assigned.[17]



(*R*)-**3f** (*R*,*S*)-**4f** (2)

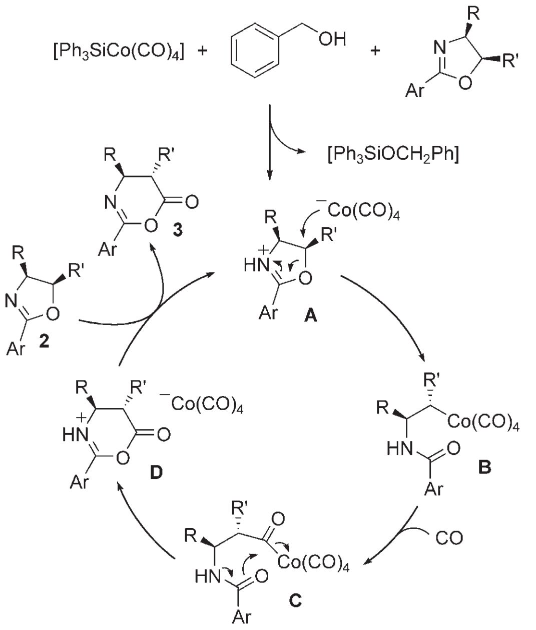
In addition to 4-substituted oxazolines, we attempted the carbonylation of 2-(4-*tert*-butylphenyl)-5-methyl-2-oxazoline, **2h** [Eq. (3)]. This substrate suffered from lower activity, and required 10 mol % catalyst to achieve only 50 % conversion.[27] This reduced reactivity, also observed by Jia,[15a] is likely due to the sterics at the 5-position, as the isomeric 4-methyl derivative was cleanly carbonylated in high conversion using only 1 mol % catalyst (Table 2, entry 1). Despite the lower conversion to oxazinone for this substrate, we examined the carbonylation of the 5*R*-methyl derivative, (*R*)-**2h**, with 10 mol % catalyst. Though yield was slightly lower than for the racemic substrate (43 % vs. 50 %), the reaction produced (*S*)-**3h** cleanly. Derivatization of these oxazinones gave products similar to the 4-substituted derivatives. Characterization of the enantiopure β-benzamido alkanamide (*S*,*S*)-**4h** using NMR spectroscopy and x-ray crystallography[17] supports the inversion of configuration at the 5-position of the oxazoline ring.



(3)

rac-**2h** (R = Me) *rac*-**3h** (R = Me) 50%
(*R*)-**2h** (R = (*R*)-Me) (*S*)-**3h** (R = (*S*)-Me) 43%

Drawing upon the mechanistic implications of the NMR studies, the carbonylation results, and the mechanisms of other carbonylation reactions, we propose a catalytic cycle for the carbonylation of oxazolines using **1** and BnOH (Scheme 2). The results of the NMR experiments indicate that the generation of an oxazolinium cobaltate ion pair **A** is facile in ether solvent.



Scheme 2. Proposed catalytic cycle for oxazoline carbonylation using **1**/BnOH system (Ar = 4-*t*BuC_6H_4).

Nucleophilic attack by the $[Co(CO)_4]^-$ at the 5-position inverts this center and creates **B**, a β-amido alkylcobalt species. Migratory insertion and uptake of CO, which are well-documented,[28] produce the acyl–cobalt species **C**. There is precedent for the ring closing of β-amido acids to give 2-oxazin-6-ones,[29] and **C** should exhibit analogous reactivity, resulting in the ion pair **D**. Ring closing through the nitrogen atom to give a β-lactam should be energetically unfavorable; no β-lactam product is observed under any conditions. The cycle is completed by proton transfer from **D** to oxazoline, regenerating **A** with extrusion of oxazinone. On the basis of preliminary in situ IR kinetic studies, ring closing is rate limiting for 4-substituted oxazolines, whereas ring opening is rate limiting for 5-substituted oxazolines. The 4-*tert*-butyl group on the aryl ring may facilitate either the protonation step (generation of **A**) or the ring-closing step (generation of **D**) or both by creating a more electron-rich substrate.

We have described a synthetic transformation for the generation of both racemic and enantiopure 4- and 5-

substituted 2-aryl-2-oxazin-6-ones via the carbonylation of oxazolines using a silylcobalt precatalyst. The oxazinones are labile compounds that can be ring opened by nucleophiles such as amines and alcohols, or hydrolyzed directly to yield β-amino acids. In addition, this work demonstrates a new methodology for the generation of $[HCo(CO)_4]$ in a controlled manner that is applicable to other areas of carbonylation chemistry. Given the ease of catalyst and substrate synthesis and the wealth of commercially available α-amino acids, the carbonylative ring expansion of oxazolines is a significant contribution to the synthesis of stereopure β-amino acid derivatives.

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