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A New Multicomponent Reaction Catalyzed by a [Lewis Acid]$^+$[Co(CO)$_4$]$^-$ Catalyst: Stereospecific Synthesis of 1,3-Oxazinane-2,4-diones from Epoxides, Isocyanates, and CO

Tamara L. Church, Christopher M. Byrne, Emil B. Lobkovsky, and Geoffrey W. Coates*

Contribution from the Department of Chemistry and Chemical Biology, Baker Laboratory, Cornell University, Ithaca, New York 14853-1301

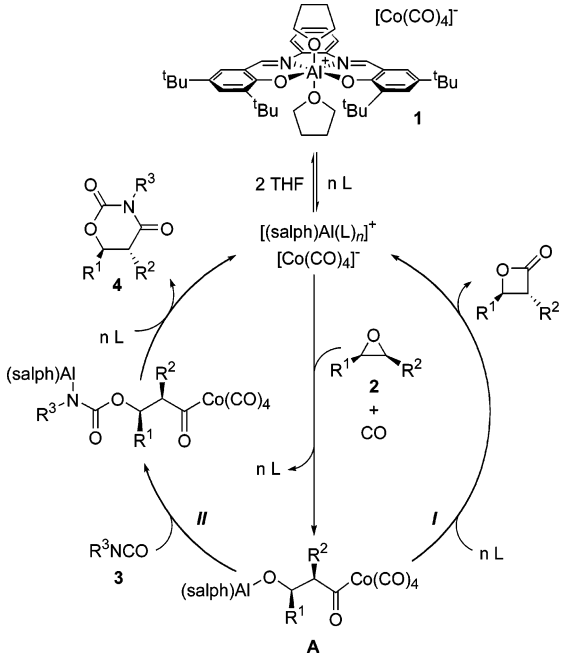
Received December 18, 2006; E-mail: gc39@cornell.edu

Abstract: The use of mechanistic information to develop a new, catalytic multicomponent reaction is described. The complex [(salph)Al(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ (**1**, salph = *N*,*N*′-*o*-phenylenebis(3,5-di-*tert*-butylsalicylideneimine), THF = tetrahydrofuran), which is known to carbonylate epoxides, aziridines, and β-lactones, was used to catalyze the synthesis of 1,3-oxazinane-2,4-diones from epoxides, isocyanates, and CO. Under optimized conditions, the reaction was both selective and high-yielding. 1,3-Oxazinane-2,4-diones were synthesized from a variety of epoxides and isocyanates, including some epoxides that do not undergo simple ring-expansion carbonylation. The best results were obtained using highly electrophilic isocyanates. The mechanism of the multicomponent reaction was investigated using labeling and stereochemistry, and the data obtained were consistent with the **1**-catalyzed formation of β-lactone and 1,3-oxazinane-2,4-dione from a common intermediate.

Introduction

Results obtained in mechanistic studies can lead to improvements upon a catalytic system through the directed variation of reaction conditions or catalyst architecture. Well-known reactions such as enantioselective amination,[1a] olefin copolymerization,[1b] hydrolytic kinetic resolution,[1c] ring-opening metathesis polymerization,[1d] asymmetric transfer hydrogenation,[1e] and asymmetric dihydroxylation[1f] have benefited from such studies. Over the past 5 years, our group has developed several catalysts that carbonylate epoxides to β-lactones.[2] These complexes, all of the form [Lewis acid]$^+$[Co(CO)$_4$]$^-$, vary considerably in activity and substrate scope. With the goal of understanding the differences between these catalysts, we have recently examined the mechanism by which [(salph)Al(THF)$_2$]$^+$[Co(CO)$_4$]$^-$ (**1**, Scheme 1, salph = *N*,*N*′-*o*-phenylenebis(3,5-di-*tert*-butylsalicylideneimine), THF = tetrahydrofuran) carbonylates epoxides (**2**) to β-lactones.[3] During this study, we found an opportunity to extend the capabilities of **1** to catalyze the coupling of epoxides, isocyanates (**3**), and CO to form 1,3-oxazinane-2,4-diones (ODs, **4**). Our study of epoxide carbonylation by **1** indicated that the catalyst resting state is a (β-aluminoxy)acylcobalt species (**A**, Scheme 1).[3] In the rate-determining step, **A** undergoes intramolecular cyclization to β-lactone (Scheme 1, path I) via a Lewis base assisted

Scheme 1. Proposed Mechanism of 1,3-Oxazinane-2,4-dione Formation from Epoxides, Isocyanates, and CO. L = Lewis base (solvent, epoxide, etc.)



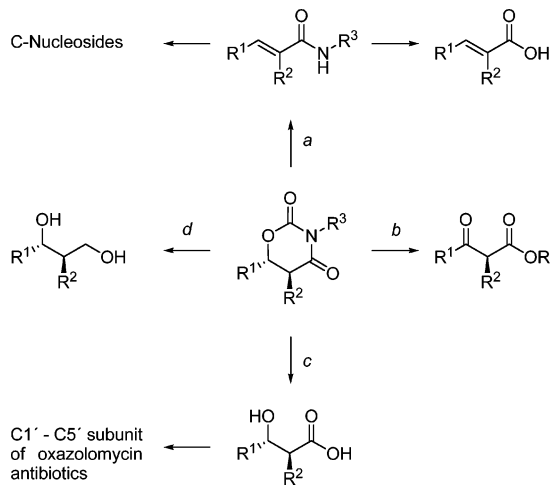
(1) For some leading references, see: (a) Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506−15514. (b) Williams, B. S.; Leatherman, M. D.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **2005**, *127*, 5132−5146. (c) Nielsen, L. P. C.; Stevenson, C. P.; Blackmond, D. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 1360−1362. (d) Choi, T.-L.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 1743−1746. (e) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97−102. (f) Wai, J. S. M.; Markó, I.; Svendson, J. S.; Finn, M. G.; Jacobsen, E. N.; Sharpless, K. B. *J. Am. Chem. Soc.* **1989**, *111*, 1123−1125.

(2) (a) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2002**, *124*, 1174−1175. (b) Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Angew. Chem., Int. Ed.* **2002**, *41*, 2781−2784. (c) Getzler, Y. D. Y. L.; Mahadevan, V.; Lobkovsky, E. B.; Coates, G. W. *Pure Appl. Chem.* **2004**, *76*, 557−564. (d) Schmidt, J. A. R.; Mahadevan, V.; Getzler, Y. D. Y. L.; Coates, G. W. *Org. Lett.* **2004**, *6*, 373−376. (e) Schmidt, J. A. R.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2005**, *127*, 11426−11435. (f) Kramer, J. W.; Lobkovsky, E. B.; Coates, G. W. *Org. Lett.* **2006**, *8*, 3709−3712.

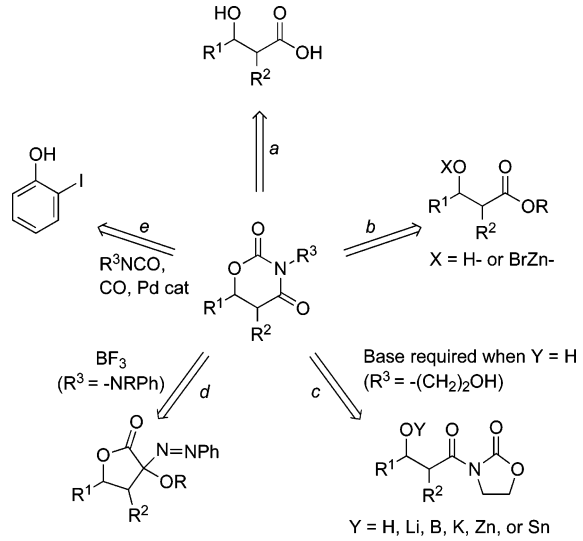
(3) Church, T. L.; Getzler, Y. D. Y. L.; Coates, G. W. *J. Am. Chem. Soc.* **2006**, *128*, 10125−10133.

10.1021/ja069065d CCC: $37.00

Scheme 2. Synthetic Uses of 1,3-Oxazinane-2,4-diones



Scheme 3. Precursors for the Synthesis of 1,3-Oxazinane-2,4-diones



ring closure, and regenerates the catalytic species. Leveraging insight gained from our mechanistic studies, we reasoned that prolonging the lifetime of intermediate **A** would enable its intermolecular reaction with electrophiles such as isocyanates (**3**).[4] Reaction of the aluminum alkoxide of **A** with an isocyanate (Scheme 1, path II), followed by ring closing, would yield a 1,3-oxazinane-2,4-dione (OD, **4**). The net result would therefore be a new, catalytic, multicomponent reaction (MCR) that forms an OD.

ODs have found use as versatile synthetic intermediates because they can be transformed, in stereospecific fashion, to a variety of functional groups (Scheme 2). They have been used in the synthesis of trisubstituted (*E*)-α,*β*-unsaturated amides (Scheme 2, path a),[5] which have in turn been elaborated to (*E*)-α,*β*-unsaturated acids[5a] and to C-nucleoside precursors.[5c] Kamino et al. have formed *β*-ketoesters from ODs (Scheme 2, path b).[6] In their total synthesis of the antibiotic neooxazolomycin, Kende et al. used an OD to form a key *β*-hydroxy-acid intermediate (Scheme 2, path c) that was difficult to produce in enantiopure form by other methods.[7] Finally, a functionalized OD has been used in the enantioselective synthesis of a linear polyol (Scheme 2, path d, $R^1 = -CH{=}CHCH_3$, $R^2 = -OBn$).[6]

A number of synthetic methods for producing ODs have been described, and these are summarized in Scheme 3. Several routes are available for the conversion of *β*-hydroxy acids to ODs (Scheme 3, path a). In general, these involve either (i) reaction with an isocyanate or cyanate, and subsequent condensation,[5c,8] or (ii) derivatization to a *β*-hydroxy amide, followed by reaction with a carbonyl equivalent such as carbonyl diimidazole or diphosgene.[9] Though high-yielding in some cases, these syntheses require at least two steps and necessarily generate byproducts. The latter is also true of OD syntheses in which a *β*-hydroxy[10] or *β*-metalloxy[11] ester is condensed with an isocyanate (Scheme 3, path b).[12] Recently, OD synthesis has been reported via the base-mediated (and, in some cases, metal-catalyzed) rearrangement of *β*-hydroxy *N*-acyloxazolidin-2-ones, which are the aldol products of *N*-acyloxazolidin-2-ones (Scheme 3, path c),[5a,b,6,7,13] and by similar rearrangements.[14] These reactions, first reported in 1989,[7b] are stereoselective and with careful choice of catalyst can produce highly stereopure ODs. Barton and Liu have also reported an unrelated rearrangement route to OD (Scheme 3, path d).[15]

In the particular case of benzo-fused ODs (Scheme 3, $-CHR^1CHR^2- = -o-C_6H_4-$), an excellent route from iodophenols is available (Scheme 3, path e).[16,17] Larksarp and Alper used a palladium-coupling strategy to construct a series of benzoxazinediones from 2-iodophenols, isocyanates, and CO.[16] Though this synthesis is restricted to benzoxazinedione formation, and does produce a coupling byproduct, it proceeds in good yields

(4) In related chemistry, the reaction of CO_2, which is isoelectronic with isocyanates, into Al-O bonds has been studied; see, for example: (a) Chisholm, M. H.; Zhou, Z. *J. Am. Chem. Soc.* **2004**, *126*, 11030−11039. (b) Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1983**, *105*, 1304−1309.

(5) (a) Feuillet, F. J. P.; Cheeseman, M.; Mahon, M. F.; Bull, S. D. *Org. Biomol. Chem.* **2005**, *3*, 2976−2989. (b) Feuillet, F. J. P.; Robinson, D. E. J. E.; Bull, S. D. *Chem. Commun.* **2003**, 2184−2185. (c) Katagiri, N.; Hirose, M.; Sato, M.; Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 933−938.

(6) Kamino, T.; Murata, Y.; Kawai, N.; Hosokawa, S.; Kobayashi, S. *Tetrahedron Lett.* **2001**, *42*, 5249−5252.

(7) (a) Kende, A. S.; Kawamura, K.; DeVita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070−4072. (b) Kende, A. S.; Kawamura, K.; Orwat, M. J. *Tetrahedron Lett.* **1989**, *30*, 5821−5824.

(8) (a) Shibuya, I.; Goto, M.; Shimizu, M.; Yanagisawa, M.; Gama, Y. *Heterocycles* **1999**, *51*, 2667−2673. (b) Paik, S.; Carmeli, S.; Cullingham, J.; Moore, R. E.; Patterson, G. M. L.; Tius, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 8116−8125. (c) Vorbrüggen, H. *Tetrahedron Lett.* **1968**, *9*, 1631−1634. (d) Testa, E.; Fontanella, L.; Cristiani, G.; Gallo, G. *J. Org. Chem.* **1959**, *24*, 1928−1936.

(9) (a) Kurz, T. *Tetrahedron* **2005**, *61*, 3091−3096. (b) Kolasa, T.; Miller, M. J. *Tetrahedron* **1989**, *45*, 3071−3080. (c) Pintye, J.; Fülöp, F.; Bernáth, G.; Sohár, P. *Monatsch. Chem.* **1985**, *116*, 857−868. (d) Shapiro, S. L.; Rose, I. M.; Freedman, L. *J. Am. Chem. Soc.* **1957**, *79*, 2811−2814.

(10) (a) Boontheung, P.; Perlmutter, P. *Tetrahedron Lett.* **1998**, *39*, 2629−2630. (b) Ohshiro, Y.; Ando, N.; Komatsu, M.; Agawa, T. *Synthesis* **1985**, 276−279.

(11) (a) Lapkin, I. I.; Semenov, V. I.; Saitkulova, G. F. *Russ. J. Org. Chem.* **1982**, *18*, 2189. (b) Saitkulova, F. G.; Semenov, V. I.; Lapkin, I. I. *Khim. Elementoorg. Soedin.* **1982**, 22−26.

(12) The electrochemically initiated condensation of a *β*-bromo amide with CO_2 has been reported to form OD; however, a large amount of α,*β*-unsaturated amide was also generated, possibly from decomposition of OD under the reaction conditions; see: Casadei, M. A.; Cesa, S.; Moracci, F. M.; Inesi, A.; Feroci, M. *J. Org. Chem.* **1996**, *61*, 380−383.

(13) (a) Feuillet, F. J. P.; Niyadurupola, D. G.; Green, R.; Cheeseman, M.; Bull, S. D. *Synlett* **2005**, 1090−1094. (b) Ito, Y.; Terashima, S. *Tetrahedron* **1991**, *47*, 2821−2834.

(14) (a) Yang, K.-S.; Chen, K. *Org. Lett.* **2002**, *4*, 1107−1109. (b) Abbas, T. R.; Cadogan, J. I. G.; Doyle, A. A.; Gosney, I.; Hodgson, P. K. G.; Howells, G. E.; Hulme, A. N.; Parsons, S.; Sadler, I. H. *Tetrahedron Lett.* **1997**, *38*, 4917−4920. (c) Narasaka, K.; Yamamoto, I. *Tetrahedron* **1992**, *48*, 5743−5754.

(15) Barton, D. H. R.; Liu, W. *Chem. Commun.* **1997**, 571−572.

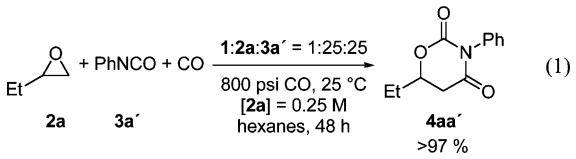
(16) Larksarp, C.; Alper, H. *J. Org. Chem.* **1999**, *64*, 9194−9200.

(17) The reaction of phenols with *N*-(chlorocarbonyl)isocyanate, followed by intramolecular Friedel−Crafts reaction, has also been shown to form benzoxazinediones; see: Hagemann, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 743−750.

and was demonstrated for several phenols and isocyanates. This reaction is formally a transition-metal-catalyzed MCR and is among a number of transition-metal-catalyzed MCRs that have been reported,[18−20] though one of only a few to use CO as a reactant.[16,19a,20a,c,g] The versatility of MCRs makes them attractive synthetic tools in organic and combinatorial chemistry.[21] A modular, atom-economic, multicomponent synthesis of other (i.e., non-benzo-fused) ODs from readily obtained starting materials, such as the one illustrated in Scheme 1 (path II), would be a versatile and convenient route to a useful synthetic building block, and we therefore pursued its development. Herein we describe a new, transition-metal-catalyzed MCR for the synthesis of OD that stemmed from the mechanistic study of epoxide carbonylation by **1**.

Results and Discussion

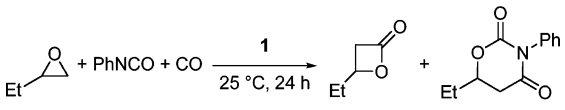
1. Reaction Development. As part of our study of β-lactone formation by **1**, we attempted the MCR under typical epoxide-carbonylation conditions;[3,22] little or no OD was detected. However, if β-lactone and OD are formed from a common intermediate **A**, then isocyanate incorporation will require conditions that slow β-lactone ring closing relative to reaction with isocyanate. Using the coupling of 1,2-epoxybutane (**2a**), phenyl isocyanate (**3a′**), and CO as a representative reaction, we screened conditions until we achieved >97% conversion to the OD **4aa′** (eq 1), with no observed β-valerolactone (β-VL) formation. Previously, we have found that Lewis basic solvents



(1)

such as THF and DME accelerate β-lactone formation (Scheme 1, path I);[3] accordingly, MCRs attempted in these solvents yielded β-lactone but no OD (Table 1, entries 9−13). The use of nonpolar, non-coordinating solvents (in which β-lactone formation is slow) enabled OD formation, and hexanes gave the best selectivity for OD among the solvents screened (Table 1, entry 1).[23] We also examined the effects of temperature, epoxide-to-isocyanate ratio, and catalyst loading on the MCR. Higher temperature, less catalyst, and extra equivalents of isocyanate each produced more β-lactone, and in some cases suppressed OD formation. Performing the reaction under lower pressures of carbon monoxide caused significant isomerization of epoxide to ketone, a side reaction also observed in carbonylation chemistry.[2,24] On the basis of the results of these optimization reactions, a standard set of conditions was implemented for test-scale OD syntheses: hexanes solution (1 mL, [**2**] = 0.25 M), **1**/**2**/**3** = 1:25:25, 800 psi CO, 25 °C, 48 h.

Table 1. OD Formation in Various Solvents[a]



entry	solvent	lactone[b] [%]	OD[b] [%]	selectivity[c] [%]
1	hexanes	8	40	83
2	pentane	5	24	82
3	toluene	20	10	33
4	diethyl ether	36	17	32
5	1,2-difluorobenzene	36	14	28
6	*tert*-butyl methyl ether	34	13	28
7	tetrahydropyran	74	4	5
8	acetonitrile	77	3	4
9	1,4-dioxane	>97	nd[d]	0
10	2,5-dimethyltetrahydrofuran	>97	nd[d]	0
11	1,2-dimethoxyethane	91	nd[d]	0
12	2-methyltetrahydrofuran	91	nd[d]	0
13	tetrahydrofuran	83	nd[d]	0

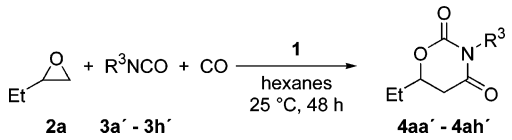
[a] Reaction conditions: 0.010 mmol **1**, 0.50 mmol each of **2a** and **3a′**, 300 psi CO, in 1.0 mL of dry solvent at 25 °C for 24 h. [b] Conversion with respect to epoxide, determined by ^{1}H NMR spectroscopy of crude reaction mixture (see experimental section for details). β-VL and OD were the only epoxide-derived products. [c] Value is equal to 100 × [OD]/([lactone] + [OD]). [d] nd = none detected.

2. Substrate Scope. Having optimized the yield of **4aa′** from the MCR (see eq 1), we sought to establish this reaction as a general route for the coupling of epoxides, isocyanates, and CO to build a family of structurally and functionally diverse ODs. While CO is structurally invariable, there are many readily available epoxides and isocyanates to which this system is applicable, and we varied each component in turn.

We found that the nature of the isocyanate had a strong influence on the reaction (Table 2). Reactions performed with aryl isocyanates having varying para substituents revealed a direct correlation between the electrophilicity of the isocyanate and the selectivity of OD formation. Similarly to the unsubstituted PhNCO (entry 1), aryl isocyanates with electron-withdrawing groups in the para position (entries 2−4) gave complete conversion of epoxide to OD, with no β-lactone formation. In fact, the very electrophilic isocyanate **3b′** reacted completely with **2a** and CO in only 12 h under the standard reaction conditions. Conversely, the presence of electron-donating groups (entries 5 and 6) reduced catalytic efficiency, lowering both selectivity and overall conversion of epoxide. These observations are consistent with the pathway shown in Scheme 1, as more electrophilic isocyanates react quickly with **A** and therefore allow path II to dominate. Despite this, we examined the MCR with alkyl isocyanates (entries 7 and 8) to

(18) A recent issue of Tetrahedron was devoted to multicomponent reactions: *Tetrahedron* **2005**, *61*, 11299−11519.
(19) For reviews of transition-metal-mediated cycloaddition and heterocycle formation, including multicomponent examples: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127−2198. (b) Frühauf, H.-W. *Chem. Rev.* **1997**, *97*, 523−596. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49−92.
(20) For some representative examples, see references 16, 18, and: (a) Kondo, T.; Nomura, M.; Ura, Y.; Wada, K.; Mitsudo, T.-A. *J. Am. Chem. Soc.* **2006**, *128*, 14816−14817. (b) Siamaki, A. R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2006**, *128*, 6050−6051. (c) Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530−6531. (d) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786−7787. (e) Cao, C.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 2880−2881. (f) Goodman, S. N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4703−4705. (g) Muraoka, T.; Kamiya, S.; Matsuda, I.; Itoh, K. *Chem. Commun.* **2002**, 1284−1285. (h) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228−3230. (i) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467−473.
(21) For several useful reviews, see: (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, *10*, 1471−1499. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem.−Eur. J.* **2000**, *6*, 3321−3329. (d) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (e) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831−844.
(22) Typical epoxide carbonylation conditions: 1,2-epoxybutane, 1.25 M in THF, [epoxide]/[**1**] = 100:1, P_{CO} = 300 psi, T = 25 °C.
(23) As **1** is only sparingly soluble in hexanes, stirring was essential to the success of the reaction.
(24) Molnar, F.; Luinstra, G. A.; Allmendinger, M.; Rieger, B. *Chem.−Eur. J.* **2003**, *9*, 1273−1280.

Table 2. Formation of 1,3-Oxazinane-2,4-diones Using Various Isocyanates[a]



entry	R^3	OD	β-VL[b] [%]	OD[b] [%]	selectivity[c] [%]
1	Ph	**4aa′**	nd[d]	>97	>97
2	4-O_2N-C_6H_4	**4ab′**	nd[d]	>97	>97
3	4-F-C_6H_4	**4ac′**	nd[d]	>97	>97
4	4-Br-C_6H_4	**4ad′**	nd[d]	>97	>97
5	4-MeO-C_6H_4	**4ae′**	20	60	75
6	4-Me-C_6H_4	**4af′**	14	42	75
7[e]	$PhCH_2$	**4ag′**	19	39	67
8[e]	Et	**4ah′**	15	13	46

[a] Reaction conditions: 0.010 mmol **1**, 0.25 mmol each of **2a** and **3**, 800 psi CO, in 1.0 mL of dry hexanes at 25 °C for 48 h. [b] Conversion with respect to epoxide, determined by ^{1}H NMR spectroscopy of crude reaction mixture (see experimental section for details). β-VL and OD were the only epoxide-derived products. [c] Value is equal to 100 × [OD]/([lactone] + [OD]). [d] nd = none detected. [e] Some isocyanate was converted to the corresponding trialkyl isocyanurate.

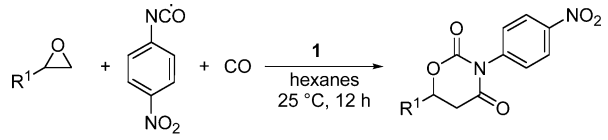
expand the functional diversity of this component. As expected, OD formation and selectivity dropped precipitously because of the reduced electrophilicity of the isocyanate reaction component. In addition, these reactions generated tribenzyl and triethyl isocyanurate, respectively. The production of these cyclic trimers suggests that electron-rich isocyanates may interact with **1** independently of epoxide. Fortunately, in most cases where side reactions accompanied the MCR, the product OD could be readily separated from the reaction mixture.[25,26]

We also incorporated an array of monosubstituted epoxides into ODs (Table 3). Variation of the epoxide component not only demonstrates the versatility of this MCR, it also diversifies the library of ODs synthesized by this method. As **2a**, **3b′**, and CO were converted to **4ab′** after only 12 h, we used isocyanate **3b′**, and a reaction time of 12 h, for test reactions with epoxides. OD formation was much less sensitive to the identity of the epoxide than of the isocyanate; high yield and selectivity were obtained in almost all cases. For example, ODs were synthesized from epoxides having shorter (entry 2) and longer (entry 3) alkyl chains than **2a**, and selectivity was only slightly reduced when a secondary alkyl substituent was present (entry 4). However, yield and selectivity suffered when the epoxide bore a tertiary alkyl substituent (entry 5). A pendant alkene (entry 6) was also successfully incorporated into a 1,3-oxazinane-2,4-dione. ODs with ether side chains were also produced in high yield (entries 7−10), though they were accompanied by small amounts of β-lactone. The MCR with epichlorohydrin (entry 11) was selective, but slower than that with other epoxides; it was only 49% complete after 12 h and only 70% complete after 24 h. Ester functionalities were also incorporated effectively into ODs (entries 12 and 13). Unfortunately, styrene oxide (entry 14) proved a problematic substrate, yielding neither β-lactone nor OD under these conditions.[27]

The attempted formation of OD from glycidyl butanoate (**2o**, Scheme 4) gave an unusual result. Following the test-scale

(25) See Supporting Information for details.
(26) We were unable to separate OD **4ah′** from triethylisocyanurate.
(27) Though most of the epoxide was unchanged following the reaction, small amounts of styrene and unidentified compounds were produced.

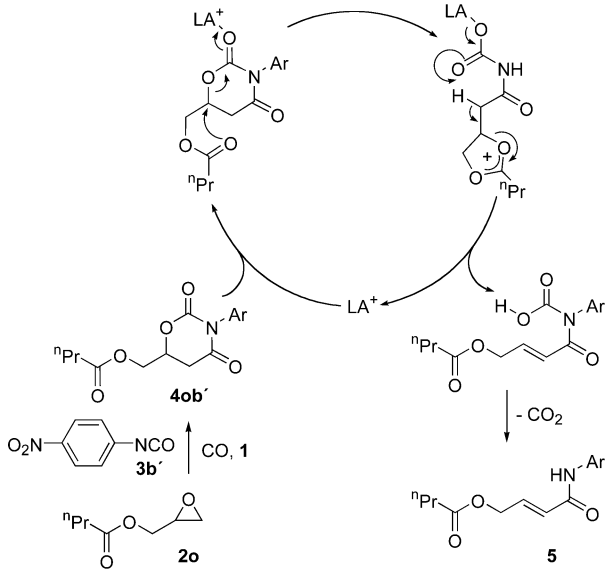
Table 3. Formation of 1,3-Oxazinane-2,4-diones Using Various Monosubstituted Epoxides[a]



entry	R^1	OD	lactone[b] [%]	OD[b] [%]	selectivity[c] [%]
1	Et	**4ab′**	nd[d]	>97	>97
2	Me	**4bb′**	nd[d]	>97	>97
3	^{n}Bu	**4cb′**	nd[d]	>97	>97
4	*c*-C_6H_{11}	**4db′**	3	94	97
5	^{t}Bu	**4eb′**	9	10	53
6	$(CH_2)_2CH{=}CH_2$	**4fb′**	nd[d]	>97	>97
7	$CH_2OCH_2CH{=}CH_2$	**4gb′**	6	94	94
8	CH_2O^nBu	**4hb′**	2	>97	>97
9	CH_2OBn	**4ib′**	8	80	88
10	$CH_2OSiMe_2{}^tBu$	**4jb′**	3	97	97
11[e]	CH_2Cl	**4kb′**	nd[d]	70	>97
12	$(CH_2)_2CO_2{}^nPr$	**4lb′**	nd[d]	>97	>97
13	$(CH_2)_3OC(O)^nPr$	**4mb′**	nd[d]	>97	>97
14	Ph	**4nb′**	nd[d]	nd[d]	na[f]

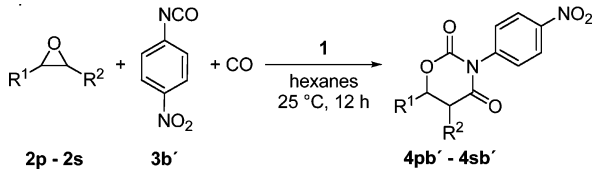
[a] Reaction conditions: 0.010 mmol **1**, 0.25 mmol each of **2** and **3b′**, 800 psi CO, in 1.0 mL of dry hexanes at 25 °C for 12 h. [b] Conversion with respect to epoxide, determined by ^{1}H NMR spectroscopy of crude reaction mixture (see experimental section for details). Lactone and OD were the only epoxide-derived products. [c] Value is equal to 100 × [OD]/([lactone] + [OD]). [d] nd = none detected. [e] Reaction time was 24 h. [f] na = not applicable.

Scheme 4. MCR of **2o**, **3b′**, and CO to Yield **4ob′**, and a Possible Mechanism for Its Decay to Form the Crotonamide **5** (LA^+ = Lewis Acid)



reaction of **2o** with **3b′** and CO, the ^{1}H NMR spectrum of the crude reaction mixture showed a trace of β-lactone, along with a major product whose spectrum was similar to those of related ODs (multiplets at 3.01, 3.04, and 4.94 ppm; pseudodoublets at 7.42 and 8.34 ppm). However, efforts to isolate this compound uniformly returned (*E*)-4-(4-nitrophenylamino)-4-oxobut-2-enyl butanoate, **5** (Scheme 4). As OD **4ob′** appeared by ^{1}H NMR spectroscopy to be the initial product of the reaction, we conclude that **5** was produced by its decomposition. Though other ODs can be induced to form crotonamides in the presence

Table 4. Formation of 1,3-Oxazinane-2,4-diones Using Disubstituted Epoxides[a]



entry	R^1, R^2	OD	lactone[b] [%]	OD[b] [%]	selectivity[c] [%]
1	*cis*-Me_2	*trans*-**4pb′**	11	89	89
2[d]	*trans*-Me_2	*cis*-**4pb′**	nd[e]	19	>97
3	*cis*-$(CH_2)_3$-	*trans*-**4qb′**	nd[e]	>97	>97
4	*cis*-$(CH_2)_4$-	*trans*-**4rb′**	nd[e]	>97	>97
5	*cis*-$(CH_2)_6$-	*trans*-**4sb′**	nd[e]	nd[e]	na[f]

[a] Reaction conditions: 0.010 mmol **1**, 0.25 mmol each of **2** and **3b′**, 800 psi CO, in 1.0 mL of dry hexanes at 25 °C for 12 h. [b] Conversion with respect to epoxide, determined by ^{1}H NMR spectroscopy of crude reaction mixture (see experimental section for details). Lactone and OD were the only epoxide-derived products. [c] Value is equal to 100 × [OD]/([lactone] + [OD]). [d] Reaction was run for 24 h. [e] nd = none detected. [f] na = not applicable.

of heat or base,[28] only **4ob′** undergoes this reaction during purification attempts. Notably, the ester-substituted ODs **4lb′** and **4mb′** do not form crotonamide under these conditions, as both were easily isolated. On the basis of the critical role played by the position of the ester substituent in the elimination, we propose that it participates in the reaction, possibly through anchimeric assistance.[29,30] A plausible mechanism for this process is shown in Scheme 4; we have previously observed a related rearrangement in β-lactones produced from glycidyl esters.[2e]

OD was also formed from 1,2-disubstituted epoxides (Table 4). Both *cis*- and *trans*-2,3-epoxybutane were converted to OD (entries 1 and 2) with good selectivity. The former, *cis*-**2p**, was completely converted to product in 12 h, whereas *trans*-**2p** reacted very slowly, producing only a trace of OD over the same period. Even after 24 h, only 19% of the epoxide was converted to OD. The alicyclic epoxides of cyclopentene (entry 3) and cyclohexene (entry 4) were converted cleanly to OD after 12 h. Cyclooctene oxide (entry 5), however, was unchanged following the reaction. The success of the MCR with cyclopentene oxide and cyclohexene oxide is significant because the β-lactones from cyclohexene oxide and the trans-ring-fused β-lactone from cyclopentene oxide have not been prepared by epoxide carbonylation. The trans-ring-fused β-lactones of these epoxides, in particular, are inaccessible under most circumstances.[31,32] As ODs can be converted to many of the same moieties as β-lactones (for example, β-hydroxyacids, Scheme 2c), this MCR offers a route to structures inaccessible via β-lactone chemistry.

As a complement to the test-scale syntheses, we performed the MCR with two substrates on a larger scale and isolated the OD products. The reaction of 4-bromophenyl isocyanate (**3d′**, 1.25 mmol), propylene oxide (**2b**, 1.25 mmol), catalyst **1** (0.050 mmol), and CO (800 psi) in 5.0 mL of dry hexanes yielded 0.250 g of pure **4bd′** after crystallization, representing 70% yield. Similarly, the MCR of **2a**, **3a′**, and CO on the 2.5-mmol scale gave pure **4aa′** in 71% yield.

3. Mechanism. Having found the **1**-catalyzed MCR of epoxides, isocyanates, and CO to be a useful and general reaction, we carried out several experiments to probe its mechanism. First, to rule out OD formation via a β-lactone intermediate rather than directly from the starting materials, we attempted the synthesis of OD from a β-lactone. When β-VL was combined with isocyanate **3b′**, catalyst **1**, and CO, no reaction occurred, even after 48 h at 60 °C. This is in accord with the prior observations that **1** reacts with β-lactone more slowly than with epoxide and that **1** reacts with β-lactone at the β carbon (rather than at the carbonyl group, which would be required for OD formation).[33] As OD is not generated from β-lactone under the reaction conditions, β-lactone cannot be an intermediate in OD formation.

The CO-derived carbonyl group in the product heterocycle was located using the MCR of **2a**, **3b′**, and ^{13}CO to form **4ab′**-^{13}C. The ^{1}H NMR spectrum of this compound showed additional splitting of both methylene signals compared to that of unlabeled **4ab′**. The coupling constants for these splittings were 6.4 and 7.4 Hz, consistent with a $^2J_{C-H}$ value.[34,35] Further, in the ^{13}C NMR spectrum of **4ab′**-^{13}C, the resonance at 167.8 ppm was very large, indicating the presence of the isotope label. This chemical shift is consistent with an amide carbonyl but downfield of the range for a carbamate carbonyl.[34] Both of these results suggest that CO is incorporated adjacent to the less substituted C atom of the OD, consistent with the reaction pathway shown in Scheme 1.

Crucial to the utility of ODs as synthetic intermediates is the ability to form them with a high degree of stereocontrol. Thus the stereochemical outcome of the new MCR informs on its utility as well as its mechanism. The relative stereochemistry of the ODs formed from disubstituted epoxides was assigned on the basis of ^{1}H NMR spectroscopic coupling constants. The pair of methine protons in compounds formed from the reaction of CO and **3b′** with cis-disubstituted epoxides *cis*-**2p**, **2q**, and **2r** split one another with $^3J = 12 \pm 1$ Hz, consistent with trans ring fusion, and with coupling constants for previously characterized *trans*-5,6-disubstituted 1,3-oxazinane-2,4-diones.[13b,15] Conversely, those in the OD produced from *trans*-**4pb′** had $^3J = 4.1$ Hz, consistent with a *cis*-5,6-disubstituted 1,3-oxazinane-2,4-dione.[13b] Therefore in all cases, cis/trans stereochemistry was interconverted during OD formation. For the case of (*rac*)-**4qb′**, which was produced from the coupling of isocyanate **3b′**, cyclopentene oxide, and CO, this result was confirmed by X-ray analysis (Figure 1).[25] The *trans* ring fusion evident in this structure suggests that only one stereocenter of the starting

(28) For example, when **4ab′** was heated to 90 °C in $CDCl_3$ for 4 days, 50% conversion to the elimination product was observed. The OD **4bb′** was completely converted to *N*-(4-nitrophenyl)-(*E*)-crotonamide after 3 hours at 0 °C in the presence of NaO^{s}Bu.

(29) Winstein, S.; Buckles, R. E. *J. Am. Chem. Soc.* **1942**, *64*, 2780−2786.
(30) Smith, M. B.; March, J. *March's Advanced Organic Chemistry*, 5th ed.; John Wiley & Sons, Inc.: New York, 2001.
(31) Using semiempirical methods, we have calculated the trans-ring-fused β-lactone from cyclopentene oxide to be approximately 45 kcal/mol higher in energy than the cis-ring-fused form (see ref 2e).
(32) Sander, Maguire, and co-workers have reported observing trans-ring-fused 7-oxabicyclo[4.2.0]octan-8-one in an argon matrix using IR spectroscopy; see: Sander, W.; Strehl, A.; Maguire, A. R.; Collins, S.; Kelleher, P. G. *Eur. J. Org. Chem.* **2000**, 3329−3335.
(33) Getzler, Y. D. Y. L.; Kundnani, V.; Lobkovsky, E. B.; Coates, G. W. *J. Am. Chem. Soc.* **2004**, *126*, 6842−6843.
(34) Silverstein, R. M.; Webster, F. X. *Spectrometric Identification of Organic Compounds*, 6 ed.; John Wiley & Sons, Inc.: New York, 1998.
(35) Though $^2J_{C-H}$ and $^3J_{C-H}$ values are generally comparable in magnitude,[34] the methylene unit of the 1,3-oxazinane-2,4-dione ring is directly adjacent to one carbonyl group and three carbons from the other. Thus the J_{C-H} at this position is expected to be a $^2J_{C-H}$ or a $^4J_{C-H}$ value.

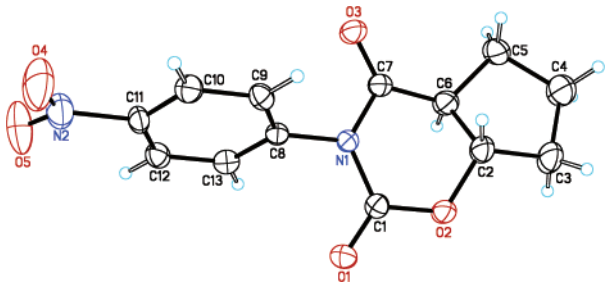


Figure 1. ORTEP structure of OD (*rac*)-**4qb′** showing the trans stereochemistry of ring fusion. Thermal ellipsoids drawn at the 30% probability level.

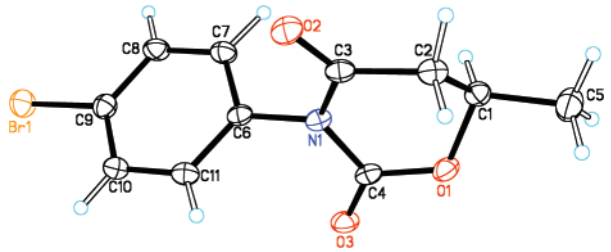
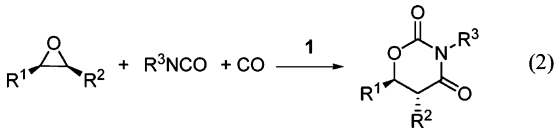


Figure 2. ORTEP structure of (*R*)-**4bd′** showing the absolute stereochemistry at the stereogenic center. Thermal ellipsoids are drawn at the 40% probability level.

epoxide was inverted, as has been shown to be the case in β-lactone formation catalyzed by **1**.[2a−c,36]

The absolute stereochemistry of a monosubstituted OD was investigated using the reaction of (*R*)-propylene oxide ((*R*)-**2b**), 4-bromophenyl isocyanate (**3d′**), and CO. Following the MCR of these compounds, the product OD, **4bd′**, was crystallized from EtOAc and examined by X-ray diffraction (Figure 2). The OD had (*R*) stereochemistry, indicating that the MCR occurs with retention of stereochemistry at the stereogenic carbon. As the X-ray structure of **4qb′** showed that OD is formed with inversion at a single C atom of the epoxide, the inverted center in the product OD must be the one β to the oxygen atom, adjacent to the inserted carbon monoxide (eq 2). These results



(2)

are consistent with the stereochemical outcome of epoxide carbonylation to β-lactone by **1**,[2a−c] and support the formation of β-lactone and OD from a common intermediate, **A**.

Though a kinetic analysis of the MCR was not carried out, the trend of more electrophilic isocyanates returning higher selectivity for OD suggests that the reaction of intermediate **A** with isocyanate is rate-determining. However, in the screening reactions described above, the selectivity for OD **4aa′** was not improved by extra equivalents of isocyanate; rather, the yields of both β-lactone and OD increased. Though an increase in OD formation at higher isocyanate concentration is consistent with a rate-determining isocyanate incorporation, the increased β-lactone production is surprising. We have previously noted that Lewis bases such as THF accelerate β-lactone formation by **1** and have attributed this to their ability to stabilize the aluminum cation formed upon ring closure.[3] Isocyanates may also be able to fulfill this role, increasing β-lactone production. Because isocyanate concentration impacts both competing pathways in this reaction, a careful balance is necessary for selectivity. Additionally, more electron-rich isocyanates are doubly disadvantaged for OD formation—they react more slowly with intermediate **A** and more effectively accelerate β-lactone formation.

(36) An exception to this trend is observed in β-lactone formation from cyclopentene oxide. Whereas carbonylation of this cis epoxide to the trans β-lactone has not been observed, it has been carbonylated to the cis β-lactone.[2e] This reaction was proposed to occur via a cationic intermediate.

Conclusion

A mechanistic study of epoxide carbonylation to β-lactones by $[(\text{salph})\text{Al}(\text{THF})_2]^+[\text{Co}(\text{CO})_4]^-$ led us to the development of a new three-component reaction that combines epoxides, isocyanates, and carbon monoxide to form 1,3-oxazinane-2,4-diones. The reaction is atom-economic, as all of the atoms in the starting materials are present in the product. With careful choice of reaction conditions, ODs can be selectively produced in high yield using this method. The reaction tolerates a variety of substitutions on the epoxide component, and is fastest and most selective when electron-poor isocyanates are employed. Further, the coupling is stereospecific, with configuration being retained α to the ring oxygen, and inverted β to the ring oxygen. Thus enantiopure ODs can be formed using the appropriate chiral epoxide. Stereochemical and labeling evidence support the formation of both β-lactone and OD from a common intermediate. Larksarp and Alper have previously demonstrated a catalytic, carbonylative MCR route to benzoxazines,[16] and the present method provides an ideal complement to this reaction. We are currently working toward including new substrate classes in the scope of this reaction.

Experimental Procedures

General Considerations. All air- and/or water-sensitive reactions were carried out under dry nitrogen using an MBraun UniLab drybox or standard Schlenk line techniques. All syringes were gastight and were dried overnight in a glassware oven prior to use. NMR spectra were recorded on Varian Mercury 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz), Bruker ASX 300 (^{1}H, 300 MHz; ^{13}C, 75 MHz), or Varian INOVA-400 (^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometers and referenced versus residual nondeuterated solvent shifts. HRMS analyses were performed on a JEOL GCMate II, using EI+ ionization. X-ray crystallographic data were collected using a Bruker X8 APEX II (Mo Kα, $\lambda = 0.71073$ Å) at 173(2) K, and frames were integrated with the Bruker SAINT+ program. The absolute configuration of (*R*)-3-(4-bromophenyl)-6-methyl-1,3-oxazinane-2,4-dione (*R*)-**4bd′** was determined by refining an enantiomorph-sensitive Flack parameter $x = 0.007(8)$ using 1341 measured Friedel pairs.[37]

Materials. Hexanes, pentane, toluene, and diethyl ether were dried and degassed over columns of alumina and copper.[38] Tetrahydrofuran was dried over columns of alumina and degassed by freeze−pump−thaw cycles. 1,2-Dimethoxyethane, 1,4-dioxane, 2-methyltetrahydrofuran, 2,5-dimethyltetrahydrofuran, and tetrahydropyran were refluxed with and distilled from Na/benzophenone under atmospheric pressure of N_2, and degassed by freeze−pump−thaw cycles. *tert*-Butyl methyl ether was stirred with Na/benzophenone, degassed by freeze−pump−thaw cycles, and vacuum transferred. Acetonitrile was stirred with CaH_2, degassed by freeze−pump−thaw cycles, and vacuum transferred. 1,2-Difluorobenzene was stirred with P_2O_5, degassed by freeze−pump−thaw cycles, and vacuum transferred. The catalyst

(37) Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876−881.
(38) Glass Contour Systems, Laguna Beach, CA, 92652.

$[(salph)Al(THF)_2]^+[Co(CO)_4]^-$ (**1**, salph = *N*,*N*′-*o*-phenylenebis(3,5-di-*tert*-butylsalicylideneimine), THF = tetrahydrofuran) was prepared according to the literature procedure.[2a] Labeled ^{13}CO was purchased from Cambridge Isotope Labs, Inc., with the aid of a research grant, and used as received. Cyclohexylethylene oxide (**2d**),[39] *tert*-butyl ethylene oxide (**2e**),[40] *n*-propyl 4,5-epoxypentanoate (**2l**),[2e] and 4,5-epoxypentyl butyrate (**2m**)[2e] were prepared according to published procedures. (*R*)-PO ((*R*)-**2b**) was isolated from *rac*-PO (*rac*-**2b**) using the method of Jacobsen.[41] Liquid epoxides were stirred with CaH_2 and vacuum distilled prior to use, and solid epoxides were used as received. Liquid isocyanates were dried over P_2O_5 and vacuum transferred, whereas solids were used as received. β-VL[42] was prepared from 1,2-epoxybutane and CO using catalyst **1**, washed through Celite with diethyl ether, and distilled. It was then stirred for 1 week with 4-Å molecular sieves, vacuum transferred onto CaH_2, stirred for 1 week, and vacuum transferred.

Procedure for the Screening of Solvents for OD Formation. A custom-fabricated, six-chamber, high-pressure reactor, which has been described,[2d,33] was used for all test-scale syntheses. The reactor was dried at 120 °C under vacuum for 16 h, refilled with N_2, and brought into a glove box. Each chamber was charged with 0.010 mmol of catalyst **1**, 0.50 mmol each of epoxide and phenyl isocyanate, and 1.0 mL dry solvent. Once all chambers were loaded, the reactor was sealed, removed from the glovebox, and pressured to 300 psi with CO. After stirring at 25 °C for 24 h, the reactor was placed on dry ice and vented slowly. Crude reaction mixtures were analyzed by ^1H NMR spectroscopy as follows: to each reaction mixture, 1−2 mL of $CDCl_3$ were added to dissolve all of the products, as most ODs were insoluble in hexanes. An aliquot of the resulting solution was filtered through Celite 545 to remove catalyst residue, and the sample was diluted with $CDCl_3$. The ^1H NMR spectrum of this solution was recorded, and the signals for OD, β-lactone, and epoxide were integrated. Conversion to OD was calculated by determining the ratio of [OD] versus the sum of [OD], [lactone], and [epoxide].

Procedure for the Test-Scale Formation of ODs. Test-scale synthesis of ODs was performed in a manner similar to the solvent-screening reactions. The reactor was dried at 120 °C under vacuum for 16 h, refilled with N_2, and brought into a nitrogen glovebox. Each chamber was charged with 0.010 mmol of catalyst **1**, 0.25 mmol each of the epoxide **2** and the isocyanate **3**, and 1.0 mL dry hexanes. Once all chambers were loaded, the reactor was sealed, removed from the glovebox, and pressured to 800 psi with CO. After stirring at 25 °C for the indicated time, the reactor was placed on dry ice and vented slowly. Crude reaction mixtures were analyzed by ^1H NMR spectroscopy using the same method as for the solvent screening reactions.

Representative Procedure for the Synthesis of 4bd′. A 60-mL, stainless steel, high-pressure Parr reactor was dried at 120 °C under vacuum for 16 h, refilled with N_2, and brought into a nitrogen glovebox. Catalyst **1** (43.7 mg, 0.050 mmol) was weighed into an oven-dried glass insert, and a stir bar was added. Dry hexanes (5.0 mL), **2b** (88.0 μL, 1.26 mmol), and **3d′** (248 mg, 1.25 mmol) were added. The reactor was sealed, removed from the glovebox, and pressured with 800 psi CO. After stirring at 25 °C for 48 h, the reactor was vented slowly. The reaction mixture was poured into a round-bottom flask, rinsed with CH_2Cl_2, and the solvents were removed by rotary evaporation. The resulting solid was washed through silica with ethyl acetate to remove catalyst residue, and the filtrate was concentrated under reduced pressure. It was then dissolved in CH_2Cl_2, and layered with hexanes to afford 0.250 g of crystalline 3-(4-bromophenyl)-6-methyl-1,3-oxazinane-2,4-dione, **4bd′** (isolated yield = 70%). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56 (2 H, d, ^3J = 6.3 Hz), 2.81 (1 H, dd, ^2J = 17.1 Hz, ^2J = 11.1 Hz), 2.94 (1 H, dd, ^2J = 17.1 Hz, ^2J = 3.6 Hz), 4.81 (1 H, m), 7.07 (2 H, pseudo-d), 7.59 (2 H, pseudo-d). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4, 38.6, 71.3, 123.3, 130.2, 132.8, 133.7, 151.2, 167.9. HRMS (EI): *m*/*z* calcd ($C_{11}H_{10}NO_3{}^{79}Br$), 282.9831; found, 282.9834; calcd ($C_{11}H_{10}NO_3{}^{81}Br$), 284.9824; found, 284.9825.

Acknowledgment. This work was generously supported by the National Science Foundation (Grant CHE-0243605) and the Department of Energy (DE-FG02-05ER15687). T.L.C. thanks the Natural Sciences and Engineering Research Council (NSERC) Canada for a Postgraduate Fellowship. We are grateful to Cambridge Isotope Laboratories, Inc. for a research grant to aid in the purchase of ^{13}CO. We are indebted to Dr. J. Schmidt and Mr. D. Treitler for epoxide synthesis and to Dr. I. Keresztes for performing the HRMS analyses.

Supporting Information Available: Isolation and characterization details and ^1H NMR spectra of new compounds; crystal structure data for compounds (*rac*)-**4qb′** and (*R*)-**4bd′**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA069065D

(39) Vyvyan, J. R.; Meyer, J. A.; Meyer, K. D. *J. Org. Chem.* **2003**, *68*, 9144−9147.
(40) Mischitz, M.; Kroutil, W.; Wandel, U.; Faber, K. *Tetrahedron: Asymmetry* **1995**, *6*, 1261−1272.
(41) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936−938.
(42) Noels, A. F.; Herman, J. J.; Teyssie, P. *J. Org. Chem.* **1976**, *41*, 2527−2531.