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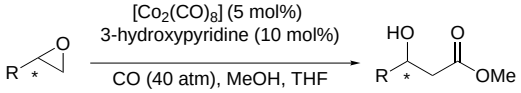
Enantiopure β-Hydroxy Morpholine Amides from Terminal Epoxides by Carbonylation at 1 atm**

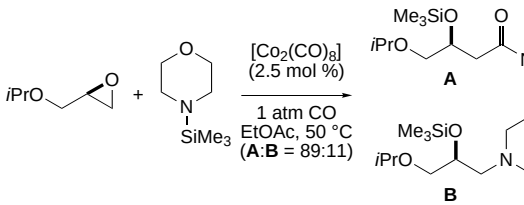
Steven N. Goodman and Eric N. Jacobsen*

As a consequence of the recently developed hydrolytic kinetic resolution (HKR) reaction,[1] a wide variety of terminal epoxides are now readily accessible in enantiopure form. The synthetic utility of this family of chiral building blocks is certainly well established, yet it is likely that new and valuable reactivity remains to be uncovered. In that context, we have sought to develop practical methodology to effect elaboration of these compounds to more highly functionalized chiral intermediates. In 1999, we reported the $[Co_2(CO)_8]$-catalyzed carbonylation of enantiomerically enriched epoxides under 40 atm of CO, to afford β-hydroxy methyl esters in good yield [Eq. (1)].[2] However, the relatively high CO pressure precludes its widespread application in laboratory and industrial settings, and the scope of nucleophiles that could be employed to trap the acylcobalt intermediate was in fact quite limited.[3] As a result, we became interested in devising complementary methodology that would afford general access to broadly useful β-hydroxy carbonyl derivatives under mild conditions.



(1)

The accelerating effect of silyl groups on cobalt-catalyzed carbonylation reactions has been documented.[4] Most relevant to the present study, Tsuji and co-workers described the carbonylative opening of racemic epoxides by *N*-silylamines at low pressures of CO.[5] We sought to extend this methodology to the direct generation of morpholine amides, which, like Weinreb amides, are intermediates with widespread utility in synthesis because of their ability to effect clean acyl transfer to a variety of nucleophiles without product overreduction.[6,7] The reaction of isopropyl glycidyl ether with 4-(trimethylsilyl)morpholine in the presence of 2.5 mol% $[Co_2(CO)_8]$ provided the anticipated β-silyloxy morpholine amide derivative in 58% yield under 1 atm of CO. However, approximately 30% of the crude product mixture was identified as the corresponding amine-opened product.[8] Variation of solvent and reaction conditions provided slight improvement in selectivity, with the use of ethyl acetate and a reaction temperature of 50°C affording best results (80:20 amide:amine ratio). Selectivity for the carbonylation pathway was improved further by carrying out the reaction under scrupulously anhydrous conditions, leading to product formation in an 89:11 amide:amine ratio [Eq. (2)].



(2)

Despite substantial effort to optimize the reaction conditions further, it was not possible to suppress formation of the amine by-product completely. Fortunately, a workup procedure involving simple treatment of the crude product mixture with aqueous acid effectively removed both the amine and the cobalt catalyst. This practical protocol was applied successfully to a variety of epoxides to afford synthetically useful yields of β-hydroxy morpholine amides isolated in >95% purity without chromatography (Table 1).

The transformation is compatible with a variety of functional groups, including ethers, olefins, halides, and esters. Reactions proceeded with no compromise of the optical purity of the starting epoxides, and carbonylations were completely regioselective for the terminal position. However, epoxides bearing sp^2-hybridized α-carbon substituents fared

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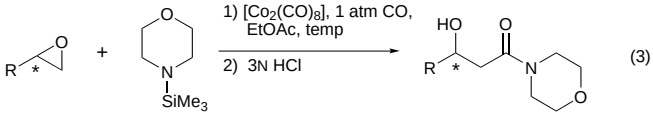
Table 1. Carbonylation of enantioenriched terminal epoxides to generate morpholinoamides [Eq. (3)].[a]

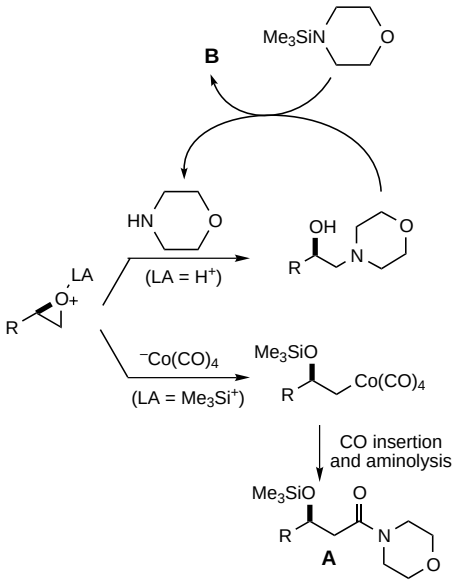


Entry	R	T [°C]	t [h]	Crude ratio [amide:amine]	Yield[b] [%]
1	CH_3	25	12	87:13	67
2	CH_3	25	12	86:14	72[c]
3	CH_2CH_3	25	12	89:11	82
4	$(CH_2)_3CH_3$	50	5	92:8	85
5[d]	$CH_2{=}CHCH_2CH_2$	25	24	88:12	80
6	iPrOCH_2	50	4	89:11	85
7[d]	BnOCH_2	50	8	83:17	79
8[d]	ClCH_2	25	12	80:20	75
9[d]	nPrCO_2CH_2	50	12	80:20	56[e]

[a] All reactions were performed with enantioenriched epoxide (1 mmol; > 99% *ee*) and 4-(trimethylsilyl)morpholine (1.3 mmol) in EtOAc (1.5 mL), using 2.5 mol% [$Co_2(CO)_8$], unless noted otherwise. [b] Yield of pure product after aqueous workup. [c] Reaction performed on 5 mmol of epoxide; product isolated as the trimethylsilyl ether by distillation of the crude mixture. [d] 5 mol% [$Co_2(CO)_8$] was used. [e] Product isolated by column chromatography.

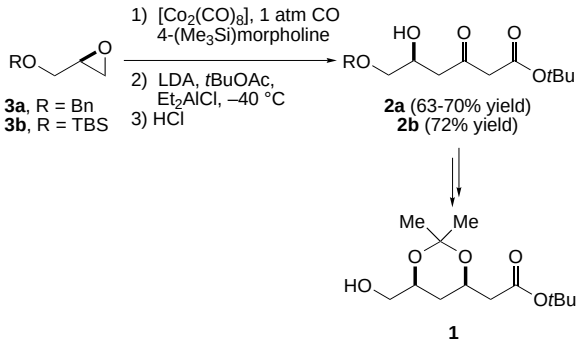
poorly as substrates: methyl glycidate and 3,4-epoxybutanone reacted slowly, affording significant amounts of amine by-product; styrene oxide underwent ring-opening with poor regioselectivity; and butadiene monoepoxide was unreactive.

We propose that amide and amine products are generated by distinct catalytic mechanisms (Scheme 1).[9] The amide pathway is most likely promoted by the catalyst $[R_2N(SiMe_3)_2]^+[Co(CO)_4]^-$, as proposed initially by Tsuji and co-workers (Scheme 1, LA = $SiMe_3$ or possibly $R_2N(SiMe_3)_2$).[5] This complex bears both Lewis acidic and strongly nucleophilic components well-suited for epoxide activation and ring-opening. In contrast, amine formation is attributable to the presence of trace unsilylated morpholine. Thus, addition of catalytic amounts of morpholine or water (to hydrolyze 4-(trimethylsilyl)morpholine in situ) led to large increases in the amount of amine by-product formation (up to 31:69 ratio of amide:amine with 20 mol% water). It is likely that catalysis by a Brønsted acid such as $[R_2NH_2]^+[Co(CO)_4]^-$ gives rise to the amine product.[10] As expected, treatment of epoxides such as isopropyl glycidyl ether with morpholine and a catalytic amount of morpholinium hydrochloride led to exclusive formation of the amine adduct at room temperature.



Scheme 1. Pathway to amide and amine products.

The utility of the morpholine amide products in acyl transfer reactions was illustrated in a concise synthesis of β-ketoester **2,** a known intermediate in the synthesis of **1** (Scheme 2). Acetonide **1** is the standard building block for



Scheme 2. Synthesis of β-ketoester **2**, an intermediate in the synthesis of acetonide **1**.

HMG-CoA reductase inhibitors such as compactin, mevinolin, and synthetic analogues such as Lipitor and Crestor. We envisioned that β-ketoester **2** could be obtained from the morpholine amide prepared from glycidyl ether derivatives by a simple acetate enolate homologation.

Unfortunately, no general method for adding enolates to amides was available.[11] Although the addition of lithium enolates to Weinreb amides is well-precedented,[12] morpholine amides are less electrophilic and were found to be unreactive toward these nucleophiles. In contrast, use of more reactive aluminum enolates afforded the corresponding δ-hydroxy-β-ketoesters cleanly. In a one-pot procedure, benzyl glycidyl ether **3a** was transformed to the corresponding morpholine amide, then treated with the aluminum enolate of *t*BuOAc to afford **2a** in 63–70% overall yield (Scheme 2). This reaction sequence was performed with resolved epoxide

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on multigram scale to provide enantiopure **2a**. Similar results were obtained for *tert*-butyldimethylsilyl (TBS) glycidyl ether **2b** (72% yield of isolated product over two steps). Given the ready availability of enantiopure terminal epoxides[1] and the relative simplicity and efficiency of the overall sequence, this route appears to provide an attractive alternative to existing routes to **2**.[13]

In summary, we have developed a mild and efficient carbonylation protocol for the conversion of optically active epoxides to β-hydroxy morpholine amides. The methodology is effective with a variety of epoxides obtained readily by the HKR, and pure products can easily be isolated simply by treatment of the crude product mixture with aqueous acid. In addition, the discovery that aluminum enolate derivatives add cleanly to morpholine amides provides a valuable new approach for the preparation of synthetically valuable δ-hydroxy-β-ketoesters.

Experimental Section

General carbonylation procedure**:** $[Co_2(CO)_8]$ (8.5 mg, 0.025 mmol) under a nitrogen atmosphere was added to an oven-dried 10-mL Schlenk flask equipped with a stirbar and septum. The atmosphere was exchanged for CO (vacuum/fill 3×) from a double balloon affixed to the stopcock sidearm. Ethyl acetate (1.5 mL) was added, and the solution stirred for ten minutes. 4-(Trimethylsilyl)morpholine (0.23 mL, 1.3 mmol) and epoxide (1.0 mmol) were added sequentially, and the septum was replaced with a greased glass stopper. The reaction mixture was stirred at the desired temperature for the specified length of time, at which point 3N HCl (aq) (1.5 mL) was added to the reaction mixture at room temperature. After the mixture had been stirred for ten minutes, the layers were separated, the aqueous layer was extracted with EtOAc (15 mL), and the combined organic layers were washed with brine (2 mL). The aqueous layers were further extracted with EtOAc (2×15 mL each). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure to provide the β-hydroxy morpholine amide as a clear to yellow oil.

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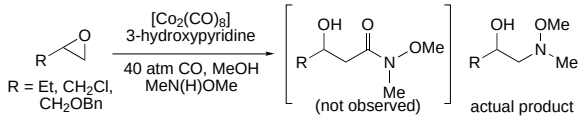

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[8] Application of the conditions documented by Tsuji and co-workers led, in our hands, to formation of significant levels of amine by-products. This reactivity pathway was not noted in the original report.

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