

Nucleophilic Metal Complexes as Acylation Catalysts: Solvent-Dependent “Switch” Mechanisms Leading to the First Catalyzed Staudinger Reaction

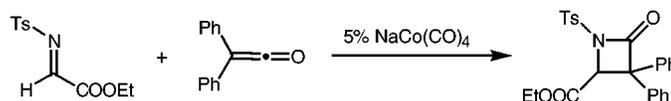
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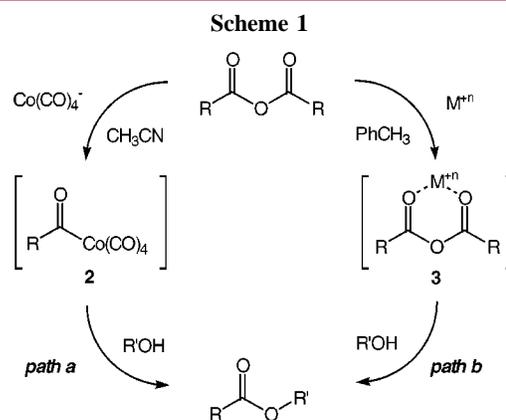
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ABSTRACT



Catalytic acylation using complex transition metal salts $MCo(CO)_4$ is demonstrated. Surprisingly, a solvent-dependent mechanistic “switch” results in a Lewis acid-based acylation mechanism in nonpolar media and a nucleophilic mechanism in polar organic media. These observations lead to the first example of a catalyzed Staudinger reaction to form β -lactams.

The remarkable diversity and specificity of catalyzed reactions underpin much of modern organic chemistry. For example, many catalysts operate as Lewis acids, as Lewis bases, or less commonly as a combination of the two.¹ Almost unheard of is the scenario in which a change in solvent fundamentally transforms a catalyst from acting primarily as a Lewis acid to a Lewis base or vice versa. For example, complex transition metal salts $X_m Y_n$, in which both X and Y are metal-centered units, are potentially bifunctional species wherein X^{+n} may act as a Lewis acid and counterion Y^{-m} as a nucleophile or Lewis base.² In this report, we present catalyzed acylations in which the *solvent* determines whether a soluble transition metal salt functions mainly as a Lewis acid-based or, alternatively, as a nucleophile-based catalyst. We found that salts, such as $NaCo(CO)_4$ (**1a**), provide the first examples of metal complexes acting as nucleophiles to catalyze standard acylation reactions in polar aprotic solvents including CH_3CN (path a, Scheme 1).³ Most interestingly, in nonpolar solvents it is the Lewis acidic counterion that becomes primarily responsible for catalysis



(path b, Scheme 1), resulting in an unusual mechanistic “switch”. We also demonstrate that the lessons learned from

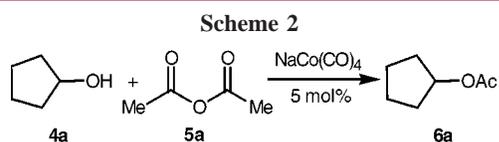
(1) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; Dover: New York, 1987; Chapter 3.

(2) We have previously reported a novel reaction pathway divergence in the Lewis acid-catalyzed reactions of acylaziridines, see: Ferraris, D.; Drury, III.; W. J.; Cox, C.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 4568.

(3) Complexes $MCo(CO)_4$ (**1**) react with alkyl halides through nucleophilic displacement followed by carbonyl insertion, see: Kerr, W. J. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1995; p 4633. Acylcobalt intermediates react with alcohols stoichiometrically to afford esters: Tkatchenko, I. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 8, p 101.

our system can be rationally applied to a new class of catalyzed acylations, namely the reaction of imines with ketenes to form β -lactams (the Staudinger reaction).⁴ Although for mechanistic reasons the Staudinger reaction was presumed not to be amenable to Lewis acid- or nucleophile-based catalysis,⁵ we show that by modification of the polarity of the imine, nucleophiles can efficiently catalyze this process.

Cyclopentanol (**4a**) was chosen as a standard alcohol for screening **1a** as an acylation catalyst (Scheme 2). We found



that a small amount of **1a** (5 mol %) catalyzes the acylation of **4a** with acetic anhydride (**5a**) in a number of different solvents to afford ester **6a** in good to excellent yields after 72 h (Table 1).

Table 1. Solvent Effects on NaCo(CO)_4 -Catalyzed Acylation of Cyclopentanol (Scheme 2)

Entry ^b	Solvent	% conversion	
		32 h	72 h
1	Toluene	64	95
2	Benzotrifluoride	42	90
3	CH_2Cl_2	22	50
4 ^a	Anisole	42	92
5 ^a	THF	47	90
6 ^a	CH_3CN	58	88

^a 1 equiv of 2,6-di-*tert*-butylpyridine added to the reaction. ^b Under all conditions examined, the background rates remained minimal (<3% after 72 h).

In coordinating solvents such as CH_3CN , completion of the reaction was reached only upon addition of 2,6-di-*tert*-butylpyridine as a stoichiometric base,⁶ whereas solvents of low polarity required no additive. Surprisingly, the reaction rates varied noticeably depending on the solvent used, with

(4) For recent applications, see: (a) Georg, G. I.; Ravikumar, V. T. In *The Organic Chemistry of β -Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; p 295. (b) Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure Appl. Chem.* **1987**, 59, 485. (c) Yamasaki, N.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1986**, 1013. (d) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1985**, 26, 3783.

(5) The Staudinger reaction is believed to be a two-step process in which nucleophilic attack of an imine on a ketene is followed by ring closure of a zwitterionic intermediate. Catalysis in such reactions generally must compete with inherently high uncatalyzed reaction rates. See: (a) Lecea, B.; Arrastia, I.; Arrieta, A.; Roa, G.; Lopez, X.; Arriortua, M. I.; Ugalde, J. M.; Cossío, F. P. *J. Org. Chem.* **1996**, 61, 3070. (b) Arrieta, A.; Ugalde, J. M.; Cossío, F. P.; Lecea, B. *Tetrahedron Lett.* **1994**, 35, 4465. (c) Cossío, F. P.; Ugalde, J. M.; Lopez, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, 115, 995. (d) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. S. *J. Am. Chem. Soc.* **1991**, 113, 5784.

(6) In the absence of base the reaction reached ~30% conversion after 72 h. Added di-*tert*-butylpyridine under standard conditions did not catalyze the reaction.

the highest rates observed in either coordinating, highly polar solvents (for example CH_3CN) or in solvents of low polarity and donicity (such as toluene).⁷ In media of intermediate character (anisole, CH_2Cl_2 , or THF), slight relative rate suppression was observed, whereas background rates remained minimal under all conditions examined. The apparent dichotomy of solvent dependence on reaction rates indicated that the solvent may be fundamentally affecting the reaction mechanism.

To investigate the possibility that Na^+ acts as a Lewis acid in nonpolar solvents, we substituted $\text{NaB}(p\text{-Ph-CF}_3)_4$ for **1a** and found both to be equally effective^{8a} as catalysts in toluene as well as in benzotrifluoride (BTF).^{8b} Na^+ is preceded to behave as a Lewis acid (albeit rarely) in nonpolar solvents in the presence of weakly coordinating counterions.⁹ The addition of 15-crown-5 to reactions in nonpolar solvents (entry 4, Table 2) slows the reaction down to the background

Table 2. Acylation of Alcohols with Acetic Anhydride Using NaCo(CO)_4 Catalyst

Entry ^a	Alcohol R =	Solvent	% Yield ^b	Time
1 ^c		Toluene ^d	quant.	12 h
2 ^{c, g}		CH_3CN	98	12 h
3 ^{c, g}		THF ^e	quant.	12 h
4 ^f		Toluene	12	24 h
5		Toluene	95	72 h
6 ^g		CH_3CN	88	72 h
7 ^g		THF	90	72 h
8		Toluene	94	12 h
9 ^g		CH_3CN	quant.	12 h
10 ^g		THF	98	12 h
11		Toluene	97	12 h
12 ^g		CH_3CN	99	12 h
13 ^g		THF	95	12 h

^a All reactions were run with 10 mol % of NaCo(CO)_4 as catalyst. ^b Yields of purified products. ^c Benzoic anhydride was also used as an acylating agent with equivalent yield after 18–24 h. ^d BTF can be substituted in all reactions for toluene with similar yields. ^e Anisole can be substituted for THF in all reactions with similar yield. ^f Reaction carried out with 10 mol % of 15-crown-5. ^g 1 equiv of 2,6-di-*tert*-butylpyridine added.

rate, indicating that in these solvents it is the counterion (such as Na^+) that is primarily responsible for catalysis. In contrast

(7) (a) Solvent polarity scales were taken from: Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*, 2nd. ed.; VCH: Weinheim, 1998. (b) The rate constants for the acylation of benzyl alcohol were determined in toluene ($k_{\text{rel}} = 2.7$), CH_3CN ($k_{\text{rel}} = 2.0$), and THF ($k_{\text{rel}} = 1.0$). Benzyl alcohol was chosen for kinetic studies for ease of HPLC and GC product analysis. Similar results were obtained for cyclopentanol, with somewhat lower overall rates; for details see the Supporting Information.

(8) (a) Under standard reaction conditions the formation of the acylated products was determined by ^1H NMR, GC, or HPLC at specified time intervals. (b) α, α, α -Trifluorotoluene is commonly referred to as benzotrifluoride.

(9) For example, Na^+ has been used as a catalyst in alkylation reactions: Gobbi, A.; Landini, D.; Maia, A.; Penso, M. *J. Chem. Soc., Perkin Trans. 2* **1996**, 2505.

to acylation in CH_3CN , the rate of reaction in nonpolar solvents was maintained over time as the acetic acid byproduct does not significantly influence the Lewis acidity of the metal ions (Na^+ , K^+).¹⁰ In further support of our mechanistic hypothesis (Scheme 1), we obtained IR evidence for chelation of Na^+ to benzoic anhydride (complex **3**, $\text{R} = \text{Ph}$).¹¹ The two characteristic carbonyl bands in BTF (1792 and 1730 cm^{-1}) merged gradually into one band of intermediate wavenumber (1779 cm^{-1}) during addition of $\text{NaB}(p\text{-Ph-CF}_3)_4$. Note that chelation of other Lewis acids to anhydrides is precedented.¹²

Alternatively, in aprotic or coordinating solvents such as THF, CH_3CN , or anisole, the reaction pathway becomes nucleophilic in nature (Scheme 1, path a). As expected, the addition of 15-crown-5 had no effect on the rate of reaction in THF or CH_3CN . Under these conditions, the cobaltate anion (but not the anion of $\text{NaB}(p\text{-Ph-CF}_3)_4$) is catalytically active and the Lewis basic environment results in effective sequestration of the cationic counterion. To provide support for the proposed nucleophilic mechanism, we first determined that a cobalt acyl species was a plausible intermediate. A solution of acetic anhydride and **1a** was mixed in BTF, and the resulting complex **2** ($\text{R} = \text{CH}_3$) was characterized by IR.¹³ The spectral data were indicative of an acyl cobalt species (IR stretch at 1729 cm^{-1}) consistent with precedent.^{14a} Consequently, when complex **2** was dissolved in a solution of cyclopentanol, the stoichiometric acylation reaction was complete in a matter of minutes. We obtained further evidence supporting nucleophilic catalysis in polar solvents by employing 1 equiv of Collman's reagent ($\text{Na}_2\text{Fe}(\text{CO})_4$ **1b**), a more basic nucleophile than **1a**.^{14b} In this case no catalyzed reaction took place under the standard conditions, an outcome that disfavors a purely base-catalyzed pathway. The substrates used in this study, as outlined in Table 2, include primary and secondary alcohols.

Especially intriguing is the use of the complex salt cobaltocenium cobaltate **1d** as an acylation catalyst (Figure 1).¹⁵ As expected, in toluene and BTF the cobaltocenium

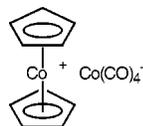


Figure 1. Cobaltocenium cobaltate **1d**.

cation is responsible for the catalytic acetylation of cyclopentanol, whereas in CH_3CN it is the cobaltate anion. For example, $\text{Cp}_2\text{Co}^+\text{PF}_6^-$ (**1c**) is an active catalyst in toluene but not in CH_3CN .¹⁶ Thus, cobalt is the catalytic agent in

(10) Remarkably, $\text{KCo}(\text{CO})_4$ showed essentially the same reactivity as its Na^+ analogue, demonstrating that K^+ is also a competent Lewis acid under the specified conditions.

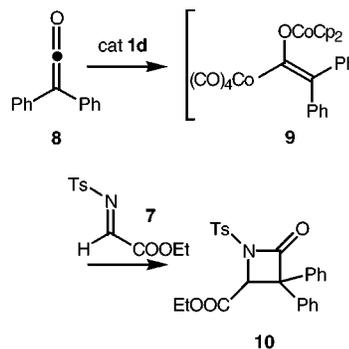
(11) (a) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 256.

(12) Viard, B.; Poulain, M.; Grandjean, D.; Amaudrut, J. *J. Chem. Res.* **1983**, 853.

two different forms and oxidation states. A question arises as to why metal carbonyl anions are acylation catalysts for alcohols in solvents such as CH_3CN but not in toluene or BTF. In toluene, we propose the acetic acid byproduct (and possibly the alcohol reactant) may be strongly hydrogen bonded to the metal carbonyl anions, thus diminishing their reactivity. In CH_3CN , the alcohol should be largely hydrogen-bonded to the solvent, leaving the anion free to react.^{7a} Thus, an acylation involving only aprotic materials may proceed by nucleophilic catalysis in nonpolar solution.

To test our hypothesis rationally, we sought an acylation process in which neither the reactant nor the product could donate hydrogen bonds. An optimal example would be the Staudinger reaction, namely the acylation of imines by ketenes to form β -lactams, involving only aprotic starting materials.^{4,5} Our approach to making this reaction catalytic for the first time involves using a much less nucleophilic imine through attachment of electron-withdrawing groups onto the imine nitrogen and α to the imine unit. We determined that electron-deficient α -imino ester **7**¹⁷ does not react with diphenylketene **8**^{18a} at room temperature. However, we found that 5 mol % of **1d** catalyzes the addition of **7** to **8** to afford β -lactam **10** in 85% yield after only 5 min in BTF at room temperature (Scheme 3).^{18b}

Scheme 3



A catalytic nucleophile entering the picture can do two things: either it can add to the ketene to form metalloenolate **9**, thus effectively reversing the polarity of the reaction, or it can reversibly add to **7** and restore its nucleophilicity.

(13) Under an inert atmosphere, 0.1 mmol of $\text{NaCo}(\text{CO})_4$ was added to 1 mmol of acetic anhydride in 3 mL of BTF and the solution was refluxed 1 h. Excess reagents were removed under vacuum, and the residue was transferred into an IR cell.

(14) (a) Haasz, F.; Bartik, T.; Galamb, V.; Palyi, G. *Organometallics* **1990**, *9*, 2773. (b) For a review of this reagent, see: Collman, J. P. *Acc. Chem. Res.* **1975**, *8*, 342.

(15) Bockman, T. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1989**, *111*, 4669.

(16) By use of 10 mol % of **1c** in 2 mL of toluene and CH_3CN , respectively, the acylation of benzyl alcohol with acetic anhydride (1 mM each) was complete in toluene after 24 h. In CH_3CN , however, no product formation was observed.

(17) Tschaen, D. H.; Turos, E.; Weinreb, S. M. *J. Org. Chem.* **1984**, *49*, 5058.

(18) (a) Lund, E. A.; Kennedy, I. A.; Fallis, A. G. *Can. J. Chem.* **1996**, *74*, 2401. (b) Using catalyst **1a** gave comparable results in this reaction. Upon addition of 1 equiv of 15-crown-5, the reaction was not inhibited, indicating that catalysis is primarily nucleophilic in nature.

Kinetic experiments indicate that the rate of reaction is *independent* of imine concentration over a 1–10 mM range, an observation consistent with rate-determining formation of **9** and its fast reaction with **7**. Stirring together ketene **8** with 1 equiv of cobaltate **1d** produces an immediate color change and putative generation of metal enolate **9**,¹⁹ which upon protonation with 1 equiv of di-*tert*-butyl-pyridinium triflate produced acyl cobalt species **2**, as characterized by IR.^{14a} In this case the mechanistic “switch” is different; the reaction apparently proceeds through an electrophilic, rather than a nucleophilic, imine. Further studies are underway involving other low-valent metal complexes to examine the

(19) For example, upon addition of 1 equiv of **1b** to **8** in BTF, the characteristic ketene IR band at 2100 cm⁻¹ disappears. Attempted ¹H NMR studies on the nature of **9** were thwarted by small amounts of apparently paramagnetic impurities.

scope of the catalyzed acylations and Staudinger reactions and will be reported shortly.

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Supporting Information Available: General experimental procedures and spectral data for new compound **10**. Also included are kinetic data and graphs for the acylation of alcohols and for the Staudinger reaction. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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