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Multicatalytic Synthesis of α-Pyrrolidinyl Ketones via a Tandem Palladium(II)/Indium(III)-Catalyzed Aminochlorocarbonylation/Friedel−Crafts Acylation Reaction

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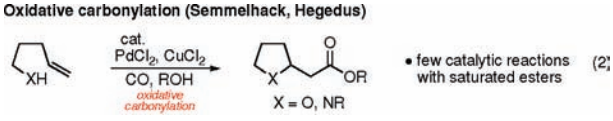
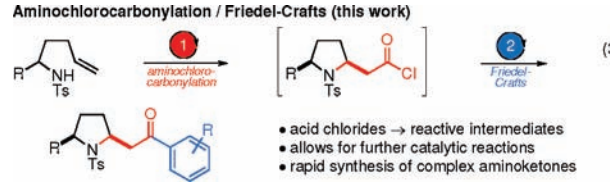
As a manifestly practical science, synthetic organic chemistry counts as one of its primary objectives the invention of increasingly rapid, efficient, and economical strategies to access valuable molecular constructs. To this end, chemists have long been interested in tandem or cascade reactions, which deliver substantial increases in molecular complexity via single-pot operations without the need for intermediate workups or purifications.[1] Recently, there has been growing interest in the development of related *catalytic* multistep processes, whereby one or more catalysts promote two or more distinct chemical transformations in a single flask.[2,3] Known as tandem-, cascade-, or sequential-catalysis, depending on the precise experimental details, such "multicatalytic" processes offer the potential to significantly advance the field of synthesis by helping to alleviate dependency on strictly iterative processes. This potential notwithstanding, the range of chemistries that have been exploited for multicatalytic purposes is quite narrow. With this in mind, our group is exploring the development of new multicatalytic processes with the broad goals of (1) developing highly efficient strategies for accessing privileged organic architectures and especially (2) inventing new chemical technologies that facilitate these processes (eq 1).

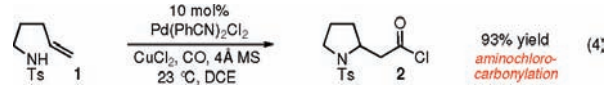
In this regard, we were attracted to the palladium(II) oxidative carbonylation chemistry developed by Semmelhack[4] and Hegedus[5] as an intriguing platform for multicatalytic design. Oxidative carbonylations are attractive transformations because they engender rapid increases in molecular complexity by the conversion of simple unsaturated alcohol or amine substrates to complex heterocyclic products (eq 2). Surprisingly, however, most reports of oxidative carbonylations detail termination by an alcohol nucleophile (usually as solvent) to generate carboxylic ester products.[6]



As useful as these transformations are, saturated esters are not efficient participants in many catalytic processes and thus do not readily lend themselves to multicatalytic methods. We were thus intrigued by the notion of diverting the oxidative carbonylation manifold to generate more reactive carbonyl products, which could then serve as viable intermediates for further catalytic operations. We report herein the finding that acid chlorides can be formed under oxidative carbonylation conditions and that these products participate in a tandem multicatalytic process involving Friedel−Crafts acylation (eq 3). Importantly, the products of this highly efficient multicatalytic sequence are α-pyrrolidinyl ketones, a motif encountered in numerous biologically active natural isolates.[7]



Encouraged by the reports by Tsuji and Tkatchenko that $PdCl_2$ in the presence of CO can effect the transformation of alkenes to β-chloro acid chlorides,[8] we reasoned that subjecting pentenyl amines to catalytic oxidative carbonylation conditions with the exclusion of alcohol should result in pyrrolidinyl acid chlorides. In fact, we found that when *N*-tosylpentenamine **1** was added slowly to a solution containing 10 mol % $Pd(PhCN)_2Cl_2$ and 3 equiv of $CuCl_2$ in dichloroethane (DCE) under a CO atmosphere, acid chloride **2** was isolated in 93% yield after filtration (eq 4). Notably, we saw only trace amounts of the amide adduct resulting from acylation of **1** by the acid chloride product **2**.



Next, in an effort to incorporate this aminochlorocarbonylation reaction into a useful multicatalytic process, we explored the possibility of employing the pyrrolidinyl acid chloride products for Lewis acid-catalyzed Friedel−Crafts acylation.[9] A screen of Lewis acidic reagents revealed indium(III) triflate[10] as a superior acylation catalyst in DCE at 23 °C. Importantly, the presence of indium(III) triflate and an electron-rich aromatic did not interfere with the aminochlorocarbonylation reaction. As such, we found it possible to execute a tandem aminochlorocarbonylation/Friedel−Crafts reaction by the slow addition of an amino substrate to a mixture of an aromatic nucleophile, 10 mol % $Pd(PhCN)_2Cl_2$, 10 mol % $In(OTf)_3$, $CuCl_2$, and 4 Å molecular sieves in DCE under a CO atmosphere. The β-pyrrolidinyl ketone products from this tandem process were isolated in good to high yields and with excellent diastereoselectivities (Table 1).

Importantly, a variety of electron-rich aromatic nucleophiles readily participate in this multicatalytic process, including aryl ether (entries 1−3), aryl bromide (entry 3), pyrrole (entry 4), thiophene (entry 5), and indole (entry 6) motifs.

This multicatalytic reaction also appears to be general in regard to substrate scope (Table 1). In addition to terminal olefinic substrates (entries 1−6), substrates bearing nonterminal olefins proved to be viable in this process, thus allowing the generation of products bearing substantial stereochemical complexity (entries 7

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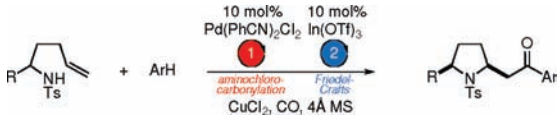
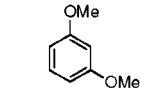
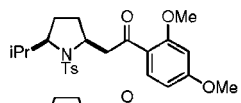
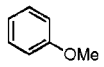
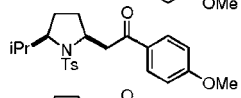
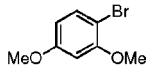
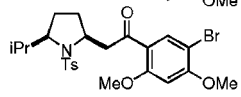
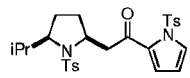
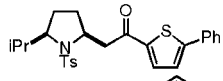
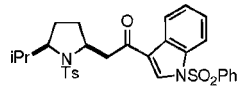
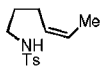
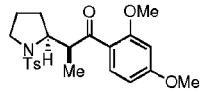
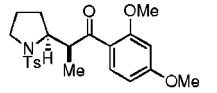
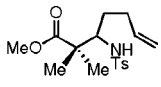
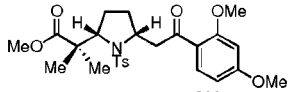
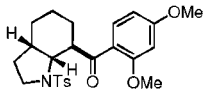
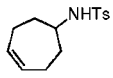
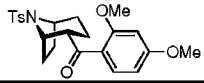
and 8). Surprisingly, in these cases the *E* and *Z* olefins give rise to the same product diastereomer, an observation that we attribute to thermodynamic equilibration via a retro-Mannich/Mannich addition process.[11] In addition, a substrate formally arising from a Mannich reaction was found to participate efficiently to produce the complex keto ester adduct shown in entry 9. Most interestingly, cyclic olefins were also ready participants in this tandem process, thus providing access to valuable fused or bridged bicyclic keto pyrrolidine products (entries 10 and 11).

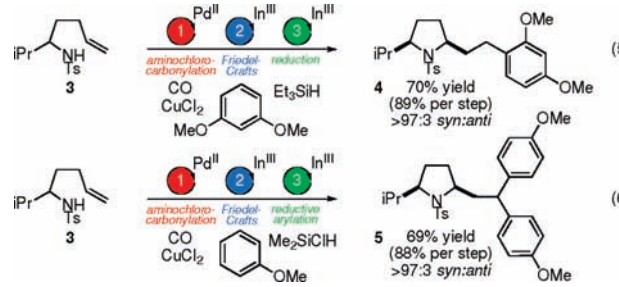
Table 1. Multicatalytic Synthesis of Pyrrolidinyl Ketones[a,b]



Entry	Substrate / ArH	Product	% yield	d.r.
1			85	96:4
2			92	>97:3
3			66	>97:3
4			88[c]	>97:3
5			91	>97:3
6			72	>97:3
7			70	93:7
8[d]			58	>97:3
9			74	95:5
10			85	>97:3
11			75	>97:3

[a] Reactions were performed by syringe-pump addition of the substrate to a suspension of 10 mol % $PdCl_2(PhCN)_2$, $CuCl_2$ (3 equiv), 10 mol % $In(OTf)_3$, 4 Å molecular sieves, CO (1 atm), and aromatic nucleophile (5 or 10 equiv) in DCE at 23 °C. [b] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixtures. [c] 3:1 regioselectivity. [d] 20 mol % $In(OTf)_3$ was used.

Finally, we have found it possible to merge this tandem reaction with additional catalytic transformations to realize three-step multicatalytic processes. For example, upon completion of the tandem aminochlorocarbonylation/Friedel−Crafts sequence with substrate **3** and dimethoxybenzene, addition of triethylsilane to the mixture effected an $In(OTf)_3$-catalyzed ketone reduction[12] to provide pyrrolidine adduct **4** in 70% yield (89% per step) with high diastereoselectivity (eq 5). Alternatively, addition of chlorodimethylsilane precipitated a reductive arylation reaction to produce diaryl pyrrolidine **5** in an efficient 88% per step yield (eq 6).



In conclusion, we have developed the first catalytic aminochlorocarbonylation and have successfully incorporated this reaction into doubly and triply catalytic processes involving Friedel−Crafts acylation. We are currently exploring these and related multicatalytic processes.

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Supporting Information Available: Experimental procedures, product characterization data, and a CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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