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Ruthenium-Catalyzed Intramolecular Hydrocarbamoylation of Allylic Formamides: Convenient Access to Chiral Pyrrolidones

Nicolas Armanino and Erick M. Carreira*

Laboratorium für Organische Chemie, ETH Zürich, CH-8093 Zürich, Switzerland

Supporting Information

ABSTRACT: An attractive strategy for the synthesis of saturated nitrogen-containing heterocycles is described herein, involving the implementation of ruthenium-catalyzed intramolecular hydrocarbamoylation of olefins. The process proceeds by formal C−H bond cleavage of an allylic formamide followed by construction of a new C−C bond in a reaction that is characterized by complete atom-economy. The method is particularly valuable in conjunction with the numerous efficient strategies available for the preparation of optically active allylic formamides.

Pyrrolidones and the related pyrrolidines are common motifs in a variety of important structures including alkaloids,[1] top-selling drugs, and other bioactive molecules (Figure 1).[2] Despite their broad applications, methods for their synthesis rely heavily on a well-established set of C−C bond-forming reactions[3] and, more recently, hydroamination reactions.[4] Propelled by our interest in identifying and investigating new bond-forming catalytic reactions, we now report a ruthenium-catalyzed hydrocarbamoylation for the construction of substituted pyrrolidones from easily accessible allylic formamides (Figure 1).

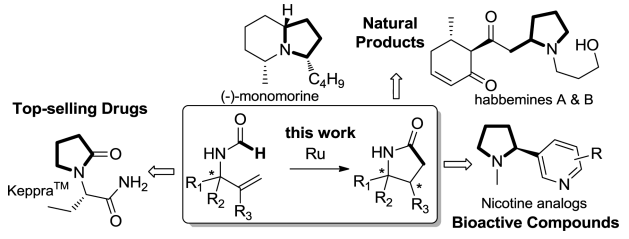

Figure 1. Intramolecular hydrocarbamoylation and potential synthetic applications.

Hydroacylation reactions constitute an important set of transformations that have a long history.[5] These reactions allow the formation of C−C bonds in a single step with complete atom-economy.[6] Since the pioneering work of Bosnich[7] and Sakai[8] on intramolecular hydroacylation for the synthesis of cyclopentanones, recent advances in intra- and intermolecular hydroacylation have led to the discovery of efficient catalyst systems for this reaction on a range of substrates.[9] Of particular interest for fine chemicals synthesis, intramolecular hydroacylation has been studied for the preparation of heterocycles.[10] Most notably, Dong's approach of replacing the olefin moiety with a ketone allowed the preparation of lactones by carbonyl hydroacylation.[11] Although hydroacylation reactions have been extensively studied, the related hydroesterification[12] and particularly the hydrocarbamoylation reactions, which one could also contemplate for heterocycle synthesis, have been the subject of only limited investigations. In this regard, the inherent difficulties finding catalysts able to perform hydroesterification or carbamoylation without suffering competitive, irreversible decarbonylation have hampered their development in complex molecule synthesis.

To date, two catalyst manifolds to effect hydrocarbamoylation have been investigated. The first involves the use of ruthenium−carbonyl complexes for intermolecular coupling of formamides and simple alkenes under harsh conditions and high pressures of CO.[13] The narrow substrate scope observed has limited their utility largely to the manufacture of industrial bulk chemicals. Milder conditions for the intermolecular reaction are achieved by Chang's insightful use of a pyridine directing group.[12e,14] This auxiliary-based approach, however, precludes its employment in an atom-economical, intramolecular fashion. The second venue developed for this transformation involves the use of nickel catalysts, which has been largely limited to alkyne substrates.[15] This method, however, is not compatible with amides bearing a free N−H bond due to the highly reactive nature of the catalyst and the requirement for use of a protecting group.

Recognizing the power of this transformation for the synthesis of heterocycles from readily available allylic formamides, we set out to explore this reaction with **1a** as a test substrate (Table 1). Initial screening of a range of complexes based on Rh, Fe, Os, Pd, and Ru identified $Ru_3(CO)_{12}$ as a competent catalyst in combination with halide additives.[16] As expected, no reaction took place in the absence of the ruthenium catalyst (entry 2). The amount of iodide additive was optimized to 15 mol% (entries 1, 3−5), and both NaI and Bu_4NI could be used interchangeably (entry 6). While we found it was not necessary to perform the reaction in a carbon monoxide-filled autoclave, initial purging of the reaction mixture with CO by sparging dramatically increased the conversion and consistently resulted in cleaner product formation (entry 7). A screen of solvents over a range of temperatures revealed DMF as the optimal choice for the reaction, while other solvents such as DMSO (entry 8) gave lower yields. The catalyst loading and temperature of the reaction could also be lowered (entries 9, 10), albeit at a cost in yield.

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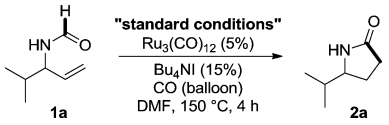
Table 1. Optimization of the Cyclization Reaction[a,b]



entry	deviation from the standard conditions	conv (%)	yield (%)
1	standard conditions[a]	>99	92
2	no $Ru_3(CO)_{12}$	0	–
3	0% Bu_4NI	15	trace
4	5% Bu_4NI	40	36
5	10% Bu_4NI	84	78
6	NaI instead of Bu_4NI	>99	92
7	no CO (under Ar)	53	10
8	DMSO as solvent	>99	51
9	only 3% $Ru_3(CO)_{12}$	>99	87
10	reaction at 120 °C	>99	77

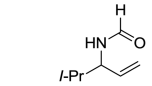
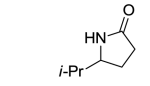
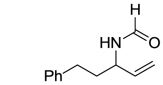
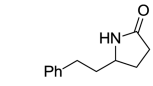
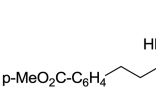
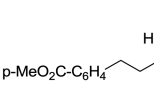
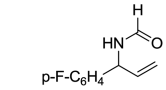
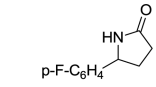
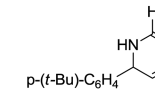
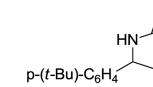
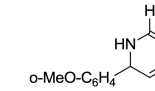
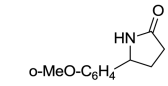
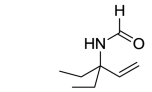
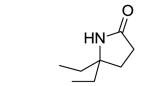
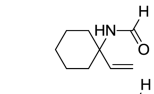
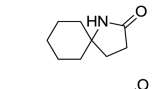
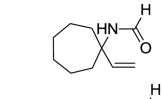
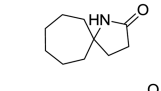
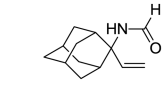
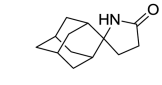
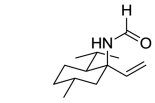
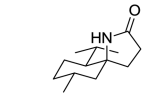
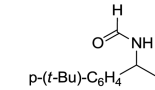
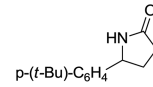
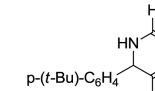
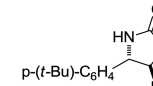
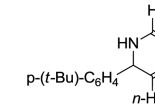
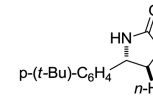
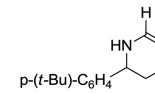
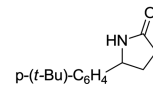
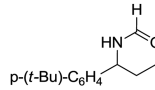
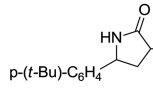
[a]Standard conditions: suspension of **1a** (0.08 mmol), $Ru_3(CO)_{12}$ (5 mol%) and Bu_4NI (15 mol%) in DMF (0.25 mL) in a septum-capped vial was purged with CO (balloon) and the vial then heated to 150 °C for 4 h. [b]Conversion and yield were determined by ^1H NMR against 1,4-dimethoxybenzene as an added standard.

With the optimal conditions in hand, we turned our attention to the scope of the reaction (Table 2). The cyclization to pyrrolidones could be performed on an array of substrates including both alkyl- and aryl-substituted secondary formamides. Aryl groups bearing both electron-withdrawing (entries 3, 4) and electron-donating groups (entry 6) at various positions of the ring were well tolerated. In those cases, no side reactions arising from insertion into the aryl C−H bonds were observed. The reaction was also compatible with substrates where the amine is positioned at a fully substituted carbon (entries 7−11), allowing easy access to spirocycles and chiral pyrrolidones (entry 11) that contain tetrasubstituted stereogenic carbon centers.

We were pleased to find that both 1,2- and 1,1-disubstituted olefins were competent substrates in the reaction and furnished the desired pyrrolidones in good yields (entries 12−14).[17] It is noteworthy that 1,1-disubstituted substrates gave the product in high diastereoselectivity, favoring the thermodynamically more stable *trans*-substituted pyrrolidone. This stands in contrast with the observations made by Sakai for rhodium-catalyzed intramolecular hydroacylation, in which the *cis*-product is preferentially formed.[8a] When employing homoallylic (entry 15) and bis-homoallylic (entry 16) formamides as substrates, we observed exclusive formation of the pyrrolidones and no sign of the corresponding piperidones. In the case of homoallylic formamide this can be explained by an *exo*-type cyclization. By contrast, in the bis-homoallylic substrate this must arise from an olefin transposition that precedes the cyclization event. In no case, however, did we observe isomerization of the olefin toward conjugation with the formamide.

We then explored the preparation of enantioenriched pyrrolidones. The impressive collection of strategies developed for the preparation of optically enriched allylic amines has rendered them readily available,[18] in particular through allylic amination[19,20] and addition to sulfinyl-imines[21] as well as enzymatic methods.[22] To demonstrate the convenience of our combined method, we synthesized the enantioenriched chiral pyrrolidone (*S*)-**2d** in two steps from the known racemic allylic alcohol (Scheme 1). The intermediate allylic amine generated from the iridium-catalyzed asymmetric amination[20] was converted directly in a single pot into the formamide, which was obtained in 88% ee. This was then conveniently cyclized utilizing ruthenium-catalyzed hydrocarbamoylation to give the

Table 2. Substrate Scope under Standard Conditions[a]

entry	substrate	product	yield[b]
1			87 %
2			81 %
3			74 %
4			77 %
5			74 %
6			75 %
7			90 %
8			87 %
9			70 %
10			87 %
11			79 %
12[c]			70 %
13[d]			82 %
14[e]			74 %
15[c]			81 %
16[c]			66 %

[a]See Supporting Information for reaction conditions. [b]Isolated yield of the product after column chromatography. [c]Product obtained as a 1:1 mixture of diastereomers. [d]Product obtained in 20:1 dr. [e]Product obtained in 8:1 dr.

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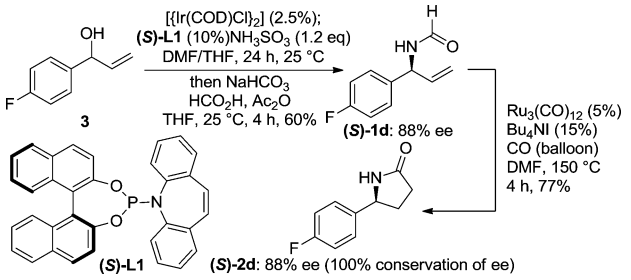
Scheme 1. Preparation of Chiral Pyrrolidone (*S*)-2d



product pyrrolidone with complete conservation of optical purity.

The pyrrolidones obtained also feature a convenient synthetic handle in the form of the free amide N−H bond for further functionalization. In fact, we found that ruthenium-catalyzed cyclization requires a free amide N−H bond. Attempts involving cyclization with various tertiary amides failed to yield cyclized product. This indicates that a free N−H bond plays an important role in the mechanism of the reaction, a feature that complements the nickel-catalyzed reactions.

On the basis of these observations and in accordance with previous reports,[13b] we propose a possible mechanism that involves initial insertion of the active ruthenium catalyst into the N−H bond of **I** to give **II** (Figure 2). This process has been

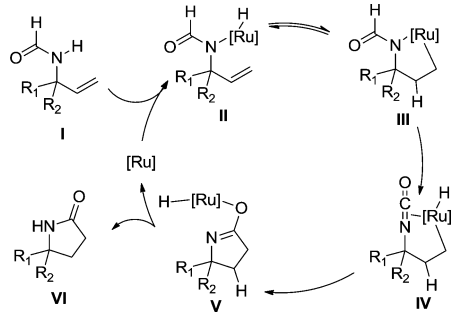
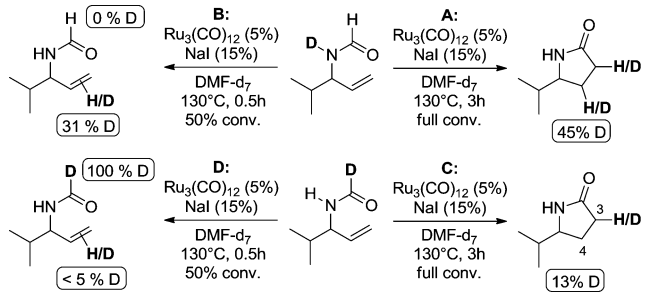


Figure 2. Proposed catalytic cycle.

reported for ruthenium−carbonyl clusters and has been shown to benefit from the additive effect of electron-rich ligands,[23] in particular halides.[24] Intermediate **II** is poised to undergo reversible insertion of the olefin to give **III**. This ruthenacycle can undergo *β*-hydride abstraction of the proximal formamide C−H bond to give **IV**, which is suggested to undergo attack of the nucleophilic alkyl moiety onto the electrophilic carbonyl carbon to give **V**. Finally, release of the product with proton transfer regenerates the active catalyst.

To gain additional mechanistic insight, we conducted a number of experiments with deuterium-labeled substrates (Scheme 2).[25] The use of the substrate with N−D in the cyclization reaction (Scheme 2, experiment A) afforded product with significant deuterium incorporation (45%) at C2 and C3. This observation suggests that olefin hydrometalation is reversible and nonselective, leading to label scrambling. Consistent with this result, when the reaction was interrupted at 50% conversion (experiment B), the olefin in the recovered starting material was shown to incorporate 31% deuterium label. We then repeated the same process for the substrate bearing C−D at the formyl carbon (experiments C and D). In the experiments, recovered substrate at 50% conversion showed

Scheme 2. Deuterium Labeling Experiments



no deuterium loss from the formyl position, indicating that breaking of the formyl C−H bond is irreversible in the catalytic cycle. In the product pyrrolidone, this label was only found to a minor extent on C(3) and not at all on C(4); the appearance of less than complete incorporation at C3 is consistent with the fact that C3 proton and deuterium in the product would be susceptible to exchange with the starting amide N−H (Figure 2).[26] In summary, the observations are in line with the mechanism involving initial activation of the N−H bond, as opposed to a direct activation of the formamide C−H bond.

In conclusion, we have reported a new intramolecular cyclization of allylic formamides. The reaction involves formal ruthenium-catalyzed insertion into the formamide C−H bond and concomitant C−C bond formation by olefin hydrocarbamoylation. The reaction exemplifies complete atom-economy since all atoms of the starting material are present in the product. Finally, the reaction presents a convenient method for the preparation of enantioenriched chiral pyrrolidones, particularly when used in conjunction with asymmetric allylic amination protocols.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectroscopic data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

carreira@org.chem.ethz.ch

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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