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# Pyrrolidine as a Cogwheel-Like Scaffold for the Deployment of Diverse Functionality Through Cycloaddition Reactions of Metallo-1,3-Dipoles in Aqueous Media

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**Abstract**—The reaction of glycinatocopper complexes with cinnamaldehydes under mildy basic aqueous conditions, affords polysubstituted prolines, which can be systematically modified in a number of chemoselective transformations. © 2000 Elsevier Science Ltd. All rights reserved.

Pyrrolidines and their substituted derivatives figure prominently in the structures of a large number of bioactive molecules (see, for example, refs 1 and 2). The presence of an α-carboxy group as in the ubiquitous proteinogenic amino acid L-proline,[3] extends the importance of the pyrrolidine ring into the realm of proteins with important consequences.[4–6]

There are a plethora of methods for the stereocontrolled synthesis of substituted pyrrolidines and prolines (for recent reviews see refs 7 and 8). Proline and pyroglutamic acid have been commonly used in conjunction with the synthesis of natural products (for selected examples, see refs 9–12), or compounds with pharmacological activities[13] (see also refs 14 and 15), such as enzyme inhibitors, agonists, and antagonists of receptors. The involvement of L-proline as a pivotal amino acid that confers conformational rigidity in peptide sequences has also instigated extensive studies in search of peptidomimetics[16–19] with improved biological profiles.

In spite of the large number of reported syntheses of pyrrolidines and prolines, few have addressed polyfunctionality (for selected syntheses of polysubstituted prolines, see refs 20–25) and diversity (for the generation of polyfunctional pyrrolidine libraries, see, for example, refs 26 and 27). We considered the pyrrolidine ring as an ideal template upon which to deploy diverse functional groups and pharmacophores. The resulting polyfunctionalized pyrrolidines could be viewed as a cogwheel-type scaffold with potential for interaction with biological receptors in a multivectorial dimension.

The condensation of glycinatocopper complexes with various electrophilic species under weakly basic conditions has been known for many years.[28] For example, the enolate generated from *N*-pyruvylideneglycinato copper II reacts with aldehydes to give β-hydroxy-α-amino acids.[29,30] Asymmetric versions of this reaction are also known.[31,32]

A lesser exploited reaction is the condensation of glycinato metal complexes with α,β-unsaturated carbonyl compounds. Casella and co-workers[33,34] reported cycloadditions of such complexes with activated olefins such as acrylonitrile, acrylates, and acrolein, to give substituted prolines as a mixture of diastereomers. Grigg and co-workers[35,36] also studied related cycloadditions with Cu(II), Zn(II) and Cd(II) complexes of *N*-pyruvylideneglycine, and concluded that the enolate formed under basic conditions constituted a metallo-1,3-dipole. They argued in favor of a concerted $4\pi + 2\pi$ cycloaddition with monosubstituted olefins, rather than a two-step Michael addition sequence as originally proposed[33,34] (for reviews on related cycloadditions, see refs 37–41) (Fig. 1).

We report our studies on the synthesis, characterization, and further functionalizations of tetra-substituted prolines arising from the reaction of *N*-pyruvylideneglycinato

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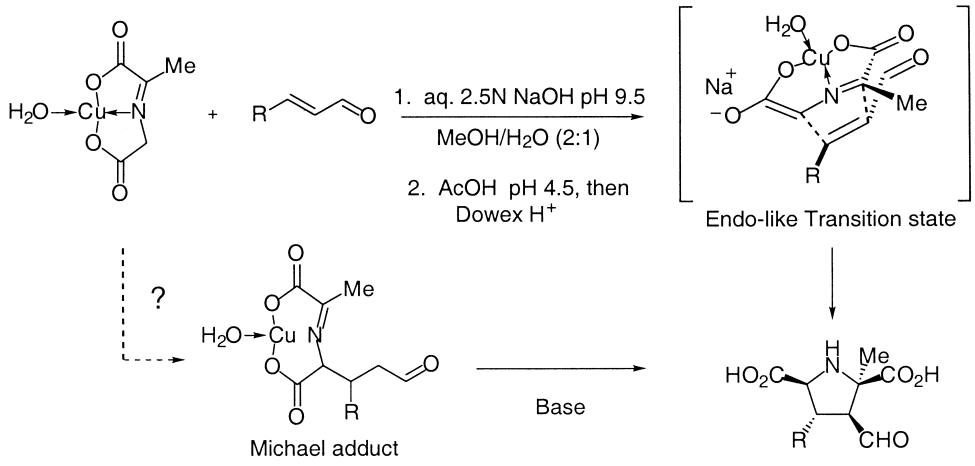
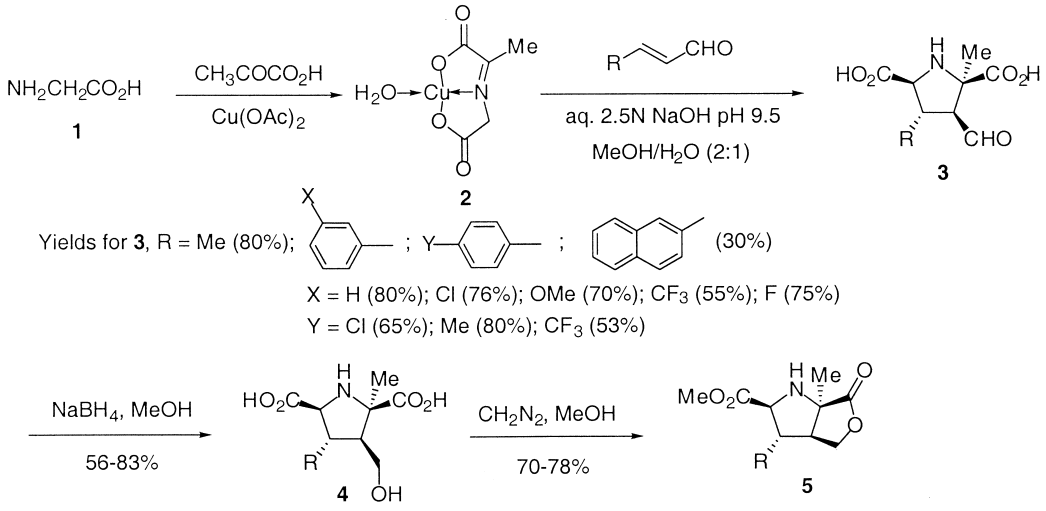



**Figure 1.** Concerted and stepwise reactions.



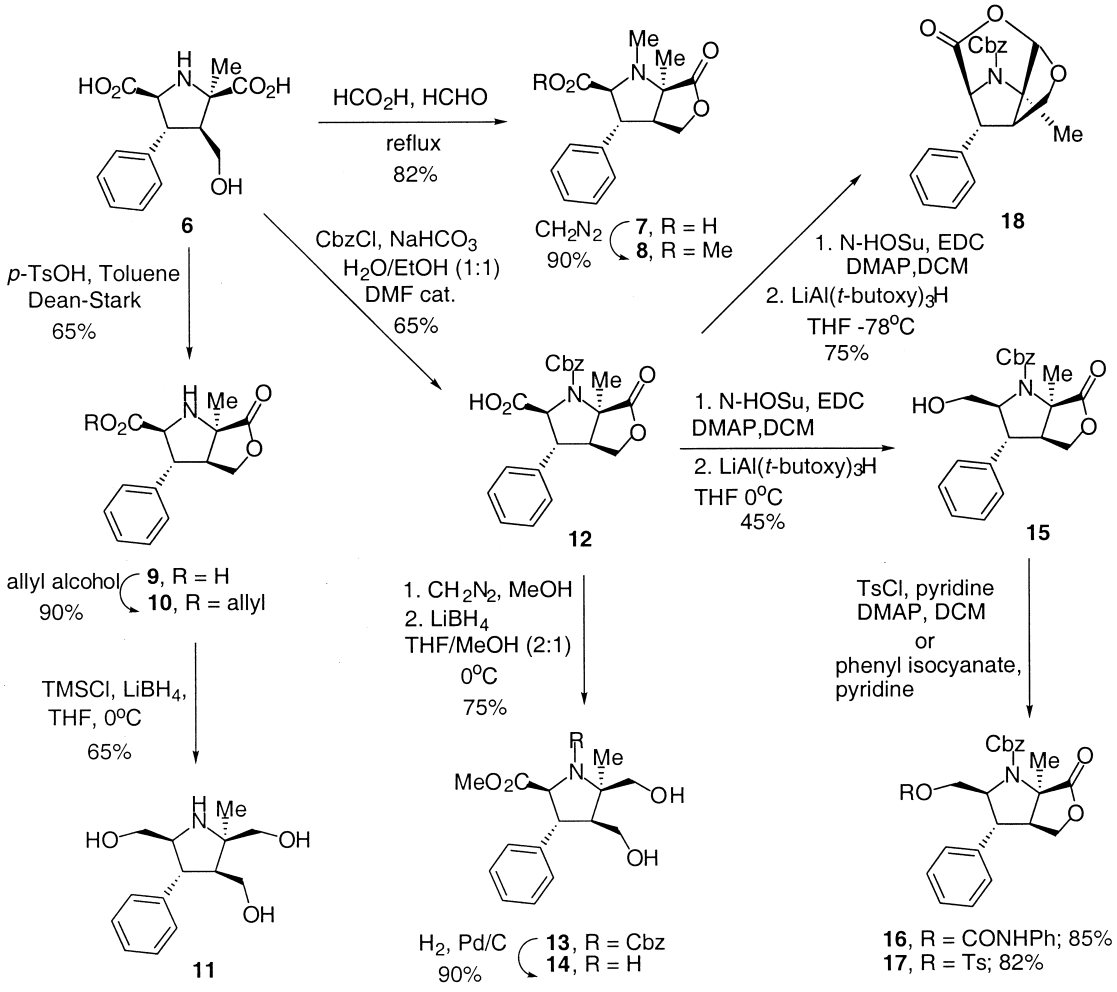

**Scheme 1.**

copper II complex with a variety of α,β-unsaturated aldehydes. Scheme 1 shows the generality of the cyclocondensation for a series of substituted cinnamaldehydes. Because the products are polyfunctional, we chose to study a number of chemoselective transformations that would differentiate the functional appendages and offer opportunities for further modification. Thus, each cycloadduct **3** was reduced to the corresponding alcohol, which was in turn esterified to the lactone esters **5**. With few exceptions, yields for each step were excellent and the isolation of intermediates was facile. The relative configuration of the cycloadducts was proven by detailed NOE studies and by an X-ray crystal structure of a derivative.

Subsequent chemical transformations were done with the phenyl analogue **6** as illustrated in Scheme 2. *N*-Methylation under Clarke–Eschweiler conditions led initially to the *N*-methyl lactone **7**, which could be esterified to **8**. In an effort to maintain the basic pyrrolidine NH intact, the lactone **9** was transformed into the allyl ester **10** and the latter reduced to the triol **11**.

In order to differentiate the carboxyl group from the vicinal *bis*-hydroxymethyl appendage, **6** was transformed into the *N*-Cbz derivative with concomitant lactonization to give **12**. Esterification and chemoselective reduction of the lactone gave the diol **13**, which could be successfully converted to the diol ester **14**, in which one of the original carboxyl groups was maintained.

The active ester derivative of **12** could in turn be chemoselectively reduced to the hydroxymethyl lactone **15**, which was easily functionalized as the phenylcarbamate **16** and the tosylate **17**, simply to demonstrate the potential for functionalization with the aim of introducing diversity. Surprisingly reduction of the active ester **12** at −78 °C led to an unusual tricyclic lactone acetal **18** in excellent yield (Scheme 2).



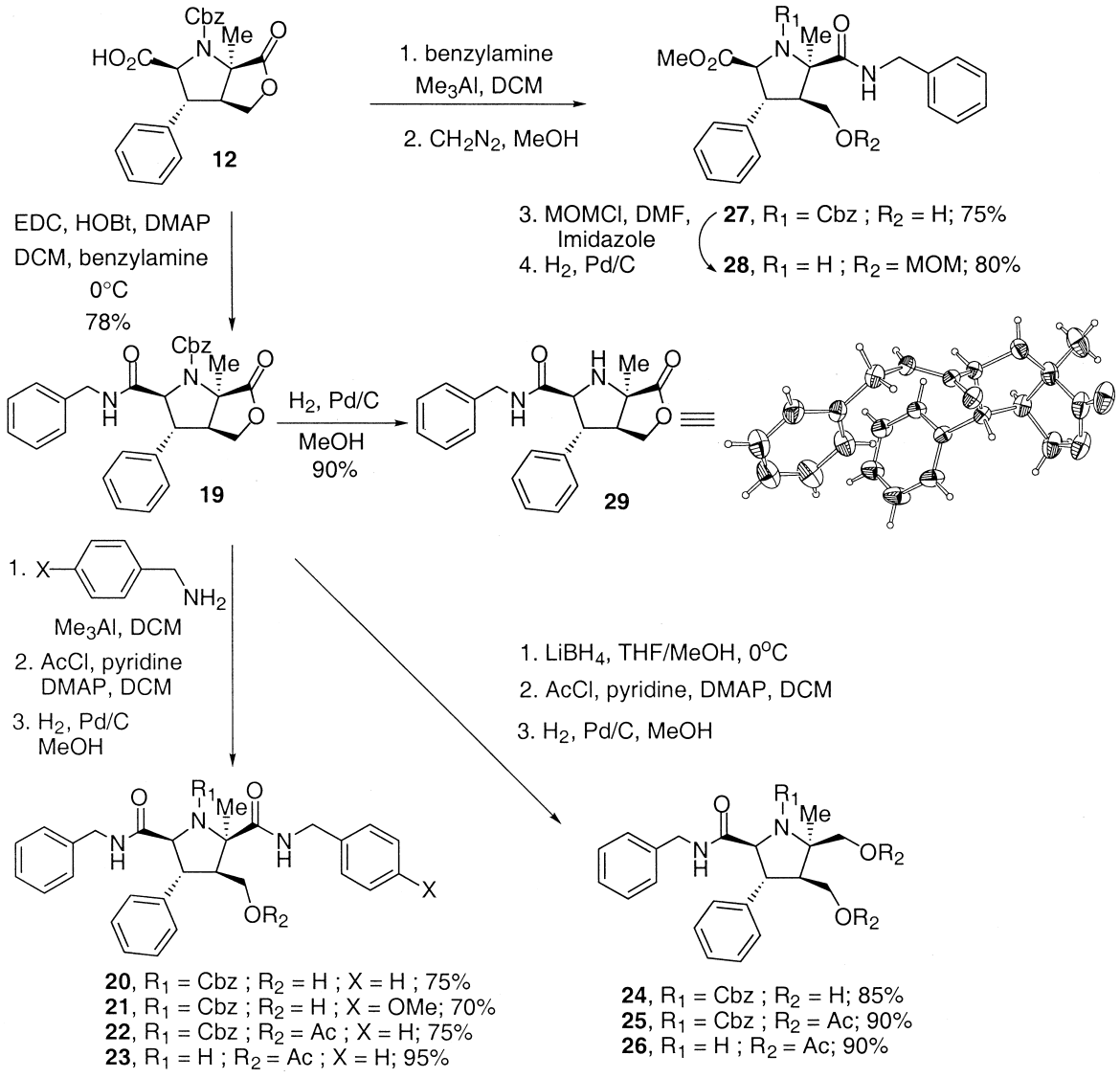

**Scheme 2.**

The availability of intermediates in which the carbonyl groups of the original diacid could be differentiated allowed us to explore diversity with amide appendages (Scheme 3). Thus, the free carboxylic group in **12** was readily transformed into the benzylamide **19**, which was subjected to lactone ring opening with other amines to give the mixed amides and their acetate esters **20–23**. Alternatively, esterification of the diol **24** resulting from the reduction of the lactone group in **19** led, as expected, to the diacetates **25–26.** The Cbz-group in **19** was removed to give the lactone amide analogue **29** cleanly. An X-ray crystal structure of **29** confirmed the configurational assignment of the cycloaddition products.

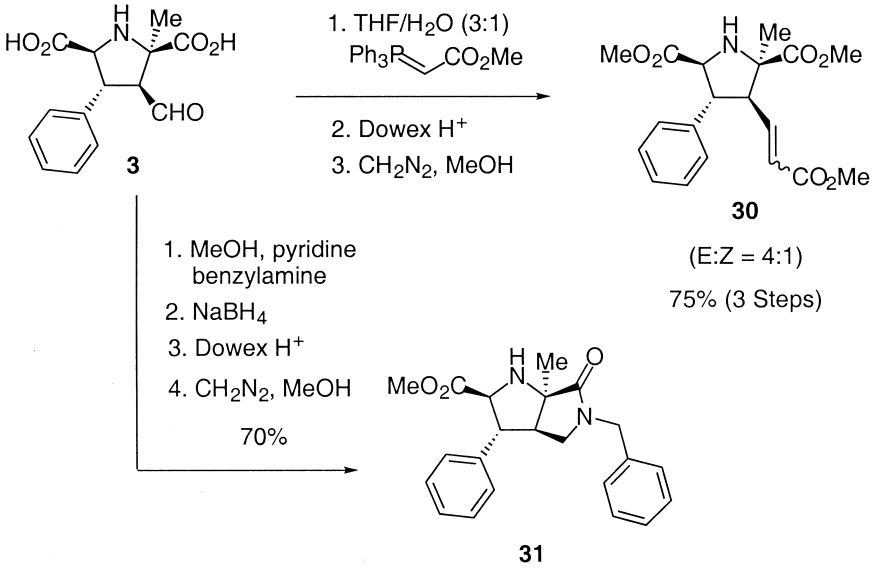
The order of amide formation could be changed by first opening the lactone in **12** with benzylamine to give **27** after esterification (Scheme 3). Transformation of the primary alcohol to the MOM ether and hydrogenolysis gave the pyrrolidine analogue **28**.

The presence of an aldehyde group in the original cycloadduct, suggested the exploration of a Wittig reaction with the aim of extending the substitution at that position. Indeed, treatment of **3** under conditions of the Wittig reaction in aq THF,[42,43] followed by esterification, gave the adduct **30** as a mixture of E/Z isomers (Scheme 4). Reductive amination on the other hand, followed by esterification led to the γ-lactam analogue **31** in excellent overall yield.

Taken individually, each of the transformations shown in the Schemes 2–4, represents a routine operation. However, the possibility to effect chemoselective reactions utilizing multiple functionality on the pyrrolidine scaffold offers a unique opportunity to explore diversity. Given the generality of the cycloaddition reaction (Scheme 1), many of these transformations can be done in a combinatorial protocol. Already, the products shown in Schemes 2–4 represent unique scaffolds deployed with a variety of functional groups as potential pharmacophores (amides, esters, ethers, carbamates, sulfonates, etc.) that may exhibit enzyme or receptor-based activity. Libraries of related pyrrolidines[20–25] can now be envisaged since the issues of compatibilities, chemoselectivities, and optimizations have been demonstrated in this work.[44] The synthesis and screening of a library of highly functionalized pyrrolidines




**Scheme 3.**




**Scheme 4.**

through cycloadditions on solid phase has been reported by the Affymax group.[26,27]

## Acknowledgement

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