

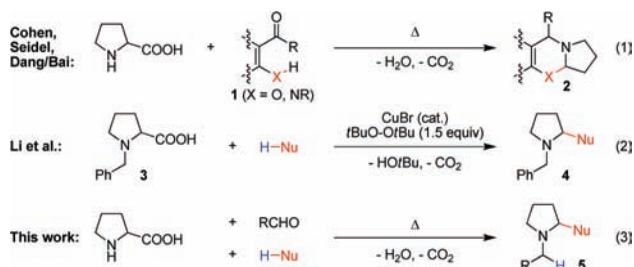
Nontraditional Reactions of Azomethine Ylides: Decarboxylative Three-Component Couplings of α -Amino Acids

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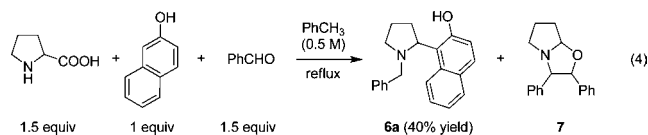
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Decarboxylative reactions of α -amino acids with carbonyl compounds were first reported in 1862 in what is now known as the Strecker degradation.¹ The intermediacy of azomethine ylides was first suggested by Rizzi² and later established by Grigg who provided detailed insights into the mechanism of dipole formation.³ Inter- and intramolecular [3+2] cycloadditions of azomethine ylides are widely used in synthesis.^{4,5} Here we report a three-component decarboxylative α -functionalization of amino acids that involves a new reaction pathway for azomethine ylides.



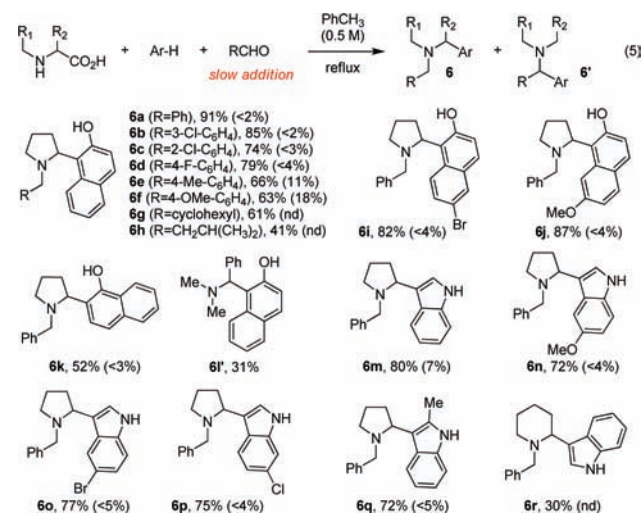
The potential of azomethine ylides to engage in nonpericyclic reactions has not yet been evaluated to an appreciable extent. One such reaction is that of proline with sterically congested 2-hydroxyacetophenones to form products **2** ($R = \text{Me}$, $X = \text{O}$, eq 1), previously reported by Cohen.⁶ We recently reported the reaction of aminobenzaldehydes (e.g., **1**, $R = \text{H}$, $X = \text{NH}$) with proline as part of a study on the formation of amins via redox neutral reactions between secondary amines and aminobenzaldehydes.^{7a} Subsequently, a related reaction was described by Dang and Bai.⁸ Concurrently, Li and co-workers reported interesting reactions of *N*-benzylated amino acids (e.g., **3**) with various nucleophiles (eq 2).⁹ These decarboxylative reactions require superstoichiometric amounts of oxidant and a metal catalyst while giving rise to synthetically useful products **4**.¹⁰ Azomethine ylides, possibly bound to a metal catalyst, were proposed as intermediates in this reaction. Given our interest in developing redox-neutral transformations^{7,11} and due to the growing appreciation for redox economy,¹² we were intrigued by the idea of using in situ generated azomethine ylides in related reactions with what would constitute nontraditional dipolarophiles (eq 3).¹³



We began our studies by evaluating the reaction between proline, benzaldehyde, and β -naphthol (eq 4). Simple heating of a mixture of the three components in toluene at reflux led to the formation of the desired product **6a**, albeit in only 40% yield. Not surprisingly, ¹H NMR analysis of the crude reaction mixture indicated the presence of significant quantities of the known compound **7**,¹⁴

resulting from the [3+2] cycloaddition of the intermediate azomethine ylide with excess benzaldehyde. Formation of the undesired compound **7** could be suppressed completely by delivering the aldehyde slowly via syringe pump over 18 h. In this instance, product **6a** was isolated in excellent yield (91%). Additionally, trace amounts of a regioisomeric product were observed (*vide infra*). The scope of this reaction is summarized in Chart 1. Proline and other amino acids readily underwent three-component reactions with aromatic or aliphatic aldehydes and different naphthol and indole derivatives. In most cases, the desired regioisomer **6** was strongly preferred over **6'**. Interestingly, *N*-methyl indole, generally considered a stronger nucleophile as compared to unsubstituted indole,¹⁵ did not participate in this reaction. A reaction with sarcosine resulted in the exclusive formation of **6l**.

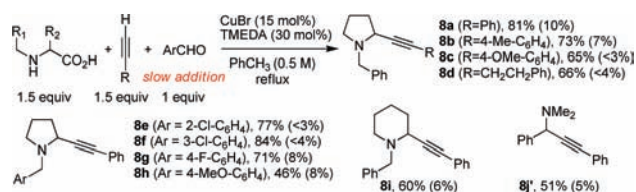
Chart 1. Reactions of Azomethine Ylides with Naphthols and Indoles^{a,b}



^a Reactions were performed on a 1 mmol scale. The aldehyde was added via syringe pump over 18 h. The yields for the regioisomeric products are given in parentheses. ^b 1.3 equiv of each, amino acid and aldehyde was used.

In another set of experiments, we evaluated alkynes as nucleophiles in this process (Chart 2). Catalytic amounts of CuBr and tetramethyl ethylenediamine (TMEDA) were employed to generate copper acetylides which function as the active nucleophiles in this process. As in the case of indoles and naphthols, no oxidant or preformed *N*-alkylamino acid derivatives were required. Terminal alkynes readily underwent decarboxylative coupling reactions with proline and different benzaldehydes. Pipecolic acid and sarcosine were also viable substrates in this reaction, and good regioselectivities were observed in most cases.¹⁶

Nitroalkanes also engaged in reactions with azomethine ylides (eq 6). Compounds **9** were isolated in moderate yields; only one regioisomeric product was observed in each case.

Chart 2. Reactions of Azomethine Ylides with Alkynes^a

^a See footnote a in Chart 1.

A proposed mechanism for the decarboxylative three component coupling reaction is outlined in Figure 1. Condensation of proline with an aldehyde results in the formation of oxazolidin-5-one **10**, a known intermediate in the subsequent decarboxylative formation of the azomethine ylide **11**.^{3d} Protonation of the dipole by the pronucleophile H–Nu results in the formation of ion pairs **12** or **12'** which then collapse into products **5** or **5'**. A concerted pathway for the direct transformation of **11** into **5** or **5'** cannot be ruled out for certain substrates. This proposed mechanism readily explains the formation of the two regioisomers and suggests that the regioselectivity of this reaction depends on the charge distribution in the azomethine ylide **11**, in addition to potential steric factors. R-groups with electron-withdrawing character appear to stabilize dipoles with a higher partial negative charge in the benzylic position. This favors protonation of the benzylic position and ultimately leads to the formation of regioisomer **5**, in accordance with what was observed for the *m*-Cl-phenyl bearing product **6b**. In contrast, azomethine ylides bearing aromatic R-groups with electron-donating character gave rise to the formation of an increased amount of the regioisomer **5'**, which was the case for the *p*-MeO-phenyl bearing substrate **6f**. However, even in the latter case, regioisomer **5** was still formed predominantly.

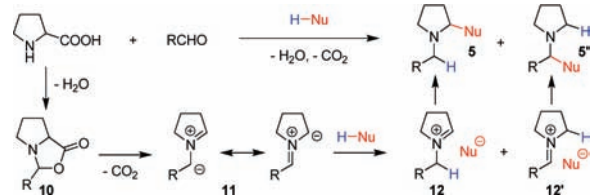
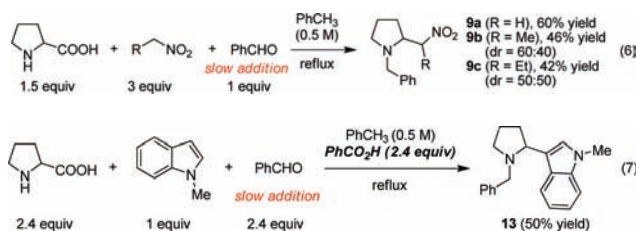


Figure 1. Proposed mechanism for the reaction of azomethine ylides with pronucleophiles.



The mechanism depicted in Figure 1 provides a satisfying explanation for the failure of *N*-methylindole to engage in this reaction. If the protonation of dipole **11** is indeed a prerequisite for nucleophilic attack, the scope of this reaction might be extended to other nucleophiles simply by addition of an acid promoter. The latter could serve to protonate dipole **11**, form an iminium ion related to **12**, and subsequently react with nucleophiles that would otherwise fail to add to azomethine ylides. Indeed, in the presence of benzoic acid, reaction of *N*-methyl indole with proline and benzaldehyde gave rise to the formation of product **13** in 50% yield (eq 7).¹⁷

In summary, we have introduced a new mode of reactivity for azomethine ylides. The latter act as a convenient source for iminium

ions for Friedel–Crafts type alkylations, Mannich reactions, and alkylation. Widespread application of these and related reactions is anticipated as they offer an opportunity for the rapid generation of molecular complexity.

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Supporting Information Available: Experimental procedures and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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