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A proline-catalyzed asymmetric Robinson annulation reaction

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Abstract

A single-step enantioselective synthesis of the Wieland–Miescher ketone (**5**) is presented. We show that L-proline as well as a number of other chiral amines can act as catalysts of both steps of the Robinson annulation reaction. Other chiral amines are identified as catalysts of Michael and aldol addition reactions.

Enantiopure Wieland–Miescher (W.M.) ketone (**5**) has proven to be a particularly useful synthon for the construction a variety of biologically active compounds including steroids, terpenoids, and more recently taxol.[1] We recently disclosed an antibody aldolase-catalyzed Robinson annulation reaction of 2-methylcyclohexane-1,3-dione with methyl vinyl ketone in aqueous medium.[2] This one-flask annulation provided the W.M. ketone in $>95\%$ ee. While the antibody efficiently catalyzed the cyclodehydration step of this reaction with a rate enhancement exceeding 10^6, catalysis of the alkylation or Michael addition step was very modest, $k_{cat}/k_{un} = 125$. An intriguing aspect of this study was that both antibody and the traditional catalysts for W.M. ketone preparation, L-proline, use an enamine-based reaction mechanism. Provided the success of antibody catalysis of both steps of the annulation reaction and the reported utility of rubidium salts of L-proline in asymmetric Michael addition reactions,[3] we examined the potential of L-proline to catalyze the entire annulation reaction. We anticipated that the Michael addition step could be facilitated by formation of the proline-imine of **1**, the enamine of **2**, or both. To examine the general potential of chiral amine catalysis of these reactions, we have also screened a library of chiral amines using this transformation as the read out.

While routes to enantiopure W.M. ketone continue to be developed,[4] the most convenient synthesis involves modest modifications of the procedure first developed in the early 1970s.[5] In the optimized procedure,[6] 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (**3**) is prepared by heating 2-methylcyclohexane-1,3-dione (**2**) with methyl vinyl ketone (**1**) in aqueous acetic acid at 75°C for 1 h after which **3** is purified. The cyclodehydration of **3** catalyzed by L-proline is then performed at 25°C by simple stirring under argon for 120 h. Enantioselection in the cyclization

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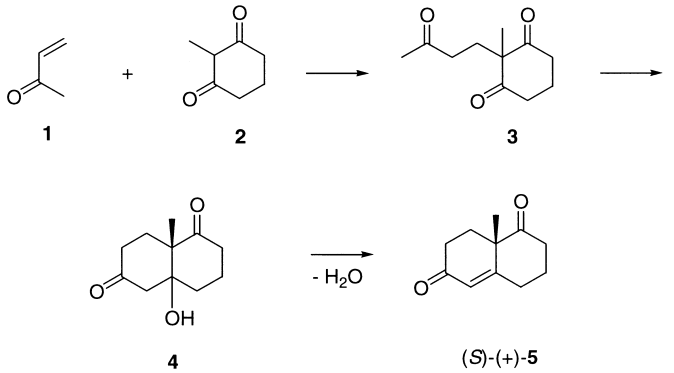
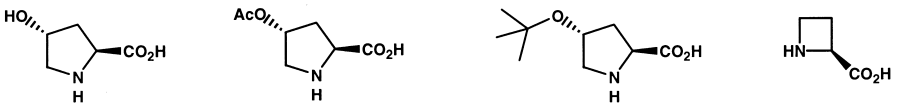
step of pro-chiral **3** en route to **5** is in the order of 70% ee. Fractional crystallization then provides the desired (*S*)-antipode of **5** with high enantiopurity.

To examine the potential of L-proline to achieve the entire Robinson annulation sequence (**1**+**2**→**5**), a variety of reaction conditions were explored that involved changes in the molar ratios of **1** and **2**, solvent, and temperature. These studies yielded a single-step annulation that provided **5** in 49% yield and 76% ee in 89 h.[7] Thus, like the mechanistically similar catalytic antibody, proline can also catalyze the entire annulation sequence providing the W.M. ketone more rapidly and with an overall yield and enantiomeric purity similar to that of the two-step reaction sequence (Scheme 1).

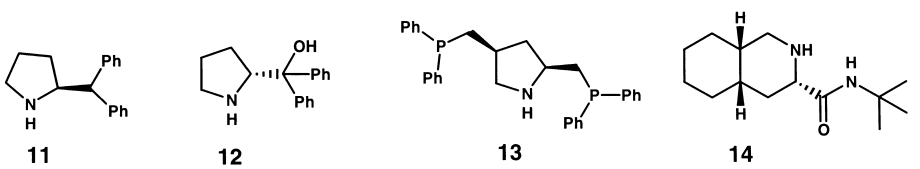


Scheme 1.

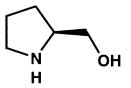
We then studied the potential of other commercially available proline-like derivatives for their ability to catalyze this reaction sequence.[8] Compounds **7**–**10** demonstrated an activity similar to proline in the transformation (**1**+**2**→**5**). Compounds **7**–**9** provided **5** with ee's ranging from 60 to 75%, while **10** provided the product with considerably lower optical purity, $<10\%$ ee. Several other amino acids containing primary amines were not catalysts of this transformation.



To further examine the potential for amine catalysis of this reaction sequence, we screened 16 additional commercially available chiral amines.[8] Of these compounds only those bearing a cyclic secondary amine demonstrated reactivity in this screen and these catalysts could be placed into two classes. The first class of catalysts consists of compounds **11**–**14**. These compounds were shown to catalyze the Michael addition reaction of (**1**+**2**→**3**). In these reactions products **4** and **5** were not detected.



The second class of catalysts consists of compounds **15**–**18**. These compounds were shown to catalyze the transformation (**1**+**2**→**3**+**4**) but not the dehydration of **4** to **5**. In independent assays, these catalysts were active in the transformation of **3** to **4**, where again formation of **5** was not observed.[9] Examination of the structure/activity relationships of the catalysts reported here, suggests that chiral compounds containing a secondary amine of the pyrrolidine-type and a carboxylate functionality are the most efficient catalysts of this asymmetric annulation reaction. The carboxylic acid functionality appears to be key to the dehydration step, at least when the reactions are performed at ambient temperatures.



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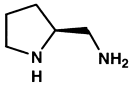

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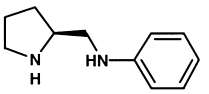

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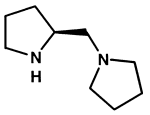

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In summary, chiral secondary amines, particularly pyrrolidine-like molecules are catalysts of Michael and aldol reactions.[10] We believe the potential of molecules such as these to act as asymmetric organic catalysts has not been sufficiently exploited. Our proline-catalyzed direct asymmetric aldol reaction,[11] MacMillan's amine-catalyzed asymmetric Diels–Alder reaction,[12] and the Robinson annulation reaction reported here are recent examples of asymmetric amine catalysis facilitated by imine and enamine type reaction mechanisms. These results underscore an interplay between mechanistic enzymology and asymmetric organic catalysis that may enable the creation of diverse and efficient organocatalysts for a wide variety of reactions.[13]

Acknowledgements

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7. A solution of L-proline (0.32 g, 2.8 mmol) and 2-methyl-1,3-cyclohexadione (1 g, 7.9 mmol) in 50 mL of anhydrous DMSO was stirred under argon at 35°C until the ketone and proline were completely dissolved. To this solution freshly distilled methylvinyl ketone was slowly added dropwise (0.99 mL, 11.9 mmol). The reaction was vigorously stirred at this temperature for 89 h and then quenched with ethyl acetate/saturated ammonium chloride. The organic layer and aqueous layer were separated with an addition of brine. The aqueous phase was extracted several times with ethyl acetate, and combined organic extracts were dried over magnesium sulfate, filtered, and evaporated in vacuo. Crude product was purified by column chromatography using hexane:ethyl acetate (3:2, then 1:1) to afford the ketone (0.69 g) as a syrup in 49% yield and 76% ee. Optical purity was determined as previously described.[2a] Optical yield was maintained in reactions performed up to 35°C and decreased at higher temperatures.
8. Screening reactions were performed essentially as described above but at ambient temperature using 30 mol% catalyst. L-α-Methyl-benzylamine and several other amino acids have previously been shown to be catalysts of the aldol addition and or condensation step, see Refs. 5a and 1a.
9. With catalyst **18**, a small amount of **5** was detected.
10. The use of pyrrolidine as a reagent for the conversion of **3** to **±5** was reported many years ago, see: Ramachandran, S.; Newman, M. S. *Org. Synth.* **1961**, *41*, 38.
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13. We have now determined that several of the catalysts reported here can be used to catalyze direct intermolecular asymmetric aldol and Mannich reactions. The results of these studies will be reported in due course.