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Enantioselective Synthesis of α-Quaternary Mannich Adducts by Palladium-Catalyzed Allylic Alkylation: Total Synthesis of (+)-Sibirinine

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Supporting Information

ABSTRACT: A catalytic enantioselective method for the synthesis of α-quaternary Mannich-type products is reported. The two-step sequence of (1) Mannich reaction followed by (2) decarboxylative enantioselective allylic alkylation serves as a novel strategy to in effect access asymmetric Mannich-type products of "thermodynamic" enolates of substrates possessing additional enolizable positions and acidic protons. Palladium-catalyzed decarboxylative allylic alkylation enables the enantioselective synthesis of five-, six-, and seven-membered ketone, lactam, and other heterocyclic systems. The mild reaction conditions are notable given the acidic free N−H groups and high functional group tolerance in each of the substrates. The utility of this method is highlighted in the first total synthesis of (+)-sibirinine.

The Mannich reaction, first discovered in the early 20th century, is among the most robust reactions known to produce nitrogen-containing compounds. In a classic intermolecular Mannich reaction, an aldehyde, an amine, and an α-acidic carbonyl compound react to form a β-amino carbonyl compound.[1] Recent progress in this area, including modified imine donors and well-explored catalyst systems, has made available a wide variety of asymmetric α-functionalizations of carbonyl compounds.[2] To date, asymmetric Mannich-type reactions to establish α-quaternary carbonyl compounds have been limited to stabilized enolates[3] (e.g., 1,3-dicarbonyl compounds). To our knowledge, the lone exception is a proline-catalyzed Mannich reaction with branched aldehydes.[4] Despite the importance of the Mannich reaction, only a handful of asymmetric α-aminomethylation reactions have been reported.[5] Enders et al.[5a] employed enantiomerically pure α-silyl ketones for regio- and diastereoselective syntheses of Mannich bases. Córdova et al.[5c] developed a proline-catalyzed asymmetric Mannich reaction that provides α-aminomethylated α-tertiary ketones in excellent enantioselectivities. The only example of enantioselective all-carbon quaternary center formation in this area is the palladium(II)-catalyzed aminomethylation of β-keto esters (i.e., **II**, R = CO_2t-Bu) performed by Sodeoka et al.;[5d] however, the reported enantioselectivities are only moderate (up to 68% ee). To date, there are no reports of enantioselective catalysis leading to α-quaternary aminomethyl "Mannich" adducts bearing only a single carbonyl moiety (i.e., **II**, R = alkyl).

The regioselectivity of enolate formation, potential subsequent enolization, and difficulty in controlling enantioselectivity under conditions that proceed through the thermodynamically favorable enolate all pose significant challenges to those trying to access enantioenriched α-quaternary Mannich adducts[6] of α-alkyl-substituted ketones (Figure 1A). To overcome these challenges, we envisioned a strategy wherein the alkylation, not the aminomethylation, would be performed last (Figure 1B).

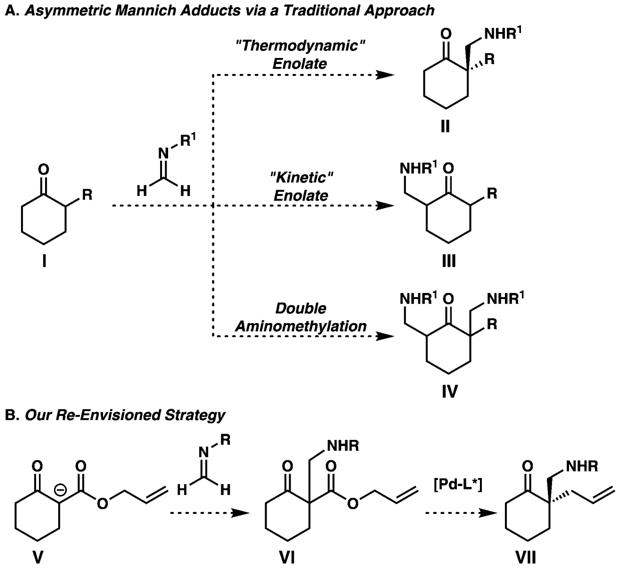

Figure 1. Contrasting approaches to access α-quaternary "Mannich" products.

Over the course of the past decade, our group has demonstrated decarboxylative palladium-catalyzed asymmetric alkylation of β-keto esters as a powerful tool to access quaternary centers with high enantioselectivities.[7] The extensive substrate scope and broad functional group compatibility of this transformation[8,9] encouraged further exploration of palladium catalysts in the synthesis of amine-containing substrates, thereby facilitating access to enantioenriched bioactive alkaloids or pharmaceutical candidates. We therefore sought to implement our well-studied, reliable

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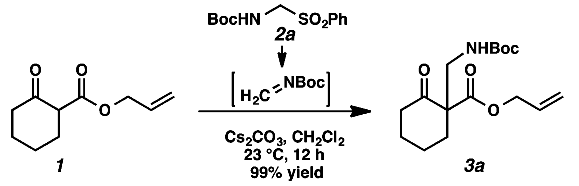
alkylation chemistry in a simple yet powerful strategy for the synthesis of α-quaternary Mannich products in an enantioselective fashion. Our plan is outlined in Figure 1B. Introduction of an aminomethyl group to β-keto ester **V** using classical Mannich chemistry (**V** to **VI**), followed by an asymmetric allylic alkylation reaction, would provide the enantioenriched α-quaternary ketone product **VII**. Compound **VII** can be thought of as an α-aminomethylation product of the so-called "thermodynamic" enolate of compound **I**. We imagined that successful exploration of this inverted strategy would enable rapid, stereocontrolled total syntheses of (−)-isonitramine and (+)-sibirinine.[10−12]

To introduce the aminomethyl moiety, we employed sulfonylmethyl carbamates (e.g., **2a**) as versatile and readily available imine precursors.[13] In the presence of Cs_2CO_3, the Boc-protected imine generated from **2** reacted with β-keto ester **1**[14] to smoothly afford β-aminoketone **3a**, quantitatively, at ambient temperature (Scheme 1). In a similar manner, we obtained other protected aminoketones **3b−g** in good to excellent yields.[15]

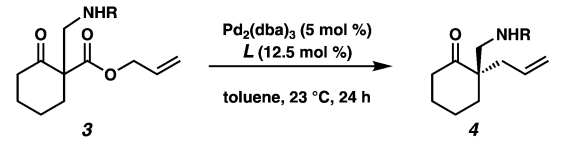
Scheme 1. Synthesis of β-Keto Ester 3a

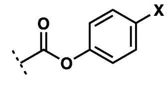


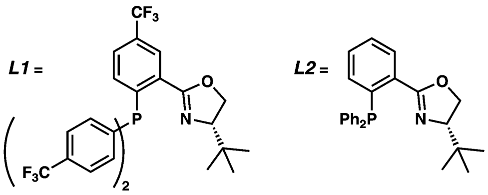
With β-keto esters **3a−g** in hand, our investigation into this substrate class commenced in the context of palladium-catalyzed allylic alkylation as shown in Table 1. We found that exposure of Boc-protected substrate **3a** to a catalytic phosphinooxazoline[16]−palladium(0) complex in toluene at ambient temperature afforded the desired product **4a** in 94% yield and 86% ee (entry 1). Cbz-protected **3b** also gave an excellent yield and ee (entry 3). It is important to note that we did not detect any *N*-alkylated side products, a result that highlights the mild nature of our reaction conditions.[17] Arylcarbamates **3c−e** gave slightly decreased enantioselectivities in the products (entries 4−6). Changing from carbamate to benzoyl or tosyl protecting groups resulted in poor ee (entries 7, 8) presumably due to their ability to coordinate to the catalyst and/or the enhanced acidity of the N−H proton. We found that the more electron-withdrawn ligand, **L1**, gave higher enantioselectivity. In the case of (*S*)-*t*BuPHOX **L2** (Table 1, entry 2), we observed diminished ee.

As outlined in Table 2, we have found that a broad range of ketones and amides (e.g., **5a-g**) can easily be converted into enantioenriched tetrasubstituted Mannich-type products (e.g., **7a−i**) with this two-step strategy. For all substrates, the first step proceeded in good to excellent yields (72−99%). In the allylic alkylation, 2-phenyl-2-propenyl-substituted **7a** was obtained in high yield (91%) and excellent enantioselectivity (90% ee). Cycloheptanone **6b** proved to be a good substrate and the corresponding α-quaternary cycloheptanone **7b** was isolated in 93% yield and 87% ee, while cyclopentanone **6c** gave a slightly lower enantioselectivity (82% ee). Vinylogous ester **6d** and tetralone **6e** afforded α-quaternary vinylogous ester **7d** and tetralone **7e** in 70% yield and 92% ee, and 74% yield and 93% ee, respectively. Heterocyclic ketone scaffolds were found to be competent substrates for this transformation, as 4-

Table 1. Optimization of the Amine Protecting Group[a]

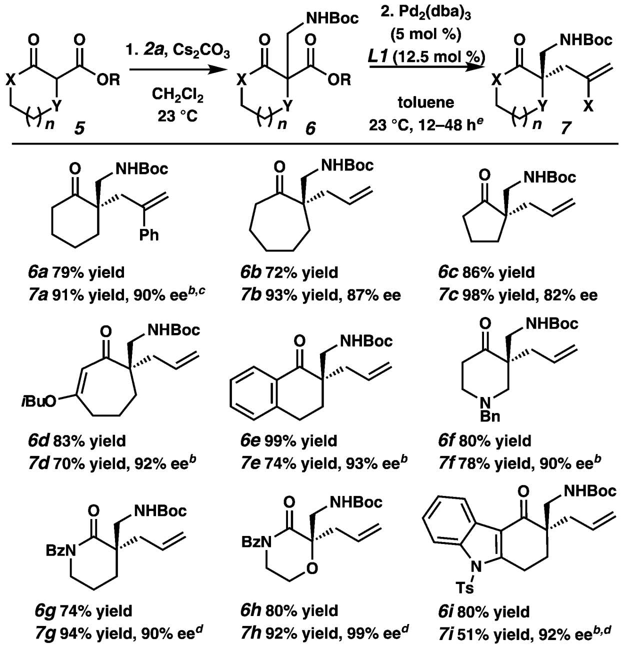


entry	R (3→4)	ligand	yield (%)	ee (%)[b]
1	Boc (*3a*→*4a*)	*L1*	94	86
2	Boc (*3a*→*4a*)	*L2*	ND[c]	80
3	Cbz (*3b*→*4b*)	*L1*	96	86
4	 X = OMe (*3c*→*4c*)	*L1*	91	83
5	X = H (*3d*→*4d*)	*L1*	90	77
6	X = F (*3e*→*4e*)	*L1*	84	77
7	Bz (*3f*→*4f*)	*L1*	ND[c]	56
8	Ts (*3g*→*4g*)	*L1*	54	24



[a]Reaction performed with 0.2 mmol of **3**, 5 mol % of $Pd_2(dba)_3$ (dba = dibenzylideneacetone), 12.5 mol % of ligand at 0.033 M in toluene at 23 °C. [b]Determined by chiral SFC analysis. Absolute stereochemistry has been assigned by anology,[8] except in entry 3, which was assigned by conversion into (−)-isonitramine. [c]A yield was not determined.

Table 2. Two-Step Synthesis of α-Aminomethyl Carbonyl Compounds from β-Oxo Esters[a]

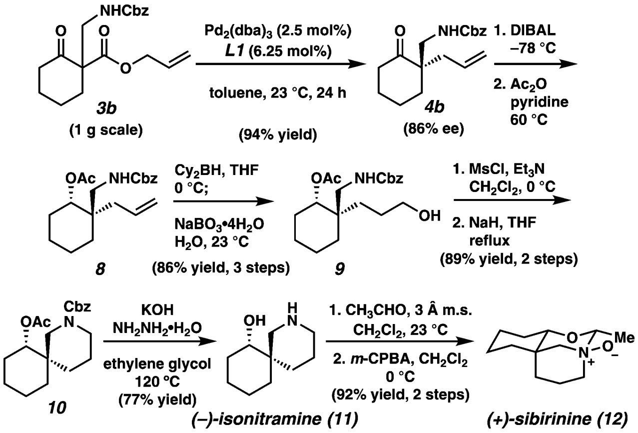


[a]Reaction conditions for step 2: **6** (1 equiv), $Pd_2(dba)_3$ (5 mol %), and **L1** (12.5 mol %) in toluene (0.033 M) at 23 °C for 12−48 h. [b]$Pd_2(pmdba)_3$ (pmdba = bis(4-methoxybenzylidene)acetone) was used instead of $Pd_2(dba)_3$. [c]Enantiomeric excesses were determined by chiral SFC analysis. [d]Reactions were performed on **6g**, **6h**, and **6i** at 40 °C. [e]For individual reaction times, see Supporting Information.

piperidinone **7f** was isolated in 78% yield and 90% ee. Lastly, we were pleased to find that, under slightly elevated reaction temperatures (40 °C), the desired lactam **7g**, morpholinone **7h**, and carbazolone **7i** were obtained in moderate to excellent yields (51−94%) and excellent enantioselectivities (90−99% ee).

In order to exhibit the utility of our method for generating interesting and useful chiral building blocks, the first total synthesis of (+)-sibirinine (**12**) was carried out (Scheme 2).

Scheme 2. Natural Product Synthesis



(+)-Sibirinine is a tricyclic alkaloid featuring an *N*,*O*-acetal, a tertiary amine *N*-oxide, and two pairs of vicinal stereocenters, including an all-carbon quaternary center. Asymmetric allylic alkylation using 1 g of **3b** proceeded with one-half of the typical catalyst loading without any loss of enantioselectivity. Reduction of *β*-amino ketone **4b** with diisobutylaluminum hydride (DIBAL), followed by acetylation of the resulting alcohol, yielded carbamate **8** as a single diastereomer. Hydroboration of the terminal alkene in carbamate **8** provided primary alcohol **9** in 86% yield over three steps. Cyclization of the mesylate derived from primary alcohol **9** smoothly delivered spirocycle **10**. Removal of the acetyl and Cbz groups using potassium hydroxide furnished (−)-isonitramine (**11**) in 77% yield. Treatment of (−)-isonitramine (**11**) with excess acetaldehyde yielded the desired hemiaminal, which was smoothly oxidized by *m*-CPBA to give (+)-sibirinine (**12**) in 92% yield over two steps. Notably, conversion of (−)-isonitramine to (+)-sibirinine can be accomplished in one pot by forming the hemiaminal intermediate under an oxygen atmosphere, albeit in diminished yield. Spectral data of **11** and **12** were identical to those previously reported.[11,12] Our synthesis of (−)-isonitramine confirms the absolute stereochemistry of **4b**.[11]

In summary, we have developed an inverted approach to the synthesis of *α*-quaternary and tetrasubstituted tertiary Mannich-type products by strategic enolate formation to give products in moderate to excellent yields and good to excellent ee. This chemistry tolerates a variety of ketone, amide, and vinylogous ester functionalities even in the presence of basic tertiary amines and relatively acidic N−H moieties. Multiple ring sizes as well as aromatic and heteroaromatic scaffolds are also accessible via this strategy. Furthermore, this method enables the efficient construction of spirocyclic amine-containing scaffolds, as illustrated in our synthesis of the alkaloids (−)-isonitramine and (+)-sibirinine. The first total synthesis of (+)-sibirinine was accomplished in 11 steps and 36% overall yield from commercially available diallyl pimelate. Further studies expanding the scope and applications of this two-step Mannich-like methodology are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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