

Direct Catalytic Asymmetric Mannich Reactions for the Construction of Quaternary Carbon Stereocenters

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S Supporting Information

ABSTRACT: Herein, we report a Zn-ProPhenol catalyzed Mannich reaction using α -branched ketones as nucleophilic partners for the direct enantio- and diastereoselective construction of quaternary carbon stereocenters. The reaction can be run on a gram-scale with a low catalyst loading without impacting its efficiency. Moreover, the Mannich adducts can be further elaborated with complete diastereocontrol to access molecules possessing complex stereotriads.

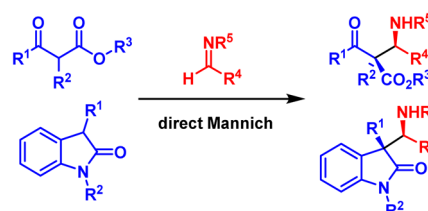
One of the modern challenges for the synthetic chemist is the fast, selective, and atom-economic access to molecular complexity starting from simple and widely available starting materials.¹ The Mannich reaction is an important tool for C–C bond formation.² Moreover, it is also one of the most robust ways to produce nitrogen-containing compounds which are ubiquitous in nature. All-carbon quaternary stereocenters are also a common feature of natural products, and their construction still represents a synthetic challenge, especially in a catalytic enantioselective fashion.³ In this context, we report herein the first direct asymmetric Mannich reaction that allows the use of α -branched ketone donors. This atom-economic transformation provides an efficient enantio- and diastereoselective access to chiral β -amino ketones decorated with a quaternary carbon stereocenter.

The Mannich reaction was discovered in the early 20th century and has received a lot of attention, especially in the context of the total synthesis of alkaloids.⁴ Despite its synthetic importance, the first examples of catalytic enantioselective Mannich reaction only appeared in the late 1990s.⁵ These reactions require preformed enolates such as silyl enol ethers that are reacted with an imine activated by a chiral Lewis acid catalyst. One serious drawback of this approach is the preparation and the instability of the preformed enolates. A more effective and atom-economic approach was later introduced by directly using an unmodified carbonyl donor.⁶ This strategy really became popular with the advent of organocatalysis.⁷ Bimetallic catalysis has also emerged as a powerful way to perform direct enantioselective Mannich reactions.⁸ However, the use of ketones as donors for such reactions is so far limited to methyl ketones, cyclohexanones, or α -hydroxyketones.^{6–9}

The formation of α -quaternary carbonyl compounds using a direct Mannich reaction has been limited to the use of easily enolizable ketones¹⁰ such as 1,3-dicarbonyl compounds¹¹ or 3-substituted oxindoles¹² (Scheme 1a). To the best of our

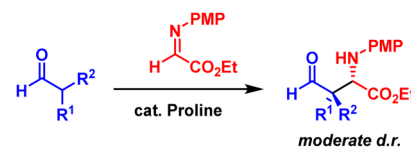
Scheme 1. Direct Mannich Reactions Forming Quaternary Carbon Stereocenters

a) Stabilized enolates

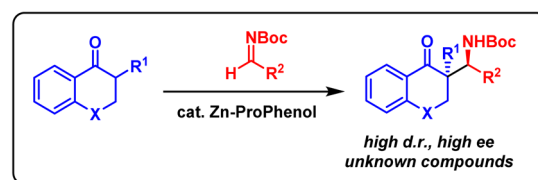


b) Non-stabilized enolates

Only reported example, Barbas and coworkers:



This work:



knowledge, the lone exception is a proline-catalyzed reaction using branched aldehydes developed by Barbas and coworkers¹³ (Scheme 1b). However, this reaction proceeds with poor to moderate diastereoselectivities and is restricted to the use of *N*-PMP-protected glyoxylate ethyl ester as acceptor. In this respect, we wished to develop the first direct catalytic enantioselective Mannich reaction allowing the use of a broad array of α -branched aromatic ketones together with a broad range of imine acceptors.

The ProPhenol ligand is part of the aza-hemicrown family of ligands and forms dinuclear main group metal catalysts when treated with alkyl metal reagents such as Et_2Zn . The Zn-ProPhenol catalytic system has proven to be particularly efficient for a range of enantioselective aldol and Mannich reactions.^{8c} However, the scope of donors that is compatible with this catalytic system is mostly limited to methyl ketones (acetophenones, acetone, methyl vinyl ketone, methyl ynone) or unsubstituted α -hydroxy carbonyl compounds. Very

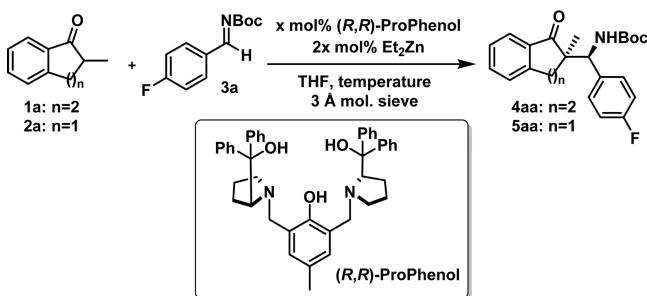
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recently, we reported the use of more substituted ketones¹⁴ for Mannich-type reactions, but so far, the formation of quaternary stereogenic centers using this strategy has remained elusive.

Our recent work with fluorinated aromatic ketones^{14a} led us to wonder about the special importance of the fluorine atom concerning the reactivity/selectivity for this Mannich reaction. Could α -branched ketones substituted with simple alkyl substituents be suitable for related processes using our Zn-ProPhenol catalytic system? A priori, such alkyl substituents should deactivate the ketone partner for both steric and electronic reasons, thus significantly impacting the outcome of the reaction. With these challenges in mind, we initiated our studies with 2-methyl tetralone **1a** to explore the feasibility of such a transformation (Table 1). Pleasingly, when **1a** was

Table 1. Optimization of the Reaction Conditions^a



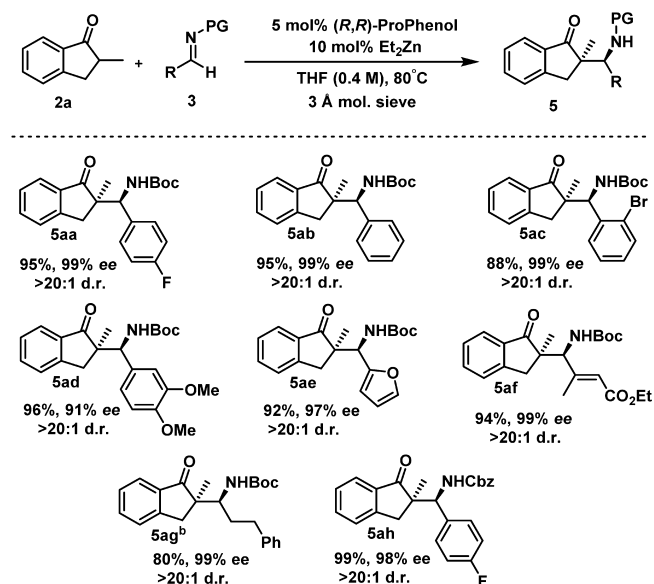
entry	1	<i>x</i>	[conc.], T	yield ^b	dr ^c	ee ^d
1	1a	20	(0.4 M), 60 °C	28%	>20:1	97%
2	1a	20	(0.4 M), 80 °C	76%	>20:1	96%
3 ^e	1a	20	(1.0 M), 80 °C	93%	>20:1	99%
4 ^e	1a	10	(1.0 M), 80 °C	75%	> 20:1	95%
5	2a	20	(0.4 M), 60 °C	99%	>20:1	99%
6	2a	10	(0.4 M), 60 °C	91%	>20:1	99%
7 ^e	2a	10	(0.4 M), 80 °C	99%	>20:1	99%
8 ^e	2a	5	(0.4 M), 80 °C	95%	>20:1	99%

^aReaction conditions: 0.20 mmol **1a** or **2a**, 0.24 mmol **3a**, *x* mol % (*R,R*)-ProPhenol, 2*x* mol % Et₂Zn (1 M in hexanes), 3 Å molecular sieves (5 mg), in THF for 40 h at the indicated temperature and concentration. ^bIsolated yield. ^cDetermined by ¹H NMR analysis. ^dDetermined by HPLC on a chiral stationary phase. ^eReaction time is 16 h.

reacted with Boc-protected aldimine **3a** in the presence of 20 mol % of the Zn-ProPhenol catalyst in THF at 60 °C, the desired Mannich product **4aa** was obtained with very promising selectivities, albeit in low yield due to a poor conversion (entry 1). When the reaction temperature was raised to 80 °C, a better conversion was observed, and remarkably, the selectivities were not affected (entry 2). Increasing the concentration of the reaction was beneficial too (entry 3), and the catalyst loading could be reduced to 10 mol % to afford **4aa** with only a slightly reduced yield (entry 4). Under similar reaction conditions, 2-methyl indanone **2a** proved to be more reactive than **1a** (entries 5–7), and **5aa** was also obtained with excellent selectivities. Pleasingly, the catalyst loading could even be lowered to 5 mol % without impacting the efficiency of the reaction (entry 8).

We selected **2a** to evaluate the generality of the reaction concerning the imine partner using our optimized conditions. A variety of aromatic Boc-aldehydes were successfully reacted under our optimized reaction conditions to afford highly functionalized β -amino ketones **5ab**–**5ag** (Scheme 2). Both

Scheme 2. Scope of the Reaction^a

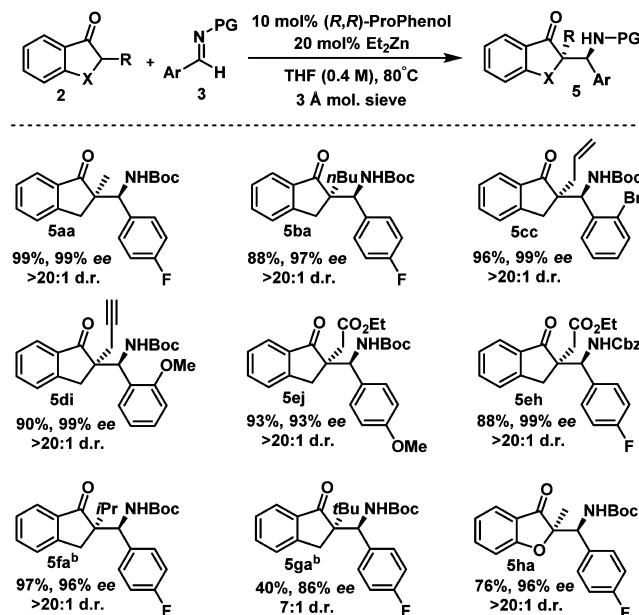


^aReaction conditions: 0.20 mmol **2a**, 0.24 mmol **3**, 5 mol % (*R,R*)-ProPhenol, 10 mol % Et₂Zn (1 M in hexanes), 3 Å molecular sieves (5 mg), in THF (0.4 M) at 80 °C for 16 h. ^bReaction run at 70 °C.

electron-withdrawing and electron-donating groups were tolerated on the aromatic ring as well as heteroaromatic imines. The reaction is not restricted to aromatic imines; vinyl imine **3f** and alkyl imine **3g** gave the Mannich products **5af** and **5ag** in high yields and selectivities. Finally, Cbz-protected imines can be used with similar efficiency which allows the use of orthogonal protecting group strategies.

We then investigated several 5-membered aromatic ketones for this direct Mannich reaction (Scheme 3). Indanones **2a**–**e**

Scheme 3. Scope of the Reaction^a

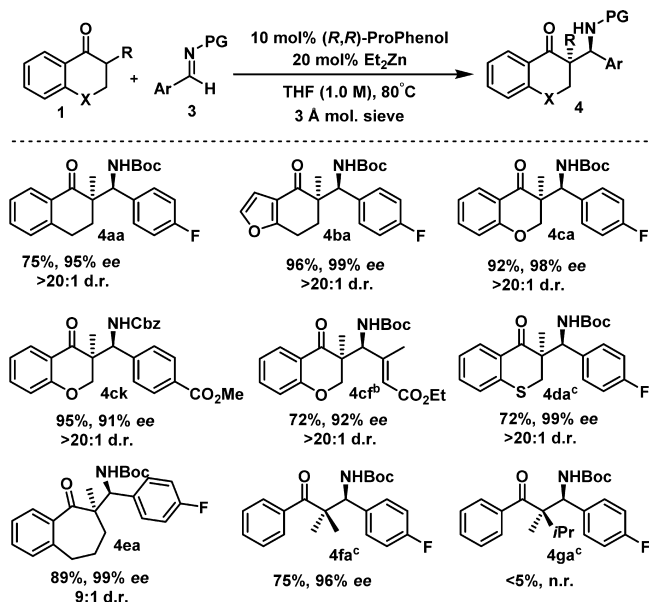


^aReaction conditions: 0.20 mmol **2**, 0.24 mmol **3**, 10 mol % (*R,R*)-ProPhenol, 20 mol % Et₂Zn (1 M in hexanes), 3 Å molecular sieves (5 mg), in THF (0.4 M) at 80 °C for 16 h. ^bReaction run in THF (1.0 M).

which are substituted with linear alkyl groups are competent partners, and the Mannich products **5aa–5eh** were obtained in good yields together with perfect selectivities. Notably, an ethyl ester and a free terminal alkyne are well tolerated under these reaction conditions. Substitution with a branched alkyl group did not impact the efficiency of the reaction as shown with **5fa**. Importantly, even a *tert*-butyl substituent could be used to afford **5ga** possessing two adjacent quaternary carbons. 3-Coumaranones are important heterocyclic compounds that are found in numerous natural products and bioactive compound.¹⁵ In this context, we were pleased to see that 3-coumaranone **2h** could be used for this direct Mannich reaction.

Moreover, this method was extended to other important aromatic ketones (Scheme 4) such as tetralone **1a–b** and 4-

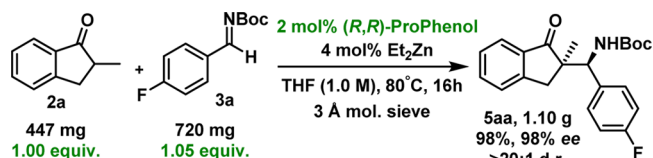
Scheme 4. Scope of the Reaction^a



chromanone **1c** which afforded the Mannich products **4aa–4cf** with similar levels of efficiency.¹⁶ Thiochromanone **4d**, possessing a coordinating sulfur atom that could potentially poison the Zn-catalyst, was also successfully used, but in this case, the innate diastereoselectivity of the reaction was 2.6:1. However, the two diastereoisomers could be easily separated by chromatography, and the major diastereoisomer **4da** was isolated in 72% yield together with excellent selectivities. Benzosuberone **4e** was also a competent partner for this Mannich reaction. Finally, challenging acyclic substrates were attempted for this reaction. Pleasingly, isobutyrophenone afforded β -amino ketone **4fa** in good yield and high enantioselectivity. However, only traces of the Mannich product were detected when the highly hindered phenone **4g** was reacted under these reaction conditions, the remainder being unreacted starting material.

To showcase the scalability and the practicality of the process, we performed a gram-scale reaction using **2a** and 1.05 equiv of imine **3a** (Scheme 5). Pleasingly, the catalyst loading could be reduced to only 2 mol % without impacting the

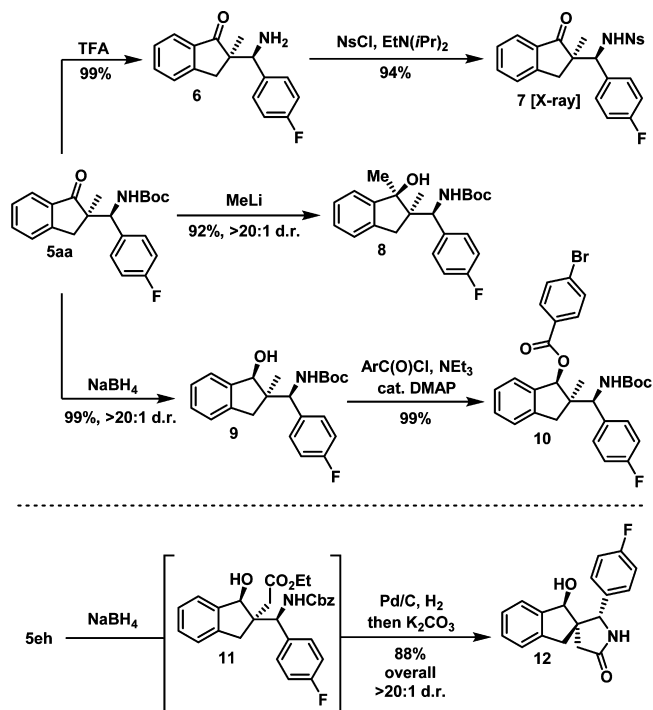
Scheme 5. Gram-Scale Reaction



outcome of the reaction, and **5aa** was obtained with comparable excellent yield and selectivities.

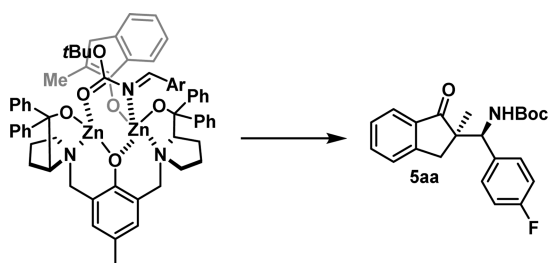
We then attempted to further elaborate the Mannich products **5** to demonstrate their synthetic utility (Scheme 6).

Scheme 6. Synthetic Applications



First, the Boc protecting group was quantitatively removed with trifluoroacetic acid in dichloromethane at room temperature. Of note, this type of reaction is usually plagued by retro-Mannich processes that were not observed in this case. Then, primary amine **6** can be further functionalized, and a protecting group switch to a *para*-nosyl group afforded compound **7** from which crystals were grown. The relative and absolute configuration of **7** derived from **5aa** was unambiguously established by X-ray crystallographic analysis, and by analogy, the same configuration was assigned to all compounds **4–5**. To account for the stereochemical outcome of the reaction, we propose a transition state where the Boc-imine is engaged via two-point binding with the dinuclear catalyst as shown in Scheme 7. When **5aa** was reacted with MeLi at -78 °C in THF, a diastereoselective addition of the methyl group was achieved to form **8** possessing three contiguous stereocenters and featuring two vicinal tetrasubstituted carbons. The use of MeMgCl instead of MeLi led to a sluggish reaction under similar conditions and to decomposition when the reaction temperature was increased. Additionally, a diastereoselective reduction of **5aa** with NaBH₄/methanol at 0 °C was also developed. The seemingly hindered neopentyl secondary alcohol **9** could then be acylated under standard conditions

Scheme 7. Proposed Transition-State for the Formation of Saa



using DMAP as a catalyst. A diastereoselective reduction of ketone **5eg** was also performed using our optimized reaction conditions, and **11** was used for the next step without chromatography purification. Removal of the Cbz protecting group under hydrogenolysis in methanol directly followed by the addition of K_2CO_3 led to the complex spirolactam **12** in excellent yield.

In summary, we have developed the first direct asymmetric Mannich reaction using α -branched ketones. This strategy allows an enantio- and diastereoselective access to a range of functionalized β -amino ketones featuring an all-carbon quaternary stereocenter. The reaction exhibits many interesting features: the preactivation of the reaction partners is not required; the reaction is highly atom-economic and can be run on a gram-scale with a low catalyst loading. Moreover, two convenient and orthogonal protecting groups can be used on the imines with similar efficiency. Finally, the Mannich adducts can be further elaborated to complex molecules possessing three contiguous stereogenic centers with complete control of diastereoselectivity. The extension of this strategy to the synthesis of quaternary carbon in acyclic systems is a major goal of our future efforts and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b01187.

Experiment details, compound characterization data, and spectra (PDF)

Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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