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Catalytic Asymmetric Mannich Reactions with Fluorinated Aromatic Ketones: Efficient Access to Chiral β -Fluoroamines

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Abstract

Herein, we report a Zn-Prophenol catalyzed Mannich reaction using fluorinated aromatic ketones as nucleophilic partners for the direct enantio- and diastereoselective construction of β -fluoroamine motifs featuring a fluorinated tetrasubstituted carbon. The reaction can be run on a gram-scale with a low catalyst loading without impacting its efficiency. Moreover, a related aldol reaction was also developed. Together, these reactions provide a new approach for the preparation of pharmaceutically relevant products possessing tetrasubstituted C–F centers.

Graphical abstract

A Zn-Prophenol catalysed direct Mannich reaction using α -fluoroketones allows the efficient construction of β -fluoroamine motifs with high enantio- and diastereoselectivities (up to 99% *ee*, >20:1 d.r.). A stereocomplementary aldol reaction is also described.

Keywords

β -fluoroamines; asymmetric catalysis; Mannich reaction; Zn-Prophenol; tetrasubstituted C–F centers

Fluorinated molecules are ubiquitous among marketed agrochemicals and pharmaceuticals.^[1] Indeed, the introduction of fluorine into bioactive molecules can modulate crucial factors such as solubility, lipophilicity or metabolic stability thus significantly impacting their bioavailability.^[2] In this context, the β -fluoroamine motif is a privileged structural motif which is of great importance in medicinal chemistry and found in numerous drug candidates.^[3] It is well established that a β -fluoro substitution lowers the pK_a of the neighboring amines which can then improve many pharmacological properties.^[4]

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For this reason, catalytic asymmetric methods providing a rapid access to β -fluoroamine building blocks are highly valuable.^[5]

Asymmetric fluorination methods have been developed exponentially over the last decade.^[6] However, the diastereoselective and enantioselective introduction of a fluorine atom into a molecule still represents a formidable challenge, especially under catalytic conditions.^[6d] The direct functionalization of simple and readily available fluorinated building blocks represents a complimentary approach for the selective synthesis of complex fluorinated molecules.^[7] Moreover, this approach is also more convergent in essence and is well-suited for the synthesis of libraries of fluorinated compounds. Along these lines, we report a Zn-Prophenol catalyzed Mannich reaction using fluorinated aromatic ketones as nucleophilic partners for the direct enantio- and diastereoselective construction of β -fluoroamine motifs.

The ProPhenol ligand is a salient member of the relatively rare aza-hemicrown family of ligands and forms dinuclear main group metal catalysts when treated with an alkyl metal reagent such as Et_2Zn .^[8] The Zn-Prophenol catalytic system has been used for an array of enantioselective aldol- and Mannich-type reactions with great success.^[8a] However, the scope of donors that can be used is so far mostly limited to methyl ketones (acetophenones,^[8b] acetone,^[8c] methyl vinyl ketone,^[8d] methyl ynones^[8e]) or unsubstituted α -hydroxy carbonyl compounds.^[8f-h] In this respect, we wished to extend the scope of the Zn-Prophenol catalyzed reactions to more substituted donors. To this purpose, we selected substituted α -fluoroketones because it was expected that the fluorine atom would have an activating effect by increasing the acidity of the ketone without being too bulky. Moreover, the obtained products would then possess a valuable tetrasubstituted C-F stereogenic center^[6a-c] which is difficult to form by traditional deoxyfluorination reactions and that is usually installed *via* asymmetric electrophilic fluorination.^[6]

The utilization of enolates of α -fluoroketones is extremely limited and enantioselective reactions involving such species are almost nonexistent.^[7] To the best of our knowledge, their use in asymmetric direct aldol reactions is so far limited to fluoroacetone (Scheme 1a).^[9] Concerning the direct Mannich reaction, highly activated fluorinated dicarbonyl compounds such as β -ketoesters have been used.^[10] However, a direct Mannich reaction using α -fluoroketones that proceeds with both high diastereo- and enantioselectivity is unprecedented. We are aware of only one report of an enantioselective Mannich reaction using α -fluoroketones but the reaction proceeds with poor diastereoselectivities to afford the *syn*-Mannich adduct as the major diastereoisomer (Scheme 1a).^[11] Furthermore, a severe drawback of this method is the requirement of an impractical mesyl protecting group on the nitrogen which is not trivial to remove in order to reveal the β -fluoroamine motif. In this respect, we report herein the first enantio- and *anti*-diastereoselective Mannich reaction using α -fluoroketones (Scheme 1b). Conveniently, our method uses an easy to remove Boc-protecting group on the nitrogen atom.

We initiated our studies with fluoroindanone **1a** as a model substrate because its cyclic structure was expected to lead to a well geometrically-defined zinc enolate (Table 1). When **1a** was reacted with 1.2 equivalent of Boc-protected aldimine **2a** in the presence of 20 mol% of a Zn-Prophenol catalyst, the desired Mannich product **3aa** was obtained as a single

diastereoisomer in 61% yield and perfect enantioselectivity (entry 1). When the reaction was run in diethyl ether, a better conversion was observed (entry 2). Increasing the reaction temperature or the reaction concentration has a positive effect on the outcome of the reaction (entry 3–4). Combining these two effects allowed the use of only 10 mol% of the Zn-Prophenol catalyst to give **3aa** with the same efficiency (entry 5). We then switched to aldimine **2b** to finish the optimization process because of its increased stability toward long-term storage and its solid nature. Under similar reaction conditions, imine **2b** led to a slightly higher yield than **2a** together with high selectivities. Interestingly, increasing the reaction temperature to 60°C gave full conversion to **3ab** without diminishing neither the diastereoselectivity or the enantioselectivity (entry 7). Under these reaction conditions, the catalyst loading could even be lowered to 5 mol% without impacting the efficiency of the reaction (entry 8). Finally, the reaction time could be reduced to 18h by running the reaction at 80°C (entry 9). The high selectivities obtained at such temperature are noteworthy.

We then evaluated the generality of the reaction concerning the imine partner. A variety of aromatic Boc-aldimines were successfully reacted with fluoroindanone **1a** using 10 mol% of the Zn-Prophenol catalyst (Scheme 2). Both electron-withdrawing and electron-donating groups were tolerated in *ortho*, *meta* and *para* position of the aromatic ring. Heteroaromatic imines also gave the desired product in high yields and selectivities. Of note, the sulfur atom of the thiophene moiety did not poison the Zn catalyst. Boc-imines derived from aliphatic aldehydes were not tolerated using our optimized reaction conditions because of a fast isomerization to the corresponding ene-carbamates. Finally, deactivated dimethoxy-substituted indanone **1b** was also successfully used for this reaction. The relative and absolute configuration of **3ag** was established by X-ray crystallographic analysis^[12] and by analogy the same configuration was assigned to all compounds **3**. Interestingly, the method reported by Tan and coworkers provides the *syn*-product as the major diastereoisomer^[11] which makes our two methods complementary.

We then investigated other fluorinated ketones for this reaction (Scheme 3). Fluorotetralones **1c–e** are competent partners and afforded the Mannich products in quantitative yields together with perfect selectivities. Fluorochromanone **1f** as well as fluorobenzosuberone **1g** worked with similar efficiency under these reaction conditions. Acyclic fluoroketone **1h**, derived from butyrophenone, also afforded the Mannich product **3hb** in high yield as a 3:1 mixture of diastereoisomers, both of them being formed with high enantioselectivities. The relative configuration of the major diastereoisomer was tentatively assigned to the *syn*-isomer based on ¹H-¹⁹F NMR coupling constants. Overall, this result might arise from a preferential formation of the *E*-enolate which minimizes dipole-dipole interactions followed by a highly enantioselective addition to the imine.

To showcase the scalability and the practicality of the process, we performed a gram-scale reaction using **1a** and 1.1 equivalent of imine **2b** (Scheme 4). Pleasingly, the catalyst loading could be reduced to only 2 mol% without impacting the outcome of the reaction and **3ab** was obtained with comparable excellent yield and selectivities.

We then attempted to further elaborate the obtained products **3** to demonstrate their synthetic utility. We developed a quantitative and diastereoselective reduction of compound **3ab** using

L-selectride. Poor to moderate diastereoselectivities were obtained with other classes of reducing agents such as NaBH₄ or DIBAL–H. Moreover, a selective addition of MeMgCl was also discovered. The use of AlMe₃ in combination with the Grignard reagent allowed the diastereoselective delivery of the methyl group to afford **5** which was isolated in 83% yield after silica gel chromatography. When AlMe₃ was omitted, the reaction proceeded with a poorer diastereoselectivity. The relative configurations of compounds **4** and **5** were established by NOE analysis^[13] and in both cases the addition to the ketone took place from the less hindered face to afford *trans*-β-fluoroalcohols.

Finally, we wished to develop a related aldol reaction using fluoroketones **1** and we report herein our preliminary results in this direction. When **1a** was reacted with α-branched aldehyde **6** in the presence of 20 mol% of a Zn-Prophenol catalyst, the desired aldol products were isolated in good yield and selectivities (Scheme 6). The use of triphenylphosphine oxide as a Lewis basic additive^[14] was crucial to increase the inherent diastereoselectivity of the reaction. The catalyst loading for a single run that is required for this reaction is mitigated by the ability to recover the (*R,R*)-Prophenol ligand in nearly quantitative yield by a simple extraction protocol.^[15]

The relative and absolute configuration of **8** derived from **7aa** was unambiguously established by X-ray crystallographic analysis.^[12] Interestingly, the absolute configuration of the tertiary fluoride in aldol products **7** is the opposite compared to the Mannich product **3** when the same (*R,R*)-Prophenol ligand was used. This unexpected result may relate to the ability of the *N*-Boc protected imines to engage in a two-point binding with the dinuclear catalyst which is not possible in the case of the aldehyde (Scheme 7). Of note, this reaction gives access to the *trans*-products and is complementary to a related detrifluoroacetylative aldol reaction affording the *syn*-diastereoisomers.^[7e]

In summary, we have developed a highly enantio- and diastereoselective Mannich reaction with fluoroketones using our dinuclear Zn-Prophenol catalyst. The reaction can proceed on a gram-scale with a low catalyst loading thus providing an efficient access to medically relevant chiral β-fluoroamines. Moreover, a related direct aldol reaction was also reported. Together, these two complementary methods enabled the straightforward preparation of product containing valuable tetrasubstituted C–F stereocenters. The stereocomplementarity of the Mannich versus aldol process is most intriguing and delineating mechanistic details of these processes is a major goal of our future efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- 12.

Crystallographic data for **3ag** and **8**: CCDC1425281 and CCDC 1425244 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

13.

See the supporting information for details.

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15.

See the supporting information of reference 8a for the extraction procedure.

a) Reported state of the art for enantioselective Mannich and aldol reactions using α -fluoroketones:

b) This work:

Scheme 1.

Development of unprecedented *anti*-selective direct Mannich and aldol reactions using α -fluoroketones.

Scheme 2.

Scope of the reaction concerning the imine partner.^[a]

[a] Reaction conditions: 0.20 mmol **1**, 0.24 mmol **2**, 10 mol% (*R,R*)-Prophenol, 20 mol% Et₂Zn (1M in hexanes), 3 Å molecular sieves (5 mg), in THF (0.4 M) at 60°C for 40 h. [b] Reaction run at 80°C for 18h.

Scheme 3.

Scope of the reaction concerning the α -fluoroketone partner.^[a]

[a] Reaction conditions: 0.20 mmol **1**, 0.24 mmol **2**, 10 mol% (*R,R*)-Prophenol, 20 mol% Et_2Zn (1M in hexanes), 3 Å molecular sieves (5 mg), in THF (0.4 M) at 80°C for 18 h. [b] Reaction run with 20 mol% (*R,R*)-Prophenol, 40 mol% Et_2Zn (1M in hexanes) in Et_2O (0.4 M) at 40°C for 40h.

Scheme 4.
Gram-scale reaction.

Scheme 5.
Synthetic applications.

Scheme 6. Development of a related aldol reaction.^[a]

[a] Reaction conditions: 0.20 mmol **1a**, 0.40 mmol **6**, 20 mol% (*R,R*)-Prophenol, 40 mol% $\text{Ph}_3\text{P}(\text{O})$, 40 mol% Et_2Zn (1M in hexanes), 3 Å molecular sieves (5 mg), in Et_2O (0.2 M) at 23°C for 40 h. [b] Reaction run using 0.60 mmol of **6c**.

Scheme 7.

Proposed binding-modes of an aldehyde and a Boc-imine to a Zn-Prophenol catalyst.

Table 1

Optimization of the reaction conditions.^[a]

entry	imine	x	solvent, T	yield ^[b]	d.r. ^[c]	ee ^[d]
1	2a	20	THF (0.2 M), 23°C	61%	>20:1	98%
2	2a	20	Et ₂ O (0.2 M), 23°C	77%	>20:1	97%
3	2a	20	THF (0.4 M), 23°C	78%	>20:1	98%
4	2a	20	THF (0.2 M), 40°C	68%	>20:1	95%
5	2a	10	THF (0.4 M), 40°C	70%	>20:1	97%
6	2b	10	THF (0.4 M), 40°C	81%	>20:1	99%
7	2b	10	THF (0.4 M), 60°C	97%	>20:1	99%
8	2b	5	THF (0.4 M), 60°C	98%	>20:1	99%
9 ^[e]	2b	5	THF (0.4 M), 80°C	98%	>20:1	99%

^[a]Reaction conditions: 0.20 mmol **1a**, 0.24 mmol **2**, x mol% (*R,R*)-Prophenol, 2x mol% Et₂Zn (1M in hexanes), 3 Å molecular sieves (5 mg), in THF for 40 h at the indicated temperature and concentration.

^[b]Isolated yield.

^[c]Determined by 1H-NMR analysis.

^[d]Determined by HPLC on a chiral stationary phase.

^[e]Reaction time was 18h.