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Enantioselective Aldol Reactions with Masked Fluoroacetates

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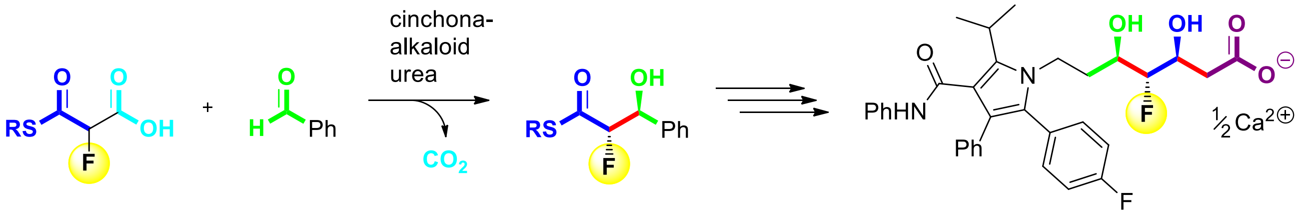
The incorporation of fluorine into organic molecules represents a versatile tool to influence its properties. The resulting increase in lipophilicity, activity and metabolic stability is particularly important for pharmacologically active substances.[1] However, fluorine containing natural products are hardly reported[2] and synthetic methodologies for its stereoselective introduction are limited.[3] One long-standing unsolved challenge is the enantioselective aldol reaction of fluoroacetate, which provides access to medicinally relevant polyketides and statins.

Herein, we present the development of fluoromalonic acid halfthioesters (F-MAHT) as biomimetic fluoroacetate surrogates as well as their application in highly stereoselective aldol reactions.[4,5] Under mild organocatalytic conditions, the α-fluorinated addition products were generated in good yields and diastereoselectivities and with up to 99% *ee*.



up to 99% yield
up to 17:1 d.r.
up to 99% *ee*

fluorinated Atorvastatin

>20:1 d.r.
> 99% *ee*

Scheme 1: Enantioselective Aldol reactions with masked fluoroacetates.

Furthermore, we demonstrated the synthetic value and versatility of the methodology by exploiting the unique reactivity of the thioester moiety of the products. Transformation into an aldehyde allowed us to perform consecutive aldol reactions to access fluorinated polyketide substructures, including a fluorinated analogue of top-selling cholesterol-lowering drug Atorvastatin (Lipitor®, Sortis®).

[1] I. Ojima *Fluorine in Medicinal Chemistry and Chemical Biology*, Blackwell Publishing Ltd, **2009**.
[2] M. C. Walker, M. C. Y. Chang, *Chem. Soc. Rev.* **2014**, *43*, 6527-6536.
[3] X. Yang, T. Wu, R. J. Phipps, F. D. Toste, *Chem. Rev.* **2015**, *115*, 826-870.
[4] J. Saadi, H. Wennemers, *Eur. Pat. Appl.* EP14192710, **2014**.
[5] J. Saadi, H. Wennemers, *Nat. Chem.* **2016**, *8*, 276-280.