

SYNLETT Spotlight 388

(*S*)- α,α -Diphenylprolinol Trimethylsilyl Ether

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This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Aneta Wróblewska was born in Bełchatów (Poland) in 1987. She received her M.Sc. degree in chemistry in 2011 working in the group of Prof. Grzegorz Mlostoń at the University of Łódź (Poland). Currently, she is continuing her research work in the same group and her interests focus on new, optically active, polyheterocyclic catalysts for asymmetric synthesis, based on the proline platform.

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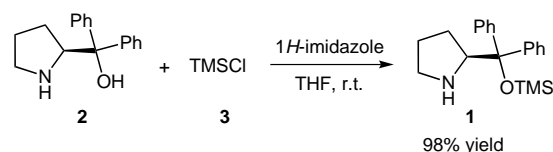
Introduction

One of the most important sections of modern organic chemistry is asymmetric synthesis, and in this field particularly attractive are problems relating to asymmetric catalysis. In the recent two decades, special attention is focused on (*S*)-proline and its derivatives, which are known as versatile organocatalysts ('aminocatalysts').^{1,2} It was found that the introduction of the protecting silyl moiety into the prolinol structure results in a remarkable increase of catalytic activity, thus allowing decrease in catalyst loading and shorter reaction times without compromising the level of enantioselectivity.³ In addition, this modification leads to significant broadening of the substrate scope. First examples of applications of the *O*-silyl prolinol derivatives in asymmetric synthesis were independently reported by Hayashi³ and Jørgensen.⁴ Since then these compounds have been used efficiently as 'privileged catalysts'^{2b} in diverse organic transformations,

such as epoxidations, aldol, *anti*-selective Mannich, Friedel–Crafts and Diels–Alder reactions, etc.^{5,6} Probably, the most prominent representative of diarylprolinol derivatives containing the silyl moiety is (*S*)- α,α -diphenylprolinol trimethylsilyl ether (**1**).

Preparation

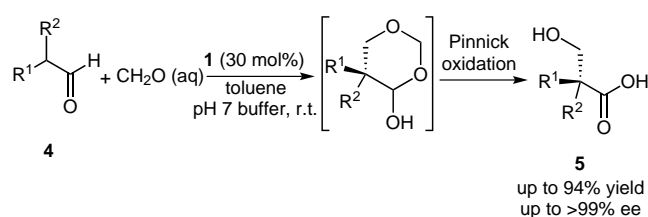
A straightforward synthesis of compound **1** is based on the *O*-protection of commercially available (*S*)- α,α -diphenylprolinol (**2**) with trimethylsilyl chloride (**3**) at room temperature in the presence of imidazole.⁷



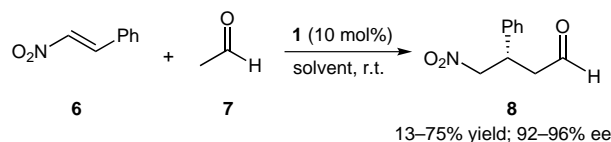
Scheme 1

Abstracts

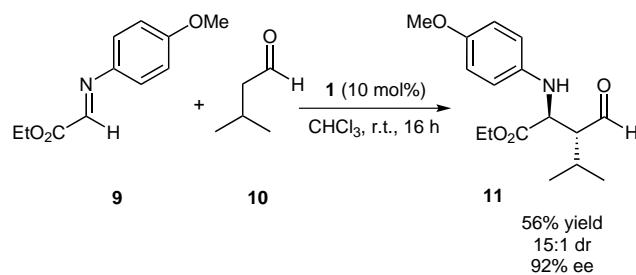
(A) Optically active β -hydroxy acids **5** can be prepared via enantioselective hydroxymethylation of aldehydes **4** in the presence of catalytic amounts of **1**. In this reaction, initially formed α -substituted β -hydroxy aldehydes are smoothly oxidized yielding corresponding β -hydroxy acids with excellent enantioselectivity and yields.^{8a} For an example of a Brønsted acid assisted regio- and enantioselective direct *O*-nitroso aldol reaction catalyzed by **1**, see ref. 8b.



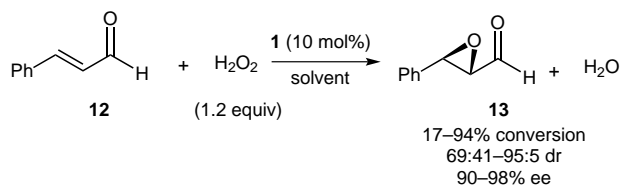
(B) Michael reaction of β -nitrostyrene (**6**) with acetaldehyde (**7**) catalyzed with **1** afforded α -substituted γ -nitro aldehyde **8** in nearly optically pure form and in high yield. The best result was obtained using 1,4-dioxane as a solvent.^{9a} In a recent report, significant modification of the generally accepted mechanism of the organocatalyzed Michael addition of aldehydes to nitro alkenes in the presence of **1** was postulated by D. Seebach and co-workers.^{9b}



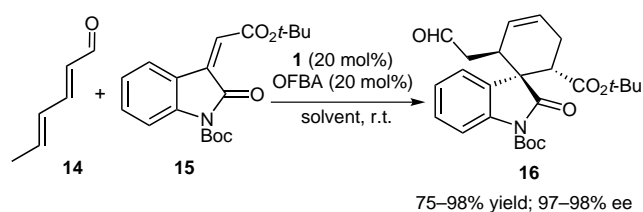
(C) *anti*-Selective Mannich reaction can be performed using **1** as an efficient organocatalyst. Thus, reaction between ethyl *N*-*p*-methoxyphenyl-protected α -iminoglyoxylate **9** and isovaleraldehyde (**10**) in the presence of **1** leads to α -amino acid derivative **11**. This product was formed in good yield and with high enantioselectivity and diastereoselectivity. The reaction was also observed to occur in a similar manner in water.^{10a} For other examples of the *anti*-selective Mannich reaction with fluorinated aldimines, see ref. 10b.



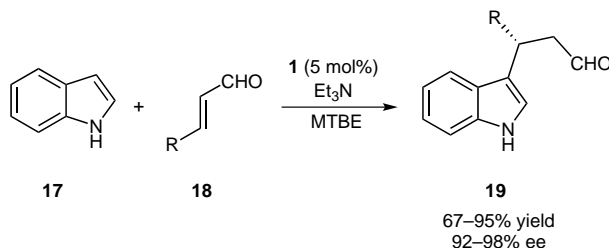
(D) (*S*)- α,α -Diphenylprolinol trimethylsilyl ether (**1**) is reported as a useful organocatalyst for the asymmetric epoxidation of α,β -unsaturated aldehydes. In the reaction with cinnamic aldehyde (**12**), hydrogen peroxide was applied as an efficient oxidizing agent. High levels of enantioselectivity were observed for reactions performed both in water or in water–alcoholic solutions in the presence of 10 mol% of **1**.¹¹



(E) Compound **1** can be used as an efficient organocatalyst for [4+2] cycloadditions (Diels–Alder reactions). A dieniminium derivative formed in situ from **1** and the unsaturated aldehyde **14**, in the presence of *o*-fluorobenzoic acid (OFBA), undergoes Diels–Alder reaction with diverse dienophiles, e.g. the α,β -unsaturated ester **15**, yielding expected [4+2] cycloadducts of type **16**. These relatively complex molecules were formed with an excellent stereocontrol leading to ee values of >97%.¹²



(F) The asymmetric Friedel–Crafts alkylations of indole (**17**) with α,β -unsaturated aldehydes **18** were carried out in the presence of **1** using methyl *tert*-butyl ether (MTBE) as a solvent. It was observed, that these reactions occurred efficiently without addition of a traditional Lewis or protic acid. Probably, the presence of triethylamine enhances the nucleophilicity of **17** by deprotonation or by an activating hydrogen-bond interaction with the NH group present in the indole molecule.¹³



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