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Pyrrolidine-linker-camphor assembly: bifunctional organocatalysts for efficient Michael addition of cyclohexanone to nitroolefins under neat conditions

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ABSTRACT

A simple and convenient strategy was developed to synthesize a new class of pyrrolidinyl–camphor based bifunctional organocatalysts possessing varying functional linkers. Catalytic screening of these camphor–pyrrolidine linked derivatives for asymmetric Michael reaction of cyclohexanone with β-nitrostyrene was carried out. Various aryl- and heteroaryl-nitroolefins, ketones as well as aldehydes gave the corresponding Michael adducts in high chemical yields (up to 95%) and exceptionally high diastereo- (*syn*/*anti* up to 99:1) and enantioselectivity (up to 95%) using catalyst **6** under solvent-free conditions.

1. Introduction

Michael reaction of ketones with nitroolefins represents an unquestionable convenient access to γ-nitroketones, which are valuable building blocks in organic synthesis.[1] The adducts serve as useful precursors for various functionalized organic compounds that are found to be pharmacologically active and can selectively block presynaptic dopamine receptors.[2] Much attention has been directed toward the design and application of organocatalysts recently.[3] Of the developed organocatalysts in asymmetric catalysis,[4] proline and its derivatives have proven to be effective protocols via the enamine catalysis.[5,6] The organocatalytic asymmetric Michael addition of a carbonyl compound with nitroolefins was pioneered by List and Barbas independently.[3h,i] Later on Alexakis[3j] and Kotsuki[3f] have shown that 2,2′-bipyrrolidine and pyrrolidine–pyridine systems could serve as powerful asymmetric catalysts. Most of the organocatalytic reactions require the use of organic solvents, i.e., DMSO, DMF, *i*-PrOH, MeOH, hexanes, toluene, and $CHCl_3$, which are not environmentally friendly. Historically, the metric to measure reaction success has been the chemical yield. Although chemical yields will remain imperative, alternative measures include the 'greenness' of a reaction, or *E* factor,[7a] and the volume productivity.[7b] The *E* factor, introduced by Sheldon, is defined as the ratio of the weight of waste to the weight of product, while the volume productivity is the grams of product per liter of reaction medium. The *E* factor for many pharmaceuticals has been estimated to exceed 100.[7c,d] The largest contributors to the magnitude of *E* factor are organic solvents, many of which are ecologically harmful and require expensive remediation. A pressing challenge facing organic chemists, therefore, is to advance new processes that are not only efficient, selective, and of high yielding but also environmentally friendly.[7e] An alternative strategy to reduce the *E* factor of reactions and their impact on the environment is to conduct the reaction under solvent-free conditions. Among the benefits of solvent-free processes are cost savings, decreased energy consumption, reduced reaction times, and a large reduction in reactor size and capital investment. The study of asymmetric catalysis under solvent-free conditions was inspired by the potential environmental benefits and the economic incentives. In addition, solvent-free Michael addition of cyclohexanone to nitrostyrene is a convenient access to important intermediates in organic synthesis.[8,9] Accordingly considerable efforts have been directed toward the development of organocatalytic systems in solvent-free conditions. Representative catalysts include pyrrolidine based phosphine oxide,[3a] aliphatic-aromatic diamine,[8a] recyclable pyrrolidine systems,[8b,e,f,h] thiourea derivatives,[8d,i] and chiral ionic liquids.[9b–e] Most of the above mentioned catalysts suffer from the limitations of long reaction time, high molecular weight, and tedious catalyst preparation. The development of alternative trivial and eco-friendly organocatalysts for Michael addition is desirable.

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2. Results and discussion

2.1. Design and preparation of organocatalysts

In this advancing field of organocatalysis, there has always been a high demand for more diverse organocatalysts encompassing the qualities of enhanced stereoselectivity, inert to air as well as water and easy preparation using readily accessible inexpensive starting materials. Over the past few years, we have been actively involved in the development of a series of camphor-based pyrrolidinyl organocatalysts.[10] These pyrrolidine linked camphor assembly have proven efficacies in organocatalytic asymmetric synthesis. The fundamental idea in designing these pyrrolidine–camphor based catalysts relies on the assumption that the pyrrolidine moiety plays a crucial role in enamine formation. The nucleophilic component is accompanied by a rigid bicyclic camphor scaffold that serves as an efficient stereocontrolling element.[11] In addition, with these pyrrolidine–camphor derived organocatalysts available, we would like to study the structure–stereoselectivity relationship. We would like to assess the impact of the linker functionality between the camphor skeleton and the pyrrolidine ring on the stereoselectivity of the reaction.

In these catalytic systems the pyrrolidine structural unit and camphor scaffold were linked with appropriate functionalities, such as amine, amide, and sulfide linkers (Fig. 1). We were interested to see whether the variation in the linker functionality will have an impact on the stereoselectivity of the reaction. We have also presumed that modification in the linker via various functionalities may contribute significantly toward the diastereo- and enantioselectivity of the reaction. Preliminary screening of these pyrrolidinyl–camphor bifunctional organocatalysts led to the conclusion that, the newly designed organocatalyst **6** showed promising results. The reaction of cyclohexanone **7a** with various aryl- and heteroaryl-nitroolefins proceeded smoothly with excellent diastereoselectivities (up to 99:1 *syn*/*anti*) and with good to excellent enantioselectivities (up to 95% ee) during the asymmetric transformation.

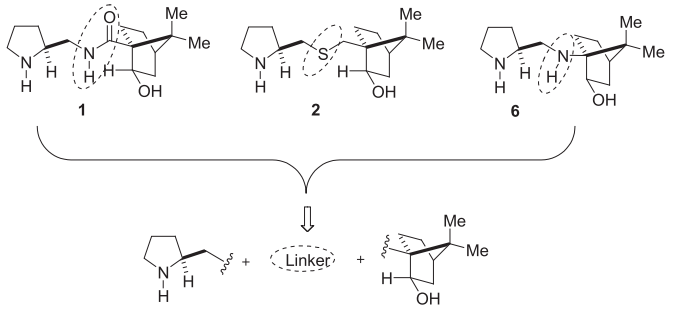


Fig. 1. Structures of various pyrrolidinyl–camphor based organocatalysts.

The organocatalysts **1** and **2** were easily prepared on a gram scale quantities by means of standard protocols developed previously in our laboratory.[10c,e,g] The preparation of the organocatalyst **6** starts with reductive amination of (*S*)-*tert*-butyl 2-formylpyrrolidine-1-carboxylate **3** and aminoketone **4**.[12] The reductive amination was successfully carried out using a mild reducing system of Ti(*i*-PrO)$_4$ and NaBH$_4$. The reaction proceeds through an intermediate titanium(IV) complex, which is either reduced directly or via equilibration of transient iminium species.[13] This synthetic route preparation can be carried out with ease for up to a quantity of 4.0 g without any difficulty. The Boc-protected procatalyst **5** obtained, can be easily deprotected by a known standard protocol using TFA–DCM to inherit the pyrrolidine–camphor based catalyst **6** with a chemical yield of 79% (Scheme 1).

The structure of the newly designed catalyst **6** was fully characterised by IR, ^{1}H, ^{13}C NMR, HRMS analyses and the absolute stereochemistry was further confirmed by a single X-ray structure analysis (Fig. 2).[18]

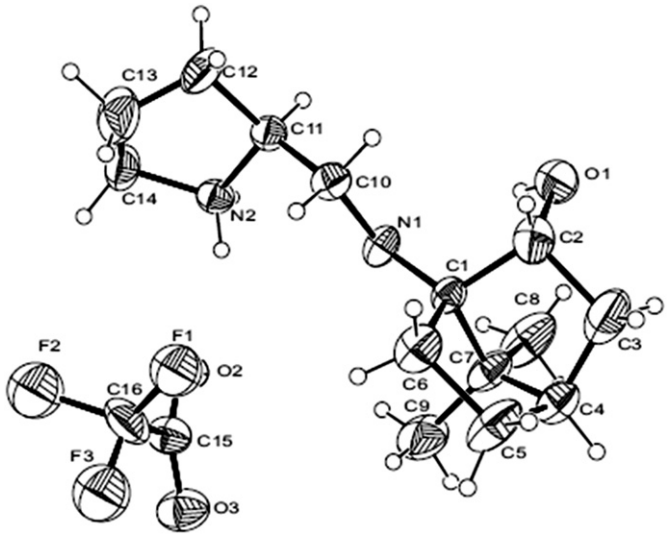


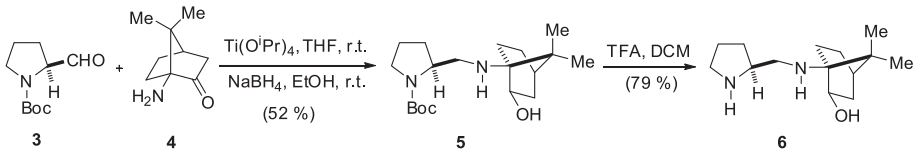
Fig. 2. ORTEP diagram of pyrrolidinyl–camphor based organocatalyst **6** as a TFA salt.

2.2. Screening of organocatalysts and optimization of reaction conditions

Catalytic screening for the previously developed and the newly designed pyrrolidine–camphor based organocatalyst **6** was carried out (Table 1). It was found that organocatalysts **1**, **2**, and **6** catalyzed the reaction of cyclohexanone **7a** with *trans*-β-nitrostyrene **8a** conveniently under neat conditions.

Organocatalyst **1** having an amide linker took about 24 h to give moderate diastereoselectivity (*syn*/*anti*) 79:21 and an enantioselectivity of 57%. Whereas, sulfide linker catalyst **2** took almost 3 days to give a good diastereoselectivity (*syn*/*anti*) 94:6 and an enantioselectivity of 85%. On the other hand, catalyst **6** outperformed the other pyrrolidine–camphor based organocatalysts in terms of reaction rate, chemical yield, and selectivity of the product formation (Table 1, entries 1–3). A very high diastereoselectivity (*syn*/*anti*) 97:3 and an enantioselectivity of 90% was obtained using organocatalyst **6** for Michael addition of cyclohexanone **7a** to *trans*-nitrostyrene **8a** within 14 h.

We next carried out the optimization studies for the reaction of cyclohexanone **7a** with *trans*-β-nitrostyrene **8a** in various solvents (Table 2).



Scheme 1. Synthesis of organocatalyst **6**.