Tetrahedron: *Asymmetry* 25 (2014) 473–477

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Sugar amide-pyrrolidine catalyst for the asymmetric Michael addition of ketones to nitroolefins

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ARTICLE INFO

Article history:
Received 21 January 2014
Accepted 5 February 2014

ABSTRACT

New sugar amide-pyrrolidine derivatives possessing the furano form of the carbohydrate template were designed and developed as efficient and stereoselective organocatalysts for asymmetric Michael additions of ketones to nitroolefins at room temperature. Good yields and high selectivities were achieved with catalyst **2** under solvent-free and additive-free reaction conditions.

1. Introduction

Over the past few years, organocatalysis has witnessed remarkable advances and great attention has been given to the design and application of small privileged organic molecules to construct asymmetric carbon—carbon and carbon—hetero atom bonds for the preparation of enantiomerically pure compounds.[1] The Michael addition is widely recognized as one of the most efficient and powerful synthetic tools for the stereoselective construction of carbon—carbon bonds for the formation of stereoenriched adducts with multiple stereogenic centers in a single step.[2] In particular, the use of nitroolefins as Michael acceptors has received attention for the efficient formation of chiral γ-nitro carbonyl compounds, which serve as versatile building blocks for the synthesis of complex organic molecules.[3] A wide variety of proline based organocatalysts have been developed with a distinct range of selectivities. Among these pyrrolidine–triazoles,[4] pyrrolidine–tetrazoles,[5] pyrrolidine–thioureas,[6] pyrrolidine–sulfonamides,[7] pyrrolidine–pyridines,[8] pyrrolodine–pyrazoles,[9] pyrrolidine–imidazoliums,[10] 2,2-bipyrrolidines[11,] and phosphoprolines[12] represent the major organocatalyst categories for asymmetric Michael additions. However, the use of carbohydrates as chiral templates with a pyrrolidine ring is very limited. To the best of our knowledge there have been only a few sugar-based pyrrolidine organocatalysts with the pyranose form of the carbohydrate that have been used successfully, while the furanose form of the carbohydrate in organocatalysis is unexplored.[13] In a continuation of our research interests,[4h,9,14] we have developed new sugar based pyrrolidine–amide catalysts (Fig. 1) derived from L-proline and the furanose form of D-glucose. Structurally, the designed catalysts possess a 'privileged' chiral pyrrolidine backbone (derived from L-proline), which acts as the catalytically active site and the carbohydrate template (derived from furano D-glucose), which provides a bulky environment and has additional hydrogen bonding sites for the activation of nitroolefins to furnish the Michael products with high stereoselectivity. Herein we report the synthesis and development of carbohydrate–pyrrolidine based amide catalysts for asymmetric Michael additions of ketones with various nitroolefins.

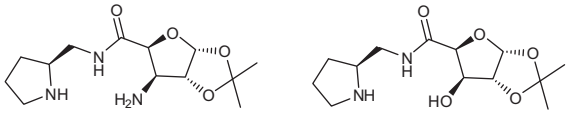

Figure 1. Structure of new sugar based organocatalysts.

2. Results and discussion

The sugar amide-pyrrolidine catalysts **1** and **2** were synthesized from the known pyrrolidine amine **3** (readily obtained from L-proline) and sugar acids **4** and **4a**, respectively (derived from furano D-glucose),[15] as illustrated in Scheme 1. Accordingly, the Cbz-protected proline amine **3** was subjected to peptide coupling with D-glucose derived acids **4a** and **4b** followed by hydrogenation using Pd/C in methanol to give the desired catalysts **1** and **2** in 84% and 82% yield, respectively (Scheme 1).

With both catalysts in hand, we tested their efficiency in a model reaction of cyclohexanone **6a** with β-nitrostyrene **7a** (Scheme 2). At first, the reaction was performed with 10 mol % of the catalyst under solvent-free conditions at room temperature. Both catalysts **1** and **2** promoted the addition with good yield

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http://dx.doi.org/10.1016/j.tetasy.2014.02.003
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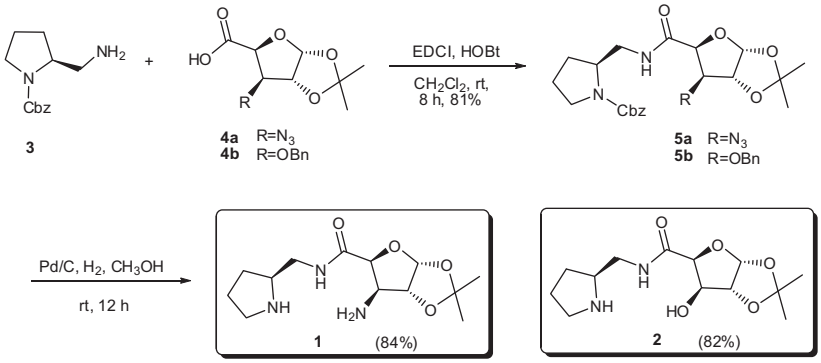
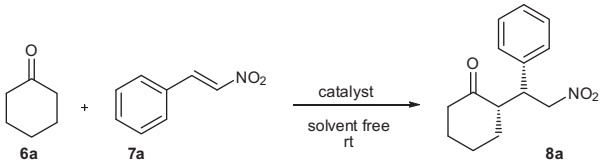


Scheme 1. Synthesis of sugar amide-pyrrolidine catalysts.



Scheme 2. Michael addition of cyclohexanone to nitrostyrene.

Table 1
Screening of catalysts[a]

Entry	Catalyst	mol %	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	**1**	10	36	85	9:1	18
2	**2**	10	36	88	92:8	66
3	**1**	15	36	90	9:1	21
4	**2**	15	36	91	91:9	70
5	**2**	20	24	94	98:2	91
6	**2**	30	24	95	98:2	91

[a] Reaction conditions: cyclohexanone (5 mmol), nitrostyrene (1 mmol).
[b] Isolated yields.
[c] Determined by the ^{1}H NMR of the crude product.
[d] Determined by chiral HPLC.

and diastereoselectivity, while the enantioselectivity obtained was moderate for catalyst **2** (Table 1, entry 2) and very low for catalyst **1** (Table 1, entry 2). In order to improve the efficacy, screening experiments were conducted by varying the catalyst loading and the results are summarized in Table 1. The best result was observed with 20 mol % of catalyst **2** (Table 1, entry 5); catalyst **1** gave good yields and diastereoselectivities but poor enantioselectivities (Table 1, entry 3). The observed low efficacy of catalyst **1** may be due to the formation of enamines in the presence of a primary amine group in the carbohydrate template, which also activates the ketone along with the secondary amine of the pyrrolidine ring.

With these observations, we then conducted solvent screening experiments using catalyst **2** (20 mol %) and investigated the scope of different solvents such as CH_2Cl_2, toluene, hexane, CH_3CN, THF, dioxane, and H_2O. The reaction times, yields, and selectivities of **2** differed significantly and the results are summarized in Table 2. The reaction proceeded well in solvents such as $CHCl_3$, THF, dioxane, and MeOH resulting in the Michael adduct in good yield, diastereoselectivity, and enantioselectivity (Table 2, entries 1, 5, 6, and 7). However in other solvents, the reaction was found to be less productive (Table 2, entries 2–4 and 8). The results of the solvent screening experiments were found to be inferior in all respects when compared to the solvent free conditions.

In order to evaluate the effect of additives, we next conducted additive screening experiments using various acid additives such as TFA, HCOOH, PhCOOH, CSA, CH_3COOH, and *p*TSA under solvent-free reaction conditions. As shown in Table 3, these experiments resulted in the formation of the desired Michael product in moderate to good yields and diastereoselectivities, whereas the enantioselectivities obtained in all respects were very low. This may be due to the fact that catalysts bearing intramolecular hydrogen bonding sites do not require any additives for high reactivity and stereoselectivity, while an acidic co-catalyst is critical for catalysts lacking an intramolecular proton donor.

Table 2
Screening of solvents using **2**[a]

Entry	Solvent	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	$CHCl_3$	60	72	95:5	92
2	Toluene	72	69	8:2	63
3	Hexane	72	73	8:2	68
4	CH_3CN	55	76	93:7	79
5	THF	60	85	92:8	86
6	Dioxan	52	82	85:15	90
7	MeOH	56	78	93:7	88
8	H_2O	50	64	92:8	60

[a] Reaction conditions: cyclohexanone (5 mmol), nitrostyrene (1 mmol), solvent (0.5 mL), catalyst **2** (20 mol %).
[b] Isolated yields.
[c] Determined by the ^{1}H NMR of the crude product.
[d] Determined by chiral HPLC.

In order to explore the scope and the limitations of the Michael reaction, various nitroolefins and ketones were studied using catalyst **2** with the optimized reaction conditions and the results are summarized in Table 4. All of the β-nitrostyrenes, irrespective of the nature of the substituents on the aryl group, reacted efficiently with cyclohexanone (Table 4, entries 1–8) to give the corresponding Michael adducts in good yields and with high diastereoselectiv-

Table 3
Screening of additives[a]

Entry	Additive	Time (h)	Yield[b] (%)	*syn*/*anti*[c]	ee[d] (%)
1	TFA	24	81	82:18	42
2	HCOOH	24	78	75:25	39
3	PhCOOH	30	84	85:15	61
4	CSA	24	70	8:2	53
5	CH_3COOH	30	75	7:3	57
6	*p*TSA	30	72	85:15	48

[a] Reaction conditions: cyclohexanone (5 mmol), nitrostyrene (1 mmol), additive (5 mol %), solvent-free.
[b] Isolated yields.
[c] Determined by the ^{1}H NMR of the crude product.
[d] Determined by chiral HPLC.