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Highly Enantioselective Organocatalytic Addition of Aldehydes to *N*-(Phenylmethylene)benzamides: Asymmetric Synthesis of the Paclitaxel Side Chain and Its Analogues

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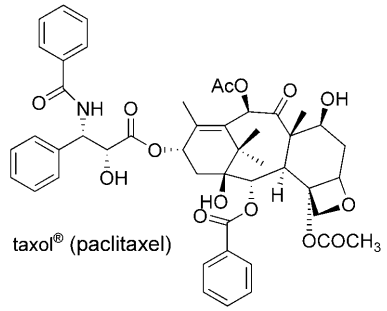
Abstract: A simple highly enantioselective organocatalytic addition of aldehydes to *N*-(phenylmethylene)benzamides is presented. The application of (*R*)-proline as the catalyst and subsequent oxidation of the protected α-hydroxy-β-benzoylaminoaldehydes (92–99% *ee*) gives access to esterification-ready phenylisoserine derivatives such as the protected paclitaxel (taxol) side chain. Esterification of these derivatives with baccatin III gives access to the cancer chemotherapeutic substance paclitaxel and its analogues that do not exist in nature.

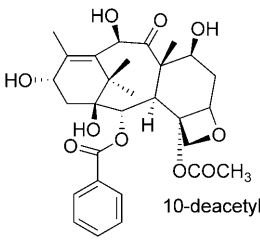
Keywords: aldehydes · asymmetric catalysis · (phenylmethylene)-benzamides · organocatalysis · taxol

Introduction

Mannich reactions rank among the most versatile class of transformations in organic chemistry.[1,2] Development of efficient and practical catalytic asymmetric variants of such reactions is a critical aim in chemical synthesis.[3] In particular, organometallic complexes have been used successfully as catalysts for indirect catalytic asymmetric Mannich-type reactions.[4] Direct catalytic Mannich-type reactions between ketones and preformed imines are also catalyzed by organometallic complexes with high enantioselectivity.[5] In the field of organocatalysis,[6] List and co-workers reported the first direct metal-free catalytic Mannich reaction in 2000.[7a] However, despite the intense research on the catalytic enantioselective Mannich reaction,[7–9] the organocatalytic enantioselective addition of aldehydes to *N*-(phenylmethylene)-benzamide has not been reported. This transformation would be important and useful since according to retrosynthetic analysis (Scheme 1) it would provide a direct entry to valuable α-hydroxy-β-amino acids, which are present in natural products such as paclitaxel (taxol).[10] Moreover, there are only a few examples of the employment of protected α-oxyacetaldehydes as donors in organocatalytic Mannich-type reactions.[7u,v,8e]

Esterification of the furnished derivative of the (2*R*,3*S*)-phenylisoserine side chain with a protected form of deacetylbaccatin III, an abundant natural product obtained from various Taxus species, would give access to paclitaxel and its analogues.[11]





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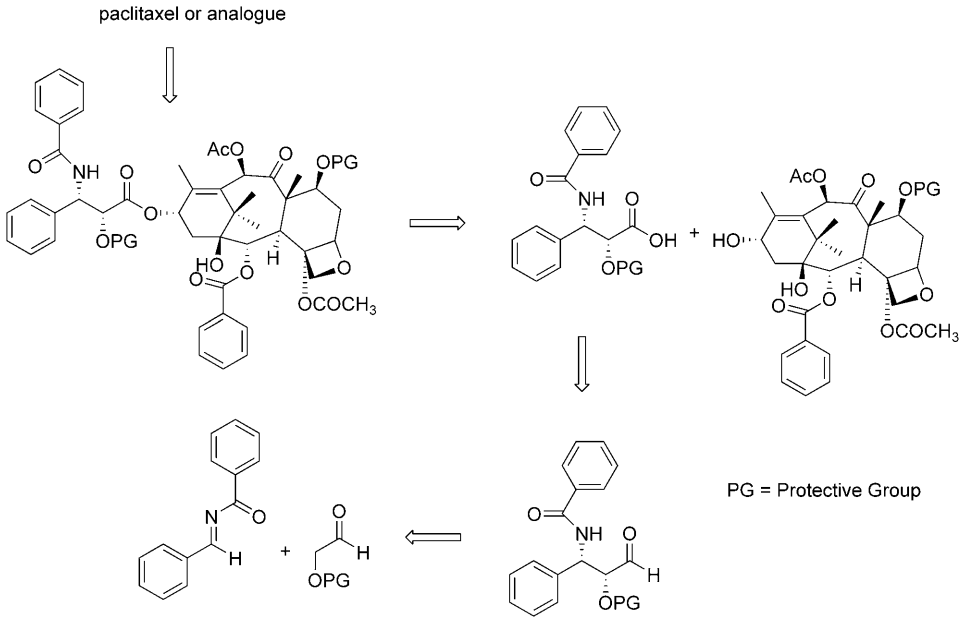
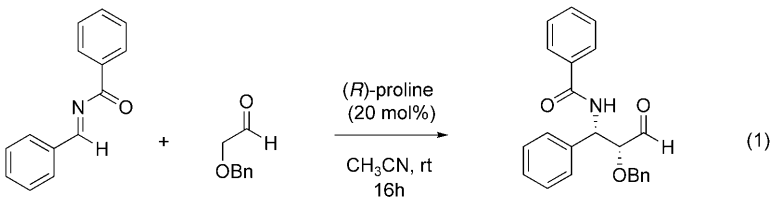


Scheme 1. Retrosynthetic analysis for a three-step synthesis of protected paclitaxel.

While deacetylbaccatin III can be obtained from Taxus species, the side chains of paclitaxel and taxane derivatives are prepared by chemical synthesis.[11,12] Asymmetric induction in the industrial transformations is generally achieved by employing chiral auxiliaries. Thus, catalytic methods[11] and in particular organocatalytic methods[6] that avoid the use of toxic catalysts would be highly desirable for the synthesis of paclitaxel side chain analogues. Herein, we report the first example, to the best of our knowledge, of a highly enantioselective amino acid-catalyzed addition of aldehydes to *N*-(phenylmethylene)benzamides.

Results and Discussion

In an initial catalyst and solvent screen for the chiral amine-catalyzed reaction between *N*-(phenylmethylene)benzamide (**1a**) and α-benzyloxyacetaldehyde (**2a**), we found that amino acid derivatives catalyzed the formation of 2-benzyloxy-3-benzoylamino-3-phenylpropanals **3a** (*syn* isomer) and **3a′** (*anti* isomer) (see the Supporting Information). To our delight, (*R*)-proline catalyzed the formation of 2-benzyloxy-3-benzoylamino-3-phenylpropanal **3a** in 68% yield with 95:5 (*syn*:*anti*) d.r. and 99% *ee* in CH_3CN at room temperature using nearly stoichiometric amounts of acceptor and donor ([Eq. (1)]).

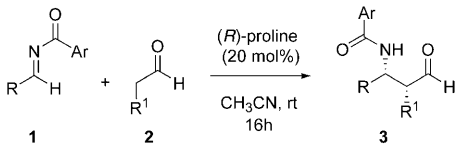


Proline derivatives also catalyzed the transformation. For example, (*S*)-hydroxyproline gave the corresponding product *ent*-**3a** in 65% yield with 90:10 d.r. and 97% *ee*. Encouraged by these results, protected 2-hydroxy-3-benzoylamino-3-phenylpropanals **3** with the same stereochemistry as the phenylisoserine side chan of paclitaxel were prepared by using (*R*)-proline as the catalyst and CH_3CN as the solvent (Table 1).

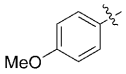
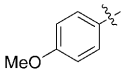
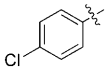
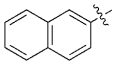
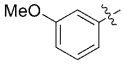
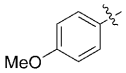
The aldehyde products **3** were assembled in an asymmetric fashion with good to high diastereoselectivity (75:25–95:5 d.r.) and high enantioselectivity (92–99% *ee*). Both protected α-oxyaldehydes and aliphatic aldehydes were successfully used as substrates. The reaction was also performed on a large scale without loss of stereoselectivity but a slight decrease in yield. Subsequent oxidation of the protected 2-hydroxy-3-benzoylamino-3-phenylpropanals **3** gave the corresponding protected esterification-ready (2*R*,3*S*)-phenylisoserine derivatives **4** in high yields. For example, protected α-hydroxy-β-aminoaldehyde **3a** was oxidized to the corresponding paclitaxel side chain **4a**[13h] in 82% yield (Scheme 2). We next embarked on the semisynthesis of paclitaxel,[13] which is currently used to treat patients with lung, ovarian, breast cancer, head and neck cancer, advanced forms of Kaposi's sarcoma, and the prevention of restenosis.[14] Esterification of **4a** with protected 7-triethylsilylbaccatin III **5**[11] produced the corresponding orthogonally protected C-2′,C-7-protected paclitaxel **7**, which can be readily deprotected, in 60% yield. All structural and characterization data were in agreement with known literature values.[13h] The employment of orthogonal protective groups is advantageous since it allows further controlled modification of the taxol to give analogues. Finally, paclitaxel was synthesized after deprotection of **7** in 76% yield. The (2*R*,3*S*)-phenylisoserine derivative **4a** was also converted to the corresponding methyl ester **6a**, which is an excellent precursor for the coupling with protected 7-triethylsilylbaccatin III **5**.[13h]

To shed more light on the initial step of the (*R*)-proline-catalyzed reaction between imines **1** and protected α-oxyaldehydes, we performed density functional theory (DFT) calculations by using the Gaussian 03 software package[15] and the B3LYP functional.[16] Geometries were optimized

Table 1. Catalytic assembly of 2-hydroxy-3-benzoylamino-3-phenylpropanals **3**.[a]



1 **2** **3**

Entry	R	Ar	R^1	Product	Yield [%][b]	d.r.[c]	*ee* [%][d]
1			OBn	**3a**	68	95:5	99
2			OBn	**3b**	64	88:12	99
3			OBn	**3c**	65	95:5	99
4			OBn	**3d**	50	85:15	94
5			OBn	**3e**	61	90:10	98
6			OBn	**3f**	60	90:10	96
7			OBn	**3g**	66	75:25	96
8			Me	**3h**	68	85:15	92
9			OTBS	**3i**	68[e]	80:20	98

[a] Experimental conditions: A mixture of **1** (0.25 mmol), **2** (0.27 mmol), and (*R*)-proline (20 mol%) was stirred at room temperature in CH_3CN (1.0 mL). [b] Isolated yield of **3** after silica gel column chromatography. [c] Determined by H^1 NMR analysis of the crude reaction mixture. [d] Determined by chiral-phase HPLC analysis. [e] Reaction run for 23 h. Bn = benzyl, TBS = *tert*-buthyldimethylsilyl.

with the double-zeta basis set 6–31G(d,p), and characterized with frequency calculations. Final energies were obtained with the larger basis set 6–311+G(2d,2p) and corrected for zero-point effects obtained from the frequency calculations. The transition state search was conducted by using the QST3 algorithm.[17] The effect of solvation in CH_3CN was calculated by using an IEF-PCM model with the dielectric constant of acetonitrile.[18] As a representative case for the calculations, we considered the initial step of the (*R*)-proline-catalyzed reaction between *N*-(phenylmethylene)benzamide (**1a**) and methyl-protected α-oxyaldehyde.[19] A favorable six-membered metal-free Zimmermann–Traxler transition state (TS) with an energy of 9.1 kcal mol^{-1} in CH_3CN relative to that of the reactant was found that gives the correct stereochemistry of the product (Figure 1). The six-membered transition state is stabilized by hydrogen bonding between the nitrogen of the *N*-(phenylmethylene)benzamide with a *trans*-configuration and the carboxylic acid group of (*R*)-proline. Hence, the reaction worked best in polar aprotic solvents.

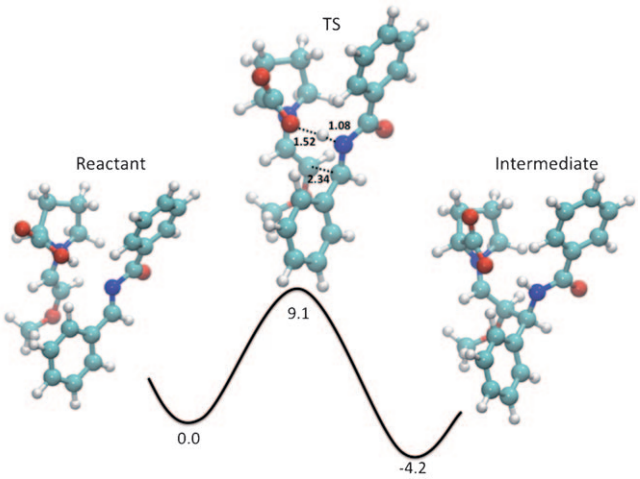


Figure 1. DFT-optimized geometries of the initial reaction steps (kcal mol^{-1}).

Conclusion

In summary, we have developed a highly enantioselective catalytic asymmetric addition of aldehydes to *N*-(phenylmethylene)benzamides. This transformation was employed in the short synthesis of phenylisoserine derivatives and the cancer chemotherapeutic substance paclitaxel. Analogues of the paclitaxel side chain that do not exist in nature could be readily made following this modular route. We are continuing to explore the potential of this method in structure–activity relationship tests of paclitaxel analogues and in diversity oriented synthesis. The results of these investigations will be reported in due course.

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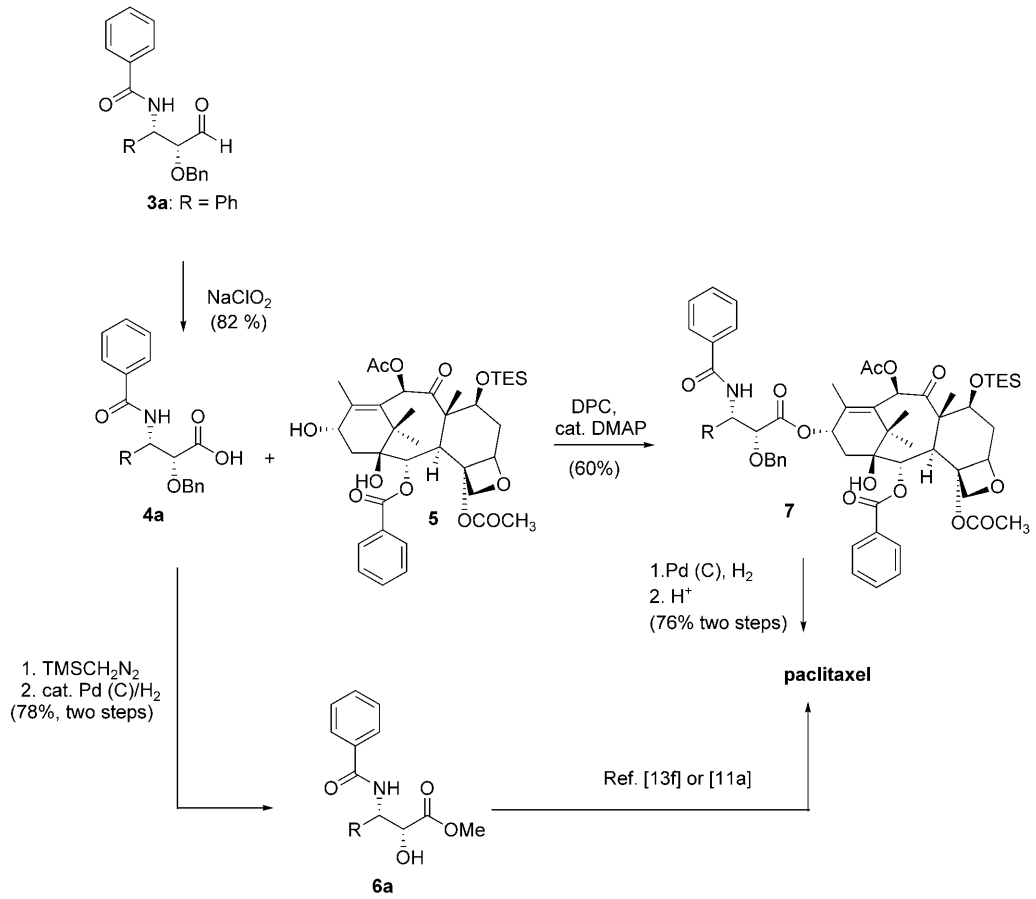

Scheme 2. Synthesis of protected paclitaxel **7**. Ac = acetyl, Bn = benzyl, DPC = di(2,2′-pyridyl)carbonate, DMAP = 4-dimethylaminopyridine, TES = triethylsilyl, TMS = trimethylsilyl.

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