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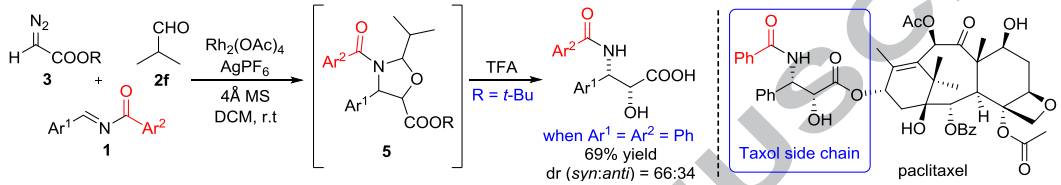

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A convenient one-pot approach to Paclitaxel (Taxol) side chain *via* 1,3-dipolar cycloaddition of carbonyl ylides and *N*-benzoylbenzyl imines

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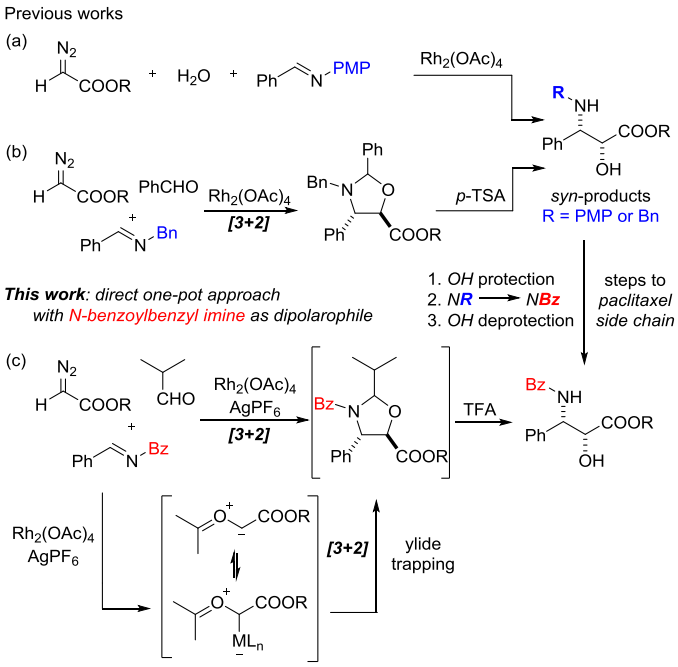
ABSTRACT

An efficient cascade approach to *α*-hydroxy-*β*-amino acid derivatives is reported, which goes through a 1,3-dipolar cycloaddition of carbonyl ylides and *N*-benzoylbenzyl imines and followed by hydrolysis under acidic conditions. This is the first example of using *N*-benzoylbenzyl imine as dipolarophile for 1,3-dipolar cycloaddition with carbonyl ylide, which provides a direct and convenient access for the one-pot synthesis of paclitaxel side chain and its derivatives.

Introduction

α-Hydroxy-*β*-amino acids and their derivatives are the indispensible moieties of many biological molecules and natural products.[1] The side chain of paclitaxel is one of the most famous examples, which plays an important role in semi-synthesis of paclitaxel.[2] As a result, considerable efforts have been made to develop a convenient and efficient route for the direct construction of this framework. In the recent decades, Sharpless aminohydroxylation[3], Sharpless dihydroxylation[4] and selective ring-opening of epoxides or aziridines with proper nucleophiles[5] are the practical methods to synthesize the *α*-hydroxy-*β*-amino acid derivatives. Moreover, the metal-catalyzed multi-component reactions[6] of imines with in situ generated ylide *via* Mannich type addition[7] and 1,3-dipolar cycloaddition of carbonyl ylide[8] have also been utilized to build the skeleton of *α*-hydroxy-*β*-amino acids.

Among these advances toward the *α*-hydroxy-*β*-amino acid derivatives, approaches to the direct and efficient synthesis of paclitaxel side chain are rare, and the substrate scope is limited.[9] Either in ylide trapping reaction[10] (Scheme 1a) or 1,3-dipolar cycloaddition reaction[11] (Scheme 1b), only *N*-aryl or *N*-benzyl imines are demonstrated, which means additional modifications including protection and deprotection procedures are needed to finally deliver the paclitaxel side chain from these products. Inspired by these works and as the continuation of our interest in



Scheme 1. Rh(II) catalyzed multi-component reactions. (a) three-component reaction of imine, EDA and water. (b) 1,3-dipolar cycloaddition of EDA, aryl-aldehyde and benzylidenebenzylamine. (c) one-pot route to paclitaxel side chain.
PMP= *p*-methoxyphenyl. EDA=ethyl diazoacetate. Bz=benzoyl.

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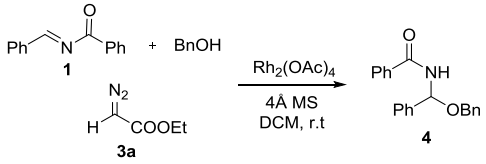
paclitaxel side chain synthesis[10], we envisioned that 1,3-dipolar cycloaddition of carbonyl ylide and imine is one of the most practical strategies to achieve this protocol[8,11,12] and if the protecting group can be replaced with benzoyl, the paclitaxel side chain could be obtained efficiently in a step-, time-, and energy-saving manner. To our knowledge, there have been only a few examples on multi-component reactions involving the imine with *N*-benzoyl or other strong electron withdrawing group[13], which remains a great challenge for us to accomplish this route. Herein we report a new convenient one-pot approach to paclitaxel side chain *via* 1,3-dipolar cycloaddition of carbonyl ylides and *N*-benzoylbenzyl imines (Scheme 1c).



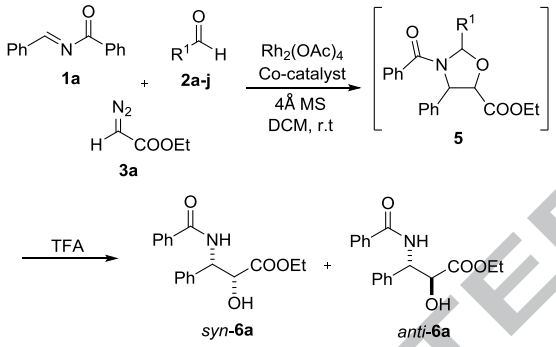
Scheme 2. Reaction of *N*-benzoylbenzyl imine and benzyl alcohol.

Result and discussion

We first investigated the $Rh_2(OAc)_4$ catalyzed coupling reaction of *N*-benzoylbenzyl imine, ethyl diazoacetate (EDA) and water according to our previous work.[10] Unfortunately, the target product was not achieved and only hydrolyzed product of *N*-benzoylbenzyl imine was observed. Benzyl alcohol also failed to perform the reaction and only addition product[13b] **4** was obtained in this condition, which indicated that *N*-benzoylbenzyl imine was unstable in the presence of water or alcohol (Scheme 2). Therefore, we attempted to carry out the 1,3-dipolar cycloaddition of imine **1a** and carbonyl ylide which generated from **2a** and **3a** in the absence of protic nucleophiles (entries 1 and 2, Table 1). The corresponding oxazolidine **5** was smoothly constructed and detected by LC-MS, and two diastereoisomers of *α*-hydroxy-*β*-amino ester **6a** were successfully isolated through column chromatography after treated with trifluoroacetic acid in 40% yield and low diastereoselectivity (*syn*:*anti* = 30:70).

To ascertain the generality of this cycloaddition process, we surveyed a variety of Lewis acid co-catalysts[14] which have been proven to have a great effect on both diastereoselectivity and yield[15] (entries 2 to 5, Table 1), and the $AgPF_6$ gave the better result. Next, the aldehyde part was investigated. When using aryl aldehydes with electron donating groups such as *p*-methoxy and *o*-methyl (entries 7 and 10, Table 1), the yield moderately increased with a loss of diastereoselectivity. On the other hand, aromatic aldehydes with strong electron withdrawing groups such as *p*-trifluoromethyl and *p*-nitro gave rise to significant decrease of yield (entries 8 to 9, Table 1). To our surprise, the aldehyde substrates were not limited to aromatic aldehydes. When aliphatic aldehydes were used (entries 11 to 15, Table 1),

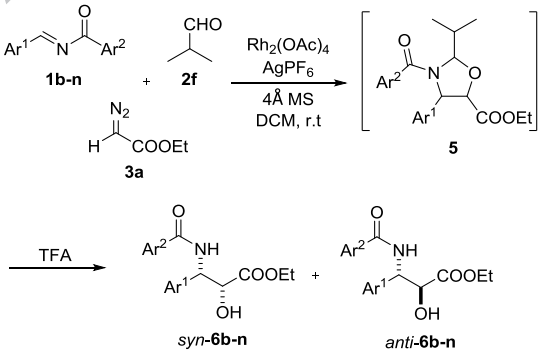
Table 1. Optimization of 1,3-dipolar cycloaddition.



entry[a]	R^1	co-catalyst	yield (%)[b]	dr[c] (*syn*:*anti*)
1	Ph(**2a**)	-	40	30:70
2	Ph	$Zn(OTf)_2$	33	58:42
3	Ph	$AgPF_6$	48	52:48
4	Ph	$Cu(OTf)_2$	31	55:45
5	Ph	AgOTf	33	55:45
6	Ph	*p*-TsOH	15	22:78
7	*p*-$MeOC_6H_4$(**2b**)	$AgPF_6$	45	31:69
8	*p*-CF_3-C_6H_4(**2c**)	$AgPF_6$	26	43:57
9	*p*-NO_2-C_6H_4(**2d**)	$AgPF_6$	trace	N.A
10	*o*-Me-C_6H_4(**2e**)	$AgPF_6$	47	40:60
11	*i*-Pr(**2f**)	$AgPF_6$	78	58:42
12	Bn(**2g**)	$AgPF_6$	trace	N.A
13	Cyclohexyl(**2h**)	$AgPF_6$	71	56:44
14	*n*-Pr(**2i**)	$AgPF_6$	76	58:42
15	*t*-Bu(**2j**)	$AgPF_6$	65	50:50

[a] The reaction was carried out with imine **1a** (1 equiv.), aldehyde **2a-j** (1.5 equivs.), $Rh_2(OAc)_4$ (2.0 mol%), co-catalyst (10 mol%) and 4Å MS in CH_2Cl_2 at room temperature with addition of EDA **3a** (1.5 equivs.) over 1h. Then TFA (3 equivs.) was added and stirred overnight to hydrolyze oxazolidine **5**.
[b] Isolated yield (two diastereoisomers).
[c] Determined by ^1H NMR spectroscopy of the crude reaction mixture.

Table 2. 1,3-Dipolar cycloaddition of isobutyraldehyde **2f**, EDA **3a** and *N*-benzoylbenzyl imine derivatives **1b-n**.



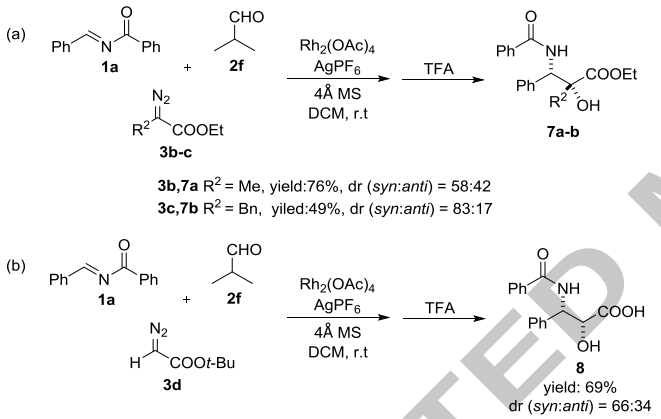
entry[a]	Ar^1	Ar^2	yield (%)[b]	dr[c] (*syn*:*anti*)
1	*m*-MeC_6H_4	Ph	56(**6b**)	58:42
2	*o*-BrC_6H_4	Ph	42(**6c**)	52:48
3	*p* -BrC_6H_4	Ph	56(**6d**)	54:46
4	*p* -$MeOC_6H_4$	Ph	51(**6e**)	49:51
5	*p* -MeC_6H_4	Ph	47(**6f**)	50:50
6	*p* -ClC_6H_4	Ph	53(**6g**)	55:45
7	*p* -$CF_3C_6H_4$	Ph	trace(**6h**)	N.A
8	Ph	*m*-BrC_6H_4	42(**6i**)	53:47
9	Ph	*p*-MeC_6H_4	48(**6j**)	54:46
10	Ph	*o*-FC_6H_4	54(**6k**)	45:55
11	Ph	*p*-$MeOC_6H_4$	52(**6l**)	60:40
12	Ph	*p* -ClC_6H_4	57(**6m**)	52:48
13	Ph	*p*-$NO_2C_6H_4$	trace(**6n**)	N.A

[a] The reaction was carried out with imine **1b-n** (1 equiv.), aldehyde **2f** (1.5 equivs.), $Rh_2(OAc)_4$ (2.0 mol%), $AgPF_6$ (10 mol%) and 4Å MS in CH_2Cl_2 at room temperature with addition of EDA **3a** (1.5 equivs.) over 1h. Then TFA (3 equivs.) was added and stirred overnight to hydrolyze oxazolidine **5**.
[b] Isolated yield (two diastereoisomers).
[c] Determined by ^1H NMR spectroscopy of the crude reaction mixture.

the desired product was obtained in apparently increasing yield with slightly promoted diastereoselectivity. Isobutyraldehyde **2f** gave the best performance, which improved the yield to 78% with 58:42 (*syn*:*anti*) diastereoselectivity. To the best of our knowledge, aliphatic aldehydes involved 1,3-dipolar cycloaddition of carbonyl ylides were very rare[11].

With the optimized reaction conditions established, a variety of imines were tested subsequently. As was shown in Table 2, in most cases, substituent imines afforded the target products in comparable yields and diastereoselectivities. However, when the imines with strong electron-withdrawing groups either on Ar^1 or Ar^2 were used, only complex mixtures were obtained and trace desired product was detected (entries 7 and 13, Table 2).

Different diazo compounds were also examined to extend the scope of this transformation (Scheme 3). Both **3b** and **3c** successfully afforded the target product **7a** and **7b**, respectively. It was notable that **3c** showed much better dr ratio (*syn*:*anti* = 83:17) than other diazo compounds. Moreover, when EDA was replaced with *tert*-butyl diazoacetate **3d**, the paclitaxel side chain **8** was successfully obtained in 69% yield with 66:34 (*syn*:*anti*) diastereoselectivity in one-pot protocol after deprotected by TFA (Scheme 3b).



Scheme 3. Scope extension of diazo components.

Conclusions

A facile and convenient approach to the *α*-hydroxy-*β*-amino acids and their derivatives has been reported, which goes through 1,3-dipolar cycloaddition and followed by hydrolysis under acidic conditions. Carbonyl ylides generated from aliphatic aldehyde and *N*-benzoylbenzyl imines are the matching components in this strategy. This method provides a direct access for the one-pot synthesis of paclitaxel side chain and derivatives of them. Further investigations of diastereoselectivity and enantioselectivity control are underway in our lab.

Acknowledgments

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Supplementary Material

Supplementary data associated with this article can be found in the online version, at…

Highlights:

- One-pot synthesis of paclitaxel side chain and its derivatives.
- Using imines with *N*-benzoyl as dipolarophile in cycloaddition with carbonyl ylide.
- Using carbonyl ylides generated from aliphatic aldehydes in this strategy.