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A Phosphane-Mediated Diastereoselective, Domino *aza*-Morita–Baylis–Hillman/Reduction Sequence Involving Water as Hydrogen Source

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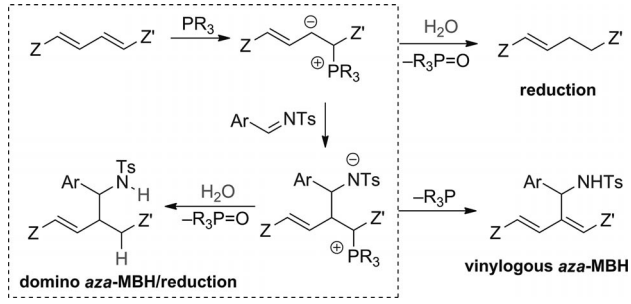
The new domino process disclosed here involves PBu_3 as both a nucleophilic and a reducing agent. The process combines suitable electron-poor dienes, *N*-tosylimines, tri-*n*-butylphosphane and water. The final products formally result from reduction of vinylogous *aza*-Morita–Baylis–Hillman adducts. The reaction proceeds with an excellent stereochemical control of the relative configurations of the newly created contiguous carbon centres.

Introduction

Wittig, Mitsunobu and Staudinger reactions are undoubtedly the most classical processes involving organophosphorus derivatives as stoichiometric reagents. In addition to these benchmark reactions, the synthetic utility of phosphorus compounds has been demonstrated by the use of trivalent phosphorus derivatives in other stoichiometric reactions,[1] including some recently disclosed reductions of olefins,[2] nitroalkanes,[3] ketones[4] and acyl cyanides.[5] Also, the reactivity of trivalent phosphorus derivatives has been utilized in a few domino sequences, which lead to pyrroles,[6] pyrrolidines,[7] cyclopropanes,[8] furanes,[9] dienes[10] or bicyclic ketones.[11] These reactions usually combine activation of an electron-poor unsaturated substrate (iminium salts, olefins, alkynes or allenes) by addition of the nucleophilic phosphane, an intermediate inter- or intramolecular transformation and, finally, a Wittig-type reaction or another mode of extrusion of phosphane oxide. The driving force of all the above processes is formation of the phosphane oxide.

Given the current interest in domino processes as a way to achieve high synthetic efficiency,[12] we intend to disclose here a new reaction sequence based on the peculiar reactivity of trivalent phosphanes. We demonstrate that phosphanes can be involved in a domino process that formally combines a vinylogous *aza*-Morita–Baylis–Hillman (MBH) type reaction[13] and a reduction step (Scheme 1). It involves water as the hydrogen source, and it is driven by oxidation of phosphorus through formal hydrolysis of a phosphonium salt intermediate.



Scheme 1. A domino *aza*-MBH/olefin reduction sequence mediated by trivalent phosphanes.

Results and Discussion

We have highlighted the domino *aza*-MBH/reduction process in Scheme 1 during our ongoing studies on the reactivity of *N*-tosylimines with doubly activated, electron-poor conjugated dienes under phosphane catalysis. These reactions usually produce pyrrolines by a catalytic multistep process based on the initial activation of the dienic substrates by the nucleophilic phosphane.[14,15] However, when considering 4-(3-oxopropenyl)chromenone (**1a**) as a potential substrate, we observed a different outcome. The reaction of **1a** with *N*-tosylbenzaldimine (**2a**) in the presence of tri-*n*-butylphosphane (20 mol-%) afforded the tosylamide-functionalized coumarin **3a** as the major product. Compound **3a** formally results from reduction of a vinylogous *aza*-Morita–Baylis–Hillman adduct, and, therefore, the observed reaction might be referred to as a "reductive *aza*-MBH reaction".[16]

The "reductive *aza*-MBH reaction" above requires stoichiometric amounts of both phosphane and water, and, consequently, additional experiments were run with stoichiometric amounts of these reagents[17] under the conditions shown in Scheme 2.[18]

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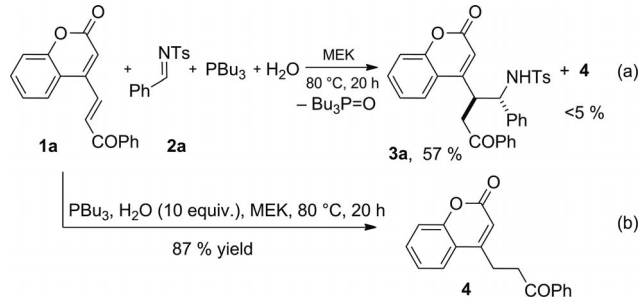


Scheme 2. A tri-*n*-butylphosphane-mediated, domino *aza*-MBH/reduction reaction and the related reduction of **1a**.

Compound **3a** was obtained as the major product (57% isolated yield), together with small amounts of side products. As mentioned in Scheme 1, plausible side reactions are the phosphane-mediated reduction of the starting olefin function,[2] as well as a vinylogous *aza*-MBH reaction.[13] Small amounts of the C=C reduction product **4** were detected indeed in the crude reaction mixture. The **4**/**3a** ratio increased when the amount of water in the reaction mixture was increased. Thus, in the presence of 2 equiv. of water, a 1:2 ratio is observed. Compound **4** could be isolated later in 87% yield, and fully characterized, from the reaction of **1a** and PBu_3 in the presence of excess water (Scheme 2b). Compound **4** is likely to be formed by hydrolysis of the zwitterionic phosphonium salt **A** (path d in Scheme 3), which is generated by α(δ′)-addition of the phosphane to the conjugated diene.

In the presence of *N*-tosylimines, the major reaction pathway should involve addition of the same intermediate, **A**, to the imine, which leads to **B**. Hydrolysis of **B**, either directly (path a) or via the corresponding phosphorus ylide (path b), will then afford the observed product **3a**. In principle, intermediate **B** might afford the vinylogous *aza*-Baylis–Hillman product also (path c); however, under the above conditions, the *aza*-Baylis–Hillman reaction was not observed at all.

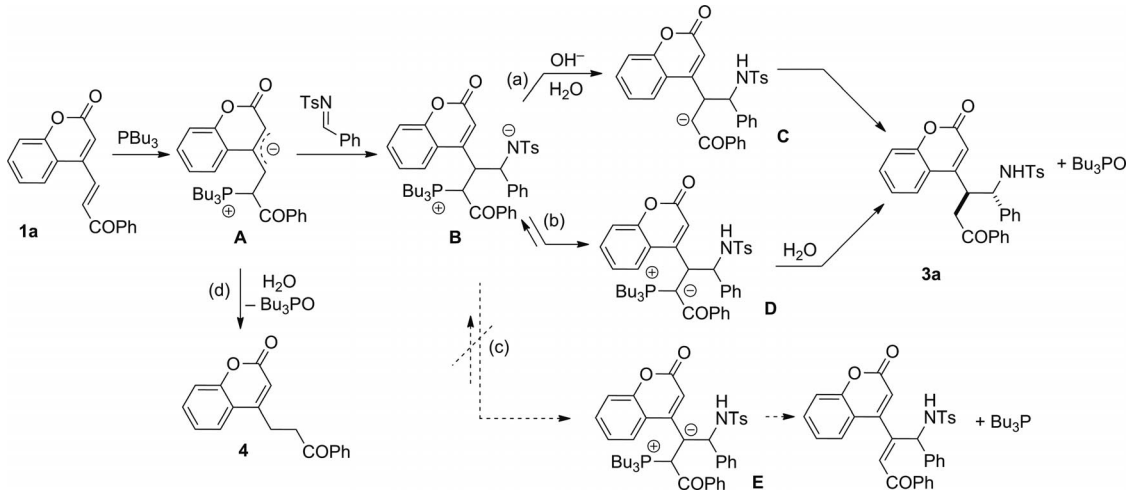
This excellent chemoselectivity suggests that, in this case, hydrolysis of the intermediate phosphonium salt **B** should be much faster than the 1,3-proton shift and phosphane elimination steps of the *aza*-Baylis–Hillman-type process (path c in Scheme 3).

We can reasonably assume that hydrolysis of the phosphonium salt **B** (path a) is favoured here since release of Bu_3PO will generate the benzoyl-stabilized carbanion **C**.[19] Also, the alternative hydrolysis pathway (b) that might be operating will involve a stabilized, benzoyl-substituted phosphorus ylide **D**.[20]

Therefore, the successful achievement of this domino sequence crucially relates to the presence of electron-withdrawing groups at both ends of the dienic unit of **1a**. According to our mechanistic proposal, initially the –OCO– function of coumarin will direct the addition of the nucleophilic phosphane to the terminal carbon [α(δ′)-addition], while the benzoyl function will favor the final hydrolysis step through either stabilization of the carbanionic intermediate **C** and/or generation of the phosphorus ylide **D**. These effects might govern the reaction outcome.

Beside the good chemoselectivity, another key feature of the domino reaction in Scheme 2 is its excellent diastereoselectivity. Indeed, although minor amounts of non-identified side products have been observed in the reaction mixture, only one of the two possible diastereomers of **3a** has been isolated. Its stereochemistry was ascertained by X-ray diffraction studies: as shown in the ORTEP drawing in Figure 1, compound **3a** displays (*S**,*S**) relative configurations of the two contiguous stereogenic centres. The origin of such high diastereoselectivity can hardly be established so far.

The good stereochemical control turns the domino reaction of Scheme 2 into a potentially synthetically useful process. Therefore, the scope of the reaction has been extended to a series of imines with aromatic or heteroaromatic substituents (Entries 1–6 in Table 1) as well as to imines with various protecting groups (Entries 7, 8). Also, the benzoyl substituent of **1a** has been replaced by a pivaloyl group in



Scheme 3. Postulated reaction pathways accounting for the observed formation of **3a** and **4**.

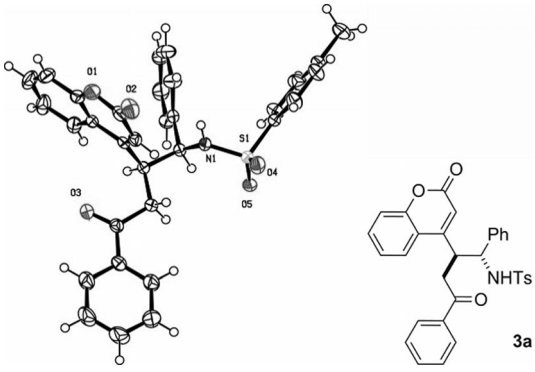
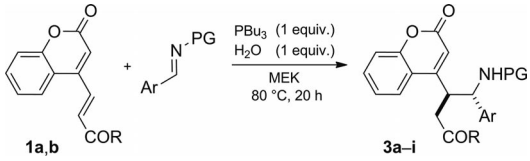


Figure 1. ORTEP view of **3a**, showing the *S**,*S** relative configurations of the stereogenic centres.

1b (Entry 9).[21] Compounds **3a**–**i** have been isolated in 30–70% yields.

Table 1. Domino *aza*-MBH/reduction reactions promoted by PBu_3.



Entry	Product	R	Ar	PG	Yield [%][a]
1	**3a**	Ph	Ph	Ts	57
2	**3b**	Ph	1-naphthyl	Ts	54
3	**3c**	Ph	2-thienyl	Ts	49
4	**3d**	Ph	4-Cl–C_6H_4	Ts	62
5	**3e**	Ph	2-Me–C_6H_4	Ts	47
6	**3f**	Ph	4-MeO–C_6H_4	Ts	24[b]
7	**3g**	Ph	Ph	4-Cl–$C_6H_4SO_2$	70
8	**3h**	Ph	Ph	4-NO_2–$C_6H_4SO_2$	32
9	**3i**	CMe_3	Ph	Ts	68

[a] Isolated yields, after chromatography. All reactions were performed on a 0.25-mmol scale. [b] The major product is the reduced compound **4** (**3f/4** ratio 35:65).

Except for Entry 6, the reductive *aza*-MBH products represent the major component of the crude reaction mixtures, which also contain variable amounts of the reduced derivative **4** shown in Scheme 2 (or the corresponding CMe_3 derivative for Entry 9).[22] Reduction of the olefinic bond becomes a competitive process when imines with lower electrophilicity are used, as, for instance, in Entry 6.

From most of the reactions in Table 1, the final products are isolated as single isomers, which shows that these domino reactions allow building of a C–C bond with excellent stereochemical control of the relative configurations of the two contiguous stereogenic carbon centres.

Conclusions

We have demonstrated a new, stereoselective phosphane-mediated domino process that formally combines a vinylogous *aza*-MBH and an olefin reduction step. As in the majority of domino processes, a subtle, proper choice of reaction partners is essential to drive the multiple-step sequence to the desired outcome. The process that has been evidenced here involves the dienic moiety of vinyl-substituted coumarins; however, other dienes with electron-withdrawing substituents at both ends might be suitable substrates as well. Extension of the method to other substrates is currently under investigation in our group.

Experimental Section

General Procedure for a Domino *aza*-Morita–Baylis–Hillman/Reduction Sequence: Tri-*n*-butylphosphane (0.25 mmol, 62 μL) was added dropwise to a solution of diene **1** (0.25 mmol) and imine (0.25 mmol) in degassed methyl ethyl ketone (MEK) (1 mL), under argon atmosphere. In initial experiments, the water content of MEK was measured as 3.2 mg/mL (0.18 mmol/mL). In other experiments, the volume of solvent was adapted, if needed, so as to have 1 equiv. of water in the reaction mixture. The reaction mixture was heated at 80 °C overnight. The crude mixture was then concentrated in vacuo and purified by column chromatography on silica gel [Combiflash apparatus, heptane-methyl *tert*-butyl ether (MTBE) gradients].

CCDC-836062 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental procedures, spectroscopic and analytical data and copies of ^1H and ^{13}C NMR spectra for all new compounds are presented.

Acknowledgments

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