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Catalytic highly enantioselective vinylogous Povarov reaction†

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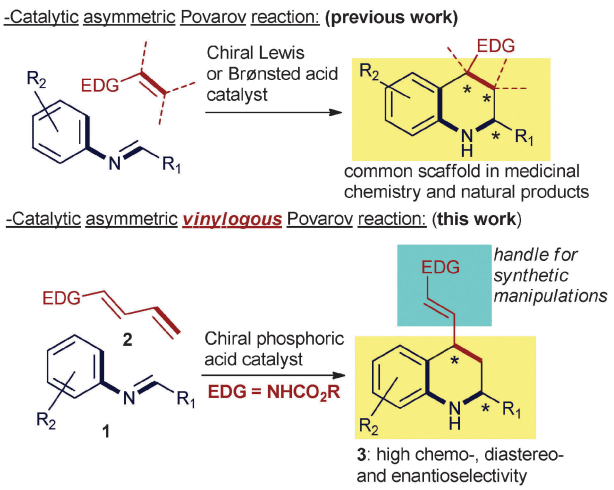
The first example of a catalytic asymmetric vinylogous Povarov reaction is presented. 1-*N*-Acylamino-1,3-butadienes react selectively at their terminal double bond in the presence of a chiral phosphoric acid catalyst, delivering highly enantioenriched 1,2,3,4-tetrahydroquinolines bearing a synthetically versatile enecarbamate group at the 4-position.

The 1,2,3,4-tetrahydroquinoline skeleton is a key structural element in medicinal chemistry, being the core of a variety of biologically active compounds (natural and synthetic).[1] Among the different methods for the preparation of 1,2,3,4-tetrahydroquinolines,[1] the inverse electron demand aza-Diels–Alder reaction between olefins and *N*-aryl imines (Povarov reaction)[2] is arguably one of the most efficient, versatile and atom-economical. The catalytic asymmetric version of this reaction has recently witnessed tremendous progress.[3] Following the exponential growth of chiral Brønsted acid catalysis,[4] various electron-rich olefins can now be engaged in catalytic enantioselective Povarov transformations, mostly by using BINOL derived phosphoric acids as catalysts.[3e–m] In all examples, to be sufficiently electron-rich for the addition to the lowered LUMO of the acid coordinated imine, the olefin bears an electron-donating group EDG, such as activated (hetero)arenes, ethers and carbamates (Scheme 1, top). These protocols complement and/or provide useful alternatives to the less studied chiral Lewis acid catalysed processes.[3a–d]

Conversely, there have been a few reports describing the non-enantioselective vinylogous counterpart of the Povarov reaction.[5,6] In these reactions, the electron donating properties of an EDG propagate through a π-system, activating for the cycloaddition a remote double bond which is not directly attached to the EDG. These protocols afford 1,2,3,4-tetrahydroquinolines bearing,



Scheme 1 Povarov reactions *vs.* vinylogous Povarov reactions.

at the 4-position, a functionality amenable to further synthetic manipulations, and thus might constitute a useful platform for the preparation of an array of products by using a single reaction. For this reason, we turned our attention towards the realisation of this transformation in a catalytic asymmetric fashion, taking advantage of our experience in chiral phosphoric acid catalysed cycloaddition reactions.[3m,7] Being conscious of the requirement of a handle for dienophile coordination to the Lewis basic phosphoryl oxygen of the catalyst,[8] we focussed on 1-carbamate substituted dienes **2** as potential dienophilic reaction partners. We were pleased to observe that in the presence of chiral phosphoric acid catalysts both the common Diels–Alder reactivity of dienes **2**[9] and the known propensity of β-alkyl enecarbamates to undergo Povarov reactions despite their steric hindrance[3g] were overridden in favour of a vinylogous reaction pathway, wherein the known Povarov reactivity of enecarbamates[3f–h] was moved to their vicinal double bond. Presumably, a combination of stereoelectronic factors controlled the chemoselectivity of the reaction,[10] allowing us to develop a highly chemo-, diastereo-, and enantio-selective cycloaddition between 1-carbamate butadienes **2** and *N*-aryl imines **1** (Scheme 1, bottom),

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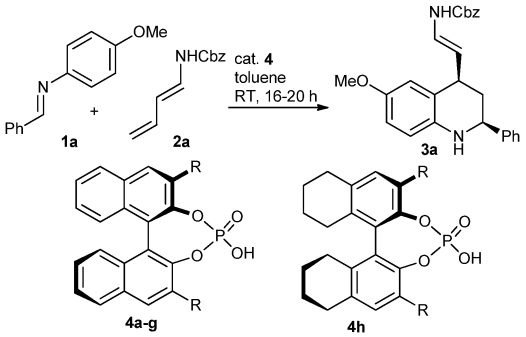
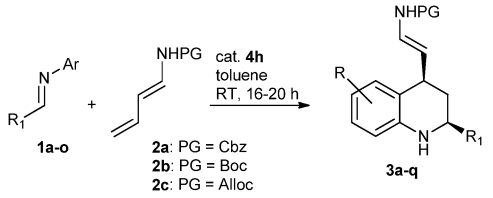
Table 1 Screening of catalysts and reaction conditions in the vinylogous Povarov reaction between imine **1a** and **2a**[a]



Entry	Cat. **4** (mol%)	R	MS[b]	Conv.[c] (%)	ee[d] (%)
1	**4a** (10)	C_6H_5	No	88	15
2	**4b** (10)	3,5-$(CF_3)_2C_6H_3$	No	78	60
3	**4c** (10)	2,4,6-(i-Pr)$_3C_6H_2$	No	72	13
4	**4d** (10)	4-$NO_2C_6H_4$	No	57	20
5	**4e** (10)	$SiPh_3$	No	30	10
6	**4f** (10)	9-Phenanthrenyl	No	49	7
7	**4g** (10)	9-Anthracenyl	No	59	92
8	**4h** (10)	9-Anthracenyl	No	80	98
9	**4h** (10)	9-Anthracenyl	4 Å[e]	84	98
10	**4h** (2.5)	9-Anthracenyl	4 Å	91	98
11	**4h** (1.0)	9-Anthracenyl	4 Å	85	98
12	**4h** (0.3)	9-Anthracenyl	4 Å	52	95

[a] Conditions: imine **1a** (0.05 mmol), catalyst **4**, dienophile **2a** (0.06 mmol), toluene (0.20 mL), RT, overnight. A single diastereoisomer was observed by ^{1}H NMR spectroscopy in the crude. [b] 20 mg molecular sieves were employed where indicated. [c] Conversion, as determined by ^{1}H NMR spectroscopy on the crude mixture. [d] Determined by chiral stationary phase HPLC. [e] Very similar results were obtained with 3 and 5 Å MS.

Table 2 Scope of the vinylogous Povarov reaction[a]



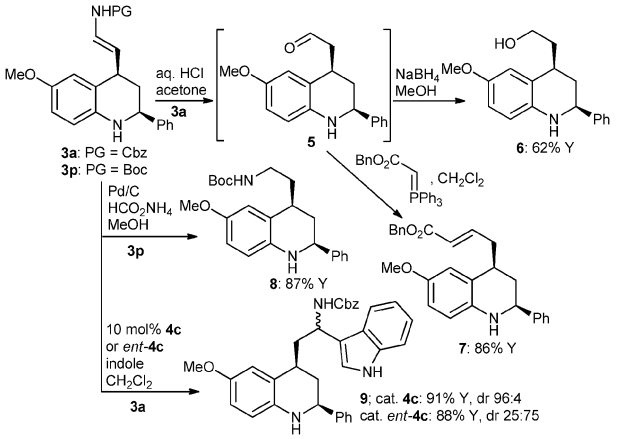
Entry	**1**	R_1	Ar	**2**	**3**-Yield[b] (%)	ee[c] (%)
1	**1a**	C_6H_5	4-$MeOC_6H_4$	**2a**	**3a**-85	98
2[d]	**1a**	C_6H_5	4-$MeOC_6H_4$	**2a**	**3a**-70	98
3	**1b**	4-BrC_6H_4	4-$MeOC_6H_4$	**2a**	**3b**-83	99
4	**1c**	2-BrC_6H_4	4-$MeOC_6H_4$	**2a**	**3c**-90	92
5	**1d**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**2a**	**3d**-78	99
6	**1e**	3,4-$(MeO)_2C_6H_3$	4-$MeOC_6H_4$	**2a**	**3e**-63	99
7	**1f**	2-Naphthyl	4-$MeOC_6H_4$	**2a**	**3f**-91	98
8[d]	**1f**	2-Naphthyl	4-$MeOC_6H_4$	**2a**	**3f**-70	>99
9	**1g**	1-Naphthyl	4-$MeOC_6H_4$	**2a**	**3g**-79	89
10	**1h**	2-Thienyl	4-$MeOC_6H_4$	**2a**	**3h**-53	87
11[d]	**1i**	i-Pr	4-$MeOC_6H_4$	**2a**	**3i**-80	99
12[d]	**1j**	$Ph(CH_2)_2$	4-$MeOC_6H_4$	**2a**	**3j**-76	84
13	**1k**	C_6H_5	C_6H_5	**2a**	**3k**-94	99
14	**1l**	4-BrC_6H_4	C_6H_5	**2a**	**3l**-74	99
15	**1m**	C_6H_5	3,4-$(MeO)_2C_6H_3$	**2a**	**3m**[e]-63	97
16	**1n**	C_6H_5	4-ClC_6H_4	**2a**	**3n**-25	98
17	**1o**	C_6H_5	3-BrC_6H_4	**2a**	**3o**[f]-60	99/99
18	**1a**	C_6H_5	4-$MeOC_6H_4$	**2b**	**3p**-89	99
19[d]	**1a**	C_6H_5	4-$MeOC_6H_4$	**2b**	**3p**-90	98
20	**1a**	C_6H_5	4-$MeOC_6H_4$	**2c**	**3q**-73	99

[a] Conditions: **1a–o** (0.15 mmol), **4h** (0.00375 mmol), **2a–c** (0.18–0.30 mmol), toluene (0.60 mL), 4 Å MS (20 mg), RT, 16–20 h. A single diastereoisomer was observed by ^{1}H NMR spectroscopy in the crude mixture. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Imine formed *in situ*. 110 mg 4 Å MS and 5 mol% **4h** were employed. [e] The 6,7-$(MeO)_2$ regioisomer was exclusively observed in the crude. [f] dr: 2.8 : 1. The 7-bromo regioisomer was exclusively observed in the crude.

which represents the first example of a catalytic asymmetric vinylogous Povarov reaction.[6,11] Importantly, the reaction renders highly diastereo- and enantioenriched 1,2,3,4-tetrahydroquinolines **3** bearing an enecarbamate moiety at the 4-position. Given the rich chemistry of enecarbamates,[12] which has been recently considerably expanded in the frame of chiral phosphoric acid catalysis,[13] this moiety bears great potential for further (one-pot) synthetic elaborations.

We started our investigations by screening a series of common (*R*)-BINOL derived phosphoric acid catalysts **4a–g**[4b-f] in the reaction between *N*-4-methoxyphenyl imine **1a** and *trans-N*-Cbz-1-amino-1,3-butadiene **2a**[9a] (Table 1, entries 1–7), in toluene as solvent. All catalysts were able to promote the reaction overnight, giving the cycloadduct **3a** in low to moderate conversion and as a single diastereoisomer. Amongst the catalysts tested, only **4b** and **4g** induced significant enantioselectivity (Table 1, entries 2 and 7). A further improvement was achieved by employing **4h**,[14] the H_8-BINOL derivative of **4g**, which gave **3a** in a nearly enantiopure form (Table 1, entry 8). With this catalyst, an enhancement in catalytic activity was observed by employing molecular sieves in the reaction (Table 1, entry 9). By using these drying agents it was possible to decrease the catalyst loading to 1 mol%, affecting only marginally conversion and enantioselectivity (Table 1, entries 10 and 11). A further decrease to 0.3 mol% lowered the conversion (Table 1, entry 12). A preliminary reaction progress kinetic analysis[15] (see ESI†) suggested that the low conversion with <1 mol% loading is not due to insufficient catalyst activity, but rather due to deactivation of the catalyst during the reaction course. Control experiments showed that this deactivation is neither due to catalyst inhibition by the product nor due to the molecular sieves. It was also confirmed that the reaction is first order in catalyst.

The scope of the reaction was then inspected (Table 2), by using the optimal catalyst **4h** at 2.5 mol% loading instead of 1 mol%, in order to employ a more robust procedure. Imines **1a–h**, derived from (hetero)aromatic aldehydes, could be employed with very good results (Table 2, entries 1–10). Variations at the aniline moiety in imines **1k–o** afforded the corresponding cycloadducts **3k–o** in variable yields, but excellent enantioselectivities in all cases (Table 2, entries 13–17). Full regioselectivity, favouring the least sterically hindered product, was observed in the reactions with imines **1m** and **1o** (Table 2, entries 15 and 17). Surprisingly, the reaction with the *N*-3-bromophenyl imine **1o** furnished the corresponding **3o** as a diastereomeric mixture at C2–C4, favouring the 2,4-*trans* isomer which was not even observed in any of the other examples. Different protecting groups in the dienophile **2**, such as the Boc and Alloc groups in **2b** and **2c**, gave results comparable to their Cbz counterpart **2a** (Table 2, entries 1, 18 and 20). The reaction was then implemented to its three-component version. Due to the sensitivity of the activity of catalyst **4h** to water, it turned out to be necessary to employ a larger amount of molecular sieves and a slightly increased catalyst loading (5 mol%). Under these conditions, products **3**



Scheme 2 Synthetic elaborations on the catalytic products.

were obtained with results comparable to the two-component procedure (Table 2, entries 2, 8 and 19), and, importantly, the reaction scope could be expanded to the unstable imines **1i,j** derived from enolisable aldehydes (Table 2, entries 11 and 12).

The relative configuration of adduct **3k** was determined as 2,4-*cis* (and *E* at the double bond) by NMR spectroscopy, whereas a comparison of the calculated (TD-DFT) with the experimental ECD spectrum[16] of this compound gave its absolute configuration as (2*S*,4*R*),[17] in line with previous phosphoric acid catalysed Povarov reactions.[3f–m,8c]

Cycloadducts **3a** and **3p** were then subjected to a few transformations at their enecarbamate moieties (Scheme 2). Hydrolysis in **3a** gave aldehyde **5**, conveniently isolated after reduction or Wittig olefination. Reduction of the double bond in Boc protected **3p** furnished the primary amine **8**, whereas addition of indole to the *N*-Cbz enecarbamate of **3a** was efficiently carried out under phosphoric acid (**4c**) catalysis.[13b,c] The stereochemistry of the newly formed chiral centre in **9** could be partially controlled by the enantiomer of the catalyst **4c** employed, and, remarkably, this transformation could be readily implemented in a one-pot process, furnishing adduct **9** in 61% yield, 96 : 4 dr and 99% ee directly from imine **1a**, dienophile **2a** and indole (see ESI†).

In summary, disclosing a new vinylogous reactivity of 1-acylamino dienes **2** towards *N*-aryl imines **1**, we have developed the first catalytic enantioselective vinylogous Povarov reaction, promoted by chiral phosphoric acids.

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