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Organocatalytic asymmetric Povarov reactions with 2- and 3-vinylindoles†‡§

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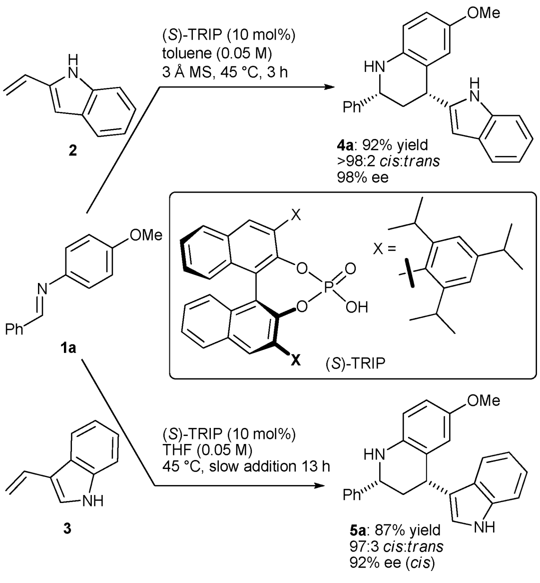
The asymmetric Povarov reaction of *N*-arylimines with 2- and 3-vinylindoles has been developed using a chiral phosphoric acid ((*S*)-TRIP) as catalyst. The peculiar reactivity of vinylindoles allowed also the disclosure of a Povarov Friedel–Crafts sequence, and the trapping of the reaction intermediate with nucleophilic species, thus providing a versatile platform for the preparation of highly enantioenriched indole derivatives.

The Povarov reaction is an inverse-electron-demand [4 + 2] cycloaddition between an *N*-arylimine (diene) and an electron-rich olefin (dienophile).[1] This transformation represents one of the most versatile entries to 1,2,3,4-tetrahydroquinolines, heterocyclic compounds which have been shown to possess a broad range of biological activity.[2] Despite their high potential, only a handful of examples describing catalytic asymmetric Povarov reactions have been reported.[3–5] Available methods make use of vinylethers or cyclopentadiene (Grieco cycloaddition)[6] as dienophiles, often in combination with chelating *N*-2-hydroxyphenyl imines activated by chiral Lewis or Brønsted acids.[4a–c] The limited range of dienophiles, together with the requirement of a specific aryl group at the imine nitrogen in some cases, pose serious limitations to the structural variety of accessible 1,2,3,4-tetrahydroquinolines. Only very recently, the range of dienophilic components was extended to also encompass enecarbamates, in a very efficient Povarov reaction catalyzed by a chiral phosphoric acid.[4d]

During our investigations on organocatalytic Diels–Alder reactions of vinylindole derivatives[7] using H-bond driven organocatalysis,[8] we observed an unprecedented inverse-electron-demand [4 + 2] cycloaddition[9] (Povarov reaction) between *N*-arylimines **1** and the double bond of 2- and 3-vinylindoles **2** and **3**. Envisaging the activation of imines by H-bond interactions with a chiral catalytic system, we set out to develop an asymmetric version of this transformation. Herein, we present our efforts towards this goal, giving the first catalytic asymmetric Povarov reaction in the vinyl(hetero)arene series. Besides, the peculiar reactivity of 2- and 3-vinylindole rendered possible the development of a Povarov–Friedel–Crafts[10] sequence, as well as the interception of the Povarov intermediate[11] with a nucleophilic species (*vide infra*).

At the outset of our studies BINOL-derived phosphoric acids[12,13] were unsurprisingly found to be the most competent catalytic systems for the asymmetric Povarov reactions with vinylindoles **2** and **3**. A thorough screening of catalyst structures and reaction conditions in the reaction with **2** was then undertaken (see ESI†). Optimised conditions derived from this screening entailed the use of (*S*)-TRIP as catalyst,[13c,14] toluene as solvent, in the presence of 3 Å molecular sieves (MS) at 45 °C, furnishing the Povarov cycloadduct **4a** derived from imine **1a** in very good yield, as a single *cis* diastereoisomer and with almost perfect enantioselectivity (Scheme 1, top). Translation of these conditions to the reaction with 3-vinylindole **3** was however not possible (see ESI†). This more electron-rich olefin was in fact found to be much more sensitive to the acidic catalyst, resulting mainly in decomposition and giving a very poor yield in the cycloadduct **5a**. Although the use of a lower temperature or pyridine as an additive[15] did not give any improvement, it was found after considerable experimentation that employing a coordinating solvent such as THF, and adding slowly a solution of the olefin to the reaction mixture over 12 h, it was possible to obtain **5a** with results comparable to **4a** (Scheme 2, bottom).



Scheme 1 Optimised reaction conditions.

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‡ Dedicated to Prof. Pelayo Camps on the occasion of his 65th birthday.

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With this set of conditions, the scope of both Povarov cycloadditions was first inspected using a range of *N*-arylimines **1a–j** derived from the condensation of 4-methoxyaniline with various aldehydes (Table 1). Schiff bases **1a–h**, obtained from aromatic or heteroaromatic aldehydes, all furnished the corresponding cycloadducts **4a–h** and **5a–h** with excellent results in terms of yields, diastereo- and enantio-selectivities, irrespective of the steric or electronic properties of the Schiff base employed (entries 1–8). Using a three-component procedure involving the formation of the imine *in situ*, even unstable imines derived from aliphatic enolisable aldehydes such as **1i** and **1j** could then be successfully engaged in these Povarov cycloadditions (entries 9,10). The simultaneous slow addition of phenethylaldehyde and **3** could overcome the instability of both imine **1j** and **3** in the presence of the acidic (*S*)-TRIP catalyst. The relative configuration of compounds **4a**, **4i** and **5i** was determined as 2,4-*cis* by NMR experiments, whereas the absolute configuration of **4a** could be assigned as 2*R*,4*R* by theoretical calculations of the ECD spectrum and $[\alpha]_D$ value, using time-dependent density functional theory (see ESI†).[16] Structural variation at the aromatic core of the 1,2,3,4-tetrahydroquinolines **4** and **5** was then achieved using Schiff bases **1k–n** derived from the combination of benzaldehyde with different anilines, which furnished smoothly the expected cycloadducts **4k–n** and **5k–n** with good results under the optimised conditions (Fig. 1). Of special interest are the cycloaddition reactions of **1l** and **1m**, which can lead to two regioisomeric products depending on the imine aromatic carbon undergoing the [4 + 2] cyclization.[11] Whereas the reactions with the *N*-2-naphthyl imine **1l** seemed to be ruled by electronic factors, rather than sterics, giving the single regioisomeric products **4l** and **5l** deriving from cyclization at the 1-naphthyl carbon, the 3,4-dimethoxyaniline Schiff base **1m** cyclised selectively at its less hindered position with 3-vinylindole **3**, while giving a nearly equimolar regioisomeric mixture with **2**.

In the reactions with 2-vinylindole **2**, the typical nucleophilic (*e.g.* Friedel–Crafts) reactivity of the C3 carbon of the indole nucleus is overridden by the Povarov cycloaddition at the C2 olefinic moiety. This reaction outcome is rather unusual, considering the known propensity of indole to undergo Friedel–Crafts type processes at C3.[10,17] Exploiting this latent reactivity of the indole moiety, the Povarov cycloadducts **4** obtained are thus susceptible to further functionalisation. Indeed, treatment of the reaction mixture with methyl vinylketone (MVK) and a mild Lewis acid catalyst, after the cycloaddition between **1a** and **2** had taken place, gave the

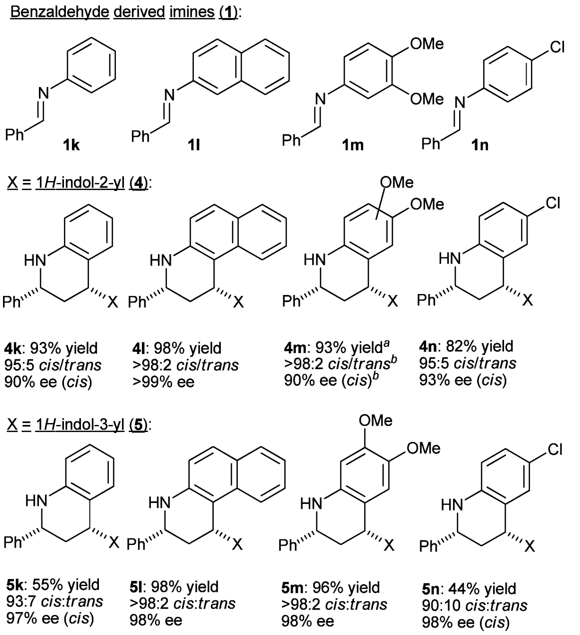
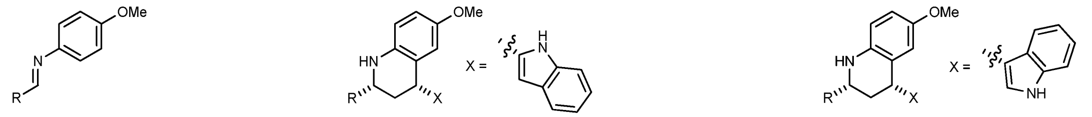


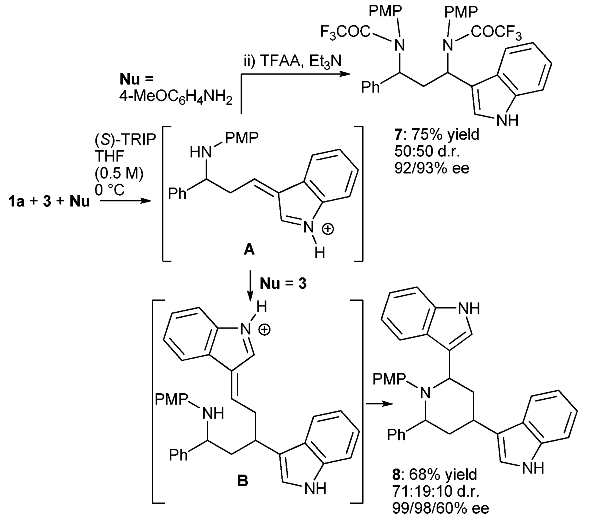
Fig. 1 [a]Refers to the mixture of regioisomers (58 : 42). [b]Refers to the 5,6-dimethoxy regioisomer.

Table 1 Scope of the catalytic enantioselective Povarov reactions of 4-methoxyaniline derived imines **1a–j** with 2- and 3-vinylindoles **2** and **3**[a]



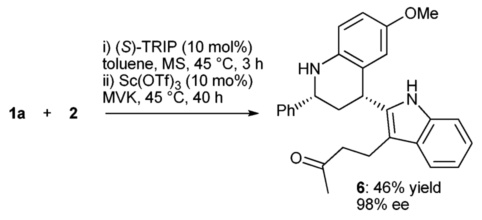
Entry	1	R	4-Yield[b] (%)	*Cis* : *trans*[c]	ee[d] (%)	5-Yield[b] (%)	*Cis* : *trans*[c]	ee[d] (%)
1	**1a**	C_6H_5	**4a**-92	>98 : 2[e]	98[f]	**5a**-87	97 : 3	92
2	**1b**	2-BrC_6H_4	**4b**-98	95 : 5	96	**5b**-96	>98 : 2	90
3	**1c**	4-BrC_6H_4	**4c**-66[g]	>98 : 2	>99[g]	**5c**-86	96 : 4	93
4	**1d**	4-MeOC_6H_4	**4d**-88	90 : 10	97	**5d**-57	95 : 5	84
5	**1e**	$3,4\text{-(MeO)}_2C_6H_3$	**4e**-96	>98 : 2	92	**5e**[h]-86	95 : 5	91
6	**1f**	1-Naphthyl	**4f**-97	>98 : 2	95	**5f**-84	>98 : 2	87
7	**1g**	2-Naphthyl	**4g**-96	>98 : 2	92	**5g**-53	98 : 2	90
8	**1h**	2-Thienyl	**4h**-91	95 : 5	>99	**5h**[h]-63	90 : 10	97
9[i]	**1i**	i-Pr	**4i**-98	>98 : 2[e]	96	**5i**[j]-90	98 : 2[e]	73
10[i]	**1j**	$Ph(CH_2)_2$	**4j**-95	>98 : 2	>99	**5j**[k]-90	>98 : 2	89

[a] Conditions for **4**: imine **1** (0.10 mmol), (*S*)-TRIP (7.5 mg, 0.010 mmol, 10 mol%), in toluene (2.0 mL), 3 Å MS (200 mg), 2-vinylindole **2** (17.2 mg, 0.12 mmol), 45 °C, 3–20 h. Conditions for **5**: imine **1** (0.10 mmol), (*S*)-TRIP (7.5 mg, 0.010 mmol, 10 mol%), in THF (2.0 mL), 45 °C, 3-vinylindole **3** (21.4 mg, 0.15 mmol) in THF (1.0 mL), slowly added (syringe pump) in 12 h, then 1 h. [b] Isolated yield after chromatography on silica gel. [c] Determined by ^{1}H NMR spectroscopy on the crude mixture. [d] Determined by chiral stationary phase HPLC, refers to the major diastereoisomer. [e] Relative configuration determined as 2,4-*cis*. [f] Absolute configuration determined as 2*R*, 4*R*. [g] After precipitation. [h] 3.0 equiv. of **3** were used. [i] Imine formed *in situ*. [j] Reaction performed in EtOAc and adding **3** all at once. [k] Reaction performed in EtOAc at rt, aldehyde and **3** were added slowly (syringe pump).



Scheme 2 Nucleophilic interception of Povarov intermediate **A**. TFAA = trifluoroacetic anhydride; PMP = 4-methoxyphenyl.

2,3-disubstituted indole derivative **6** [eqn (1)]. Despite the moderate yield, calculated over two steps, the present one pot transformation is able to afford very rapidly a rather complex 2,3-disubstituted indole.



(1)

Conversely, the high degree of stabilisation of the intermediate **A** in the reactions with 3-vinylindole **3** rendered possible its nucleophilic interception (Scheme 2).[11,18] To favour the intermolecular trapping of **A** against the intramolecular ring closure leading to the Povarov cycloadduct, reactions were performed at higher concentration. Under these conditions, using 4-methoxyaniline as the nucleophilic trapping component, the 1,3-diamine **7** could be isolated in good yield, after derivatisation with trifluoroacetic anhydride (Scheme 2). We also found that 3-vinylindole **3** itself could be employed as the intercepting agent, if added in excess (5 equiv.). In this latter case, the reaction afforded piperidine **8** resulting from intramolecular ring closure of the amine nitrogen to the second indol-3-yl stabilised cationic intermediate **B**.[19]

In conclusion, a reaction manifold was developed based on the Povarov reactivity of 2- and 3-vinylindoles with *N*-arylimines, in the presence of (*S*)-TRIP as catalyst. Taken together, the results presented here give a versatile synthetic platform for the construction of enantioenriched compounds containing an indole moiety, a very common structure in natural and bioactive molecules.

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