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Chiral Brønsted Acid-Catalyzed Enantioselective Three-Component Povarov Reaction

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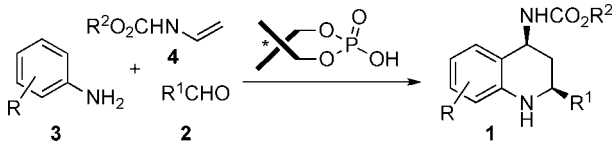
The Povarov reaction,[1] an inverse electron-demand aza-Diels−Alder (IEDDA) reaction between 2-azadienes and electron-rich olefins, allows a rapid construction of polysubstituted tetrahydroquinolines. The reaction is catalyzed by either protic or Lewis acids, and a three-component version starting from aniline, aldehyde, and olefin is known.[2] The development of an enantioselective Povarov reaction has nevertheless met with limited success. The BINOL−lanthanide complexes and aminodiol−titanium (IV) complexes developed by Ishitani and Kobayashi[3a] and Sundararajan et al.,[3b] respectively, are notable examples. More recently, Akiyama et al. reported an elegant Brønsted acid-catalyzed Povarov reaction between a vinyl ether and *N*-arylimines.[4,5] Notwithstanding these achievements, two issues still await solution: (a) *N*-arylimines derived from aliphatic aldehydes were excluded in the reported enantioselective processes, and the use of *o*-hydroxyaniline is mandatory in Akiyama's protocol; (b) an enantioselective three-component Povarov reaction remains unknown. Indeed, the complexity of the reaction mechanism and the reversibility of reaction steps often associated with multicomponent reactions (MCRs) have made the development of enantioselective MCRs a significant challenge.[6]

In continuation of our research program in the field of catalytic enantioselective MCRs,[7] we were interested in developing a catalytic enantioselective three-component Povarov reaction (Scheme 1). The enecarbamate **4**[8] was chosen as the dienophile for following

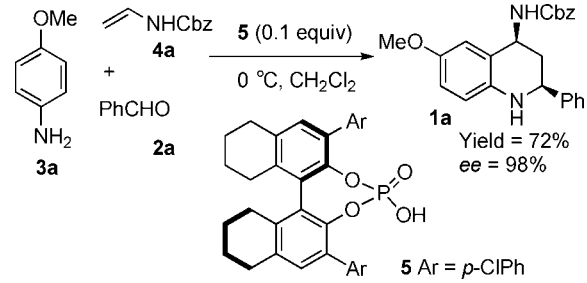
Scheme 1. Catalytic Enantioselective Three-Component Povarov Synthesis of 2,4-Disubstituted 1,2,3,4-Tetrahydroquinolines



reasons: (a) its NH function could form a hydrogen bond with the catalyst, potentially avoiding the need for the OH function in the anilines **3**; (b) the resulting product, (2,4-*cis*)-4-amino-2-alkyl(aryl)-1,2,3,4-terahydroquinoline (**1**) is an important structural subunit found in bioactive natural products[9] and drug candidates.[10] Here we report the first example of a chiral, phosphoric acid-catalyzed, highly enantioselective three-component Povarov reaction with a wide application scope and document the reversal of enantiofacial selectivity relative to Akiyama's catalytic system.

A three-component reaction involving benzaldehyde (**2a**), 4-methoxyaniline (**3a**), and benzyl *N*-vinylcarbamate (**4a**) in the presence of BINOL-derived phosphoric acids was examined (Scheme 2). After surveying the reaction conditions by varying the catalyst, solvent, temperature, and stoichiometry, we were pleased to find that the reaction performed in CH_2Cl_2 at 0 °C in the presence of 10 mol % catalyst **5** derived from octahydro-(*R*)-BINOL (see the Supporting Information for details) afforded compound **1a** (R = 6-OMe, R^1 = Ph, R^2 = Bn) as a single diastereomer[11] in 72%

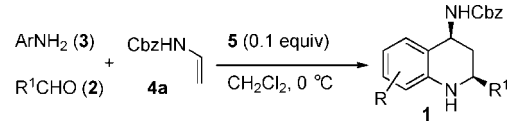
Scheme 2. Chiral Phosphoric Acid (**5**)-Catalyzed Enantioselective Three-Component Povarov Reaction



yield and 98% ee. The use of methyl *N*-vinylcarbamate (**4b**, R^2 = Me) as the dienophile under otherwise identical conditions afforded the corresponding adduct in lower yield and reduced enantioselectivity. The isomerization of enecarbamate to *N*-acylimine that would deviate from the desired reaction sequence was not observed.[12]

The scope of this Brønsted acid-catalyzed three-component Povarov reaction was next examined. As shown in Table 1, electron-neutral,

Table 1. Scope of the Enantioselective Brønsted Acid-Catalyzed Three-Component Povarov Reaction[a]



entry	R^1 (**2**)	Ar (**3**)	**1**	yield (%)[b]	ee (%)[c]
1	*p*-ClC_6H_4 (**2b**)	*p*-$MeOC_6H_4$ (**3a**)	**1b**	74	99
2	*p*-PhC_6H_4 (**2c**)	*p*-$MeOC_6H_4$ (**3a**)	**1c**	89	98
3	*p*-FC_6H_4 (**2d**)	*p*-$MeOC_6H_4$ (**3a**)	**1d**	72	99
4	*p*-MeC_6H_4 (**2e**)	*p*-$MeOC_6H_4$ (**3a**)	**1e**	64	>99
5	2-furyl (**2f**)	*p*-$MeOC_6H_4$ (**3a**)	**1f**	85	97
6	*p*-BrC_6H_4 (**2g**)	*p*-$MeOC_6H_4$ (**3a**)	**1g**	72	>99
7	*p*-NCC_6H_4 (**2h**)	*p*-$MeOC_6H_4$ (**3a**)	**1h**	75	>99
8	*p*-(*i*-Pr)C_6H_4 (**2i**)	*p*-$MeOC_6H_4$ (**3a**)	**1i**	68	>99
9	*p*-$NO_2C_6H_4$ (**2j**)	*p*-$MeOC_6H_4$ (**3a**)	**1j**	80	>99
10	*p*-$CF_3C_6H_4$ (**2k**)	*p*-$MeOC_6H_4$ (**3a**)	**1k**	79	>99
11	*i*-$PrCH_2$ (**2l**)	*p*-$MeOC_6H_4$ (**3a**)	**1l**	85	92
12	*i*-Pr (**2m**)	*p*-$MeOC_6H_4$ (**3a**)	**1m**	77	95
13[d]	Et (**2n**)	*p*-$MeOC_6H_4$ (**3a**)	**1n**	82	92
14[d]	*n*-propyl (**2o**)	*p*-$MeOC_6H_4$ (**3a**)	**1o**	90	92
15[d]	Et (**2n**)	*p*-$CF_3C_6H_4$ (**3b**)	**1p**	57	93
16	Ph (**2a**)	Ph (**3c**)	**1k**	74	99
17	Ph (**2a**)	*p*-ClC_6H_4 (**3d**)	**1r**	89	>99

[a] General conditions: aldehyde **2** (0.10 mmol), amine **3** (0.10 mmol), **4a** (0.11 mmol), and **5** (0.01 mmol) in CH_2Cl_2 (1.0 mL). [b] Yields referred to chromatographically pure product. [c] Enantiomeric excess was determined by chiral HPLC analysis. [d] Reaction performed at −30 °C.

-rich, and -poor aromatic aldehydes all served as appropriate substrates, providing diverse tetrahydroquinolines in good yields. Both the enantioselectivities (98 to >99%) and diastereoselectivities (>95:5 dr) were uniformly high. In some cases, three-component adducts were obtained in greater than 99% ee. Aliphatic aldehydes have usually been

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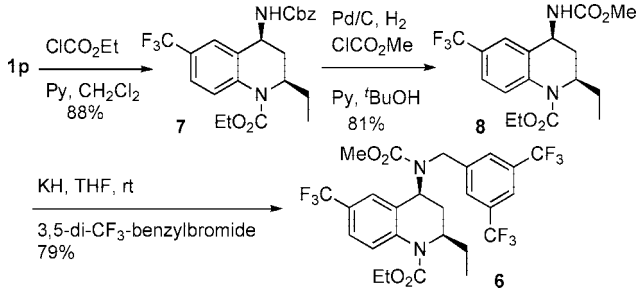
found to be poor substrates for the Povarov reaction because of the competitive isomerization of the aliphatic *N*-arylimine intermediates to the corresponding enamines.[2,13] It was thus remarkable to observe that the present catalytic process was also applicable to aliphatic aldehydes. Indeed, both α- and *β*-branched aldehydes (**2l** and **2m**, respectively) efficiently provided the corresponding tetrahydroquinolines **1l** and **1m** with excellent enantioselectivities (entries 11 and 12). The linear aldehydes **2n** and **2o** gave adducts with better yields and ee when the reaction was carried out at −30 °C (entries 13−15). A wide range of diversely functionalized anilines, including electron-poor ones (entries 15 and 17), were suitable partners to afford the corresponding adducts in moderate to high yields and excellent enantioselectivities (up to 99% ee). The absolute configuration of **1r** was unambiguously determined by X-ray analysis to be (2*S*,4*S*) (see the Supporting Information).

To illustrate the power of this novel catalytic enantioselective three-component Povarov reaction, we undertook an enantioselective synthesis of torcetrapib (**6**) (Scheme 3).[14] Reaction of 4-trifluoromethylaniline (**3b**), propionaldehyde (**2n**), and enecarbamate **4a** in the presence of a catalytic amount of **5** afforded tetrahydroquinoline **1p** in 57% yield with 93% ee (Table 1, entry 15). Ethoxycarbonylation of the secondary amine under standard conditions provided **7** in 88% yield. Deprotection of *N*-Cbz of **7** and in situ acylation of the resulting primary amine with methylchloroformate under hydrogenolysis conditions furnished **8** in 81% yield. Finally, benzylation of the secondary amide with 3,5-bis(trifluoromethyl)benzyl bromide afforded **6** in four steps in 32% overall yield.[10b,c,14]

Scheme 3. Synthesis of Torcetrapid (**6**) Featuring a Key Enantioselective Three-Component Povarov Reaction



It is interesting to note that the absolute configuration of the tetrahydroquinolines **1** is different from that obtained by Akiyama, although the chiral phosphoric acids used in both cases were derived from (*R*)-BINOL. One possible explanation for this reversal of enantiofacial selectivity could be the difference in H-bonding models (Figure 1). In Akiyama's catalytic system, the phosphoric acid activated only the electrophile via the participation of the *o*-hydroxy group.[4] The *Re*-face attack by the enecarbamate on the imine via transition state **9** would afford the (2*R*,4*R*) stereoisomer. In our case, we assumed that the phosphoric acid acted as a bifunctional catalyst that activates both the nucleophile and electrophile via transition state **10** to allow a pseudointramolecular *Si*-face attack by **4a** on the imine. To gain support for our working hypothesis, the reactions of **3a** and **2a** with benzyl *N*-methyl-*N*-vinyl carbamate (**4c**) and *N*-Cbz-2-pyrroline (**4d**) were performed. With **4c**, no reaction was observed, while with **4d**, the corresponding adduct (all-cis isomer, dr >99/1) was isolated in 30% yield with only 25% ee. These control experiments indicated that the N−H function in carbamate **4a** was essential not only for the enantioselectivity but also for the reactivity.

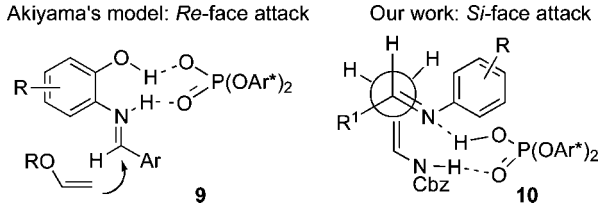


Figure 1. Activation modes and stereochemical outcomes.

In summary, we have successfully developed the first catalytic enantioselective three-component Povarov reaction. A wide variety of aromatic and aliphatic aldehydes as well as anilines with different electronic properties were tolerated. This approach combines the advantages of both MCRs and organocatalysis, leading to a highly efficient synthesis of enantiomerically enriched (2,4-*cis*)-4-amino-2-aryl(alkyl)-tetrahydroquinolines. Its application has led to the development of a short, efficient synthesis of torcetrapib.

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Supporting Information Available: Synthetic procedures, catalysis optimization, spectroscopic data, ee measurement, and X-ray data for **1r** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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