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# Direct Catalytic Asymmetric Synthesis of Cyclic Aminals from Aldehydes

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Despite the enormous advancements of asymmetric catalysis, the catalytic enantioselective generation of acetals and related compounds only recently became a possibility. Inspired by the advent of asymmetric Brønsted acid catalysis,[1,2] Antilla et al. developed phosphoric acid catalyzed syntheses of acyclic aminals and hemiaminals via additions of amides and alcohols to preformed imines.[3] Realizing the ubiquitous occurrence of stereogenic *cyclic* aminals and similar structures in drugs and other compounds of use, and the lack of available enantioselective routes toward their preparation, we became interested in this fascinating problem. Here we report a highly enantioselective direct synthesis of aminals from aldehydes, catalyzed by a new chiral phosphoric acid catalyst.

Although possibly considered metabolically unstable, cyclic aminals and acetals are relatively common structural elements of diverse commercial pharmaceuticals. A small collection is shown in Figure 1 and includes Aquamox and Thiabutazide, two members of the benzo(thia)diazine class of cyclic aminals used for the treatment of high blood pressure.[4] Other examples include Cevimeline,[5] which contains an *S,O*-acetal and is used in the treatment of dry mouth associated with Sjögren's syndrome, the *O,O*-acetal Pipoxolan,[6] an antispasmodic drug, the parasympathomimetic *N,N*-acetal Physostigmine,[7] as well as the Seebach imidazolidinone chrial auxiliary,[8] more recently used as an organocatalyst.[9]

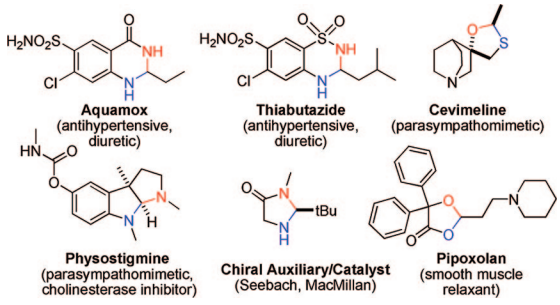
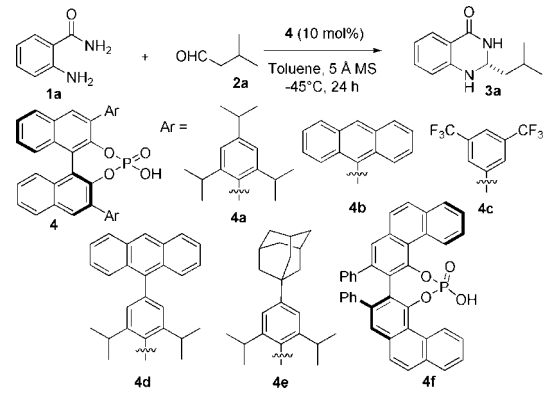



***Figure 1.*** Important compounds that contain a stereogenic cyclic acetal, thioacetal, or aminal.

We felt that especially the benzo(thia)diazine pharmaceuticals, which have been used as effective diuretic drugs since 1957 and are commonly used to treat high blood pressure, would be attractive targets.[4] The widely used protocol for their synthesis involves the condensation of substituted 2-aminobenzamide or 2-aminobenzenesulfonamide with an aldehyde in the presence of a Brønsted acid catalyst or reagent.[10] So far only achiral acids have been used in the preparation of racemic diazines. While it has been established that their enantiomers have different bioacitivtiy,[11] to the best of our knowledge, the only method to access enantiomerically enriched species has been HPLC separation.[12] A catalytic asymmetric route would be highly attractive for a possible second generation enantiomerically pure drug.

A model reaction between 2-aminobenzamide (**1a**) and isovaleraldehyde (**2a**) to furnish dihydroquinazolinone **3a** was initially established. In the presence of 10 mol% of (*S*)-TRIP (**4a**)[13] a clean and complete reaction occurred at room temperature within 12 h furnishing product **3a** in 4 er (56% ee) and in 86% yield. After optimizing the conditions (see Supporting Information, SI), a benchmark screening of different chiral phosphoric acids was carried out (Table 1). At −45 °C, (*S*)-TRIP gave up to 8 er with full conversion after 24 h (entry 1). Anthrancenyl substituted phosphoric acid **4b** gave product **3a** with an er of only 4 (entry 2). Both catalyst **4c** previously used by Akiyama et al. and VAPOL-derived phosphoric acid **4f**, which Antilla et al. utilized to catalyze the corresponding intermolecular reaction, did not improve the enantioselectivity of our reaction (entries 3 and 6). Remarkably, anthracenyl-modified TRIP catalyst **4d**, which we have previously used to catalyze the direct asymmetric Kabachnik−Fields reaction, dramatically increased the enantioselectivity to 99 er (98% ee).[14] In addition, catalyst **4e** bearing the adamantyl backbone gave high enantioselectivity.

***Table 1.*** Catalyst Investigation




| Entry | Catalyst | Yield | er[a] (ee%) |
|---|---|---|---|
| 1 | **4a** | 84% | 8 (78) |
| 2 | **4b** | 82% | 4 (60) |
| 3 | **4c** | 88% | 3 (48) |
| 4 | **4d** | 86% | 99 (98) |
| 5 | **4e** | 87% | 24 (92) |
| 6 | **4f** | 83% | 4 (60)[b] |

[a] From HPLC analysis using an OD-H column. [b] Opposite enantiomer.

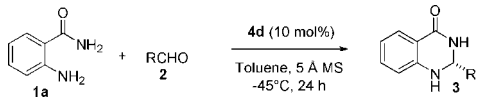
Having identified acid **4d** as a suitable catalyst, we reacted different aldehydes (**2b**−**g**) and ketone **5** under the same conditions with amide **1a** to furnish cyclic aminals **3** (Table 2). Aliphatic, α-unbranched aldehydes all gave high yields and enantioselectivities in the conversion to aminal **3** (entries 1−5). Isobutyraldehyde (**2a**) and benzaldehyde (**2g**) as representatives of α-branched and aromatic aldehydes gave somewhat lower enantioselectivities. As a highly reactive ketone, we also investigated isatin (**5**) under the standard conditions and found it to give spirocyclic product **6** in moderate enantioselectivity (12 er). In this case, (*S*)-TRIP **4a** turned out to be a superior catalyst giving product **6** in good enantioselectivity (entry 8).

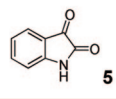
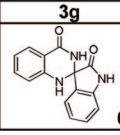
We also explored various substituted 2-aminobenzamides (**1b**−**l**) in their reaction with isovaleraldehyde (**2a**) (Table 3). The reaction



**10.1021/ja8071034 CCC: $40.75** 

***Table 2.*** Aldehyde Scope

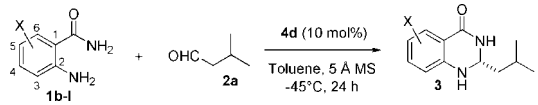


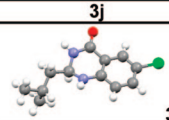
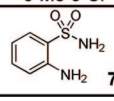
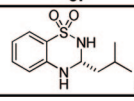

| Entry | RCHO | Product | Yield | er[a] (ee%) |
|---|---|---|---|---|
| 1 | $^t$BuCHO (**2a**) | **3a** | 86% | 99 (98) |
| 2 | $^n$PrCHO (**2b**) | **3b** | 91% | 28 (93) |
| 3 | $^t$BuCH$_2$CHO (**2c**) | **3c** | 94% | 49 (96) |
| 4 | CyCH$_2$CHO (**2d**) | **3d** | 84% | 99 (98) |
| 5 | BnCHO (**2e**) | **3e** | 80% | 39 (95) |
| 6 | $^i$PrCHO (**2f**) | **3f** | 72% | 3 (50) |
| 7 | PhCHO (**2g**) | **3g** | 67%[b] | 2 (26) |
| 8 |  **5** |  **6** | 85%[c] | 12 (84) |

[a] From chiral stationary phase HPLC analysis. [b] Reaction at −15 °C. [c] (*S*)-TRIP **4a** (10 mol%) was used as catalyst (70 °C, 4 h).

turned out to be highly tolerant to arene substitution, and essentially all investigated amides gave excellent enantioselectivities (entries 1−11). Aminal **3k** was crystallized from $CH_2Cl_2$, and its structure, including its absolute configuration, was determined from Röntgen diffraction studies. Furthermore, sulfonamide **7** gave the corresponding cyclic product **8** in excellent enantioselectivity. Aminal **8** has previously been shown to racemize at room temperature, which we confirmed.[15]

***Table 3.*** 2-Aminobenzamide Scope




| Entry | X | Product | Yield | er[a] (ee%) |
|---|---|---|---|---|
| 1 | 4-Me | **3h** | 84% | 28 (93) |
| 2 | 5-Me | **3i** | 84% | 49 (96) |
| 3 | 6-Me | **3j** | 83% | 49 (96) |
| 4 | 5-Cl |  **3k** | 90% | 49 (96) |
| 5 | 6-Cl | **3l** | 82% | 39 (95) |
| 6 | 5-Br | **3m** | 85% | 49 (96) |
| 7 | 6-F | **3n** | 90% | 99 (98) |
| 8 | 5-OMe | **3o** | 90% | 99 (98) |
| 9 | 5-OCF$_3$ | **3p** | 96% | 99 (98) |
| 10 | 3,4-Me$_2$ | **3q** | 85% | 17 (89) |
| 11 | 3-Me-5-Cl | **3r** | 79% | 24 (92) |
| 12[b] |  **7** |  **8** | 80% | 49 (96) |

[a] From HPLC analysis using an OD-H column. [b] Er measured from crude product; compound **8** racemizes upon storage at room temperature.

Finally, our methodology can also be applied to systems of practical relevance. While Thiabutazide could not be prepared using our standard conditions because of a lack of solubility of the required reagent, clean conversion occurred if the reaction was conducted in $CH_2Cl_2$ using catalyst **4e** providing (*R*)-Thiabutazide in 81% yield and 21 er (91% ee) (Figure 2). Thiabutazide proved to be configurationally stable during the reaction conditions and isolation. Similarly, (*R*)-Cyclopenthiazide, (*R*)-Bendroflumethiazide, and (*R*)-Penflutizide could be synthesized in high enantioselectivity using our methodology. (*S*)-Aquamox could also be prepared. In this case, somewhat lower enantioselectivity was achieved.[16]

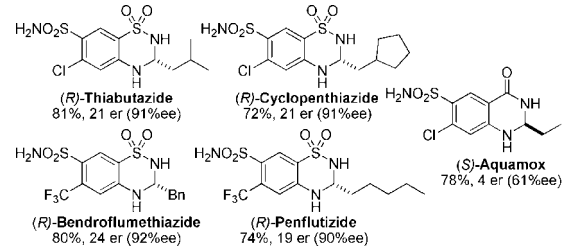



***Figure 2.*** Antihypertensive pharmaceuticals made using our new methodology.

In summary, we have developed a direct synthesis of chiral aminals from aldehydes using a phosphoric acid as catalyst. This methodology has been applied to pharmaceutically relevant compounds. Current studies in our laboratories aim at further expanding the scope of this chemistry.

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**Supporting Information Available:** Experimental procedures, compound characterization, NMR-spectra, and HPLC traces and Röntgen data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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