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Brønsted Acid Catalyzed Enantioselective Indole Aza-Claisen Rearrangement Mediated by an Arene CH−O Interaction

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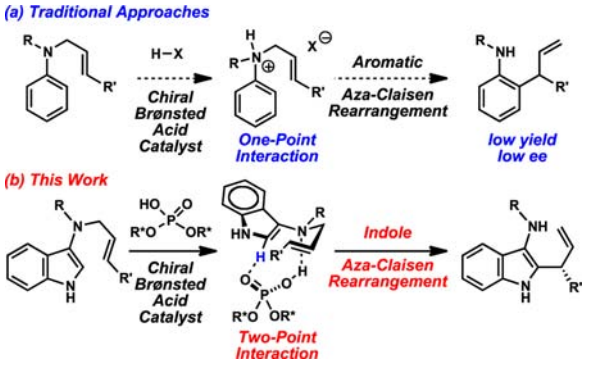
Supporting Information

ABSTRACT: Although the aromatic aza-Claisen rearrangement is a general strategy for accessing substituted aromatic amines, there are no highly enantioselective examples of this process. We report the first Brønsted acid catalyzed enantioselective indole aza-Claisen rearrangement for the synthesis of chiral 3-amino-2-substituted indoles. We present evidence for an arene CH−O interaction as a source of activation and stereoinduction, which is an unprecedented phenomenon in enantioselective Brønsted acid catalysis. The products of this reaction can be transformed into 3-aminooxindoles, which are prevalent in many biologically active small molecules.

Despite the development of several catalytic enantioselective aliphatic aza-Claisen rearrangements in recent years,[1−3] the asymmetric catalysis of aromatic aza-Claisen rearrangements remains an underdeveloped area (Scheme 1a). The paucity of enantioselective aromatic aza-Claisen rearrangements may be partially attributed to the absence of a secondary interaction for two-point binding in an aromatic amine that only contains one basic functional group. This hypothesis is supported by the observation that most enantioselective examples of aromatic oxa-Claisen rearrangements require a chiral substrate or a functionalized substrate that can undergo two-point binding with a catalyst.[4−8]

Scheme 1. Strategies for a Catalytic Enantioselective Aza-Claisen Rearrangement



We were drawn to the aromatic aza-Claisen rearrangement because of its potential for generating medicinally valuable aromatic amines.[9] Given the prevalence of indoles in biologically active molecules,[10] we were interested in developing an enantioselective [3,3]-rearrangement around the indole scaffold (Scheme 1b).[6b−d,11] The discovery of a catalytic enantioselective variant of this reaction could provide a novel approach to chiral 2-subsitituted indoles.[12]

Here, we describe the first Brønsted acid catalyzed enantioselective aromatic aza-Claisen rearrangement.[13] We also present evidence for an arene CH−O interaction as a source of activation and stereoinduction in the reaction. Our discovery establishes a new strategy for two-point interactions in catalytic enantioselective reactions of substrates with only one basic functional group.[14,15]

Based on the known Brønsted acid mediated activation of aromatic aza-Claisen rearrangements,[16] we treated *N*-allyl-3-aminoindole **1a** with a series of Brønsted acids (Table 1). In the presence of stoichiometric trifluoroacetic acid at ambient temperature, aminoindole **1a** was converted to [3,3]-rearrangement product **2a** in 82% isolated yield (entry 1). As expected, when aminoindole **1a** was heated to 100 °C in the absence of any acid, we did not observe an appreciable amount of the rearrangement product (entry 2).[2]

We exposed *N*-allyl-3-aminoindole **1a** to several chiral phosphoric acid catalysts to determine if this novel indole aza-Claisen rearrangement could be rendered enantioselective. In addition, we were hopeful that the phosphate group of these chiral Brønsted acids could provide a mechanism for dual activation of the indole substrate via a two-point interaction.[17] Upon treatment of aminoindole **1a** with 5 mol % BINOL-based phosphoric acid **3a** at 80 °C, we observed complete conversion to rearrangement product **2a**, which was isolated in 90% yield and 12% ee (entry 3). This represents a rare example of accelerating an aromatic aza-Claisen rearrangement with a catalytic amount of a chiral Brønsted acid.[18] While treatment of aminoindole **1a** with catalytic amounts of phosphoric acids **4** and **3b**−**3d** furnished 3-amino-2-sustituted indole **2a** in 80−85% yield, the rearrangement product was isolated with almost no enantiomeric excess (entries 4−7). We obtained the desired [3,3]-rearrangement product in 80% yield and 48% ee in the presence of 9-anthracenyl disubstituted Brønsted acid **3e** at 80 °C for 12 h (entry 8). Lowering the reaction temperature to 60 °C and increasing the reaction time to 36 h improved the ee to 76% without affecting the efficiency of the rearrangement (entry 9). Once catalyst **3e**

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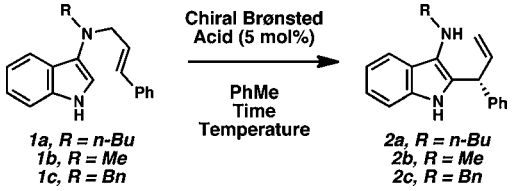
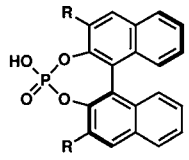
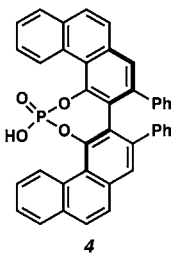
Table 1. Optimization of Catalytic Enantioselective Indole Aza-Claisen Rearrangement[c]



entry	R	catalyst	time (h)	temp (°C)	yield[a]	ee (%)
1	*n*-Bu	TFA[b]	12	23	82	–
2	*n*-Bu	–	12	100	<5	–
3	*n*-Bu	3a	12	80	90	12
4	*n*-Bu	4	12	80	80	3
5	*n*-Bu	3b	12	80	83	3
6	*n*-Bu	3c	12	80	85	5
7	*n*-Bu	3d	12	80	83	3
8	*n*-Bu	3e	12	80	80	48
9	*n*-Bu	3e	36	60	85	76
10	Me	3e	36	60	76	34
11	Bn	3e	36	60	93	90





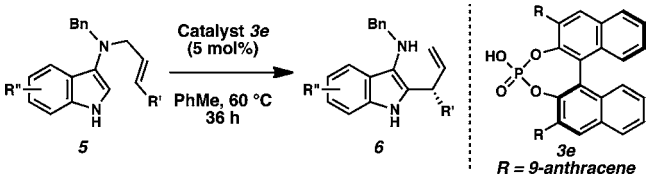
[a]Isolated yield. [b]1.1 equiv TFA (trifluoroacetic acid). [c]Reaction conditions: aminoindole **1** (0.1 mmol), 5 mol % phosphoric acid **3** or **4**, PhMe (0.1 M).

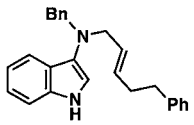
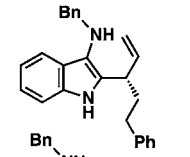
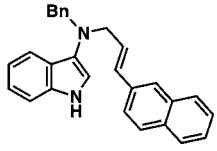
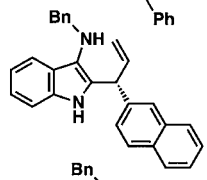
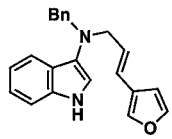
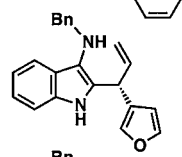
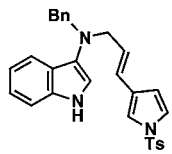
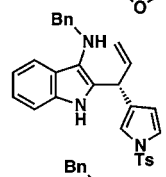
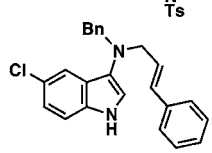
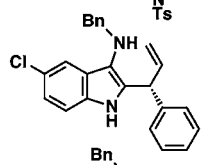
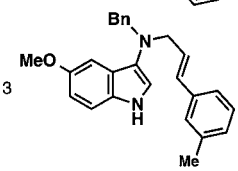
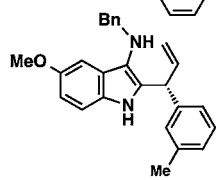
was identified as the most promising phosphoric acid, we examined the effect of modifying the ancillary substituent on the nitrogen of substrate **1**. The sterically unencumbered *N*-methyl-*N*-allyl-3-aminoindole **1b** (*R* = Me) was converted to the corresponding rearrangement product **2b** in only 34% ee (entry 10). To our delight, the *N*-benzyl-*N*-allyl-3-aminoindole **1c** (*R* = Bn) furnished the aza-Claisen rearrangement product **2c** in 93% isolated yield and 90% ee (entry 11).

A diverse range of *N*-allyl-3-aminoindoles **5** were subjected to the optimized enantioselective rearrangement conditions (Table 2). Several allylic moieties were compatible with this reaction. For example, a series of functionalized aromatic rings (R′) with electron-donating and -withdrawing groups could be incorporated into the products without affecting the efficiency of the rearrangement process (entries 2−7). While aliphatic substitution drastically lowered the stereoselectivity of the reaction (entry 8), polycyclic aromatic hydrocarbons (entry 9) and heteroaromatic functional groups (entries 10 and 11) were tolerated. We also examined the effect of electronically perturbing the indole ring system. Both electron-withdrawing and -donating groups on the indole ring were compatible with the enantioselective [3,3]-rearrangement (entries 12 and 13).

We have studied the mode of activation and stereoinduction in the [3,3]-indole aza-Claisen rearrangement. Initially, we were pleasantly surprised that chiral phosphoric acids such as **3e** could accelerate the [3,3]-rearrangement at relatively low temperatures compared to other Brønsted acid mediated aromatic aza-Claisen rearrangements,[1,2,16] while also exhibiting unprecedented levels

Table 2. Substrate Scope of Catalytic Enantioselective Indole Aza-Claisen Rearrangement[c]



Entry	Substrate	Product	Yield (%)[a]	ee (%)
1	R = H		93	90
2	R = 4-OMe		85	86
3	R = 4-Cl		84	93
4	R = 4-NO2		81	86
5	R = 3-Me		93	96
6	R = 3-F		93	93
7	R = 4-Br		86	93
8			91	22
9			89	95
10			83	85
11[b]			81	91
12			91	88
13			87	91

[a]Isolated yield. [b]Aminoindole **5** (0.1 mmol), 10 mol % phosphoric acid **3e**, PhMe (0.1 M), 60 °C, 16 h. [c]Reaction conditions: aminoindole **5** (0.2 mmol), 5 mol % phosphoric acid **3e**, PhMe (0.1 M), 60 °C.

of enantioselectivity.[19] Based on the results of our quantum chemical calculations, we believe this unusual reactivity and enantioselectivity is in part due to an arene CH−O interaction between the C2-proton and the phosphate counterion of acid **3e** (Figure 1). Although arene C−H bonds are not usually implicated in catalytic enantioselective reactions,[14] they are routinely invoked in crystal structures and biological contexts as structural controlling elements.[20]

The transition-state structure leading to the major product for the reaction of Table 2, entry 1 (R = H) was examined using DFT calculations.[21] First, a conformational search on a truncated sigmatropic shift transition-state structure and truncated phosphoric acid catalyst was performed. The lowest energy

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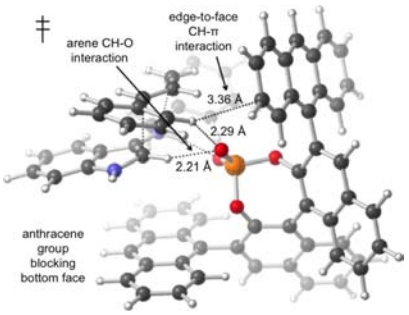
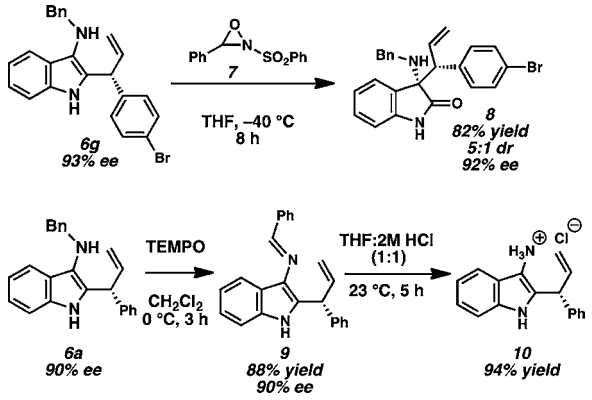


Figure 1. Transition-state structure (B3LYP/6-31G(d)) leading to the major product for the reaction shown in Table 2, entry 1 (R = H); selected distances shown in Å. The predicted free energy barrier in the gas phase is 18.7 kcal/mol.

conformation found (with M06-2X/6-31+G(d,p))[22] contained an arene CH−O interaction. The analogous transition-state structure for the full substrate and catalyst (**3e**) was then optimized (with B3LYP/6-31G(d)).[23] In the resulting structure (Figure 1), the two-point binding mode (via CH−O and NH−O interactions) organizes the adduct such that a 9-anthracene group blocks the *si* face of the substrate (bottom face), favoring allyl shift on the *re* face (top face), leading to the observed enantiomer of the product. This model is consistent with the reduced selectivity observed for catalysts with smaller and/or more conformationally mobile groups in place of 9-anthracene (Table 1). An edge-to-face CH−π interaction between the R′=Ph group of the substrate and the other 9-anthracene group, as well as a CH−O interaction between this phenyl group and the phosphate, are also present, consistent with the observation that aryl groups at this position lead to the highest selectivities for the cases examined so far (Table 2).

The 3-aminoindole structures obtained from this enantioselective [3,3]-rearrangement can be transformed into synthetically useful chiral products such as 3-aminooxindole **8** (Scheme 2). Despite the prevalence of 3-aminooxindoles in biologically

Scheme 2. Synthetic Modification of Chiral 3-Amino-2-Substituted Indoles



active molecules,[24] highly enantioselective and diastereoselective methods for accessing 3-substituted 3-aminooxindoles with two contiguous stereocenters are rare.[25] Exposure of aminoindole **6g** (93% ee) to oxaziridine **7** resulted in the formation of 3-substituted 3-aminooxindole **8** in 82% yield, 5:1 dr, and 92% ee (for the major diastereomer). The absolute and relative stereochemistry of 3-aminooxindole **8** was confirmed by X-ray crystallography. The benzyl group of aminoindole **6a** could be removed through a two-step protocol, which included a TEMPO-mediated oxidation to 3-iminoindole **9**, followed by hydrolysis under acidic conditions to unveil the HCl salt **10**.

In conclusion, we have developed a catalytic enantioselective aromatic aza-Claisen rearrangement of 3-aminoindoles for the generation of 3-amino-2-substituted indole structures. These products can be transformed into synthetically useful 3-aminooxindoles that are difficult to access by known methods. We believe this rearrangement is accelerated and organized for high enantioselectivity by an arene CH−O interaction between the C2-proton and the phosphate counterion of the chiral phosphoric acid. This class of chiral Brønsted acids may be uniquely suited for two-point interactions in Brønsted acid catalyzed reactions of substrates that contain only one basic functional group. We anticipate that this weak interaction will be useful in the design of other Brønsted acid catalyzed enantioselective reactions that were previously thought to lack a mode for high stereoinduction through one-point binding. Therefore, we are exploring this new strategy in substrate−catalyst two-point interactions for the Brønsted acid catalyzed enantioselective rearrangements of other classes of substrates. The application of this enantioselective aromatic aza-Claisen rearrangement in the synthesis of chiral indole alkaloids is also under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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