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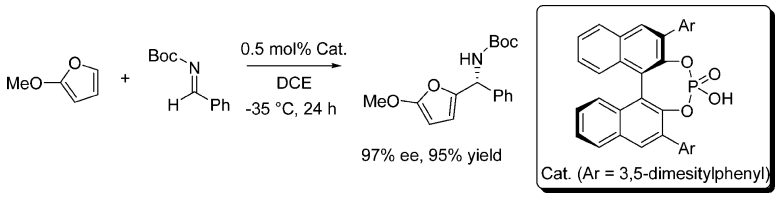

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Organocatalytic Asymmetric Aza-Friedel−Crafts Alkylation of Furan

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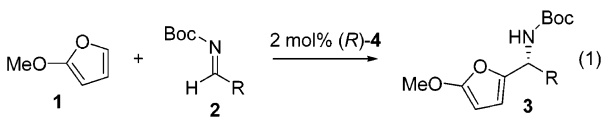
A key goal of modern organic chemistry is to both maximize the efficiency of using readily available materials and minimize the generation of waste.[1] Toward this ideal, significant contributions have been made with use of late transition metal catalysts.[1,2] Moreover, the recent rapid growth of organocatalysis has presented a new approach by using metal-free conditions.[3−7] The organocatalyzed direct aldol and related reactions are especially noteworthy as they come close to being truly ideal for C−C bond-forming reactions, which in addition to being atom-economic can be chemo-, regio-, diastereo-, and enantioselective.[3] Among these reactions, secondary amine catalysis is one of the most powerful and widely applied strategies, and a key feature of this catalysis is the activation of the nucleophilic components via enamine formation.[4] As an alternative to this strategy, we have recently developed a direct Mannich reaction via the electrophilic activation of an acceptor, an *N*-Boc-protected aldimine derivative, with a chiral phosphoric acid as the Brønsted acid catalyst.[5−7] This strategy, based on electrophilic activation, should be applicable to enantioselective transformations other than those accomplished by secondary amine catalysis. As an initial step and as a valuable chemical transformation in its own right, we present herein the highly enantioselective 1,2-aza-Friedel−Crafts reaction catalyzed by a binaphthol monophosphoric acid.

The stereoselective addition of sp^2 C−H bonds to an aldimine, a 1,2-aza-Friedel−Crafts (F−C) reaction, is an atom-economical approach to synthesizing chiral nitrogen-containing compounds that are important in organic chemistry and biochemistry.[8] In view of the significance of controlling the stereochemistry in an absolute sense, the successful cultivation of a catalytic enantioselective variant of this reaction is in high demand. Although F−C alkylation reactions that utilize metal salts with catalytic amounts of an optically active ligand have been developed recently,[9,10] to the best of our knowledge, no precedent has materialized on an asymmetric 1,2-aza-F−C reaction of aldimines promoted by organocatalysts.[11] Since optically active furan-2-ylamines are highly useful synthetic building blocks,[12−14] we focused on the development of an enantioselective 1,2-aza-F−C reaction of a furan with *N*-Boc aldimine derivatives (eq 1).



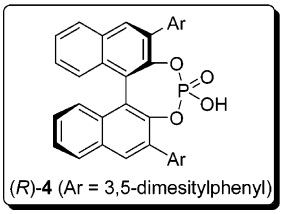


Table 1. Solvent Effect on the Aza-Friedel−Crafts Reaction (Eq 1, R = Ph)[a]

entry	solvent	temp (°C)	yield (%)[b]	ee (%)[c]
1	THF	0	70	83
2	^{i}Pr$_2$O	0	80	79
3	toluene	0	88	83
4	chlorobenzene	0	79	83
5	$CHCl_3$	0	83	84
6	CH_2Cl_2	0	82	88
7	$(CHCl_2)_2$	0	87	90
8	$(CH_2Cl)_2$	0	86	92
9	$(CH_2Cl)_2$	−20	89	95
10	$(CH_2Cl)_2$	−35	87	97

[a] All reactions were carried out with 0.1 mmol of aldimine (**2**) in 1 mL of solvent for 20 h. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis. See Supporting Information for details.

Indeed, the 1,2-aza-F−C reaction of commercially available 2-methoxyfuran (**1**) with *N*-Boc aldimine (**2**, R = Ph) proceeded smoothly under the influence of 2 mol % of the phosphoric acid catalyst ((*R*)-**4**) at 0 °C. Although various common organic solvents were tolerated by the reaction (Table 1), halogenated solvents gave better results than ethereal or aromatic solvents (entries 1−8). Among the halogenated hydrocarbons tested, 1,2-dichloroethane was found to be best in terms of enantiomeric excess (entry 8). Fortunately, lowering the reaction temperature further improved the enantioselectivity (entries 8−10). The absolute configuration of the furan-2-ylamine (**3**, R = Ph) was determined by derivatization to Boc-phenylglycine methyl ester via oxidative cleavage of the furan ring.[13] Interestingly, this ester was assigned to be of an *R*-configuration, opposite to that found previously in our direct Mannich reaction study.[7,15]

Experiments to probe the scope of the *N*-Boc aldimine component (**2**) are summarized in Table 2. The reaction was relatively less sensitive to the character of the aldimine aromatic ring in terms of enantioselectivity as well as reaction efficiency. Electron-donating and -withdrawing substitutions at the para position did not indicate any effect on the selectivity (entries 1, 4, 7−9). The existence of an ortho substituent on the aldimines did not compromise the enantioselectivity (entries 2 and 5). Meta-substituted aromatic rings were tolerated for the reaction (entries 3 and 6), and naphthyl and furyl rings were also good reaction partners (entries 10−12). Most notably, the reaction could be performed in the presence of as little as 0.5 mol % of (*R*)-**4**, and the reaction proceeded smoothly without any detrimental effect even on a gram scale (entry 13). Moreover, (*R*)-**4** could be readily recovered during purification of the product and then applied to separate reactions without any special treatment prior to use.

Finally, the synthetic utility of this transformation was demonstrated by derivatization of the furan ring to γ-butenolide (Scheme 1). Since the γ-butenolide architecture is a common building block in the synthesis of various natural products,[16] **3** represents a new entry to synthetic precursors of nitrogen-containing complex molecules. Indeed, the aza-Achmatowicz reaction[14] of **3** (R = Ph,

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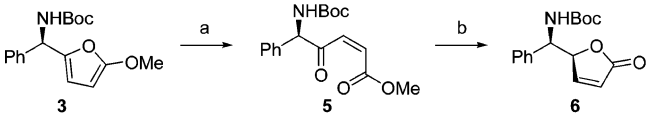
Table 2. Organocatalyzed Aza-Friedel−Crafts Reaction of Furan (**1**) with Representative *N*-Boc Aldimine Derivatives (**2**) (Eq 1)[a]

entry	R	yield (%)[b]	ee (%)[c]
1	*p*-MeO-C_6H_4-	95	96
2	*o*-Me-C_6H_4-	84	94
3	*m*-Me-C_6H_4-	80	94
4	*p*-Me-C_6H_4-	96	97
5	*o*-Br-C_6H_4-	85	91
6	*m*-Br-C_6H_4-	89	96
7	*p*-Br-C_6H_4-	86	96
8	*p*-Cl-C_6H_4-	88	97
9	*p*-F-C_6H_4-	82	97
10	1-naphthyl-	84	86
11	2-naphthyl-	93	96
12	2-furyl-	94	86
13[d]	Ph-	95	97

[a] Unless otherwise noted, reactions were carried out with 0.1 mmol of aldimine (**2**) in 1 mL of 1,2-dichloroethane at −35 °C for 24 h. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis. See Supporting Information for details. [d] The reaction was performed on a 1 g scale in the presence of 0.5 mol % of (*R*)-**4**.

Scheme 1. Synthetic Utility of Furan-2-ylamine (**3**, R = Ph)[a]



[a] Conditions: (a) NBS, $NaHCO_3$, Et_2O/H_2O, 0 °C, 30 min, 90%; (b) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, −78 °C to room temperature, 5 h, 95% (syn/anti = 85/15).

97% ee) cleaved the furan ring cleanly to form 1,4-dicarbonyl compound **5** in 96% ee. Subsequent reductive cyclization of **5** under Luche conditions led to the γ-butenolide (**6**) in 95% yield without any loss of enantiomeric excess (96% ee).

In conclusion, a new asymmetric entry of the 1,2-aza-Friedel−Crafts reaction catalyzed by the chiral phosphoric acid ((*R*)-**4**) has been described. The present reaction provided an atom-economical route to furan-2-ylamine derivatives in a highly enantioselective fashion. The synthetic utility of these products was displayed by oxidative cleavage of the furan ring (aza-Achmatowicz reaction) to form a 1,4-dicarbonyl compound (**5**) that could, in turn, be derivatized to a γ-butenolide (**6**). Further application of phosphoric acid catalysts to challenging transformations and mechanistic studies of the reactions are underway in this laboratory.

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Supporting Information Available: Representative experimental procedures and spectroscopic data for **3**−**6** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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