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Catalytic, Asymmetric, Aldol/*O*-Conjugate Addition Sequence for the Construction of Highly Substituted Furanoids

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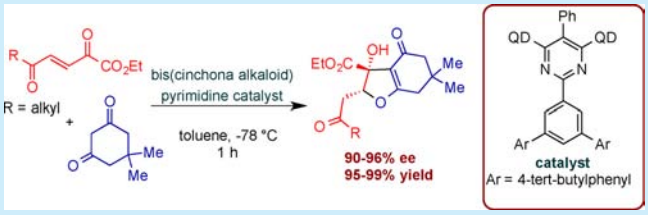
Supporting Information

ABSTRACT: A new method for the enantioselective synthesis of highly functionalized dihydrofurans has been developed. This process, related to the interrupted Feist–Bénary reaction, involves the reaction of 2-ene 1,4-diketones with dimedone in the presence of bis(cinchona alkaloid)-pyrimidine catalysts to afford dihydrofuran products in excellent yields and high diastereo- and enantioselectivities.

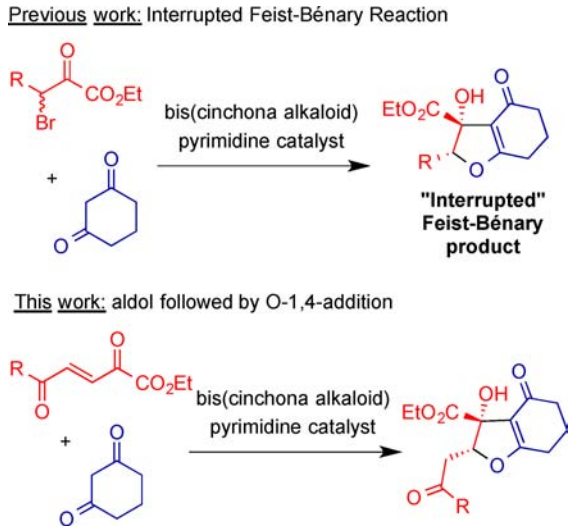


Substituted 2,3-dihydrofurans and related structures constitute an important class of organic compounds that are highly represented in both natural products and useful synthetic intermediates.[1] As a consequence, a great deal of attention has been paid to 2,3-dihydrofurans, and many approaches to their synthesis have been described in the literature.[2] Despite this fact, examples of the enantioselective construction of chiral furanoids are still scarce.[3]

Among other methods, the Feist–Bénary reaction offers a quick access to the highly substituted furans through the condensation of 1,3-dicarbonyl compounds with α-halo ketones.[4] There have been a number of reports over the past decade demonstrating the utility of Feist–Bénary reaction.[5] We previously studied the substrate scope and diastereoselectivity of the interrupted Feist–Bénary (IFB) reaction[6] and discovered the first enantioselective version of this reaction.[7] This method utilizes highly reactive α-bromopyruvates as electrophiles in a reaction with cyclic diones to produce IFB product in high efficiency. The high enantioselectivity is induced by protonated cinchona alkaloid-derived catalysts, which presumably activate the electrophile through bifurcated hydrogen bonding. We also described an asymmetric IFB reaction of α-tosyloxy ketones.[8] In addition, Jorgensen reported the multibond-forming reaction cascade that involved the IFB reaction of α-epoxy aldehydes to produce optically active 2-hydroxyalkyl-2,3-dihydrofurans.[9]

In our attempt to expand the scope of the IFB reaction, we envisioned the new concept of combining an aldol reaction with an *O*-1,4-addition step (Scheme 1). As the stereochemistry-determining step would be the initial aldol reaction, as in the IFB reaction, we predicted that bis(cinchona alkaloid)pyrimidine catalysts, similar to those successfully used in the IFB reaction, would also afford high enantioselectivity here. This new atom-economical strategy avoids the use of stoichiometric base while still affording a product with two adjacent stereocenters. Herein we describe an IFB-related, highly enantioselective reaction that involves a reaction of 2-ene 1,4-diketones and dimedone to produce chiral hydroxydihydrofurans in high efficiency.

Scheme 1. Interrupted Feist–Bénary Reaction



We began our investigations by examining the reaction of methyl ketone **1a** and dimedone (Scheme 2). To our delight, the anticipated reaction proceeded smoothly in the presence of catalytic DABCO giving complete consumption of the electrophile in 1 h at 78 °C and an excellent isolated yield of the desired product. Additionally, we observed reasonable diastereoselectivity (10.2:1 dr) favoring formation of the *cis*-isomer. Initially formed IFB product **3a** interconverts between one open and two hemiketal forms. This interconversion results in poor separation of the enantiomers by HPLC. In order to overcome this difficulty, compound **3a** was converted into mixed-methyl ketals **4a** and **5a** by treatment with PPTS in methanol. Compounds **4a** and **5a** can be separated by flash chromatography and the enantiomers of the minor, β-isomer separated readily on a chiral HPLC column.

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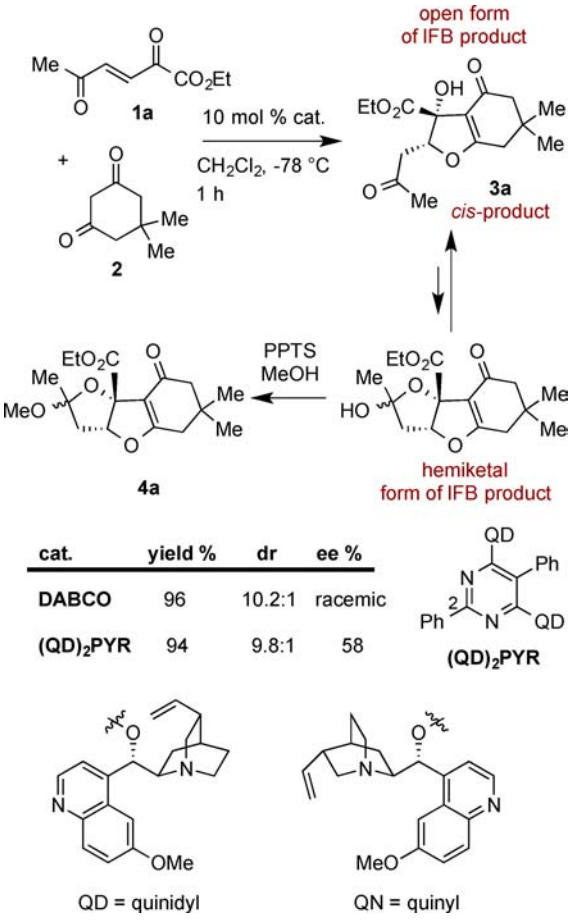
Scheme 2. Target Reaction of Electrophile 1a and Dimedone



In order to test whether a chiral catalyst could induce asymmetry in this reaction, we first tested the readily available bis(cinchona alkaloid)pyrimidine catalyst, $(QD)_2PYR$. The observed enantioselectivity of 58% was highly encouraging, so we proceeded in our attempt to improve the enantioselectivity by catalyst modification.

The nature of the 2-substituent of the catalyst proved to be essential for the high enantioselectivity in our previous studies.[7,8,10] Catalysts presenting different Ar groups at the 2-position can be readily prepared in two steps starting with 4,6-dichloro-5-phenylpyrimidine. Aryllithium addition to the most electrophilic site of the pyrimidine ring and oxidation with DDQ leads to the formation of the catalyst precursors **5a–c** (Scheme 3). Treatment of the resulting dichloropyrimidines with the appropriate cinchona alkaloid and KOH in refluxing toluene furnishes the bis(cinchona alkaloid)pyrimidine catalysts **6a–d** in high yields.

Changing the Ar substituents of the catalyst had a significant impact on the enantioselectivity of the tested reaction (Table 1). The introduction of a methoxy group in the ortho position (catalyst **6a**) resulted in a noticeable improvement in the stereoinduction (79% ee) compared to catalyst $(QD)_2PYR$. Further screening revealed that catalyst **6b**, bearing a 3,5-diphenylphenyl group, gives 85% ee. Following this trend, we attempted to modify the phenyl groups at the 3- and 5-positions of the central aryl ring. This strategy proved to be beneficial, as catalyst **6c** furnished the product in 88% ee. Finally, further improvement was realized when the catalyst

Scheme 3. Synthesis of New Catalysts

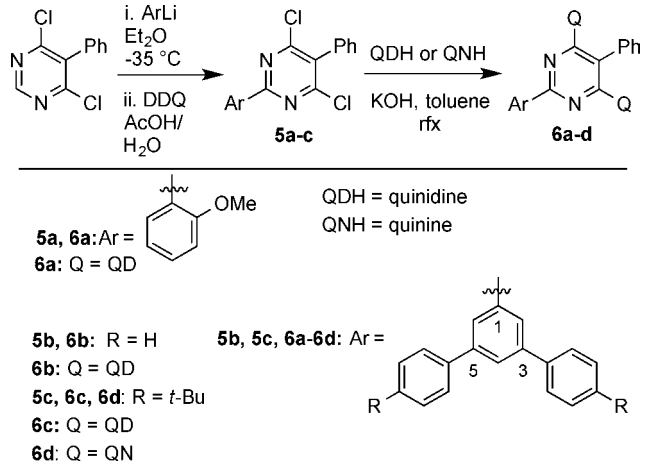


Table 1. Optimization of the Reaction of 1a and 2 in Solvent at −78 °C

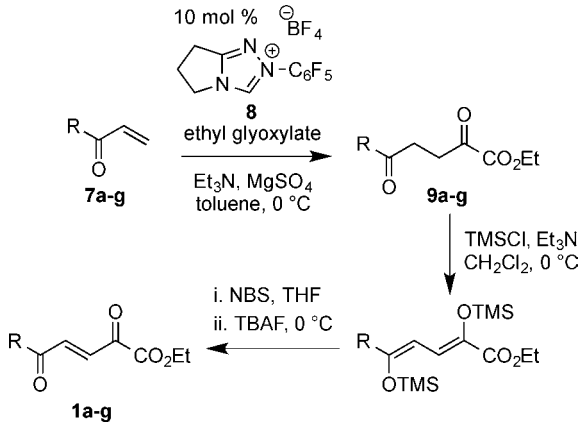
entry	catalyst	catalyst loading (mol %)	solvent	dr	% yield (% ee)[a]
1	**6a**	10	CH_2Cl_2	10.2:1	98 (79)
2	**6b**	10	CH_2Cl_2	9.8:1	97 (85)
3	**6c**	10	CH_2Cl_2	10.0:1	96 (88)
4	**6c**	5	CH_2Cl_2	9.9:1	97 (92)
5	**6c**	5	THF	10.0:1	93 (92)
6	**6c**	5	toluene	10.3:1	99 (96)

[a]Determined by HPLC analysis of the purified product **4a**.

loading was lowered from 10 to 5 mol %, and the reaction was performed in toluene instead of dichloromethane.

To demonstrate the generality of this method, we intended to expand it to other alkyl ketones. These highly reactive compounds were prepared by a straightforward procedure (Table 2). The synthesis commences with the Stetter reaction

Table 2. Synthesis of 2-Ene 1,4-Diketones 1a–g



compound	R	overall % yield from **8**
1a	Me	83
1b	Et	74
1c	*n*-Pr	68
1d	*i*-Pr	92
1e	*i*-Bu	79
1f	CH_2Bn	75
1g	CH_2OBn	54

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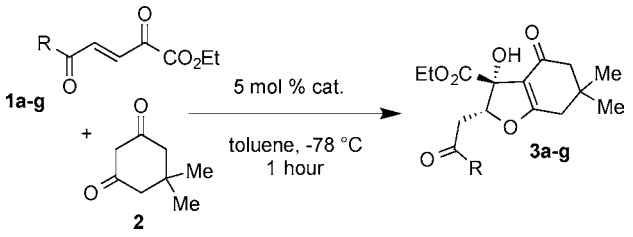
of the appropriate alkyl vinyl ketone with ethyl glyoxylate catalyzed by triazolium salt[11] **8** to produce 1,4-diketone products **9a–g**. Subsequent treatment with 2 equiv of TMSCl and triethylamine led to the formation of the corresponding bis-TMS-enol ethers. Monobromination with 1 equiv of NBS, followed by deprotection with TBAF, allowed isolation of the desired 2-ene-1,4-diketones **1a–e** in moderate to excellent yields.

To our delight, the optimal conditions developed for the reaction of **1a** proved to be general (Table 3). Variations in the

Table 3. Substrate Scope of the Reaction



entry	cat.	product	% yield	dr	% ee[a]
1	**6c**	**3b**	95	9.8:1	94
2	**6c**	**3c**	98	10.1:1	96
3	**6c**	**3d**	98	11.3:1	90
4	**6c**	**3e**	97	12.8:1	95
5	**6c**	**3f**	99	11.8:1	95
6	**6c**	**3g**	98	8.2:1	95
7[b]	**6d**	**3a**	97	9.8:1	−96
8[b]	**6d**	**3c**	98	11.0:1	−96

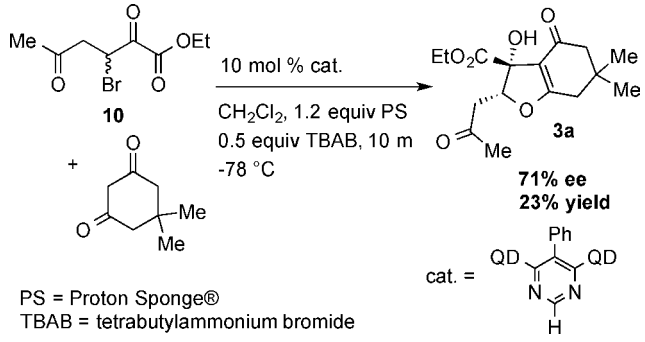
[a]Determined by HPLC analysis of the purified product **4b–g**. [b]Opposite enantiomer of **3** produced.

length of the alkyl chain have little or no influence on either the yield or enantioselectivity. Finally, by switching to the diastereomeric catalyst **6d**, derived from quinine, we were able to obtain the opposite enantiomer of the dihydrofuran product in similarly high optical purity (entries 7 and 8, Table 3). The enantioselectivity was determined by converting **3b–g** into the corresponding mixed methyl ketals **4b–g** and separating the minor ketal anomer by chiral HPLC. The yields of the anomeric mixtures of **4b–g** were generally very high, but we did not quantify these yields, as we were mainly interested in getting pure minor anomer for HPLC analysis.

In order to assign an absolute stereochemistry of the products, we performed the IFB reaction of α-bromopyruvate **10** and dimedone using previously developed reaction conditions (Scheme 4).[7] This reaction produced the desired product **3a**, although in significantly reduced yield and moderate enantioselectivity (71% ee), compared to the present method. This experiment shows that the newly developed method is complementary to the classic IFB reaction of α-bromopyruvates.

In conclusion, we have demonstrated a new approach to chiral dihydrofurans that relies on a reaction of 2-ene-1,4-diketones with dimedone. The reactions proceed in excellent yields, and the newly synthesized cinchona alkaloid-derived catalysts afford the resulting products with excellent levels of diastereo- and enantiocontrol.

Scheme 4. IFB Reaction of α-Bromopyruvate 10 and Dimedone



■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds. 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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