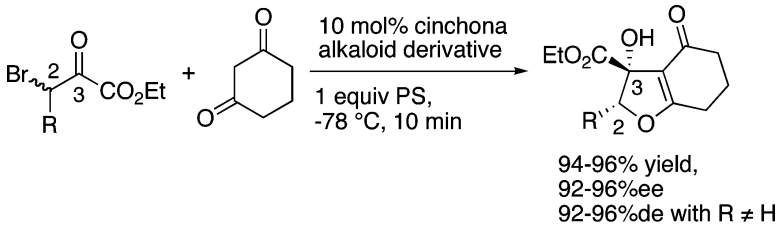
Communication

Catalytic, Asymmetric, "Interrupted" Feist–Bénary Reactions

Michael A. Calter, Ryan M. Phillips, and Christine Flaschenriem

J. Am. Chem. Soc., **2005**, 127 (42), 14566-14567• DOI: 10.1021/ja055752d • Publication Date (Web): 01 October 2005



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 4 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 10/01/2005

Catalytic, Asymmetric, "Interrupted" Feist−Bénary Reactions

Michael A. Calter,*,† Ryan M. Phillips,† and Christine Flaschenriem‡

Department of Chemistry, Wesleyan University, Middletown, Connecticut 06459-0180, and Department of Chemistry, University of Rochester, Rochester, New York 14627-0216

Received August 22, 2005; E-mail: mcalter@wesleyan.edu

Although the Feist−Bénary reaction enjoys a history of over a century and provides a convenient access to highly substituted furan derivatives, relatively few studies on the mechanism, selectivity, and synthetic applications of this reaction have appeared.[1] The Feist−Bénary reaction involves condensation of β-dicarbonyl compounds with α-haloketones to produce hydroxydihydrofurans, followed by elimination to form furans (Scheme 1). We will refer to the reaction stopping at the hydroxydihydrofuran as the "interrupted" Feist−Bénary (IFB) reaction. Several groups have studied the mechanism and scope of the IFB reaction,[2] and we recently explored its scope, diastereoselectivity, and application to the synthesis of the zaragozic acid core.[3] However, the lack of an asymmetric version of this reaction has hindered its development as a tool for modern organic synthesis. We describe here the first reported asymmetric IFB reactions, culminating with a convenient, catalytic procedure.

We discovered an enantioselective catalyst for the IFB reaction by screening a number of cinchona alkaloid derivatives in the test reaction between ethyl bromopyruvate **1** and cyclohexadione **2** (Scheme 1, Table 1). This reaction has a negligible background rate at −78 °C, but the addition of a substoichiometric amount of a tertiary amine or trialkylammonium salt causes the reaction to proceed to completion in less than 10 min. As the reaction generates an equivalent of HBr, the amine is protonated for the majority of the reaction regardless of its initial state. To avoid any formation of canonical Feist−Bénary product, our standard conditions involved the incorporation of a slight excess of Proton Sponge (PS).[4] Although quinidine itself gives low enantioselectivity, the commercially available diphenylpyrimidinyl derivative of this compound gives much improved asymmetric induction.[5] We next probed the effect of the substituent in the 2-position of pyrimidine ring. Replacement of the phenyl substituent of **4a** with a thiomethyl group led to a noticeable increase in induction, and substitution with hydrogen led to synthetically useful levels of selectivity. The use of quinine-derived catalysts led to the production of the opposite enantiomer of the product, but with an altered response of the level of induction to the size of the pyrimidine substituent. Catalyst **5d**, with the bulky *tert*-butyl substituent, gives excellent enantiocontrol for the formation of the *S*-enantiomer of **3**.

Slightly modified conditions afford excellent diastereo- and enantioselectivities in the reactions of racemic, secondary α-bromoketones (Scheme 3, Table 2). We began our explorations with these substrates by reacting racemic **6a** with varying stoichiometries of **2**. These reactions gave results consistent with one enantiomer of **6a** reacting to give **7a** at a rate 20 times greater than the other enantiomer reacts to give a 3:1 mixture of *ent*-**7a** and **8a**. The diastereoselectivity of this reaction agrees with that observed previously for the racemic reaction.[3a] The initial results also indicated that the enantiomers of **6a** do not interconvert under the reaction conditions, a necessary condition for dynamic, kinetic resolution. We reasoned that the bromide generated in the reaction could isomerize **6a** by an S_N2 mechanism if the reaction occurred in a polar, aprotic solvent. Accordingly, performing the reaction in THF led to some interconversion. We further accelerated the interconversion of the enantiomers of **6a** by the addition of 0.5 equiv of tetrabutylammonium bromide (TBABr). These conditions result in complete consumption of racemic **6a** and the production of **7a** in high yield and almost complete diastereo- and enantioselectivity. The reactions of other substituted bromoketoesters give similar results.

Scheme 1

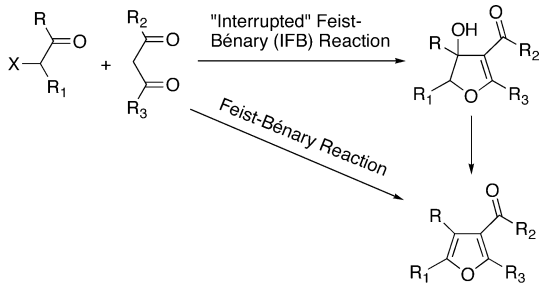


Table 1. Yields and Enantioselectivities for Scheme 2

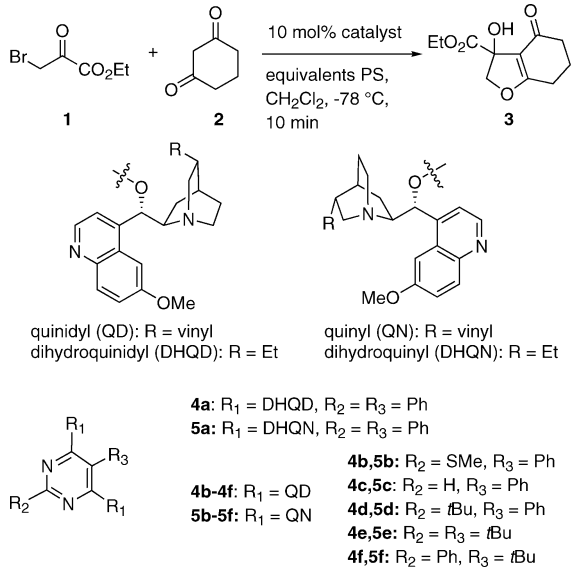
catalyst	equiv of PS	% yield **3**	% ee **3** (configuration)
	0	2	
Et_3N	0	81	
quinuclidine	0	90	
quinuclidine•HCl	0	92	
quinuclidine	1.1	99	
QDH	1.1	99	21 (*R*)
4a	1.1	89	68 (*R*)
4b	1.1	94	88 (*R*)
4c	1.1	98	91 (*R*)
4c•2HBr	0	88	92 (*R*)
4d	1.1	94	64 (*R*)
4e	1.1	96	61 (*R*)
4f	1.1	99	75 (*R*)
5a	1.1	95	82 (*S*)
5b	1.1	96	75 (*S*)
5c	1.1	93	65 (*S*)
5d	1.1	93	98 (*S*)
5e	1.1	96	14 (*S*)
5f	1.1	99	53 (*S*)

The levels of asymmetric induction observed show that the chiral amine associates with at least one of the reactants in the stereochemistry-determining step. Our previous mechanistic work on the Feist−Bénary reaction indicated that the product forms by an aldol reaction followed by rapid cyclization. The fact that the reaction in which **4c** begins and presumably remains in the protonated form throughout the entire reaction is as fast as that in which the catalyst starts as the free base suggests that the protonated form of **4c** is in

† Wesleyan University.
‡ University of Rochester.

10.1021/ja055752d CCC: $30.25

Scheme 2



Scheme 3

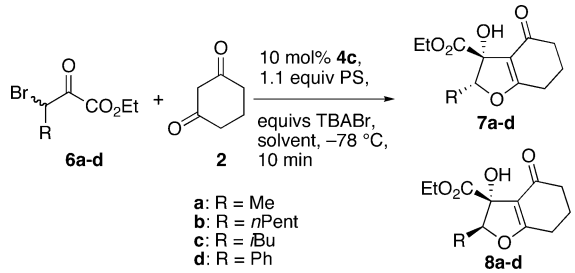
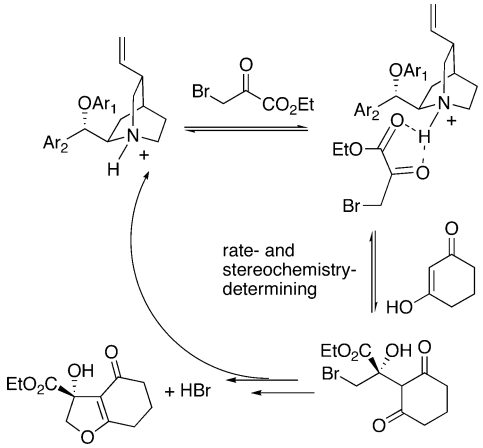


Table 2. Yields and Enantioselectivities for Scheme 3

starting material	equiv of **2**	solvent	equiv of TBABr	**7**:**8**	% yield **7** (% ee)
6a	1.0	CH_2Cl_2	0	89:11	80 (17)
6a	0.5	CH_2Cl_2	0	94:6	92 (59)
6a	0.25	CH_2Cl_2	0	99:1	89 (94)
6a	1.0	THF	0	96:4	94 (78)
6a	1.0	THF	0.5	98:2	95 (94)
6b	1.0	THF	0.5	96:4	96 (93)
6c	1.0	THF	0.5	97:3	94 (96)
6d	1.0	THF	0.5	96:4	94 (93)

fact the active catalyst. The only reasonable role we could postulate for protonated **4c** in accelerating the aldol reaction would be in forming a hydrogen bond to **1**, rendering it more electrophilic toward attack by either the enol or the enolate of **2**. Several groups have suggested that protonated cinchona alkaloids activate electrophiles by hydrogen-bond donation; in fact, Prelog proposed such a mechanism in his explanation of the reported example of a cinchona alkaloid-catalyzed asymmetric reaction.[6,7] In the most relevant example for the current case, Baiker proposed that the high induction realized in the asymmetric hydrogenation of α-ketoesters arises from delivery of hydride to one face of an α-ketoester

Scheme 4



bifurcatedly hydrogen-bonded to a protonated cinchona alkaloid, while both are absorbed on a Pt surface.[8] In the asymmetric IFB reaction, the observed induction could arise from attack of the nucleophile on the less hindered, *Re* face. The alternative rotamer of the hydrogen-bonded intermediate, which would favor *Si* face attack and formation of the opposite enantiomer, is likely disfavored by interaction between the bromine of the substrate and the pyrimidine ring of the catalyst.

In conclusion, we have discovered the first examples of a catalytic, enantioselective interrupted Feist−Bénary reaction. High enantioselectivity depends on new cinchona alkaloid catalysts and the use of an appropriate stoichiometric base. Preliminary results indicate that the reaction proceeds through a hydrogen-bonded intermediate between the protonated form of the catalyst and the electrophile. The exploration of the asymmetric addition of other nucleophiles to this intermediate is underway.

Acknowledgment. We thank the Department of Chemistry at Wesleyan University for financial support of this work.

Supporting Information Available: Complete experimental procedures and characterization data for compounds **3** and **7a**−**d**, along with details of the stereochemical proof. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Feist, F. *Chem. Ber.* **1902**, *35*, 1537−1544. (b) Bénary, E. *Chem. Ber.* **1911**, *44*, 489−492.
(2) (a) Dunlop, A. P.; Hurd, C. D. *J. Org. Chem.* **1950**, *15*, 1160−1164. (b) Canton, I. J.; Cocker, W.; McMurry, T. B. H. *Tetrahedron* **1961**, *15*, 45−52.
(3) (a) Calter, M. A.; Zhu, C. *Org. Lett.* **2002**, *4*, 205−208. (b) Calter, M. A.; Zhu, C.; Lachicotte, R. J. *Org. Lett.* **2002**, *4*, 209−212.
(4) The literature suggests that quinuclidine is more basic than PS in organic solvents, indicating that sufficient protonated **4c** is present to catalyze the reaction even in the presence of an excess of PS. See: Benoit, R. L.; LeFebvre, D.; Fréchette, M. *Can. J. Chem.* **1987**, *65*, 996−1001.
(5) Crispino, G. A.; Jeong, K.-S.; Kolb, H. C.; Wang, Z.-M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785−3786.
(6) Prelog, V.; Wilhelm, M. *Helv. Chim. Acta* **1954**, *37*, 1634−1660.
(7) For a review of protonated chiral catalysts, see: Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758−1763.
(8) (a) Baiker, A. *J. Mol. Catal. A: Chem.* **1997**, *115*, 473−493. (b) Bonalumi, N.; Bürgi, T.; Baiker, A. *J. Am. Chem. Soc.* **2003**, *125*, 13342−13343.

JA055752D