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Catalytic, Asymmetric, Interrupted Feist–Bénary Reactions of α-Tosyloxyacetophenones

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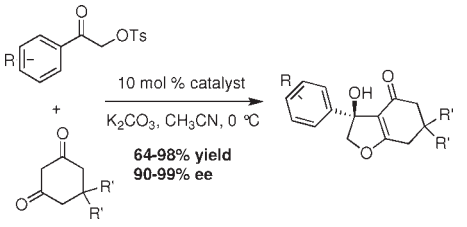
ABSTRACT



A new variant of the Interrupted Feist–Bénary (IFB) reaction uses α-tosyloxyacetophenones as electrophiles and proceeds in good yields and excellent enantioselectivities.

Substituted furanoids are common building blocks for the synthesis of many natural products and useful intermediates in organic synthesis.[1] Among other methods, the Interrupted Feist–Bénary (IFB) reaction—the condensation of α-haloketones and 1,3-dicarbonyl compounds—provides quick access to highly substituted hydroxyfuranoids from simple and easily accessible starting materials.[2] We found several years ago that β-bromo-α-ketoesters were suitable electrophiles for a asymmetric version of the IFB reaction catalyzed by bis(cinchona alkaloid)pyrimidines.[3] The ester moiety of the β-bromo-α-ketoester presumably activates the ketone carbonyl carbon for nucleophilic attack, allowing the reaction to proceed rapidly at low temperature. We also postulated that the ester carbonyl provides a second hydrogen-bond acceptor, further organizing the transition state and allowing for high enantioselectivity.[3] Indeed, all reported examples of the catalytic, asymmetric IFB reaction involve β-bromo-α-ketoesters as electrophiles.[4]

We decided to expand the scope of the catalytic, asymmetric IFB reaction to include less highly functionalized electrophiles. We chose acetophenone derivatives as our initial set of substrates (Scheme 1). In analogy to the previous work, we chose to use bromide as the leaving group. However, these simple α-bromoketones, without the adjacent, activating ester, did not afford appreciable product. Fortunately, we then discovered that ketones bearing an α-tosyloxy (OTs) group were much more reactive, and therefore we decided to explore the catalytic, asymmetric reactions of α-tosyloxyacetophenones.

We began our study using the reaction between α-tosyloxy-*p*-nitroacetophenone[5] and 1,3-cyclohexyldione to screen for the optimal catalyst (Table 1). Under standard conditions using Proton Sponge (PS) as a base and quinuclidine as a catalyst the reaction went to the completion in about 10 min and the desired product was isolated in moderate yield. As bis(cinchona alkaloid)pyrimidines proved to be effective in the parent reaction, we decided to screen the quinidine catalysts previously synthesized in our group.[3,6] These initial results indicated that catalysts with R_2 = *t*Bu (entries 1 and 2) lead to low enantioselectivity,

(1) Kilroy, T. G.; O'Sullivan, T. P.; Guiry, P. J. *Eur. J. Org. Chem.* **2005**, 4929–4949.

(2) (a) Feist, F. *Chem. Ber.* **1902**, *35*, 1537–1544. (b) Bénary, E. *Chem. Ber.* **1911**, *44*, 489–492. (c) Dunlop, A. P.; Hurd, C. D. *J. Org. Chem.* **1950**, *15*, 1160–1164. (d) Cantlon, I. J.; Cocker, W.; McMurry, T. B. H. *Tetrahedron* **1961**, *15*, 46–52. (e) Calter, M. A.; Zhu, C. *Org. Lett.* **2002**, *4*, 205–208. (f) Calter, M. A.; Zhu, C.; Lachicotte, R. J. *Org. Lett.* **2002**, *4*, 209–212.

(3) Calter, M. A.; Phillips, R. M.; Flaschenriem, C. *J. Am. Chem. Soc.* **2005**, *127*, 14566–14567.

(4) Chen, H.; Jiang, R.; Wang, Q. F.; Sun, X. L.; Luo, J.; Zhang, S. Y. *Chin. Chem. Lett.* **2010**, *21*, 167–170.

(5) Kose, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487–2489.

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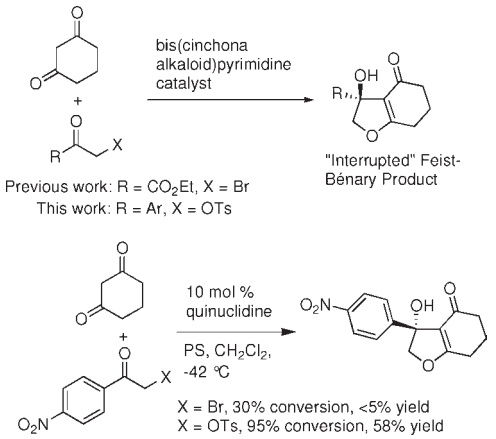
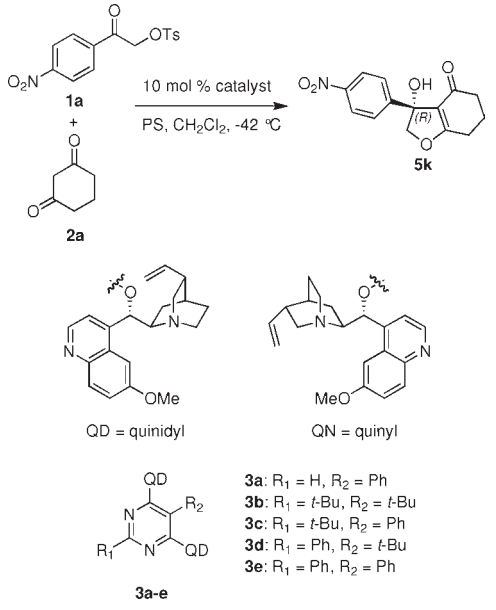
Scheme 1. Interrupted Feist–Bénary Reaction



while a catalyst with phenyl at both the R_1 and R_2 positions (entry 5) gives a promising result (74% ee). For further improvement of ee toward a synthetically useful level, we decided to synthesize new catalysts containing different aryl groups at the R_1 position.

Table 1. Target IFB Reaction



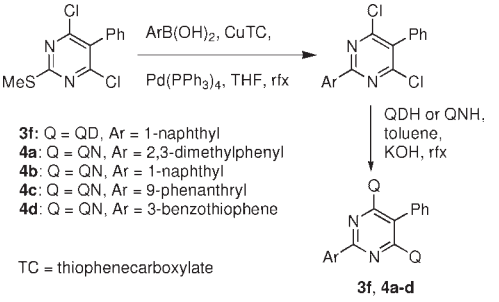
entry	catalyst	yield %	ee %[a]
1	**3a**	79	46
2	**3b**	69	11
3	**3c**	72	10
4	**3d**	81	60
5	**3e**	74	74

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

(6) (a) Calter, M. A.; Wang, J. *Org. Lett.* **2009**, *11*, 2205–2208. (b) Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xe, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785–3786.

These cinchona alkaloid-derived catalysts can be synthesized in two steps starting from commercially available 4,6-dichloro-2-methylthio-5-phenylpyrimidine (Scheme 2). Liebeskind–Srogl coupling of this substrate with aryl boronic acids allows the introduction of different aryl groups at the R_1 position.[7] The resulting dichloropyrimidines react with quinine or quinidine in the presence of KOH in refluxing toluene to afford bis(cinchona alkaloid)pyrimidine catalysts **3f** and **4a**–**d**.

Scheme 2. Synthesis of New Catalysts



Screening of these newly synthesized quinine catalysts showed that the 2,3-dimethylphenyl group noticeably improves the ee of the product (82%, Table 2). Gratifyingly, a similar catalyst containing a 1-naphthyl group gave over 90% ee in the test reaction. Other large aryl groups, like 9-phenanthryl, 3-benzothiophene, or 2-naphthyl, did not significantly improve enantioselectivity. The quinidine version of the catalyst with the 1-naphthyl substituent was also synthesized (**3f**) and gave the opposite enantiomer of the product in 96% ee.

Table 2. IFB Reaction of **1a** and **2a** in CH_2Cl_2 in the Presence of PS and 10 mol % of Catalyst at −42 °C

entry	catalyst	yield %	ee %[a]
1	**4a**	83	82 (*S*)
2	**4b**	80	92 (*S*)
3	**4c**	73	84 (*S*)
4	**4d**	79	69 (*S*)
6	**3f**	81	96 (*R*)

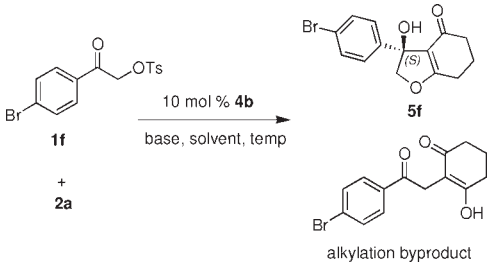
[a] Determined by HPLC analysis of the purified product.

While the IFB reaction of α-tosyloxy-*p*-nitroacetophenone proceeds smoothly at −42 °C, the less reactive α-tosyloxy-*p*-bromoacetophenone (**1f**) affords the desired product in an unsatisfying 51% yield at this temperature (Table 3, entry 1). The significant fall in the yield was caused by competing C-alkylation. To optimize the reaction conditions, we varied solvent, base, and temperature. The yield improves if the reaction is run at higher temperature (0 °C), but the enantioselectivity drops significantly in both CH_2Cl_2 and CH_3CN in the presence of PS.

(7) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979–981.

Switching from PS to K_2CO_3 allowed us to perform the reaction at higher temperature (0 °C) in acetonitrile without any loss of stereoinduction. Although reaction in CH_2Cl_2 gives a better ratio of IFB vs C-alkylation product, and as a result a better yield, the ee of the product is too low at 0 °C.

Table 3. Optimization of Reaction Conditions for Reaction of **1b** and **2a**



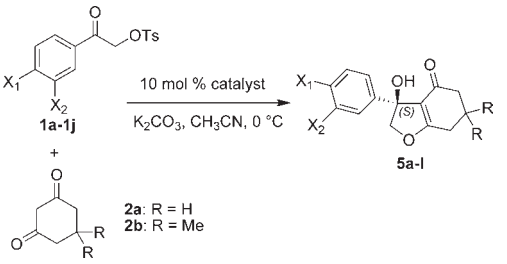
entry	base	solvent	temp (°C)	**5f**: alkylation[a]	% yield of **5f**	% ee of **5f**[b]
1	PS	CH_2Cl_2	−42	1.2:1	51	95
2	PS	CH_2Cl_2	0	9.0:1	76	82
3	PS	CH_3CN	−28	1.1:1	47	97
4	PS	CH_3CN	0	3.2:1	67	88
5	K_2CO_3	CH_2Cl_2	−28	8.9:1	73	86
6	K_2CO_3	CH_2Cl_2	0	32:1	85	80
7	K_2CO_3	CH_3CN	−28	1.2:1	50	96
8	K_2CO_3	CH_3CN	0	5.0:1	69	94

[a] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [b] Determined by HPLC analysis of the purified product.

With optimized reaction conditions in hand, we then tested the scope of the reaction by varying the substituents on the phenyl ring of the electrophile. We found that the electronic nature of the aryl group has some effect on the rate and yield but, at the same time, a very small influence on the stereochemical outcome of the reaction. Electron-withdrawing groups accelerate the reaction so that it is done faster and yields of the products are generally higher (Table 4, entries 1−5).

Most of the *p*-halo-substituted-α-tosyloxyacetophenones give IFB products in excellent ee's (entries 6−12) and good yields with the catalyst **4b**. The reaction of *p*-chloro and unsubstituted α-tosyloxyacetophenone showed reduced enantioselectivity, but it can be significantly improved by switching to the catalyst **4c** containing a 9-phenanthryl group at the R_1 position (entries 7 and 14). Meta-substituted substrates also react with only slightly reduced ee and yields. In general, in order to increase the enantioselectivity the reaction can be carried out at lower temperature (entries 3 and 16), but the yield can worsen for substrates with no electron-withdrawing group on an aromatic ring. Finally, both dimedone **2b** and cyclohexyldione **2a** function as satisfactory nucleophiles for the reaction, giving very similar results in terms of yields and enantioselectivities of the IFB products.

Table 4. Substrate Scope of IFB Reaction



entry	electro-phile	X_1	X_2	R	catalyst	product	% yield	% ee[a]
1	**1a**	NO_2	H	Me	**4b**	**5a**	98	91
2	**1a**	NO_2	H	Me	**3f**	**5a**	97	94[b]
3	**1a**	NO_2	H	Me	**4b**	**5a**	95	95[c]
4	**1b**	CN	H	Me	**4b**	**5b**	82	94
5	**1c**	CF_3	H	Me	**4b**	**5c**	87	96
6	**1d**	F	H	Me	**4b**	**5d**	76	90
7	**1d**	F	H	Me	**4c**	**5d**	73	93
8	**1e**	Cl	H	Me	**4b**	**5e**	69	84
9	**1e**	Cl	H	Me	**4c**	**5e**	71	96
10	**1f**	Br	H	Me	**4b**	**5f**	65	96
11	**1f**	Br	H	Me	**3f**	**5f**	66	96[b]
12	**1g**	I	H	Me	**4b**	**5g**	70	99
13	**1h**	H	H	Me	**4b**	**5h**	64	84
14	**1h**	H	H	Me	**4c**	**5h**	66	90
15	**1i**	H	NO_2	Me	**4b**	**5i**	78	82
16	**1i**	H	NO_2	Me	**4c**	**5i**	77	90
17	**1j**	H	Br	Me	**4c**	**5j**	61	91
18	**1c**	CF_3	H	H	**4b**	**5k**	90	98
19	**1f**	Br	H	H	**4b**	**5l**	69	94

[a] Determined by HPLC analysis of the purified product. [b] The (*R*)-enantiomer is the major product. [c] Reaction run at −42 °C.

We assigned the absolute stereochemistry of IFB product **5f**, made in the reaction catalyzed by the quinine-catalyst **4b**, by anomalous dispersion analysis of single crystal X-ray data. By analogy, the remaining IFB products were assigned as *S*-isomers if **4b** was used and *R* with quinine-derived catalyst **3f** .

In conclusion, the interrupted Feist−Bénary reaction of α-tosyloxy-acetophenones and cyclic 1,3-diketones proceeds in good to excellent yields under mild conditions. Newly synthesized bis(cinchona alkaloid)pyrimidines afford the IFB product with excellent asymmetric induction.

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Supporting Information Available. Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.