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Chiral Phosphine–Silver(I) Complex Catalyzed Enantioselective Interrupted Feist–Bénary Reaction with Ynones: The Aldol–Cycloisomerization Cascade

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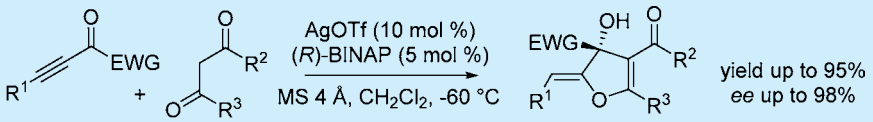
Supporting Information

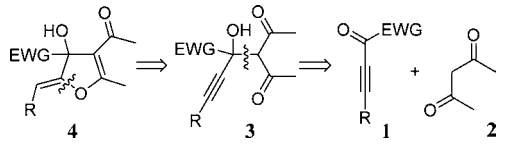


ABSTRACT: Silver-catalyzed interrupted Feist–Bénary reaction is described for the efficient enantioselective synthesis of dihydrofuran heterocycles. A new method has been developed for the silver(I)–(*R*)-BINAP complex mediated aldol–cycloisomerization cascade reaction between ynones and 1,3-diketones to provide functionalized dihydrofurans with moderate to good yields (up to 95%) and good to excellent enantiomeric excess (up to 98%). The presence of an exocyclic double bond and hydroxy group in the dihydrofuran products provides wide scope for further structural manipulation.

The 2,3-dihydrofuran core is one of the most featured motifs found in naturally occurring[1] and pharmaceutically active[1a−d,2] compounds. Functionalized dihydrofurans serve as crucial building blocks in the construction of versatile synthetic tetrahydrofurans.[3] Asymmetric protocols toward synthesis of the same are therefore always in very high demand. Ever since the first report of the Feist–Bénary reaction,[4] several strategies have been developed and modified to carry out the atom-economic condensation between 1,3-dicarbonyl motifs and suitable dielectrophiles to prepare dihydrofurans in stereoselective manner.[5−7] One familiar strategy in obtaining dihydrofurans is to arrest the usual Feist–Bénary reaction sequence at the hydroxydihydrofuran stage, thereby inhibiting the final dehydration step. It is therefore referred to as the "Interrupted Feist–Bénary" (IFB) reaction and provides access to functionalized hydroxydihydrofuran derivatives with high optical purity.[7] However, in asymmetric IFB, only cinchona alkaloid derived organocatalysts are recognized to be useful so far. The lack of investigations in this field has narrowed the scope of the asymmetric IFB approach, particularly with metal catalysis. To the best of our knowledge, there is no report on metal-catalyzed asymmetric IFB reaction.

In our continued venture toward stereoselective formulation of important heterocycles,[8] it was decided to highlight the less explored domain of enantioselective IFB reaction using silver catalysis[9] as the prospective tool. Herein, we document a new silver-catalyzed aldol–cycloisomerization cascade reaction between ynones and *β*-diketones, resulting in the enantioselective synthesis of dihydrofurans. Following the retro-synthesis (Scheme 1), it was presumed that activated ynone **1** would undergo silver-catalyzed asymmetric aldol reaction with 1,3-diketone component **2**; enolization followed by tandem *5-exo-dig* cyclization of the aldol intermediate **3** thereafter would

Scheme 1. Retro Feist–Bénary Approach



produce the dihydrofuran derivative **4**, with exocyclic double bond at the C-2 position. Reports on catalytic propargylation of 1,3-dicarbonyls followed by cycloisomerization reaction to furnish furans are abundant in literature.[6,10] Nevertheless, an account on the metal-catalyzed asymmetric synthesis of 2,3-dihydrofurans having an exocyclic double bond at the 2-position was unknown until recent days. When our research was in progress, Hu et al. reported asymmetric cycloaddition of *β*-ketoesters with propargylic esters to generate dihydrofurans bearing an exocyclic vinyl group.[6a] However, the substrate scope of this copper-catalyzed reaction is limited to terminal alkynes only.

Our investigation began with ethyl 2-oxo-4-phenylbut-3-ynoate (**1a**) and dimedone (**2a**) as the model ynone and diketone counterparts, respectively (Table 1). To a mixture of ynone **1a** (0.20 mmol) and dimedone **2a** (0.40 mmol) in dichloromethane at 0 °C was added slowly a solution of silver triflate (0.02 mmol) and (*R*)-BINAP (0.022 mmol). To our delight, within a couple of hours, the ynone was fully transformed to a pair of products. The minor one, which was later characterized to be the tetrahydro-4*H*-chromene **5aa**, decomposed in situ during the reaction course, producing

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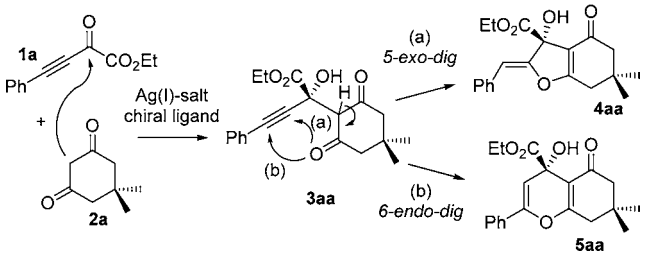
Table 1. Screening of Catalysts and Reaction Conditions[a]



entry	Ag(I) salt	ligand	time (h)	yield[b] (%)	ee[c] (%)
1[d]	AgOTf	(*R*)-BINAP	2.0	74	70
2[d]	$AgClO_4$	(*R*)-BINAP	2.0	73	70
3[d]	$AgBF_4$	(*R*)-BINAP	1.5	76	58
4[d]	$AgPF_6$	(*R*)-BINAP	1.0	72	60
5	$AgSbF_6$	(*R*)-BINAP	1.5	74	61
6	AgOAc	(*R*)-BINAP	2.0	84	20
7	AgOTf	(*R*)-T-BINAP	2.0	79	68
8	AgOTf	(*R*)-DM-BINAP	4.0	80	65
9	AgOTf	(*R*)-H_8–BINAP	4.0	82	28
10	AgOTf	(*R*)-SEGPHOS	2.0	92	34
11	AgOTf	(*R*)-DM-SEGPHOS	3.0	91	43
12	AgOTf	(*R*)-DTBM-SEGPHOS	5.0	85	41
13[e,d]	AgOTf	(*R*)-BINAP	2.0	74	70
14[e,f]	AgOTf	(*R*)-BINAP	24.0	70	83
15[e,g]	AgOTf	(*R*)-BINAP	96.0	70	90

[a]Unless otherwise mentioned, all of the reactions were carried out with ynone **1a** (0.20 mmol, 1.0 equiv), dimedone (**2a**, 0.40 mmol, 2.0 equiv), silver salt (0.020 mmol, 10 mol %), and phosphine ligand (0.022 mmol, 11 mol %) in dichloromethane at 0 °C. For additional screening with ligands, solvents, and additives, see Table S1 in the Supporting Information. [b]Isolated yield of dihydrofuran **4aa**. [c]Enantiomeric excess determined by chiral HPLC analysis. [d]These reactions, when reperformed in the presence of molecular sieves (MS 4 Å), were completed within 1 h with unaltered yields and selectivities of the IFB product. [e]Reaction carried out with 10 mol % of AgOTf and 5 mol % of (*R*)-BINAP. [f]Reaction carried out with MS 4 Å and at −40 °C. [g]Reaction carried out with MS 4 Å and at −60 °C.

highly polar uncharacterized substances. Through column chromatographic purification, only dihydrofuran **4aa** was isolated as the major product and with appreciable selectivity (74% yield, 70% ee, Table 1, entry 1). Inspired by this initial finding, an array of catalysts was examined by rational variation of commonly available silver salts and suitable chiral ligands (Table 1). A number of silver salts were assessed first in chelation with (*R*)-BINAP as the reference chiral ligand. As far the yields and selectivities are concerned, the outcomes of asymmetric IFB reactions were found to be highly dependent on the catalyst modulation. Among the silver salts, silver triflate was found to be superior over the rest, and on the other hand, among phosphine ligands, unsubstituted (*R*)-BINAP was observed to be the best. Next, optimization was carried out with several solvents, and dichloromethane showed the most promising result in this respect (Table S1, Supporting Information). Both the acidic and basic additives exhibited worsening effects on the enantiomeric ratio of the products (Table S1). Changing the ligand loading from 10 to 5 mol % fascinatingly produced dihydrofuran **4aa** with unaltered yield and selectivity (entry 13, Table 1). Use of molecular sieves (MS 4 Å) was found to accelerate the reaction rates considerably without affecting the yield and ee values (entries 1–4 and 13). It was interesting to observe that the minorly formed *6-endo-dig* cyclization product **5aa** had persisted on carrying out the reactions in the presence of MS 4 Å and was isolated in 20–25% yields. The effect of temperature over the reaction was also surveyed, and it was quite exciting to record a gradual ascent in the ee values while lowering the reaction temperature. It could be enhanced up to 90% at −60 °C (entry 15). Use of molecular sieves at that temperature was very essential for the reaction, which otherwise needs more than 7 days for completion. A combination of silver triflate (10 mol %), chiral-BINAP (5 mol %), and MS 4 Å in dichloromethane at −60 °C was thus determined to be the optimal condition for all future analysis.

To generalize and elaborate the substrate tolerance of silver-catalyzed IFB reaction, different substituted ynones (**1a–l**) and dicarbonyls (**2a–e**) were employed and effectively transformed to the corresponding dihydrofurans **4** with moderate to high yields and selectivities (Scheme 2). Owing to the highly labile nature of 4*H*-pyrans, we focused on the isolation and exploration of dihydrofuran derivatives only. 4,4-Dimethylcyclohexane-1,3-dione (**2b**) reacted smoothly with ynone **1a** to produce a regioisomeric mixture of 5,5-dimethyl- and 7,7-dimethylhexahydrobenzofurans **4ab** and **4ab′**, correspondingly (2:1 ratio, 77% yield overall). Mapping of individual molecular structures for these two regioisomers were done by HMBC experiments (see the Supporting Information). Besides the ethyl ester bearing ynone **1a**, the methyl ester analogue **1b** also worked efficiently with dimedone (**2a**) and 1,3-cyclohexanedione (**2c**) to afford the corresponding dihydrofurans **4ba** (70% yield, 87% ee) and **4bc** (73% yield, 81% ee), respectively. Compounds **4ac** and **4bc** could be synthesized with comparatively higher enantiomeric excess (95% and 91%, respectively) by reproducing the reactions at even lower temperature (−80 °C, 144 h). Ynones with *p*-nitrophenyl-, *p*-bromophenyl-, *p*-fluorophenyl-, *p*-tolyl-, *o*-tolyl-, and *p*-anisyl-substituted terminals (**1c–h**) underwent facile condensation with cyclohexanedione (**2c**). It is interesting to point out that by tuning the electronic property of the substituents the enantioselectivity could be improved up to 98% (example **4gc**). 1-Naphthyl-, 2-thiophene-yl-, and *n*-butyl-substituted ynones (**1i–k**) were also equally relevant in this process, generating highly enantioenriched dihydrofurans **4ic**, **4jc**, and **4kc**. Instead of ester, when a trifluoromethyl group was used as an activating group in the ynone **1l**, it afforded the dihydrofuran **4lc** in 58% yield and 44% ee. To our pleasure, most of these dihydrofuran products are solid and could be isolated in an almost enantiopure state after recrystallization from diethyl ether/*n*-pentane solution. Surprisingly, acetylacetone (**2d**) and cyclopentane-1,3-dione (**2e**) were realized to be unreactive under the present reaction condition. These diketones reacted with ynone **1a** only in the presence of a base like triethylamine but ended up with no selectivity (for example, **4ad** and **4ae**). The absolute stereochemistry of AgOTf-(*R*)-BINAP-catalyzed IFB reaction products was assigned to be *R* in analogy with the refined X-ray crystal structure of compound **4dc** (Figure 1).[11]

All of the reactions were carried out with 0.20 mmol of ynone **1** and 0.40 mmol of diketone **2**. Enantiomeric excess values were determined by chiral HPLC. Values in parentheses refers to the ee after recrystallization, where ee_{ML} = ee measured from mother liquor and ee_{CR} = ee measured from crystal. For diketones **2d** and **2e**, reactions were conducted at 0 °C in the presence of 10 mol % of triethylamine.

In order to verify the practical efficacy of this synthetic methodology, ynone **1a** was reacted with diketone **2c** on a

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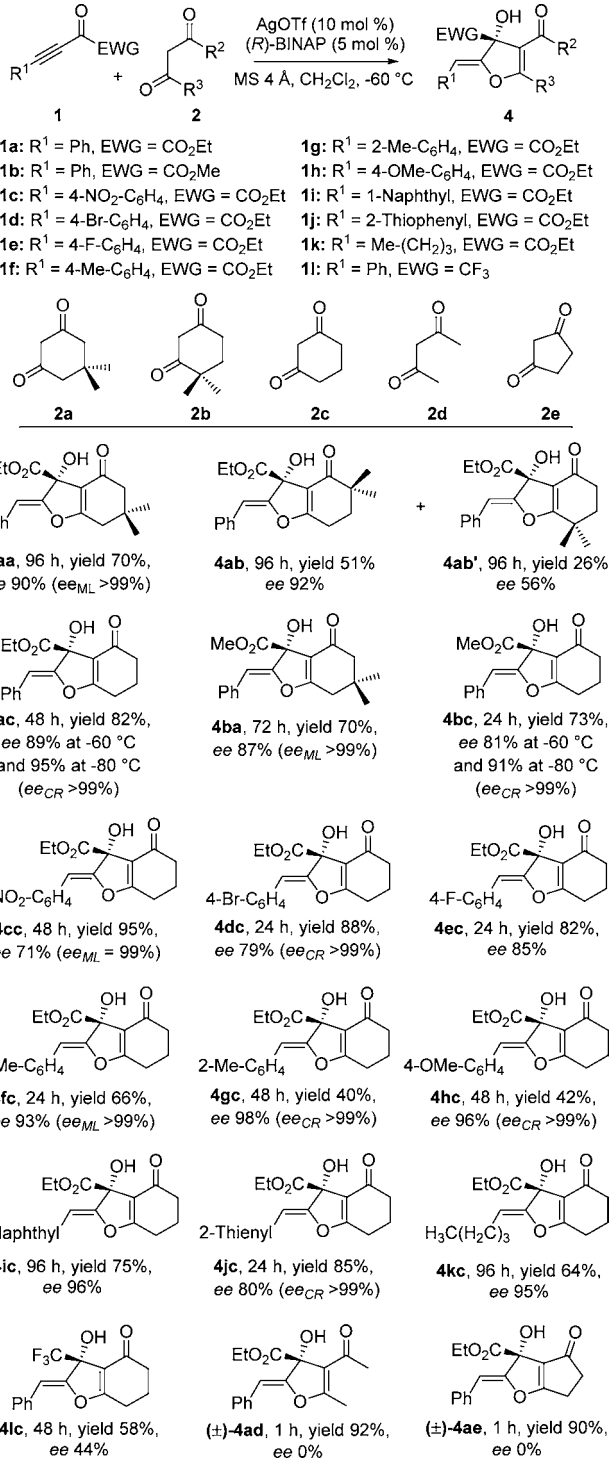
Scheme 2. Generalized Substrate Scope in Dihydrofuran Synthesis



gram scale (**1a**, 1.01 g, 5.0 mmol, Scheme 3) and in the presence of even reduced catalyst loading [AgOTf (6 mol %) and (*R*)-BINAP (3 mol %)]. The reaction was complete in 3 days; isolation followed by recrystallization furnished the dihydrofuran **4ac** in 66% overall yield and >99% enantiomeric purity. Dihydrofuran **4ac**, when subjected to Pd−C mediated hydrogenation, resulted in selective reduction of the external double bond with retained enantioselectivity (**6ac**, 73% yield, dr >95:05, ee > 99%). An interesting example of benzofuran

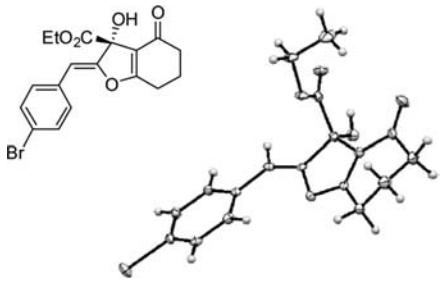
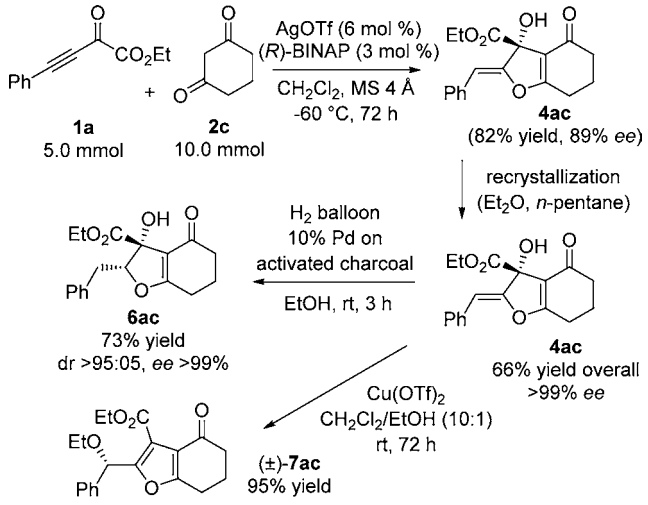


Figure 1. ORTEP of crystal (+)-**4dc**.[11]

Scheme 3. Synthetic Applications of Dihydrofuran Product 4ac[a]



[a]Absolute stereochemistry of compound **6ac** was assigned by analogy with similar hydrogenation reaction.[12].

derivative **7ac** was synthesized from compound **4ac** on treatment with ethanol and copper(II) triflate. However, racemization was a serious problem in this process.

In summary, we are pleased to report the silver-catalyzed enantioselective interrupted Feist−Bénary reaction between *β*-diketones and activated ynones for the first time. This methodology is highly efficient for the asymmetric construction of dihydrofuran derivatives with exocyclic double bond. The IFB products were obtained in moderate to excellent yields and high values of enantioselectivity. Reactions are easily upgradeable to gram scale, and enantiomeric excess can be reached >99% by recrystallization. Further studies in making use of the present protocol toward stereocontrolled total synthesis of the flavagline group of natural products are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and analytical data for all new compounds and X-ray data for compound **4dc** (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01468.

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Notes

The authors declare no competing financial interest.

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