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# Catalytic Asymmetric Domino Michael Addition−Alkylation Reaction: Enantioselective Synthesis of Dihydrofurans

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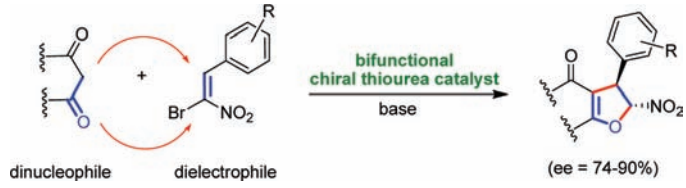
## ABSTRACT




**A catalytic enantioselective synthesis of dihydrofurans has been developed. 1,3-Dicarbonyl derivatives react with (*E*)-β,β-bromonitrostyrenes in the presence of a chiral bifunctional thiourea catalyst providing mild and efficient access to diverse polysubstituted dihydrofurans in good yields and enantioselectivities.**

Dihydrofurans are found in many naturally occurring compounds and are attractive starting materials for the synthesis of highly valuable tetrahydrofurans.[1,2] Many syntheses of enantiomerically enriched dihydrofurans have been described, but most rely on the use of multistep diastereoselective strategies using chiral auxiliaries, including oxazolidinones,[3a] sulfoximines,[3b] or sulfonium salts.[3c] Further elegant approaches include the retro-Claisen photo rearrangement of enantiopure norbornane derivatives[4a] and the nickel-catalyzed rearrangement of cyclopropanes to provide enantioenriched hydrofurans.[4b]

In addition, examples of asymmetric transition metal-catalyzed reactions employing different chiral ligands have also been described.[5]

In view of the importance of this class of molecules, and building on our previous investigations, we decided to develop a new metal-free enantioselective reaction for the fast and efficient synthesis of hydrofurans. Recently, Gouverneur and co-workers described a proline-catalyzed aldol reaction to efficiently generate acyclic chiral keto-alcohols which upon a phosphine-catalyzed cyclization provided the desired 5-membered ring.[6a] In addition, Calter et al. reported an enantioselective interrupted Feist-Benary reaction employing a cinchona catalyst.[6b,c]

Our group reported the synthesis of multisubstituted hydrofurans using a Brønsted acid catalyzed Mannich-ketalization reaction.[7] Guided by our studies on the use of diketones **1** in cascade transformations,[8] we envisioned that

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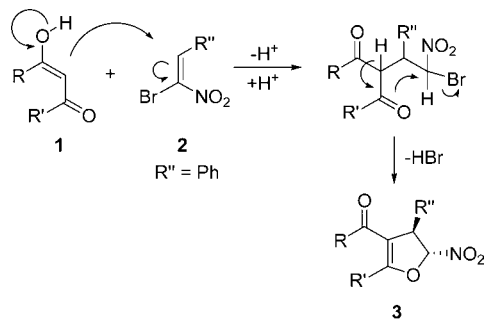
the reaction between this type of dinucleophile and bromonitrostyrene[8d] **2** could lead to the targeted dihydrofuran **3** (Scheme 1). The proposed reaction sequence would involve

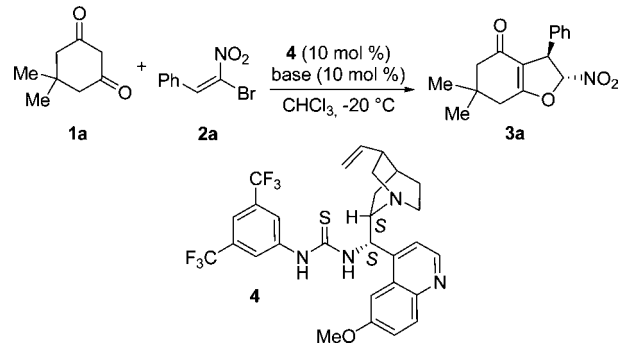
**Scheme 1.** Synthetic Approach to Dihydrofurans




the enantiocontrolled Michael addition of diketone **1** to the (*E*)-$\beta$,$\beta$-bromonitrostyrene **2a**, followed by the diastereoselective cyclization requiring nucleophilic substitution of the bromide to yield the desired polysubstituted dihydrofurans. Furthermore, it was hoped that the chiral induction may be achieved by activation of the bromonitrostyrene employing a hydrogen bond donor catalyst.[9]

To verify this hypothesis, we conducted a series of reactions between the dimedone **1a** and the (*E*)-$\beta$,$\beta$-bromonitrostyrene **2a** using different bifunctional cinchona alkaloid catalysts.[10,11] In all cases formation of the product **3a** was observed but the best enantioselectivity (77% ee) was obtained when the bifunctional thiourea **4** was used as the catalyst in chloroform at −20 °C (Table 1, entry 1).

**Table 1.** Optimization of the Reaction Conditions[a]




| entry | base | yield (%) | ee (%) |
|---|---|---|---|
| 1 | None | 20 | 77 |
| 2 | KOAc | 54 | 6 |
| 3 | $K_2CO_3$ | 86 | 78 |
| 4 | Pyridine | 59 | 58 |
| 5 | Lutidine | 63 | 74 |
| 6 | DMAP | 78 | 70 |
| 7 | DABCO | 68 | 0 |
| 8 | $Et_2NH$ | 59 | 68 |
| 9 | $Et_3N$ | 58 | 66 |
| 10 | TMEDA | 82 | 82 |
| 11[b] | TMEDA | 89 | 81 |
| 12[c] | TMEDA | 88 | 80 |

[a] Reactions were run on 0.4 mmol scale using diketone (1.0 equiv), bromonitrostyrene (1.0 equiv), thiourea catalyst **4** (10 mol %), base (10 mol %) in $CHCl_3$ (0.2 M) at −20 °C for 48 h. [b] TMEDA (20 mol %) was used. [c] TMEDA (20 mol %) and 20 mol % catalyst **4** were used.

However, the yields and conversions to the cyclic compound **3a** remained poor. Furthermore, lower temperatures caused the reaction to proceed slowly without increasing

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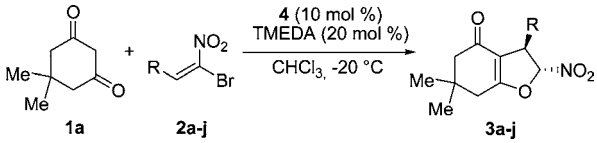
**Table 2.** Reaction between Dimedone **1a** and Various $\beta,\beta$-Bromonitrostyrenes[a]

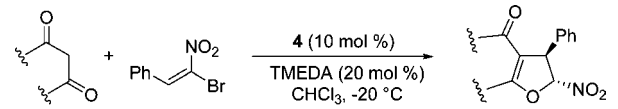



1a 2a-j 3a-j

| entry | bromonitro -styrene | product | time (h) | yield (%) | ee[b] |
|---|---|---|---|---|---|
| 1 | **2a** | | 24 | 89 | 81 (99) |
| 2 | **2b** | | 48 | 81 | 84 (99) |
| 3 | **2c** | | 72 | 83 | 66 (78) |
| 4 | **2d** | | 72 | 82 | 80 (97) |
| 5 | **2e** | | 48 | 77 | 90 (99) |
| 6 | **2f** | | 48 | 70 | 82 (99) |
| 7 | **2g** | | 48 | 72 | 80 (99) |
| 8 | **2h** | | 48 | 92 | 80 (99) |
| 9 | **2i** | | 72 | 92 | 83 (99) |
| 10 | **2j** | | 48 | 71 | 78 (86) |

[a] Reactions were run on 0.4 mmol scale using diketone (1 equiv), bromonitrostyrene (1 equiv), thiourea catalyst (10 mol %), TMEDA (20 mol %) in $CHCl_3$ (0.2 M) at −20 °C. [b] ee values in brackets are obtained after one recrystallization using isopropanol.

**Table 3.** Reaction between 1,3-Diketone Derivatives and $\beta,\beta$-Bromonitrostyrene **2a**[a]




1b-f 2a 5-8

| entry | nucleophile | product | time (h) | yield (%) | ee[b] (%) |
|---|---|---|---|---|---|
| 1 | **1b** | **5** | 48 | 82 | 80 (97) |
| 2 | **1c** | **6** | 72 | 71 | 77 (98) |
| 3 | **1d** | **7** | 72 | 67 | 86 (98) |
| 4 | **1e** | **8** | 48 | 45 | 74 |
| 5[c,d] | **1f** | **9a** | 24 | 37 | 90 |
| | | **9b** | | 42 | 92 |

[a] Reactions were run on 0.4 mmol scale using diketone (1 equiv), bromonitrostyrene (1 equiv), thiourea catalyst **4** (10 mol %), TMEDA (20 mol %) in $CHCl_3$ (0.2 M) at −20 °C. [b] ee values in brackets are obtained after one recrystallization using isopropanol. [c] Obtained as a 1:1 mixture of regioisomeres. [d] Reaction was carried out at 0 °C without base.

either the enantiomeric excesses or the yields. Looking closer at the reaction mechanism, we considered that the liberation of bromhydric acid in the reaction medium could be detrimental to the good activity of the catalyst due to the possible protonation of its basic sites. Thus, many different base additives were used in order to trap the liberated acid. When one equivalent was used, a significant drop in enantioselectivity was observed yet the conversion increased. Therefore, we investigated the amount and nature of the base needed for the reaction. Interestingly the best results were obtained when 20 mol % of tetramethylethylenediamine (TMEDA) were used in combination with either 10 mol % (Table 1, entry 11) or 20 mol % (Table 1, entry 12) of the bifunctional thiourea.[12−14] This resulted in the formation of

the desired product as a single diastereoisomer in 89% yield and with 81% enantiomeric excess.

The versatile inorganic base $K_2CO_3$ can also be used in 20 mol % quantity as it gives similar results with regard to yield and enantioselectivity (Table 1, entry 3). With the optimal conditions in hand, we carried out a series of experiments using variously substituted bromonitrostyrenes (Table 2). Both electron-rich and electron withdrawing groups were well tolerated at the *ortho*, *meta* or *para* position of the phenyl ring. In general the yields were consistently good; the lowest of which was 70% for the *m*-bromo substituted styrene (Table 2, entry 6). Enantiomeric excesses were all in the 80−90% range. Only in the case of the bulky 2-naphthyl substituent was a slight decrease observed.

The above enantioselectivies were obtained from the compounds when they were fully dissolved. When we initially carried out our analysis with the typical HPLC sample solvent, isopropanol, crystallization occurred and the enantiomeric excess increased to more than 97% ee. Therefore, we recrystallized all the compounds using isopropanol and obtained the dihydrofurans in good yields and with excellent enantioselectivities throughout.

To explore the scope of the reaction, further experiments were conducted using different dicarbonyl derivatives. The results are reported in Table 3.

The simple cyclohexanedione **1b** (Table 3, entry 1) gave results comparable with dimedone **1a**. The hydroxy coumarin **1c** (Table 3, entry 2) and its lactam analog **1d** (Table 3, entry 3) reacted well with the bromonitrostyrene to give the tricyclic compounds **6** (71% yield, 77% ee) and **7** (67% yield, 86% ee) respectively. The lactone **8** (Table 3, entry 4) was obtained in lower yield (45%) but the enantiomeric excess remained good. When the hydroxyquinone **1f** was used in the reaction two products were obtained in a 1:1 ratio. These compounds were identified as the two regioisomers **9a** and **9b** and they were isolated in 37 and 42% yields and with excellent enantioselectivies of 90 and 92% ee, respectively.

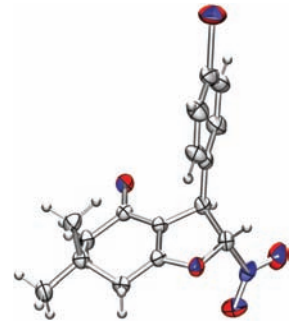


**Figure 1.** Molecular structure of **3e**. The single crystal has been obtained from isopropanol. Ellipsoids set at 50% probability.

To determine the absolute configuration of the products, X-ray analysis was performed on a single crystal of compound **3e** bearing a bromine atom on the para position of the phenyl ring. The configuration was assigned as (2*R*,3*R*).

In summary, we have developed a new enantioselective Michael addition-nucleophilic substitution reaction that enables the formation of *trans*-tetrasubstituted dihydrofuranes from easily accessible diketones and (*E*)-$\beta$,$\beta$-bromonitrostyrenes. The reactions proceed in good yields, with good enantioselectivities and with high functional group tolerance. Furthermore, this methodology demonstrates that $\beta$,$\beta$-bromonitrostyrenes are useful dielectrophilic synthons in the field of asymmetric organocatalysis.

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

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(14) Increasing the amount of base additive resulted in lower enantioselectivities.