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Phosphorus(III)-Mediated Stereoconvergent Formal [4+1]-Cycloannulation of 1,2-Dicarbonyls and *o*-Quinone Methides: A Multicomponent Assembly of 2,3-Dihydrobenzofurans

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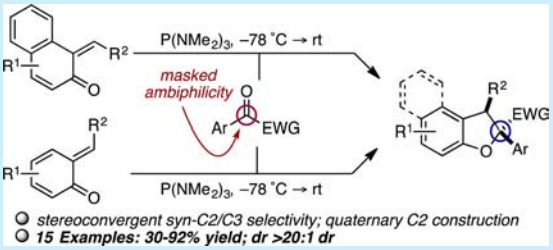
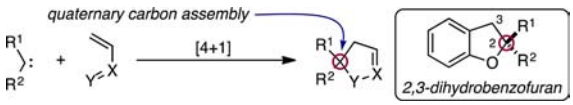
Supporting Information

ABSTRACT: A phosphorus(III)-mediated formal [4+1]-cycloaddition of 1,2-dicarbonyls and *o*-quinone methides to provide 2,3-dihydrobenzofurans is described. By exploiting the carbene-like nature of dioxyphospholenes, dihydrobenzofurans bearing a quaternary center at C2 are obtained in 30−92% yield with diastereoselectivities up to ≥20:1. This study highlights the subtle steric interactions involved in the [4+1]-cycloannulation and the impact they have on yield and stereoselectivity in dihydrobenzofuran formation.



Unlike sequential fragment coupling/cyclization approaches, pericyclic and transition-metal-catalyzed cycloadditions[1] offer convergent entry into functionalized heterocycles. Despite impressive advances in intramolecular C−H activations,[2] [3+2]-cycloadditions are still widely used for 5-membered heterocycle construction.[3] In contrast, [4+1]-cycloadditions and chelotropic processes are significantly underutilized in this context (Scheme 1).[4] Frequently, high activation energies and competing cyclopropane/aziridine formation from carbenoids/nitrenoids limit the versatility of these strategies.[5] Albeit nontrivial, addressing these challenges would enable site-specific heterocycle functionalization through the *geminal* substitution of a single carbon unit, such as 2,3-dihydrobenzofurans bearing a C2 quaternary center. The 2,3-dihydrobenzofuran ring system is an important motif present in a number of natural products and pharmaceuticals for use in the treatment of an array of maladies (Figure 1).[6] As a result, the development of new methods toward this subunit has attracted the attention of synthetic chemists for decades.[7]

Scheme 1. [4+1]-Approach toward Heterocycle Construction



Despite their utility, few existing methods provide direct access to 2,3-substituted dihydrobenzofurans in a stereoselective fashion.[7a,8] Speculating that a formal [4+1]-cycloaddition approach would rapidly install quaternary substitution at C2 while maintaining structural flexibility at C3, we sought to apply the retrosynthetic disconnect outlined in Scheme 1 by the addition of a carbenoid derivative into an *o*-quinone methide (*o*-QM).[9] While decomposition of α-diazo carbonyls using transition-metal catalysts is perhaps the most common means

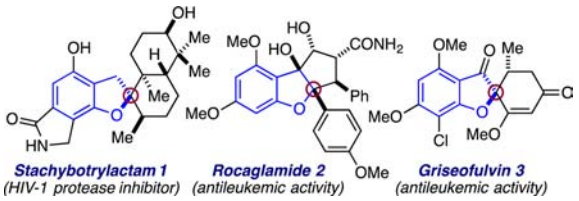
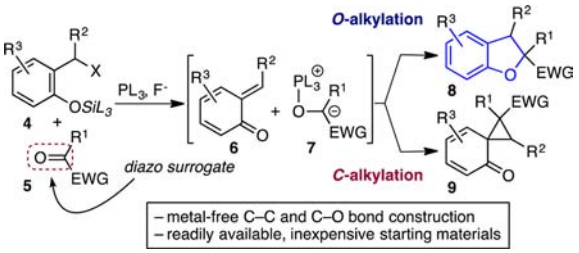


Figure 1. Biologically active dihydrobenzofuran natural products.

of accessing carbenoid reactivity,[10] this approach is often hampered by the light and heat sensitivity of diazo compounds and would likely suffer from competitive C−H arylations and cyclopropanations en route to the desired dihydrobenzofurans.[11] Inspired by recent independent studies conducted by Radosevich and He, we chose to employ a Kukhtin−Ramirez-like condensation in which the addition of a phosphine to ketone **5** bearing an α-electron-withdrawing group generates an oxyphosphonium enolate **7** that exhibits carbene-like reactivity (Scheme 2).[12] Generation of *o*-QM **6** from silyl ether **4**[9c,13] followed by 1,4-addition of **7** sets the stage for an *O*-alkylation

Scheme 2. Proposed 2,3-Dihydrobenzofuran Synthesis



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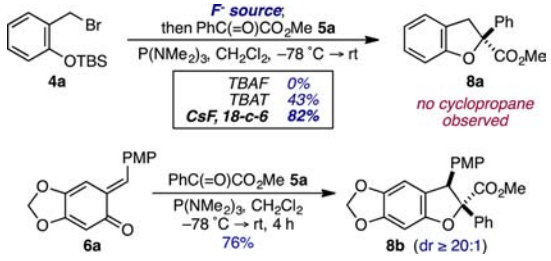
event, in which P=O bond formation acts as a thermodynamic driving force, to provide 2,3-dihydrobenzofuran **8**.[14]

At the outset of this study, we were acutely aware of the synthetic challenges this strategy carried with it, including the potential for competitive *C*-alkylation of the initial conjugate addition adduct to yield cyclopropane **9**.[9e,15] Additionally, we were concerned that the low temperature conditions required for *o*-QM generation may be incompatible with oxyphospholene formation[9c,13] and competitive self-condensation of ketone **5** would hinder dihydrobenzofuran formation.[12b] Herein, we describe the successful implementation of this [4+1]-cycloaddition strategy toward 2,3-dihydrobenzofuran construction and the development of a three-component assembly to access vicinal 2,3-substitution with a high degree of diastereoselectivity.

To evaluate our strategy outlined in Scheme 2, we examined the addition of α-ketoester **5a** to *o*-QM precursor **4a** in the presence of $P(NMe_2)_3$ and a fluoride source (Scheme 3). While TBAF led to an intractable mixture of products, we discovered that TBAT gave dihydrobenzofuran **8a** in 43% yield.[16] The yield improved to 82% using CsF and 18-c-6, and time and temperature proved critical toward minimizing *o*-QM dimer formation and self-condensation of **5a**.[12b] Allowing the reaction to warm slowly from −78 °C to room temperature, following the sequential addition of fluoride and $P(NMe_2)_3$, effectively eliminated these side reactions. Likewise, treatment of isolable *o*-QM **6a** to **5a** and $P(NMe_2)_3$ yielded *syn*-2,3-dihydrobenzofuran **8b** as a single stereoisomer in 76% yield.[17]

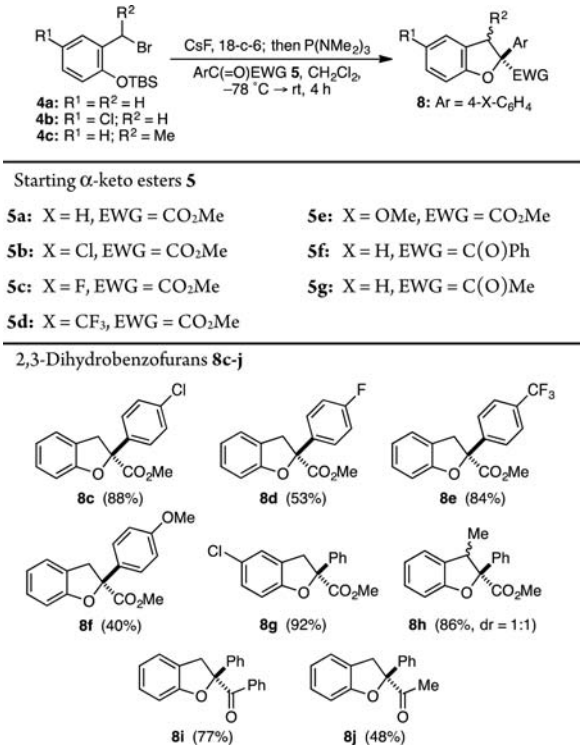
Scheme 3. Initial Findings



Excited by these initial results, we next evaluated the functional group compatibility of this approach (Scheme 4). While both electron-rich and electron-poor aryl-substituted α-ketoesters were tolerated, the yield of dihydrobenzofuran **8** was higher with electron-deficient arenes. This is consistent with a mechanism involving an initial nucleophilic addition of $P(NMe_2)_3$ to the α-ketoester as proposed by Ramirez and co-workers.[12c] Similarly, chloride substitution on **4b** gave cycloadduct **8g** in 92% yield. While benzylic substitution on **4c** did not hinder formation of **8h**, the reaction proceeded with 1:1 diastereoselectivity. Symmetrical and unsymmetical 1,2-diketones were effective as demonstrated by the conversion of benzil **5f** to **8i** in 77% yield and unsymmetrical diketone **5g** to methyl ketone **8j** in 48% as a single regioisomer. Interestingly, employing α-ketoesters bearing alkyl and vinyl β-substituents failed to provide the corresponding benzofuran in appreciable yields.

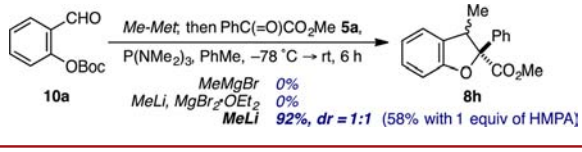
Unfortunately, synthesis of the secondary benzylic bromides proved low yielding and hampered the application of this method toward 2,3-substituted cycloadducts. To address this issue we were inspired by Pettus' work on hetero-Diels−Alder cycloadditions in which he showed that addition of Grignard reagents to Boc-protected salicylaldehyde derivatives initiates a 1,5-acyl migration/β-elimination sequence to generate the corresponding *o*-QM.[9e,18] Whereas the addition of MeMgBr or MeLi/$MgBr_2{\cdot}OEt_2$ to salicylaldehyde **10a** failed to provide dihydrobenzofuran **8h**, the addition of MeLi, followed by **5a** and $P(NMe_2)_3$, produced adduct **8h** in 92% yield (Scheme 5). Interestingly, the addition of HMPA (1 equiv) led to a decrease in the yield of **8h**, which would seem to highlight a delicate balance in metal alkoxide charge separation for controlled *o*-QM generation. This modification of Pettus' method enabled ready access to 2,3-disubstituted dihydrobenzofurans.

Scheme 4. Fluoride-Mediated *o*-QM Generation[a]



[a]Conditions: CsF (0.52 mmol) and 18-c-6 (0.52 mmol) were added to **4** (0.26 mmol) in CH_2Cl_2 (0.5 M) followed by **5** (0.34 mmol) and $P(NMe_2)_3$ (0.34 mmol).

Scheme 5. Organometallic *o*-Quinone Methide Generation



In general, good to excellent yields of the cycloadducts were obtained from various salicylaldehydes **10** and organolithium reagents (Scheme 6). Substitution on **10** did not adversely affect the formation of dihydrobenzofurans **8k−m**, as exemplified by the presence of two electron-donating groups in **8m**. Using PhLi enabled smooth *o*-QM formation to give adducts **8n−p**. Consistent with our previous results, electron-poor aryl α-ketoesters gave higher yields of **8** than their electron-rich counterparts (i.e., **8o** and **8p**). Employing phenyl acetylide gave **8q** bearing an alkyne at C3. It is also noteworthy that although the C3-methyl-substituted dihydrobenzofuran **8r** was obtained in 73% yield, employing PhLi led to a diminished yield of **8s**.

Over the course of these studies, we became acutely aware of the discrepancy between the diastereoselectivities observed for

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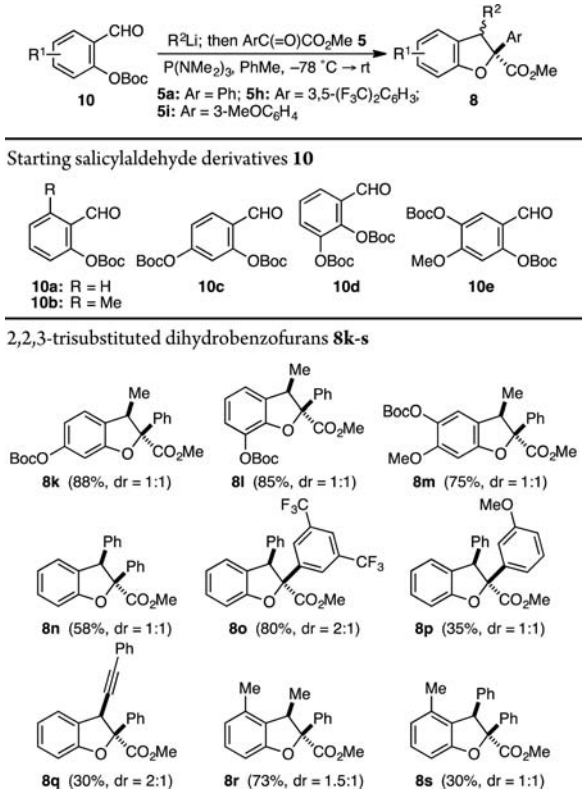
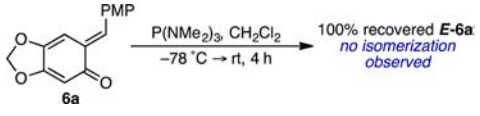
Scheme 6. Dihydrobenzofuran Assembly[a]



[a]Conditions: R^2Li (0.29 mmol) was added to **10** (0.26 mmol) in PhMe (0.2 M), followed by **5** (0.34 mmol) and $P(NMe_2)_3$ (0.34 mmol).

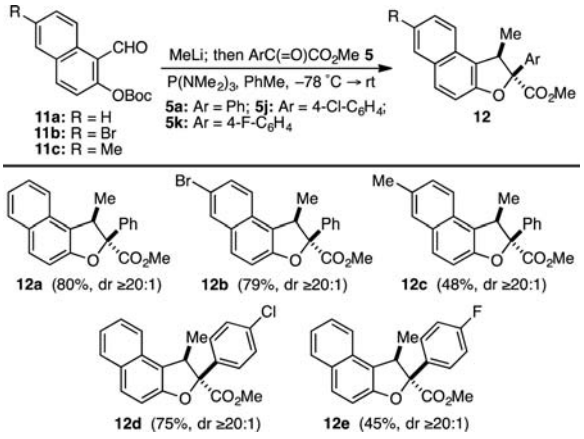
dihydrobenzofurans in Schemes 4 and 6 and the high degree of selectivity for **8b** (Scheme 3). Given that the *E*-alkylidene **6a** gave exclusively the *anti* isomer of **8b**, we speculated that *o*-QM alkylidene integrity was critical to 2,3-diastereoselectivity.[8d] Based on this assertion, it is plausible that an unselective in situ generation of the *o*-QM or rapid *E*-to-*Z* isomerization mediated by $P(NMe_2)_3$ is responsible for the low diastereoselectivities observed with those substrates in Scheme 6.[19] This is consistent with the observation that treatment of **6a**, which provided **8b** as a single stereoiosomer, with $P(NMe_2)_3$ in the absence of **5a** failed to provide the corresponding *Z*-isomer (Scheme 7). The sharp contrast in diastereoselectivity between **8b** and **8k**–**s** suggests that the selective generation of a geometrically stable *o*-QM alkylidene is critical to achieving high C2–C3 diastereoselectivity.

Scheme 7. Alkylidene Geometric Stability



To test this hypothesis further, we examined 2-hydroxynaphthaldehyde derivatives **11** with a preference for *Z*-alkylidene formation in the formation of dihydronaphthylfurans **12** (Scheme 8).[8c] Addition of MeLi to naphthaldehyde **11a** followed by **5a** and $P(NMe_2)_3$ provided **12a** in 80% yield and ≥20:1 stereoselectivity. Electron-withdrawing halogens at C6 of the naphthyl ring were well tolerated in the cycloaddition event

Scheme 8. Dihydronaphthylfuran Synthesis[a,b]

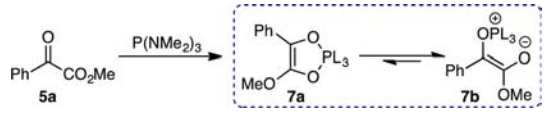


[a]Conditions: MeLi (0.28 mmol) was added to **11** (0.26 mmol) in PhMe (0.2 M), followed by **5** (0.34 mmol) and $P(NMe_2)_3$ (0.34 mmol). [b]Ratios determined by ^1H NMR (500 MHz).

leading to formation of **12b** and **12c** in excellent yield and consistently high diastereoselectivity. Employing *α*-keto esters **5b** and **5c** likewise gave the corresponding dihydronaphthylfurans **12d** and **12e** exclusively in 75% and 45% respectively. Strikingly, we observed a stereoconvergent dihydrobenzofuran assembly to the *syn*-2,3 isomer, whether employing the presumptive *Z*-alkylidene from **11** or *E*-alkylidene **6a**.

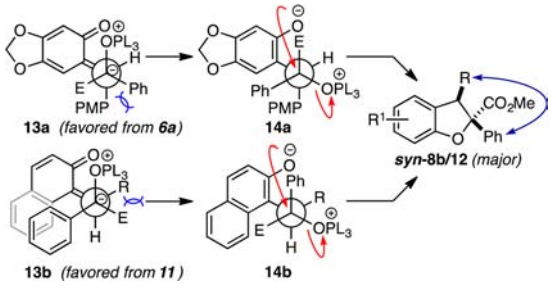
On the basis of these results, a preliminary picture arises of the stereochemical control elements in this formal [4+1]-cycloannulation. Addition of $P(NMe_2)_3$ to **5a** provides an equilibrium of oxyphospholene **7a** and zwitterion **7b** (Scheme 9). Ramirez

Scheme 9. Dioxyphospholene/Zwitterion Formation



has shown that this equilibrium favors the more nucleophilic zwitterion **7b** (L = NMe_2).[20] If we assume an electrostatic attraction between the *o*-QM carbonyl oxygen and phosphonium cation, transition states **13a** and **13b** arise from the addition of **7b** to *o*-QMs **6a** and **11**, respectively (Scheme 10). Minimizing gauche interactions orients the larger aryl group away from the *o*-QM benzenoid ring in **13a**, resulting in phosphine oxide displacement through *anti*-conformer **14a** to give ***syn*-8b**. Preference for *syn*-**12** from the *Z*-naphthyl alkylidene is potentially due to a combination of favorable *π*–*π* stacking between the aryl group on **5** and the naphthyl ring and

Scheme 10. Proposed Rationale for Diastereoselection



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minimization of Me/Ph gauche interactions in **13b**. Ultimately, this leads to the same relative *syn*-C2/C3 stereochemistry and relies on configurational stability of the alkylidene to provide high levels of stereocontrol. While speculative, this hypothesis is consistent with Ramirez's findings and rationalizes the stereoselective formation of **8b** and dihydronaphthylfurans.

In summary, we have developed an efficient and convergent [4+1]-cycloaddition approach toward the construction of substituted 2,3-dihydrobenzofurans. The flexibility of this strategy permits rapid access to a variety of structurally distinct dihydrobenzofurans bearing a quaternary center at the C2 position. Mechanistic studies and extension of this [4+1]-cycloaddition strategy to other heterocyclic frameworks are currently underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02122.

Experimental procedures and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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