

# Asymmetric Homoenate Additions to Acyl Phosphonates through Rational Design of a Tailored *N*-Heterocyclic Carbene Catalyst

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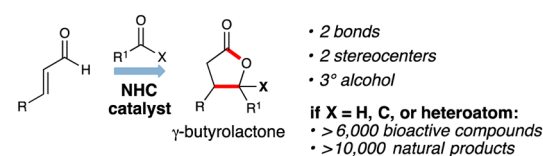
**S** Supporting Information

**ABSTRACT:** A highly selective NHC-catalyzed synthesis of  $\gamma$ -butyrolactones from the fusion of enals and  $\alpha$ -ketophosphonates has been developed. Computational modeling of competing transition states guided a rational design strategy to achieve enhanced levels of enantioselectivity with a new tailored  $C_1$ -symmetric biaryl-saturated imidazolium-derived NHC catalyst.

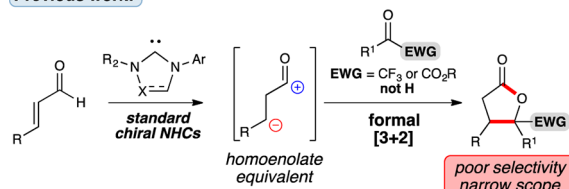
The ability to forge complex hetero- and carbocyclic systems convergently with high levels of selectivity remains a challenge in organic synthesis. Over the past two decades, *N*-heterocyclic carbenes (NHCs) have been explored intensely for the synthesis of various structural manifolds through *Umpolung* reactivity.<sup>1</sup> Since the seminal reports of NHC-homoenate reactions, there have been significant advancements in this area, with a primary focus on additions to various activated  $\pi$  systems.<sup>2,3</sup> While aldehydes and aldimines are productive substrates in a variety of reactions to produce  $\gamma$ -lactones and lactams, respectively,<sup>3a-c,4</sup> more sterically hindered, less reactive ketones and imines impose severe limitations on single NHC catalyst systems.<sup>5,6</sup> To address this challenge, new strategies and/or new catalyst design approaches are needed. One strategy is cooperative catalysis with NHCs integrating Lewis and Brønsted acids to enhance reactivity, modulate stereocontrol, and access new reactivity with previously inactive electrophiles.<sup>4c,7</sup> However, there are few examples involving the synthesis of  $\gamma$ -butyrolactones with high levels of enantioselectivity.<sup>6,7b</sup> These motifs are highly attractive given the large number of bioactive molecules and natural products with this key architectural feature (Figure 1, X = H, C, or heteroatom). *As a complementary strategy, new advances in rational N-heterocyclic carbene structure/reactivity development could provide new solutions for NHC annulations of  $\pi$  electrophiles.*

Acyl phosphonates are potential electrophiles for an NHC-catalyzed [3+2] annulation process, but are particularly challenging given the steric environment around the target carbonyl group. These phosphonates have been employed in a wide range of enantioselective processes.<sup>8</sup> Many methods have been developed to incorporate phosphonate groups due to the prevalence of the phosphinic acid group in naturally occurring and pharmaceutical compounds with antiviral, antibacterial, and anticancer properties.<sup>9</sup> In particular, the synthesis of phospho-

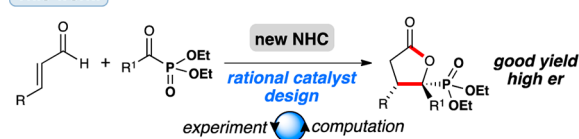
**Carbene-Catalyzed Formal [3+2] Strategy for  $\gamma$ -Butyrolactones**



**Previous work:**



**This work:**



**Figure 1.** NHC annulations of acyl phosphonates.

nates bearing  $\alpha$ -hydroxy<sup>10</sup> and  $\alpha$ -amino groups<sup>11</sup> has received significant attention.

Here we report the addition of  $\alpha,\beta$ -unsaturated aldehydes to  $\alpha$ -ketophosphonates under carbene catalysis to afford enantio-enriched  $\gamma$ -butyrolactones with a previously unreported core structure (Figure 1, X = P(=O)(OR)<sub>2</sub>). The discovery that standard chiral NHC catalysts are ineffective for this transformation resulted in the design of several new  $C_1$ -symmetric biaryl-saturated imidazolium catalysts. This scaffold was introduced by Hoveyda in an enantioselective, metal-free C–B bond-forming reaction.<sup>12</sup> Computationally guided rational catalyst design was employed to improve selectivity for this new formal [3+2] annulation process. This strategy is underutilized in the field of NHC catalysis, but several groups, most prominently Sigman et al., have demonstrated the use of correlative methods to dictate improved catalyst scaffolds for epoxidation, hetero-Diels–Alder, and other catalytic asymmetric reactions.<sup>13</sup> These efforts have resulted in enhanced catalyst performance and relate catalyst structure to the observed enantioselectivity.

**Received:** November 1, 2013

**Published:** December 3, 2013

Table 1. Optimization of Reaction Conditions

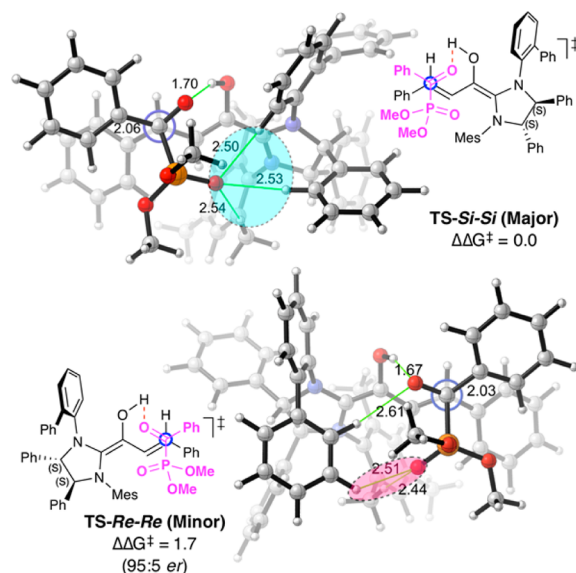
entry	azolium	base	% yield <sup>a</sup>	cis:trans <sup>b</sup>	er <sup>c</sup>
1	A	DBU	35	1:13	-
2	B	DBU	70	1:4.6	-
3	C	DBU	20	1.2:1	67:33
4	D	DBU	94	5.8:1	85:15
5	D	MTBD	79	1.8:1	90:10

<sup>a</sup>NMR yield with internal standard. <sup>b</sup>Diastereomeric ratio determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup>Enantiomeric ratio determined by HPLC analysis.

We began our studies by combining  $\alpha$ -ketophosphonate **1** with cinnamaldehyde in the presence of imidazolium precatalyst **A** and 20 mol% 1,8-diazabicyclo[5.4.9]undec-7-ene (DBU, Table 1, entry 1). Under these conditions, the desired formal [3+2] annulation product was formed in 35% yield with good selectivity for the *trans* diastereomer. To improve the efficiency, various other NHC precatalysts were examined for this transformation: the use of saturated imidazolium **B** resulted in a decrease in diastereoselectivity but a significant increase in yield (entry 2). Notably, while saturated imidazoliums are frequently employed as ligands for transition metals,<sup>14</sup> there are limited reports on the use of these NHCs as organocatalysts.<sup>7d</sup>

With this backdrop, we turned to rendering this reaction enantioselective. The use of 1,2-aminoindanol-derived triazolium catalyst **C**<sup>4b</sup> resulted in poor conversion to the lactone product with low levels of enantioselectivity (67:33 er, entry 3). Based on the success of achiral saturated imidazolium **B**, we explored the C<sub>1</sub>-symmetric biaryl-saturated imidazolium precatalyst **D**.<sup>12</sup> Under the previously explored conditions, precatalyst **D** afforded the product in excellent yield and good diastereo- and enantioselectivity (94%, 85:15 er, entry 4). A further increase in enantioselectivity was observed by switching the base from DBU to 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), affording the lactone in 79% yield and 90:10 er (entry 5).

At this stage, a new direction was required to achieve higher levels of selectivity. Faced with the typical arduous empirical approach of evaluating many new analogues of **D**, we initiated a computational investigation of the stereodetermining homoaldol step with density functional theory, B3LYP/6-31G\*.<sup>15</sup> The transition structures (TSs) that correspond to the formation of the major (*S,S*) and minor (*R,R*) enantiomer products are shown in Figure 2. In both cases, nucleophilic attack of the homoenol to the acyl phosphonate carbonyl is concomitant with deprotonation of the enol proton by the forming alkoxide.<sup>16</sup> Stereoselectivity arises from differential stabilization of the phosphonyl oxygen by the catalyst aryl protons through *nonclassical hydrogen bonds* (NCHBs).<sup>17</sup> The preorganization and anion stabilization present in these TSs are reminiscent of the oxyanion hole stabilization found in enzymes, where an array of backbone amide protons provide stabilization of the developing alkoxide.<sup>18</sup>



**Figure 2.** Transition structures with catalyst **D**. The first *Re/Si* notation refers to the homoenol face, and the second *Re/Si* refers to the electrophile face. Et groups abbreviated to Me for computational efficiency. Cyan region marks stabilizing nonclassical hydrogen-bonding interactions in the major TS, while pink marks those found in the minor. Green lines indicate electrostatic interactions. Distances are in Å and energies in kcal/mol.

Table 2. Catalyst Optimization

entry	azolium	R	% yield <sup>a</sup>	cis:trans <sup>b</sup>	er <sub>comp</sub>	er <sub>exp</sub> <sup>c</sup>
1	<b>D</b>	H	79	1.8:1	95:5	90:10
2	<b>E</b>	Me	82	2.1:1	99:1	92:8
3	<b>F</b>	Et	80	2.5:1	N/A	94:6

<sup>a</sup>NMR yield with an internal standard. <sup>b</sup>Diastereomeric ratio was determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup>Enantiomeric ratio was determined by HPLC analysis.

It was anticipated that selective destabilization of the minor TS could be achieved because the stabilization sites differ between the major and minor enantiomers (Table 2). In the minor TS, the catalyst NCHB sites are only on the terminal biphenyl meta positions (shown in pink). This is in contrast to the major TS, where there are multiple stabilizing NCHB interactions, located at the ortho positions of the catalyst backbone phenyl and the internal *N*-biphenyl (shown in cyan). The increased number of strong NCHB interactions is responsible for the computed 1.7 kcal/mol selectivity (95:5 er), which compares favorably with the experimental selectivity of  $\sim 1.0$  kcal/mol (90:10 er). While both TSs are stabilized by the mesityl methyl C–H, these protons are inferior NCHB donors compared to aryl C–H's.<sup>17</sup> Since the NCHB stabilization motif was clearly different between the

major and minor TSs, we envisioned that the installation of methyl groups at the terminal biphenyl meta positions would disrupt the phosphonyl stabilization of the minor TS but leave the major TS unchanged, thus increasing enantioselectivity.

Based on the computational prediction, catalyst E was employed in the annulation reaction. Under the previously optimized conditions with the more sterically demanding 3,5-dimethylphenyl substituent we observed an increase in enantioselectivity to 92:8 er (1.5 kcal/mol, Table 2, entry 2). This correlates well with the computationally predicted er of 99:1 (3.0 kcal/mol). Extension of the catalyst to include ethyl groups at the 3- and 5-positions of the aryl ring was explored to determine if the enantioselectivity could be further enhanced. We were pleased to find that this simple catalyst modification afforded the product in 80% yield and 94:6 er (entry 3).

We surveyed several  $\alpha,\beta$ -unsaturated aldehydes in the reaction with  $\alpha$ -ketophosphonate **1** with the optimized reaction conditions (Table 3). Both electron-withdrawing and -donating substituents were tolerated, providing the  $\gamma$ -butyrolactones in good to excellent yield and enantioselectivity (3–7, >91:9 er). In addition, enals bearing a pyridine and *N*-Me indole at the  $\beta$ -position were also accommodated. 3-Pyridyl-substituted lactone **11** was formed in slightly diminished yield but with good enantioselectivity. Likewise, the indole-substituted lactones were both produced in >65% yield, with 2-indoyl substrate **12** generated with slightly higher enantioselectivity. Variation of the  $\alpha$ -ketophosphonate was also explored. We found that electron-donating groups performed well, with lactones **14** and **15** formed in good yield and 93:7 er. Electron-withdrawing substituents afforded the products in excellent yield and enantioselectivity but with moderate diastereoselectivity (**16–18**). Other aromatic groups, such as naphthyl, also performed well in the reaction. Currently, alkyl-substituted substrates (either aldehyde or acyl phosphonate) do not provide practical levels of efficiency.

Based on our calculations, the proposed mechanism for formation of the lactone products involves initial addition of the catalyst to the aldehyde and subsequent formal 1,2-H migration to generate the extended Breslow intermediate (**I**, Scheme 1). Based on computational modeling, H-bonding between the ketone of the acyl phosphonate and the enol results in an organized transition state. Following C–C bond formation to generate enol **II**, tautomerization occurs, giving rise to acyl

### Scheme 1. Proposed Reaction Mechanism

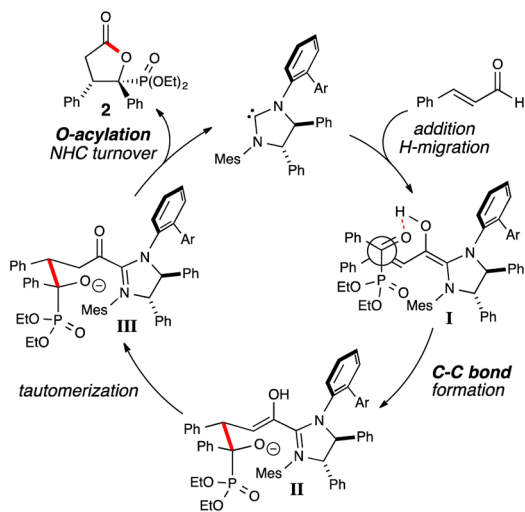
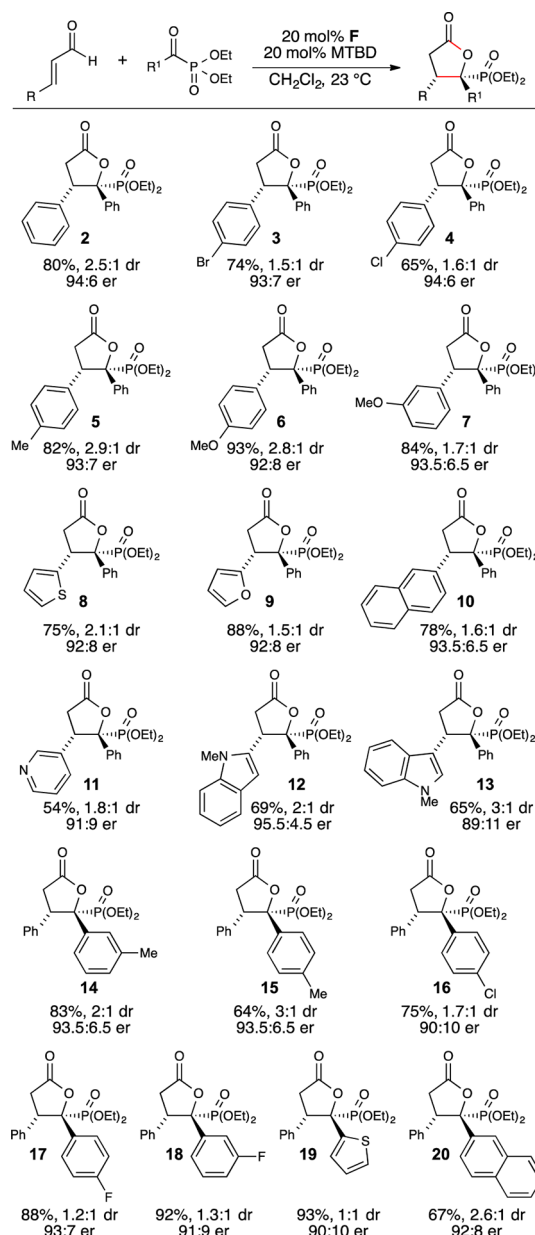


Table 3. Lactone Substrate Scope<sup>a</sup>

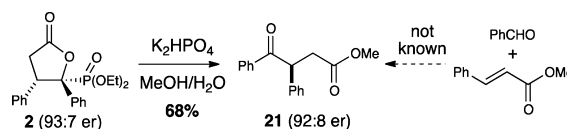


<sup>a</sup>Yields are of isolated product after column chromatography. Diastereomeric ratio determined by <sup>1</sup>H NMR spectroscopy. Enantiomeric excess determined by chiral HPLC.

azolium **III**, which then undergoes *O*-acylation to afford lactone **2** and release the NHC catalyst.

The lactone products can be converted to enantioenriched 1,4-ketoesters in a single, mild operation with almost complete transfer of chirality. Treatment of lactone **2** (93:7 er) with potassium phosphate dibasic afforded ketoester **21** in 68% yield and 92:8 er through initial opening of the lactone and a subsequent retro-phospho aldol reaction (Scheme 2). Related

### Scheme 2. Transformation to Stetter Products



1,4-carbonyl systems are often prepared through a Stetter reaction,<sup>19,20</sup> but this particular class is difficult to access through traditional methods due to the diminished reactivity of the ester and the resulting acidity of the  $\alpha$ -aryl ketone product.<sup>21</sup> This NHC-catalyzed annulation provides a potential new strategy for accessing this challenging 1,4-carbonyl manifold which in theory can be accessed through a Stetter reaction. However, to our knowledge, no general, enantioselective intermolecular Stetter reaction of aromatic aldehydes to  $\alpha,\beta$ -unsaturated esters has been reported that provides high levels of enantiocontrol at the  $\beta$ -stereocenter.<sup>21</sup>

In conclusion, a highly selective NHC-catalyzed formal [3+2] annulation of  $\alpha,\beta$ -unsaturated aldehydes with acyl phosphonates has been developed. The ineffectiveness of known NHC catalysts for this transformation resulted in the creation of new  $C_1$ -symmetric biaryl-saturated imidazolium catalysts. Computationally guided rational catalyst design resulted in enhanced enantioselectivity, allowing for the synthesis of various  $\gamma$ -butyrolactones with excellent selectivity. These saturated imidazoliums provide a new catalyst scaffold for investigating other NHC-catalyzed transformations. In addition, this new enantioselective platform provides a distinct approach to 1,4-carbonyl compounds that are difficult to access through traditional methods, where various substituents can be incorporated through the appropriate choice of the acyl phosphonate and aldehyde starting materials. Continuing investigations involving the use of these chiral saturated imidazolium catalysts in NHC-catalyzed transformations and the integration of computational methods to enhance selectivity via specific catalyst tailoring are ongoing.

## ■ ASSOCIATED CONTENT

### ● Supporting Information

Experimental procedures and spectral data for new compounds, geometries, and energies of all structures discussed. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

Financial support was generously provided by the NIH (RO1-GM073072) and Oregon State University (Stone Scholar Funds). We thank Dr. Paul Siu (Northwestern University) for assistance with X-ray crystallography.

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