Published in final edited form as:

J Am Chem Soc. 2014 January 8; 136(1): 76–79. doi:10.1021/ja410932t.

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

Ki Po Jang^a, Gerri E. Hutson^a, Ryne C. Johnston^b, Elizabeth O. McCusker^a, Paul H.-Y. Cheong^b, and Karl A. Scheidt^a

Karl A. Scheidt: scheidt@northwestern.edu

^aDepartment of Chemistry, Center for Molecular Innovation and Drug Discovery, Chemistry of Life Processes Institute, Northwestern University, Silverman Hall, Evanston, Illinois 60208

^bDepartment of Chemistry, Oregon State University, 153 Gilbert Hall, Corvallis, Oregon 97331

Abstract

A highly selective NHC-catalyzed synthesis of γ -butyrolactones from the fusion of enals and α -ketophosphonates has been developed. Computational modeling of competing transition states was employed to guide a rational design strategy and achieve enhanced levels of enantioselectivity with a new tailored C₁-symmetric biaryl saturated imidazolium-derived NHC catalyst. This new annulation is compatible with a wide range of acyl phosphonates and α,β -unsaturated aldehydes.

The ability to forge complex hetero- and carbocyclic systems convergently with high levels of selectivity remains a challenge in organic synthesis. Over the last two decades, *N*-heterocyclic carbenes (NHC) have been explored intensely for the synthesis of various structural manifolds through *Umpolung* reactivity.¹ Since the seminal reports of NHC-homoenolate reactivity, there have been significant advancements in this area with a primary focus on the additions to various activated π systems.^{2,3} While aldehydes and aldimines are productive substrates in a variety of reactions to produce γ -lactones and lactams, respectively,^{3a-c,4} more sterically hindered, less reactive ketones and imines impose severe limitations on single NHC catalyst systems.^{5,6} To address this challenge, either new strategies and/or new catalyst design approaches are needed. One such strategy is cooperative catalysis with NHCs integrating Lewis and Brønsted acids to enhance reactivity, modulate stereocontrol, and access new reactivity with previously inactive electrophiles^{4c,7} However, there still remain a limited number of examples involving the synthesis of γ -butyrolactones with high levels of enantioselectivity.^{6,7b} 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 to cooperative catalysis approaches, new advances in rational N-heterocyclic carbene structure/reactivity development could provide new solutions for NHC annulations of π electrophiles.*

Acylphosphonates 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 special phosphonates have been employed in a wide range of enantioselective processes.⁸ Many methods have been developed for the incorporation of

phosphonate groups due to the prevalence of the phosphinic acid group in naturally occurring and pharmaceutical compounds due to their antiviral, antibacterial, and anticancer properties.⁹ In particular, the synthesis of phosphonates bearing α -hydroxy¹⁰ and α -amino groups¹¹ has received significant attention. Herein we report the addition of α,β -unsaturated aldehydes to α -ketophosphonates under carbene catalysis to afford enantioenriched γ -butyrolactones with an unreported core structure until now (Figure 1, X = P(=O)(OR)₂). The discovery that standard chiral NHC catalysts are ineffective for this transformation resulted in the design of several new C₁-symmetric biaryl saturated imidazolium catalysts (see below). This scaffold was originally introduced by Hoveyda and to the best of our knowledge has not yet been reported solely a selective organocatalyst.¹² 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 and coworkers, have demonstrated that the use of correlative methods to dictate improved catalyst scaffolds for epoxidations, hetero-Diels-Alder, and other catalytic asymmetric reactions.¹³ These efforts have resulted in enhanced catalyst performance and relate catalyst structure to the observed enantioselectivity.

We began our studies by combining α -ketophosphonate **1** with cinnamaldehyde in the presence of imidazolium precatalyst **A** in the presence of 20 mol % DBU (Table 1, entry 1). Under these conditions, the desired formal [3+2] annulation product was formed in 35% yield and 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,¹⁴ **there are limited reports involving the use of these NHCs as organocatalysts**.^{7d} With this backdrop, we turned our attention toward rendering this reaction enantioselective. The use of 1,2-aminoindanol derived triazolium catalyst **C**^{4b} 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 C₁-symmetric biaryl saturated imidazolium precatalyst **D**.¹² Under the previously explored conditions, imidazolium 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 upon 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 analogs of **D**, we initiated a computational investigation of the stereodetermining homoaldol step with density functional theory (DFT), B3LYP/6-31G*.¹⁵ 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 acylphosphonate carbonyl is concomitant with deprotonation of the enol proton by the forming alkoxide.¹⁶ Stereoselectivity arises from differential stabilization of the phosphoryl oxygen by the catalyst aryl protons through *non-classical hydrogen bonds* (NCHB).¹⁷ 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.¹⁸

It was anticipated that selective destabilization of the minor TS could be achieved due to the fact that the stabilization sites differ between the major and minor enantiomer (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 of selectivity (95:5 er), which compares favorably with the experimental selectivity of ~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–Hs.¹⁷ 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 prepared and 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, entry 2). This correlates well with the computationally predicted er of 99:1 (3.0 kcal/mol). The extension of the catalyst to include ethyl groups at the 3- and 5-position 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 α,β -unsaturated aldehydes in the reaction with α -ketophosphonate **1** with the optimized reaction conditions (Table 3). Both electron-withdrawing and -donating substituents were tolerated, providing the γ -butyrolactones in good to excellent yield and enantioselectivity (**3–7**, >91:9 er). Various other aromatic systems also performed well in this transformation (**8–10**). In addition, enals bearing a pyridine and *N*-Me indole at the β -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. The variation of the α -ketophosphonate was also explored. We found that electron-donating groups performed well, with lactones **14–15** 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 acylphosphonate) do not provide practical levels of efficiency.

Based on our calculations (see above) 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, hydrogen bonding between the ketone of the acyl phosphonate and the enol results in an organized transition state. Following carbon-carbon bond formation to generate enol **II**, tautomerization occurs to give rise to acyl 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. The 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. Related 1,4-carbonyl systems are often prepared through a Stetter reaction,^{19,20} but this particular manifold is difficult to access through traditional methods due to the diminished reactivity of the ester and the resulting acidity of the α -aryl ketone product.²¹ 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 the best of our knowledge, a general, enantioselective intermolecular Stetter reaction of aromatic aldehydes

to α,β -unsaturated esters that provides high levels of enantiocontrol at the β -stereocenter has not been reported.²¹

In conclusion, a highly selective NHC-catalyzed formal [3+2] annulation of α,β -unsaturated aldehydes with acylphosphonates 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 an enhanced enantioselectivity, allowing for the synthesis of various γ -butyrolactones with excellent selectivity. These saturated imidazoliums have not been previously explored as organocatalysts and provide a new catalyst scaffold for investigation in 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, wherein the incorporation of various substituents can be achieved through the appropriate choice of the acylphosphonate and aldehyde starting materials. Continuing investigations involving the use of these chiral saturated imidazolium catalysts in NHC-catalyzed annulations and the integration of computational methods to enhance selectivity via specific catalyst tailoring are ongoing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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Carbene-Catalyzed Formal [3+2] Strategy for γ -Butyrolactones

Previous work:

This work:

Figure 1.
NHC Homo enolate Annulations of Acyl Phosphonates

Figure 2. Homoaldol transition structures involving 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 non-classical hydrogen bonding (NCHB) 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.

Scheme 1.
Proposed Reaction Mechanism

Scheme 2.

Transformation to Stetter products

^a See Supporting Information for details. *Reagents and conditions*: 20 equiv K₂HPO₄, Hexanes/MeOH/H₂O (15:1:1), 23 °C, 42 h

Table 1

Optimization of Reaction Conditions

entry	azolium	base	% yield ^d	cis:trans ^b	ex ^c
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

^d NMR yield with internal standard.^b Diastereomeric ratio determined by ¹H NMR spectroscopy (500 MHz).^c Enantiomeric ratio determined by HPLC analysis using a chiral stationary phase.

Table 2

Catalyst optimization.

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

^a NMR yield with an internal standard.^b Diastereomeric ratio was determined by ¹H NMR spectroscopy (500 MHz).^c Enantiomeric ratio was determined by HPLC analysis using a chiral stationary phase.

Table 3

Lactone substrate scope^a

^a See Supporting Information for details. Yields are of isolated product after column chromatography. Diastereomeric ratio determined by ¹H NMR spectroscopy (500 MHz) of the unpurified reaction. Enantiomeric excess determined by chiral HPLC.