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Highly Enantioselective, Intermolecular Hydroamination of Allenyl Esters Catalyzed by Bifunctional Phosphinothioureas

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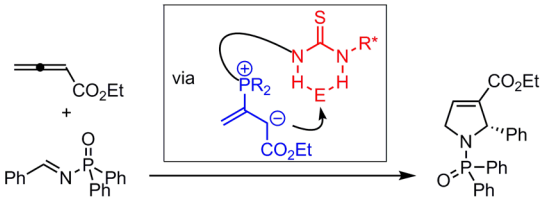
Supporting Information

ABSTRACT: Bifunctional phosphinothiourea catalysts have been developed successfully for the highly regio- and enantioselective γ-hydroamination of allenyl and propargyl esters with *N*-methoxy carbamate nucleophiles to yield α,β-unsaturated γ-amino acid ester products. In the case of propargyl ester substrates, the reaction proceeds through reversible phosphinothiourea-catalyzed isomerization to the corresponding allenyl ester. The high enantioselectivity of the process is attributed to a cooperative conjugate addition of a thiourea-bound carbamate anion to a vinyl phosphonium ion resulting from covalent activation of the allenyl ester substrate.

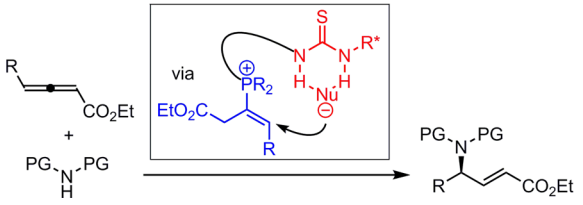
Small, polyfunctional molecules capable of cooperative activation and precise positioning of reacting partners hold tremendous potential in selective catalysis.[1] Recently, we reported the development of a family of phosphinothiourea catalysts[2] that promote imine-allene [3 + 2] cycloadditions via nucleophilic activation of the allene by the phosphine with simultaneous imine activation by hydrogen bonding to the thiourea (Scheme 1A).[3,4] We were intrigued by the potential of a complementary reactivity mode with the same family of catalysts, wherein the H-bond donor would promote formation of a reactive nucleophile by anion binding,[5,6] while the phosphine component could induce generation of an activated vinyl phosphonium electrophile (Scheme 1B).[7,8] We report here the successful development of this strategy, with the application of this new type of cooperative activation to the highly regio- and enantioselective γ-hydroamination of allenyl and propargyl esters.[9] This methodology provides practical access to synthetically valuable α,β-unsaturated γ-amino esters in highly enantioenriched form.[10]

Scheme 1. Cooperative Catalysis with Phosphinothioureas

A) Established mode of cooperative activation by phosphinothiourea: nucleophilic catalysis by phosphine/electrophile activation by thiourea



B) Proposed mode of cooperative activation by phosphinothiourea: nucleophile generation by thiourea/electrophile generation by phosphine



A survey of potential *N*-centered nucleophiles revealed that compounds with pK_a values between 8 and 10 (in H_2O) were suitable reacting partners in γ-additions to allenoate **1** catalyzed by phosphinothiourea **3a**, whereas compounds with acidities lying outside that range were unreactive.[11] Highest enantioselectivities were achieved with *O*-substituted hydroxylamine carbamate derivatives,[12] and the reaction of **1** with **2a** was selected as a model reaction for catalyst optimization studies (Table 1).

Catalysts with the general structure depicted in **3** were generally effective in the model reaction, affording the γ-adduct **4a** as the only detectable product. Variation of the identity or the stereochemistry of the α-amino acid component had little effect on enantioselectivity (entries 1−4), although the *S*-phenylalanine-*R*,*R*-amino-phosphinocyclohexane combination afforded **4a** with the highest ee (entry 1).

Improved reactivity was observed in reactions of less sterically hindered carbamate nucleophiles, and the *O*-methyl alloc variant (**2c**) provided the best balance of reactivity and enantioselectivity (entry 6). In this manner, the loading of catalyst **3a** could be reduced from 10 to 1 mol% with only a slight decrease in enantioselectivity (entries 6−7). Further improvement in reactivity was provided by reducing the steric demand of the amide component as in **3e** (entry 8). Replacement of the amide with an ethyl ester (**3f**) had a negative effect on reaction rate, but very little effect on ee (entry 9). Overall, it appears that the amino acid-derived component of **3** plays an important, albeit subtle role in the mechanism of catalysis, particularly given the observation that simplified catalyst **5** promoted the γ-addition reaction with much lower enantioselectivity (entry 10). On the basis of this analysis, **3e** was selected for further investigation.

During the course of these optimization studies, unreacted allenyl ester **1** isolated after reactions catalyzed by the phosphinothiourea catalysts was always detected as a 1:1 mixture with propargyl ester **6**. We subsequently found that phosphinothiourea **3e** (2 mol%) catalyzed the rapid interconversion of **1** and **6** in the absence of carbamate, reaching equilibrium as a 1:1 mixture within 30 min (Scheme 2).[13] It was thereby possible to

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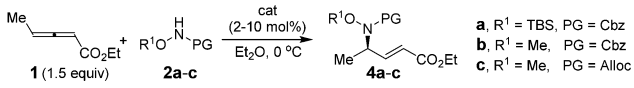
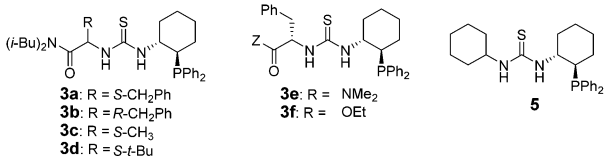
Table 1. Optimization Studies

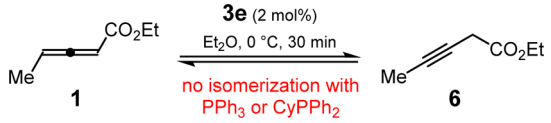




entry	Nu	cat	loading (mol %)	time (h)	yield (%)[a,c]	ee (%)
1	**2a**	**3a**	10	120	65	92
2	**2a**	**3b**	10	120	93	88
3	**2a**	**3c**	10	120	66	88
4	**2a**	**3d**	10	120	72	88
5	**2b**	**3a**	10	24	>99[b]	82
6	**2c**	**3a**	10	24	>99[b]	92
7	**2c**	**3a**	1	48	53	89
8	**2c**	**3e**	1	48	90	92
9	**2c**	**3f**	10	20	92[d]	88
10	**2c**	**5**	10	20	77	50
11	**2c**	$CyPPh_2$	10	24	36[e]	
12	**2c**	**3e**	2	24	96	93
13[f]	**2c**	**3e**	2	24	99	94
14[f]	**2c**	$CyPPh_2$	10	24	N.R.	

[a]Isolated yield, unless noted otherwise. [b]Conversion. [c]In all cases except entries 9 and 11, the γ-adduct was the only detectable product (γ/α >100:1). [d]γ/α = 50:1. [e]γ/α = 20:1. [f]Propargyl ester **6** was used instead of allenyl ester **1**.

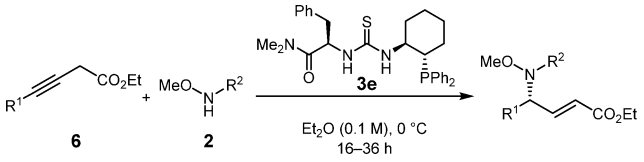
Scheme 2. Phosphinothiourea-Catalyzed Interconversion of Allenyl Ester 1 and Propargyl Ester 6

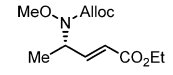
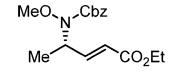
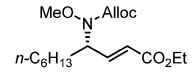
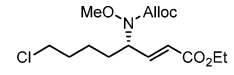
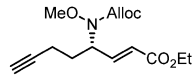
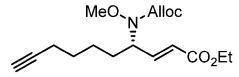
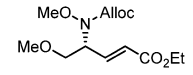
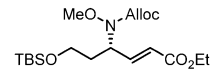
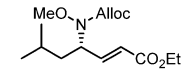
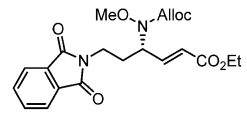
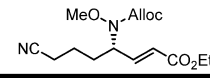


engage propargyl ester **6** in the hydroamination reaction, with slightly improved yield and enantioselectivity compared to reactions employing allenyl ester **1** (Table 1, entries 12 vs 13). Simple phosphines such as triphenylphosphine and cyclohexyldiphenylphosphine were not observed to promote the isomerization between **1** and **6**, even at higher catalyst loadings and elevated temperatures, nor did they promote hydroamination of **6** (entry 14). The use of propargyl esters such as **6** in the enantioselective reaction provides a practical advantage because they are readily prepared in a general manner and in one step by Fu's copper-catalyzed reaction of terminal alkynes with diazoacetates.[14]

The scope of the enantioselective γ-hydroamination reaction was examined under the optimized conditions identified above. Significant variation of the substitution on the propargyl ester was possible while maintaining excellent product yields and enantioselectivities (Table 2). In particular, primary alkyl chloride (entry 4), terminal alkynyl (entries 5 and 6), alkyl and silyl ether (entries 7 and 8), phthalimide (entry 10), and nitrile-containing (entry 11) propargyl esters all underwent clean reaction to afford the corresponding α,β-unsaturated γ-amino acid ester products in consistently high ee's. However, the reaction proved sensitive to the local steric properties of the alkyne, with the isobutyl-substituted derivative requiring higher

Table 2. Enantioselective γ-Hydroaminations Catalyzed by 3e

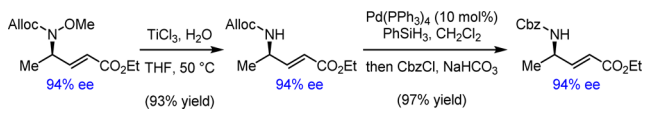


entry	Product	Catalyst loading (mol%)	Isolated yield (%)	ee (%)
1		2	99	94
2		3	92	92
3		3	94	96
4		3	95	96
5		2	85	96
6		3	96	96
7		5	90	90
8		5	79	97
9		10	87	98
10[a]		7.5	87	96
11		5	90	99

[a]CH_2Cl_2 was used as solvent.

catalyst loadings (entry 9), and branched alkynes (or their corresponding allenyl esters) proving unreactive.[11] The γ-addition products could be readily deprotected in high yields to afford the free amine with preservation of enantiomeric integrity (Scheme 3).[11]

Scheme 3. Deprotection



We propose a mechanism of catalysis for the γ-hydroamination reaction in Scheme 4. The loading of the carbamate and the allenyl ester onto the catalyst can occur in either order to generate intermediate **A**. The hydrogen-bond interaction with the carbamate is expected to lower the pK_a of the N−H bond substantially,[15] favoring proton transfer to the ion pair intermediate **B**. Addition of the catalyst-bound, deprotonated carbamate to the resulting vinyl phosphonium ion should be very facile, producing ylide intermediate **C**, which can liberate the

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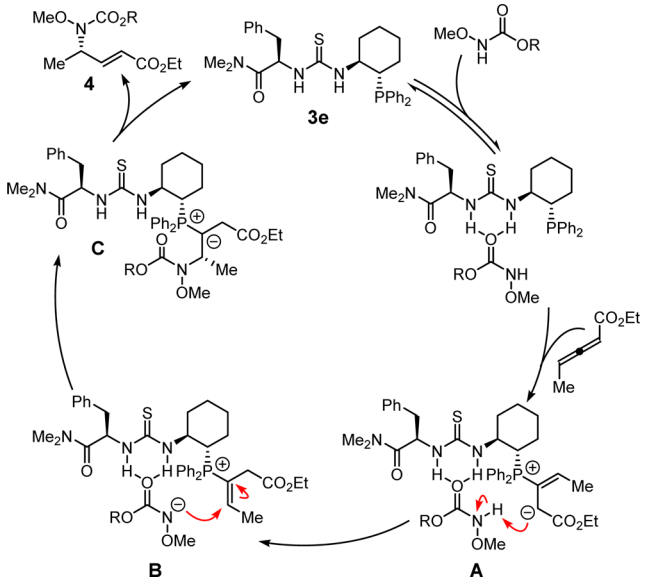
Scheme 4. Proposed Catalytic Cycle



product **4** and regenerate the active catalyst upon tautomerization and β-elimination.[2]

The utility of chiral phosphinothioureas has thus been extended into a new, anion-binding manifold with the highly enantioselective γ-hydroamination of allenyl esters. Further studies into the reactivity and selectivity of these versatile polyfunctional catalysts are ongoing.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Nucleophile and catalyst screening information, product absolute stereochemistry assignment, complete experimental procedures, characterization data, and chromatographic analyses of the catalyst and the products. 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.

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