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Phosphine-Catalyzed Allylic Substitution of Morita−Baylis−Hillman Acetates: Synthesis of N-Protected β-Aminophosphonic Acid Esters

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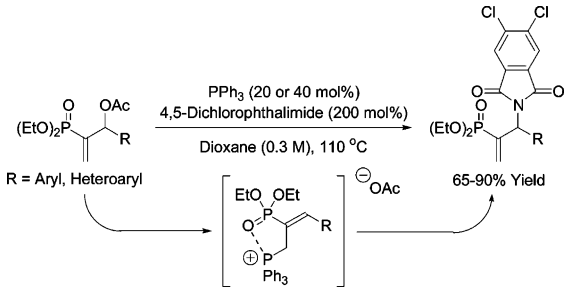
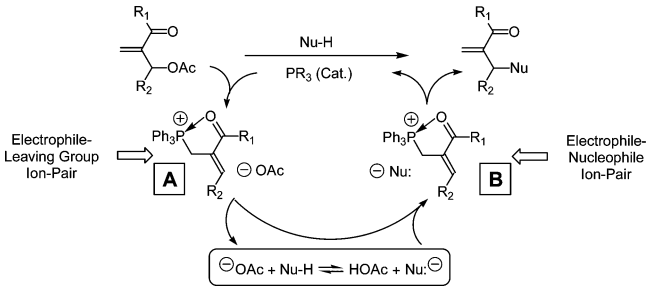


A series of *N*-protected β-amino phosphonic acid esters have been prepared by phosphine-catalyzed allylic substitution of 2-(diethylphosphonyl)-substituted allylic acetates employing 4,5-dichlorophthalimide as nucleophilic partner. These organocatalytic allylic substitutions exhibit exceptionally high levels of regiospecificity by virtue of a tandem $S_N2'-S_N2'$ mechanism.

Although transition metal catalyzed substitutions of allylic esters and carbonates have been extensively explored,[1] organocatalytic variants of such transformations have only recently begun to emerge.[2−4,5h,i] Through the use of allylic acetates decorated with anion stabilizing groups, as exemplified by Morita−Baylis−Hillman (MBH) acetates, ionic pathways for regioretentive allylic substitution may be achieved through the intervention of nucleophilic organocatalysts in successive $S_N2'-S_N2'$ processes. The feasibility of this approach was first indicated by the "two-stage" regioretentive substitution of MBH acetates, wherein stoichiometric S_N2' displacement of the acetate by DABCO is followed by treatment of the resulting DABCO adduct with a heteroatom nucleophile that engages in a second S_N2' displacement of DABCO.[2] Concurrently, it was shown that MBH carbamates and trichloroacetimidates undergo decarboxylative rearrangement in the presence of substoichiometric quantities of DABCO to afford products of regioretentive amination.[3] Later, $(DHQD)_2PHAL$ was shown to catalyze regioretentive allylic substitution of MBH acetates with sodium bicarbonate as nucleophile.[4] The corresponding MBH alcohols were produced in 25−42% yield and 54−92% enantiomeric excess. In connection with our ongoing studies involving nucleophilic phosphine organocatalysis,[5] we recently reported the first intermolecular organocatalytic allylic substitution reactions of MBH acetates, wherein the *N*- and *C*-nucleophiles 4,5-dichlorophthalimide and 2-trimethylsilyloxyfuran were found to generate allylic amines and γ-butenolides, respectively, with retention of regiochemistry.[5h,i] These studies complement corresponding palladium-catalyzed allylic substitutions of MBH acetates, which thus far are limited to phenol-based nucleophiles and suffer from incomplete regioselection.[6] Our collective studies are consistent with a catalytic mechanism in which generation of the electrophile−nucleophile ion pair **B** plays a key role in suppressing direct addition of the nucleophile to the less substituted enone moiety of the starting MBH acetate. Generation of the electrophile−nucleophile ion pair **B**, in turn, depends on the ability of acetate **A** to engage in acid−base equilibria involving deprotonation of the pronucleophile, as in the case of 4,5-dichlorophthalimide, or formation of anionic hypervalent silicon adducts, as for 2-trimethylsilyloxyfuran. Finally, an advantage associated with the use of *P*-centered nucleophilic catalysts over *N*-based nucleophiles may reside in activation of the enone **B** through internal coordination to phosphorus (Scheme 1).[7]

SCHEME 1. Plausible Catalytic Mechanism for the Regioretentive Allylic Substitution of MBH Acetates via Phosphine Catalysis



In an effort to expand this emergent class of organocatalytic allylic substitutions, the use of anion stabilizing groups in the

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(1) For a recent review, see: Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813.

(2) For regioretentive substitutions of MBH acetates mediated by stoichiometric DABCO, see: (a) Gong, J. H.; Kim, H. R.; Ryu, E. K.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 789. (b) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, 173.

(3) For regioretentive rearrangements of MBH acetates catalyzed by DABCO, see: (a) Ciclosi, M.; Fava, C.; Galeazzi, R.; Orena, M.; Sepulveda-Arques, J. *Tetrahedron Lett.* **2002**, *43*, 2199. (b) Galeazzi, R.; Martelli, G.; Orena, M.; Rinaldi, S. *Synthesis* **2004**, 2560.

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(5) For phosphine-catalyzed transformations developed in our laboratory, see: (a) Wang, L.-C.; Luiz, A.-L.; Agapiou, K.; Jang, H.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 2402. (b) Agapiou, K.; Krische, M. J. *Org. Lett.* **2003**, *5*, 1737. (c) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758. (d) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682. (e) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855. (f) Koech, P. K.; Krische, M. J. *J. Am. Chem. Soc.* **2004**, *126*, 5350. (g) Luis, A.-L.; Krische, M. J. *Synthesis* **2004**, 2579. (h) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, *6*, 1337. (i) Cho, C.-W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 6689.

(6) Enantioselective Pd-catalyzed allylic alkylation of Morita−Baylis−Hillman acetates has been reported but is restricted to phenol-based nucleophiles and suffers from incomplete regioselection: (a) Trost, B. M.; Toste, D. F. *J. Am. Chem. Soc.* **2000**, *122*, 3534. (b) Roy, O.; Riahi, A.; Hénin, F.; Muzart, J. *Tetrahedron* **2000**, *56*, 8133. (c) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2002**, *124*, 11616. (d) Trost, B. M.; Thiel, O. R.; Tsui, H.-C. *J. Am. Chem. Soc.* **2003**, *124*, 13155.

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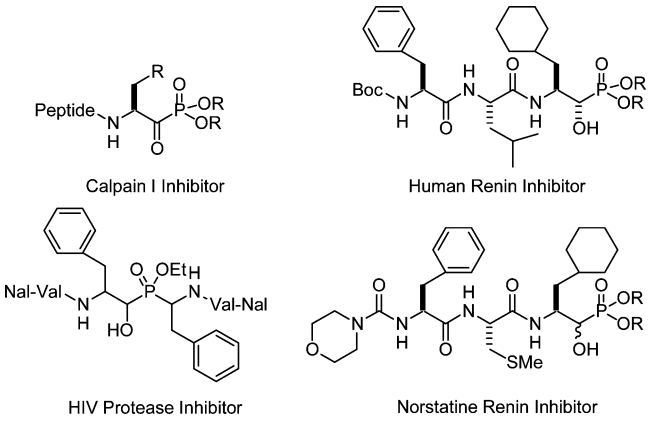
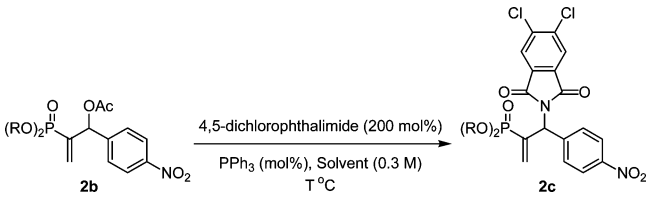


FIGURE 1. Enzyme inhibitors that embody β-aminophosphonic acid substructures.

form of phosphonic esters was explored. Here, we disclose that exposure of 2-(diethylphosphonyl)-substituted allylic acetates **1b**−**6b** to 4,5-dichlorophthalimide in the presence of substoichiometric quantities of triphenylphosphine results in regioretentive displacement of the acetate to afford β-(4,5-dichlorophthalimido)-phosphonic acid esters **1c**−**6c**.[8] Protected β-amino phosphonic acids of this type are potential precursors to β-amino acid isosteres. As exemplified by the indicated inhibitors of calpain I, human renin, HIV protease, and norstatine renin, such compounds possessing β-aminophosphonic acid substructures exhibit interesting and diverse biological properties (Figure 1).[9,10]

The preparation of substrates **1b**−**6b** for phosphine-catalyzed allylic substitution was initially attempted using a MBH-type vinylphosphonate-aldehyde coupling protocol.[11] However, attempted MBH-type couplings employing a range of different nucleophilic promoters failed to provide the desired adducts **1a**−**6a**. Direct lithiation of the vinyl phosphonate mediated by LDA in the presence of the aldehyde met with greater success.[12] The desired 2-(diethylphosphonyl)-substituted allylic alcohols **1a**−**6a** were obtained in moderate yield. Subsequent exposure of alcohols **1a**−**6a** to acetic anhydride in the presence of substoichiometric quantities of $FeCl_3$ in acetonitrile solvent delivered the phosphonyl-substituted allylic acetates **1b**−**6b** in good to excellent yields (Scheme 2).

TABLE 1. Optimization of Phosphine Catalyzed Allylic Amination of Substrate 2b



entry	R	PPh_3 (mol %)	*T* °C	solvent	yield (%)
1	Me	20−100	25	THF	nr
2	Me	20−100	65	THF	<10
3	Et	20−100	25	THF	trace
4	Et	40	65	THF	50
5	Et	20	110	1,4-dioxane	90

With substrates **1b**−**6b** in hand, optimum conditions previously determined for the phosphine-catalyzed allylic substitution of corresponding acrylate-based systems were examined.[5h] In the event, introduction of triphenylphosphine to a THF solution of **2b** (R = Me) and 4,5-dichlorophthalimide at ambient temperature failed to provide the desired substitution product **2c**, even at stoichiometric loadings of triphenylphosphine (Table 1, entry 1). A similar outcome was observed for reactions performed at elevated temperatures in THF (65 °C) (Table 1, entry 2). It was reasoned that **2b** (R = Me) might be a suboptimal substrate as a result of facile dealkylation of the methyl phosphonate via nucleophilic attack by triphenylphosphine, which would simultaneously consume the phosphine catalyst. To challenge this hypothesis, the phosphine-catalyzed allylic substitution of **2b** (R = Et) was examined. Indeed for substrate **2b** (R = Et), trace quantities of the desired reaction product **2c** could be isolated from reactions performed at ambient temperature (Table 1, entry 3), and for the reaction performed at elevated temperature (65 °C) a 50% isolated yield of phthalimide **2c** was obtained at 40 mol % loadings of triphenylphosphine (Table 1, entry 4). Finally, appreciating that phosphonates are inherently less electrophilic than their carboxy counterparts, the reaction of **2b** (R = Et) was investigated at 110 °C in dioxane solvent using 20 mol % loadings of triphenylphosphine. The product of allylic substitution was obtained in 90% yield with complete retention of regiochemistry (Table 1, entry 5).

These optimized conditions were applied to diethylphosphonyl-substituted allylic acetates **1b**−**6b**. The corresponding allylic amination products **1c**−**6c** were obtained in good to excellent yields. In each case, the products appear as single regioisomers, as determined by ^{1}H NMR analysis. As expected on the basis of the optimization study presented in Table 1, high reaction temperatures were required for complete conversion because of the diminished electrophilicity of the phosphonyl-substituted MBH acetates in comparison to those derived from methyl acrylate and methyl vinyl ketone. Accordingly, for less reactive substrates **1b** and **6b**, increased loadings of triphenylphosphine were required. Exposure of **2c** to the reaction conditions in the presence of phthalimide does not result in exchange with 4,5-dichlorophthalimide. Hence, it would appear that regiochemistry is kinetically controlled (Table 2).

In summary, we report a concise synthetic approach to *N*-protected β-aminophosphonates **1c**−**6c** via phosphine-

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SCHEME 2. Preparation of Substrates 1b-6b for Phosphine Catalyzed Allylic Substitution

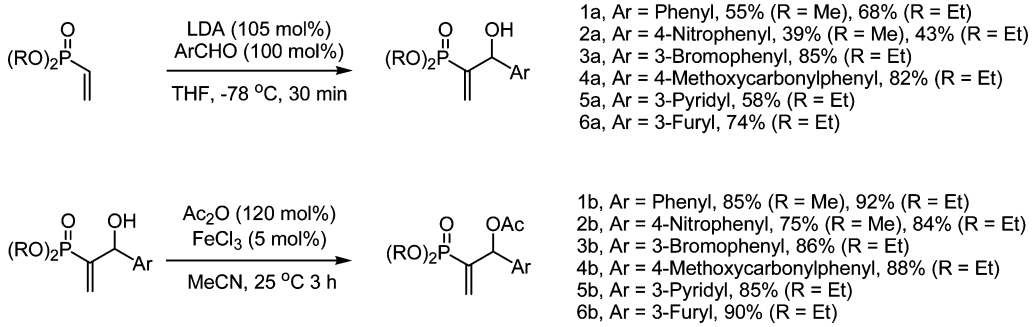
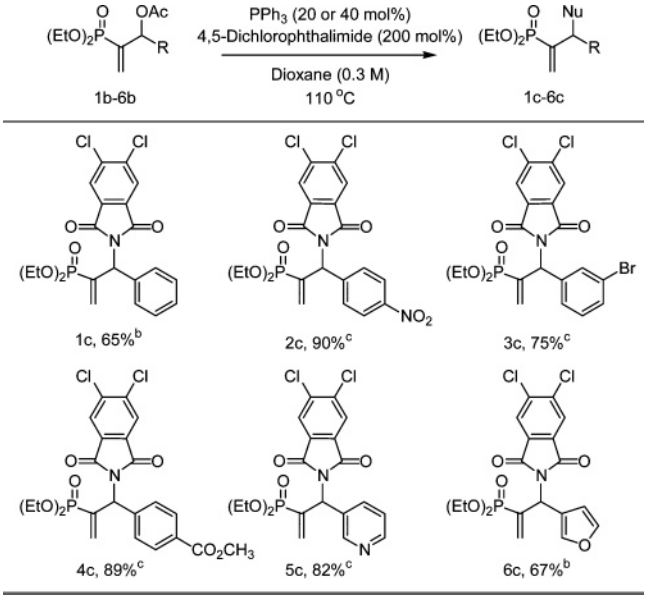


TABLE 2. Phosphine Catalyzed Allylic Substitution of Phosphonyl-Substituted Morita−Baylis−Hillman Acetates 1b−6b[a]



[a] Cited yields are of isolated material. In all cases, >95:5 regioselection is observed. See Experimental Section for a general procedure. [b] 40 mol % loadings of PPh_3 were used. [c] 20 mol % loadings of PPh_3 were used.

catalyzed allylic substitution of 2-(diethylphosphonyl)-substituted allylic acetates **1b**−**6b**, employing 4,5-dichlorophthalimide as a nucleophilic partner. Unlike the vast majority of metal-catalyzed allylic substitutions,[1] the phosphine-catalyzed transformations exhibit exceptionally high levels of regiospecificity by virtue of a tandem $S_N2'-S_N2'$ substitution mechanism. Future studies will focus on the development of related transformations, including enantioselective variants of the present transformation and application of this methodology toward the synthesis of molecules of biological and medicinal interest that incorporate the β-aminophosphonate substructures.

Experimental Section

General Procedure for Preparation of Acetates 1b−6b. To an acetonitrile solution (0.2 M) of alcohol **1a** (1 mmol, 100 mol %) at ambient temperature was added acetic anhydride (1.2 mmol, 120 mol %) followed by ferric chloride (0.05 mmol, 5 mol %). The reaction vessel was allowed to stir for 30 min, at which point saturated aqueous $NaHCO_3$ solution was added until bubbling ceased. The reaction mixture was partitioned between diethyl ether and water. The aqueous layer was extracted with diethyl ether, and the combined ethereal extracts were dried ($MgSO_4$), filtered, and evaporated onto silica gel. Purification by silica gel column chromatography provides allylic acetate **1b**.

General Procedure for Preparation of 4,5-Dichlorophthalimides 1c−6c. To a reaction vessel charged with acetate **1b** (0.5 mmol, 100 mol %), 4,5-dichlorophthalimide (1.0 mmol, 200 mol %), and PPh_3 (0.1 mmol, 20 mol %) was added a dioxane (0.3 M). The reaction vessel was placed in a heating bath at 110 °C and was allowed to stir until complete consumption of **1b** was observed by TLC analysis, at which point the reaction mixture was evaporated onto silica gel. Purification by silica gel column chromatography provides phthalimide **1c**.

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Supporting Information Available: Experimental details and spectral data for all new compounds (^1H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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