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Phosphine-Catalyzed Regiospecific Allylic Amination and Dynamic Kinetic Resolution of Morita–Baylis–Hillman Acetates

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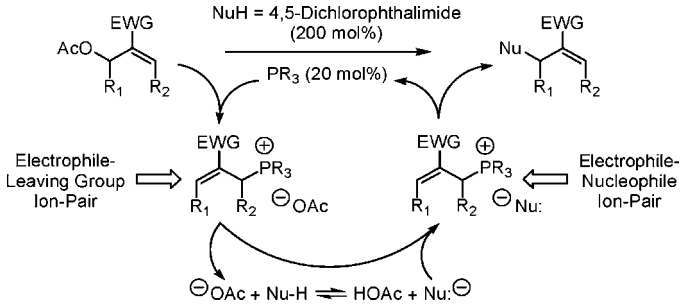
ABSTRACT



Exposure of Morita–Baylis–Hillman (MBH) acetates to tertiary phosphine catalysts in the presence of 4,5-dichlorophthalimide enables regiospecific allylic substitution through a tandem S_N2'–S_N2' mechanism. Through the use of the chiral phosphine catalyst (*R*)-Cl-MeO-BIPHEP, chiral racemic MBH acetate 4 is converted to the corresponding allylic amination product in 80% yield and 56% enantiomeric excess, thus establishing the feasibility of dynamic kinetic resolution.

Nucleophilic catalysis via conjugate addition of *N*- and *P*-nucleophiles represents an important subset of organocatalytic reactions. Beyond the Morita−Baylis−Hillman (MBH) condensation,[1] a remarkably diverse range of transformations is encompassed, including the addition of oxygen nucleophiles to activated alkenes,[2] the cross Michael cycloisomerization of activated bis(alkenes),[3] the internal redox isomerization of activated alkynes,[4] nucleophilic α- and γ-additions to activated alkynes,[5] inter- and intramolecular [3 + 2] cycloadditions,[6,7] [4 + 2] cycloadditions,[8] cycloallylation of activated alkenes,[9] and the coupling of allenic esters to activated alkenes.[10]

Recently, a two-step protocol for the amination of MBH acetates mediated by stoichiometric DABCO was reported.[11a,b]

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(2) Stewart, I. C.; Bergman, R. G.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 8696.

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(4) Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1992**, *114*, 7933. (b) Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921.

(5) (a) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *62*, 55670. (b) Trost, B. M.; Dake, G. R. *J. Am. Chem. Soc.* **1997**, *119*, 7595.

(6) (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906. (b) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1997**, *38*, 3461. (c) Zhu, G.; Chen, Z.; Jiang, Q.; Xiao, D.; Cao, P.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 3836. (d) Xu, Z.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 549. (e) Xu, Z.; Lu, X. *J. Org. Chem.* **1998**, *63*, 5031. (e) Du, Y.; Lu, X.; Yu, Y. *J. Org. Chem.* **2002**, *67*, 8901.

(7) (a) Wang, J.-C.; Ng, S.-S.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 3682. (b) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855.

(8) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.

(9) Jellerichs, B. G.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2003**, *125*, 7758.

(10) Evans, C. A.; Miller, S. J. *J. Am. Chem. Soc.* **2003**, *125*, 12394.

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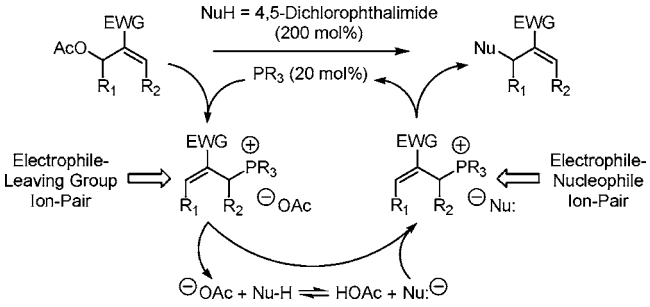
A related two-step transformation employing quinidine subsequently appeared.[11c] In the latter case, propargyl alcohol is employed as nucleophile to provide products of regioretentive allyllic substitution in 25−40% enantiomeric excess. Following reports of these stoichiometric processes, the DABCO-catalyzed decarboxylative rearrangement of MBH carbamates was demonstrated.[11d] Finally, $(DHQD)_2PHAL$ has recently been shown to catalyze regioretentive allylic substitution of MBH acetates using sodium bicarbonate as nucleophile.[11e] The corresponding MBH alcohols are produced in 25−42% yield and 54−92% enantiomeric excess.

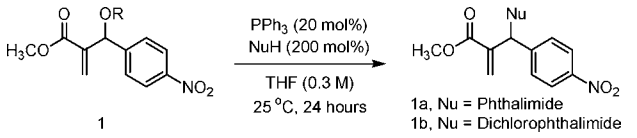
In this account, we report the first examples of phosphine catalyzed allylic amination of MBH acetates.[12] Upon exposure of MBH acetates to tertiary phosphine catalysts in the presence of 4,5-dichlorophthalimide, regioselective allylic substitution occurs through a tandem $S_N2'-S_N2'$ substitution mechanism to provide products of N-allylation.

Scheme 1. Intermolecular Phosphine-Catalyzed Regioretentive Allylic Amination



To assess the feasibility of phosphine-catalyzed allylic amination of MBH adducts, a series of acyl derivatives based on MBH adduct **1** were prepared and exposed to 20 mol % triphenylphosphine at ambient temperature in the presence of phthalimide or 4,5-dichlorophthalimide (Table 1). This survey of leaving group−pronucleophile combinations reveals a dramatic dependence on the ΔpK_a between the conjugate acid of the leaving group and the pronucleophile, presumably due to the crucial role of the acid−base reaction between the leaving group and the pronucleophile vis-à-vis generation of an electrophile−nucleophile ion pair. If the leaving group is not sufficiently basic, deprotonation of the pronucleophile does not occur. Conveniently, optimum yields were obtained using acetate as leaving group along with commercially available 4,5-dichlorophthalimide as pronucleophile. Here, a 90% yield of the amination product **1b** is obtained as a single regioisomer, as determined by ^{1}H NMR analysis. Presumably, generation of the electrophile−nucleophile ion pair enhances the fidelity of regioretention by suppressing direct addition of the nucleophile to the less substituted enone moiety of the starting MBH acetate (Table 1).

Table 1. Optimization of Phosphine-Catalyzed Allylic Alkylation of Morita−Baylis−Hillman Adducts[a]

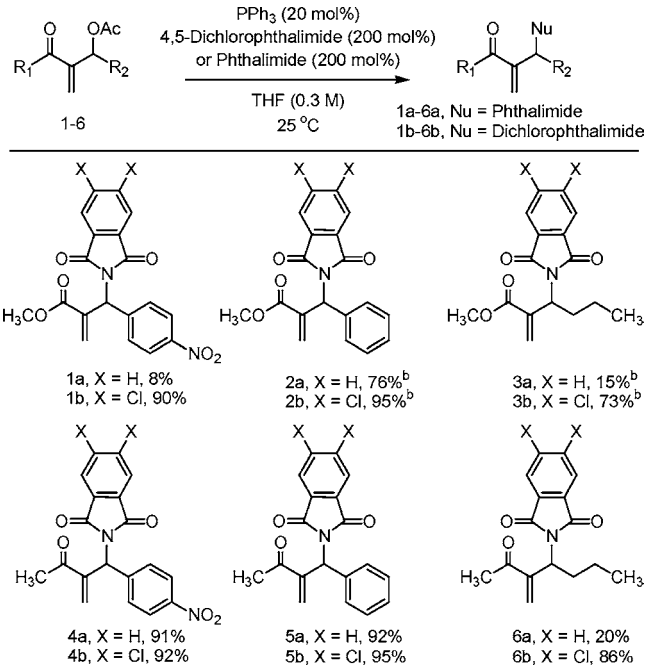


entry	substrate	nucleophile (NuH)	yield (%)
1	R = $PO(OEt)_2$	4,5-dichlorophthalimide	3
2	R = BOC	phthalimide	12
3	R = BOC	4,5-dichlorophthalimide	77
4	R = Bz	4,5-dichlorophthalimide	79
5	R = *p*-NO_2Bz	4,5-dichlorophthalimide	32
6	R = Ac	phthalimide	8
7	**R = Ac**	**4,5-dichlorophthalimide**	**90**

[a] Procedure: To a reaction vessel charged with **1** (0.5 mmol, 100 mol %), imide (1.0 mmol, 200 mol %), and PPh_3 (0.1 mmol, 20 mol %) was added THF (1.6 mL, 0.3 M). The reaction was allowed to stir at ambient temperature for 24 h, at which point the reaction mixture was evaporated onto silica gel and the product was isolated by silica gel chromatography.

Under these optimized conditions, intermolecular catalytic allylic amination of MBH acetates derived from methyl acrylate **1**−**3** and methyl vinyl ketone (MVK) **4**−**6** were explored. In each case, the corresponding allylic amination products **1b**−**6b** were obtained in good to excellent yields

Table 2. Intermolecular Phosphine-Catalyzed Allylic Alkylation of Morita−Baylis−Hillman Acetates **1**−**6**[a,b]



[a] Procedure: as described in Table 1. [b] Reaction performed at 50 °C.

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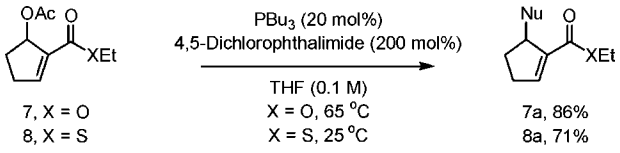
(12) For an enantioselective Pd-catalyzed allylic alkylation of Morita−Baylis−Hillman acetates using phenol-based nucleophiles, see: Trost, B. M.; Tsui, H.-C.; Toste, D. F. *J. Am. Chem. Soc.* **2000**, *122*, 3534.

as single regioisomers, as determined by ^{1}H NMR analysis. As expected on the basis of the optimization study presented in Table 1, use of phthalimide as the pronucleophile affords adducts **1a**−**6a** in diminished yield. Interestingly, the MVK-derived acetates **4**−**6**, which are more electrophilic, showed less sensitivity to the nature of the nucleophilic partner and provided excellent yields of both the phthalimide- and dichlorophthalimide-derived amination products **4a**−**6a** and **4b**−**6b**, respectively (Table 2).

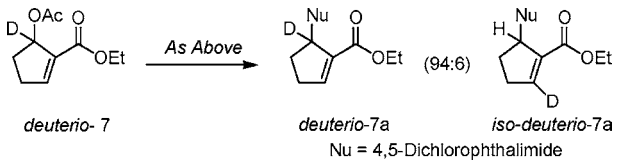
As a further demonstration of scope, catalytic amination of β-substituted MBH acetates **7** and **8** was attempted. For β-substituted α,β-unsaturated carbonyl compounds, the use of more nucleophilic trialkylphosphine catalysts is required. Gratifyingly, upon exposure of the β-substituted acetates **7** and **8** to modified reaction conditions employing tributylphosphine as catalyst, efficient conversion to the corresponding amination products **7a** and **8a** is observed (Scheme 2).

Scheme 2. Phosphine-Catalyzed Regioretentive Allylic Amination of Cyclic MBH Acetates **7** and **8**



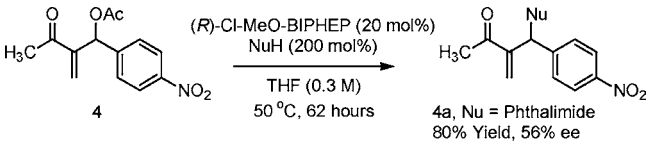
For substrates **7** and **8**, the catalyzed and uncatalyzed allylic substitution would afford identical products. To assess the extent of the background reaction, *deuterio*-**7** was prepared and subjected to standard reaction conditions. The substitution product appears as a 94:6 ratio of isomers, favoring retention of regiochemistry. This result strongly suggests that the phosphine-catalyzed tandem $S_N2'-S_N2'$ mechanism is operative (Scheme 3).

Scheme 3. Deuterium Labeling Study Corroborates Proposed Tandem $S_N2'-S_N2'$ Mechanism



As the phosphine-catalyzed allylic substitution proceeds through a mechanism involving the destruction and subsequent reconstitution of a stereogenic center, the dynamic kinetic resolution (DKR) or "deracemization" of chiral racemic MBH acetates is potentially enabled through the use of chiral phosphine catalysts. To establish the feasibility of performing such deracemizations, the racemic MBH acetate **4** was exposed to commercially available (*R*)-Cl-MeO-BIPHEP under otherwise standard conditions. The substitution product is produced in 80% isolated chemical yield and 56% enantiomeric excess (Scheme 4).

Scheme 4. Establishing the Feasibility of Deracemization via Chiral Phosphine Catalysts



In summation, Morita−Baylis−Hillman acetates are shown to engage in regiospecific allylic substitution under the conditions of nucleophilic catalysis through a tandem $S_N2'-S_N2'$ substitution mechanism. The feasibility of related catalytic deracemizations has been established. A key feature of these transformations relates to the generation of an electrophile−nucleophile ion pair, which presumably suppresses direct addition of the nucleophile to the less substituted enone moiety of the starting MBH acetate. Future studies will focus on the development of related transformations, including applications of this methodology toward the total synthesis of complex natural products.

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Supporting Information Available: Experimental details and spectral data for all new compounds (^{1}H 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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