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Highly Enantioselective and Regioselective Substitution of Morita–Baylis–Hillman Carbonates with Nitroalkanes

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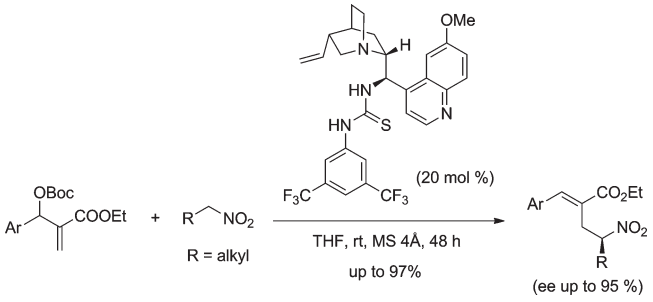
ABSTRACT



A highly enantioselective and regioselective substitution reaction of the Morita–Baylis–Hillman (MBH) carbonates with nitroalkanes catalyzed by a quinidine-derived tertiary amine–thiourea catalyst has been developed. The described method, which is different from most organocatalytic allylic substitutions of the MBH adducts to date, represents a novel approach to regioselectively functionalize the MBH adducts.

The Morita–Baylis–Hillman reaction (MBH) is one of the most important and valuable organic processes for the construction of densely functionalized products from simple precursors in a highly atom economic fashion.[1] The MBH adducts and their derivatives are very useful synthetic intermediates in organic synthesis, and organocatalytic asymmetric approaches making use of the MBH adducts have been investigated intensively in recent years. By converting the hydroxy group into a leaving group, the MBH adducts can undergo allylic substitution reactions.[2] In this context, various nucleophiles, including cyanoester,[3] 2-silyloxy furan,[4] indole,[5] oxindoles,[6] α,α-dicyano alkene,[7] butenolides,[8] and phosphine oxide,[9] have been examined in the asymmetric allylation reactions of the MBH adducts (pathway I, Scheme 1). Alternatively, an S_N2'-type reaction of a nucleophilic catalyst with the MBH adducts, followed by an S_N2 displacement of the catalyst moiety with the final nucleophile, represents another synthetic manipulation of these useful intermediates (pathway II, Scheme 1). However, examples of catalytic asymmetric

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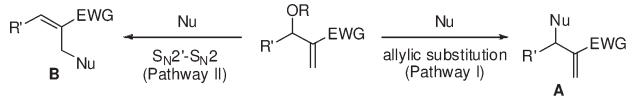
versions of this reaction reported in the literature are very limited and are mostly based on metal catalysis.[10] To the best of our knowledge, the report by Ramachandran and coworkers on the synthesis of glutamic acid derivatives employing allylic acetates under chiral phase transfer conditions was the only example based on organic catalysis in the literature.[11] As part of our research program toward the development of practical asymmetric synthetic methods, we were interested in developing organocatalytic asymmetric transformations employing the MBH adducts.[12]

Scheme 1. Conversions of the MBH Adducts



Nitroalkanes are valuable nucleophiles commonly used in organic synthesis and have been extensively investigated in asymmetric nucleophilic addition reactions.[13] Although the reactions between the MBH acetates and nitroalkanes promoted by inorganic bases have been reported by Kim and Basavaiah, respectively,[14] a catalytic asymmetric version of this reaction is unknown. Herein, we describe the first regioselective asymmetric substitution of the MBH adducts by nitroalkanes, catalyzed by cinchona alkaloid-derived bifunctional catalysts.

For the allylic substitution of the MBH adducts, a commonly accepted tandem $S_N2'-S_N2'$ mechanism[15] is illustrated in Scheme 2. The nucleophilic catalyst (a tertiary amine or phosphine) first adds to the MBH adduct in an S_N2' fashion, with the concurrent departure of the OR group, which could be utilized to activate the nucleophile. A second S_N2' reaction then affords the final product, regenerating the catalyst at the same time. In order to obtain a product of type B (Scheme 1), we hypothesize that employment of a bifunctional nucleophilic catalyst with an appropriate Brønsted acid moiety may be a viable approach. Following the initial S_N2' reaction, the hydrogen bonding interactions between the nucleophile and the Brønsted acid moiety of the catalyst are expected to direct the subsequent S_N2 substitution, thus leading to products of type B.

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(14) (a) Basavaiah, D.; Rao, J. S. *Tetrahedron. Lett.* **2004**, *45*, 1621. (b) Kim, J. M.; Im, Y. J.; Kim, T. H.; Kim, J. N. *Bull. Korean Chem. Soc.* **2002**, *23*, 657.

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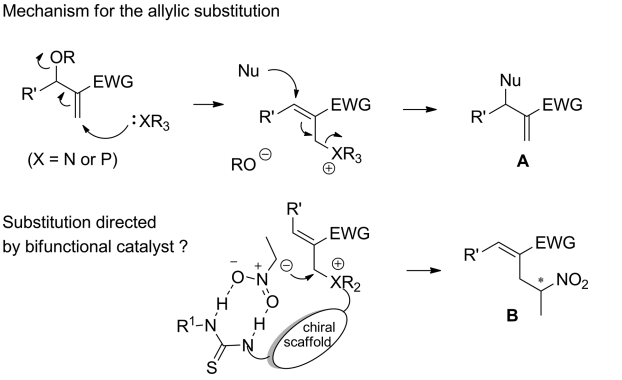
Scheme 2. Regioselectivity in the Substitution Reactions



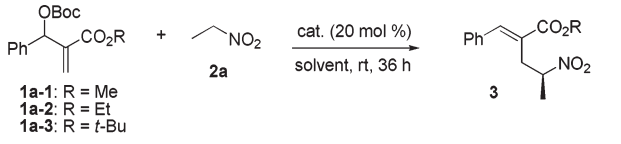
We began our investigation by choosing the reaction between nitroethane **2a** and MBH carbonates **1** as a model reaction. A number of cinchona alkaloid-derived bifunctional catalysts[16] were examined, and the results are summarized in Table 1. All the tertirary amine−thiourea catalysts, cinchonidine-derived **4**, quinine-derived **5**, and quinidine-based **6**, were able to catalyze the regioselective formation of the product **3** (Table 1, entries 1−3).[17] However, quinine-derived tertiary amine−sulfonamide **7** was found to be ineffective (Table 1, entry 4). Variation of the ester moiety in the MBH carbonates offered further improvement; employment of the ethyl ester of the MBH carbonate **1a-2** led to the formation of **3a** in 96% yield and 93% ee (Table 1, entry 5). The solvent screening was carried out (Table 1, entries 7−13), and THF was identified as the solvent of choice for the subsequent reactions.

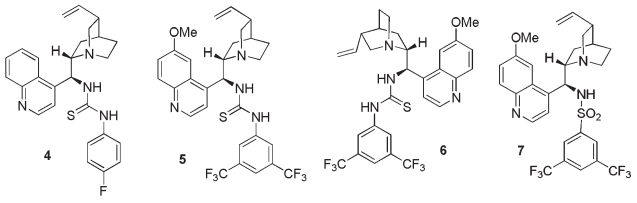
Having identified the optimal reaction conditions, we then investigated the substrate scope (Table 2). The reaction worked well for the MBH carbonates with different aromatic moieties; very good yields and excellent enantioselectivities were attainable, regardless of the electronic nature and the substitution pattern of the aryl groups (Table 2, entries 1−11). The relatively low

(16) For selected examples of this type of catalysts, see: (a) Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. (b) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (c) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. (d) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (e) Li, B.-J.; Jiang, L.; Liu, M.; Chen, Y.-C.; Ding, L.-S.; Wu, Y. *Synlett* **2005**, 603. (f) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (g) McCooey, S. H.; Connon, S. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6367. (h) Ye, J.; Dixon, D. J.; Hynes, P. S. *Chem. Commun.* **2005**, 4481. (i) Han, X.; Kwiatkowski, J.; Xue, F.; Huang, K.-W.; Lu, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 7604. (j) Zhu, Q.; Lu, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 7753. (k) Zhong, F.; Chen, G.-Y.; Lu, Y. *Org. Lett.* **2011**, *13*, 82. (l) Liu, X.; Lu, Y. *Org. Lett.* **2010**, *12*, 5592. (m) Liu, X.; Lu, Y. *Org. Biomol. Chem.* **2010**, *8*, 4063. (n) Zhu, Q.; Lu, Y. *Org. Lett.* **2009**, *11*, 1721. (o) Luo, J.; Xu, L.-W.; Hay, A. S. R.; Lu, Y. *Org. Lett.* **2009**, *11*, 437. (p) Han, X.; Luo, J.; Liu, C.; Lu, Y. *Chem. Commun.* **2009**, 2044. For reviews, see:(q) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289. (r) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. (s) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999. (t) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520. (u) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (v) Yu, X.; Wang, W. *Chem.—Asian J.* **2008**, *3*, 516. (w) Connon, S. J. *Chem. Commun.* **2008**, 2499.

(17) The reaction between **1a-2** and **2a** in the presence of 20 mol % C-9-OBz-quinidine at room temperature for two days did not yield any desired product.

Table 1. Catalyst Screening for the Regioselective Substitution of the MBH Carbonates[a]



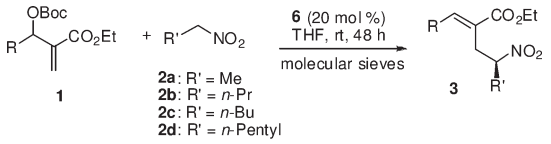


entry	R	cat.	solvent	yield (%)[b]	ee (%)[c]
1	Me	**4**	THF	75	82
2	Me	**5**	THF	71	79
3[d]	Me	**6**	THF	58	91
4[e]	Me	**7**	THF	–	–
5	Et	**6**	THF	96	93
6	*t*-Bu	**6**	THF	<5	–
7	Et	**6**	Et_2O	84	90
8	Et	**6**	CH_2Cl_2	87	90
9	Et	**6**	$CHCl_3$	96	90
10	Et	**6**	toluene	95	91
11	Et	**6**	hexane	60	92
12	Et	**6**	MeOH	76	36
13	Et	**6**	DMF	24	8

[a] The reactions were performed with **1** (0.025 mmol), nitroethane **2a** (0.25 mmol) and the catalyst (0.005 mmol) in the solvent (0.1 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reaction time was 22 h. [e] No reaction was observed.

enantioselectivity observed for the MBH carbonate with the *ortho*-substituted aryl group suggested the importance of steric hindrance in asymmetric induction (Table 2, entry 10). The reaction also tolerated the MBH carbonate containing a 2-naphthyl or 2-furyl moiety (Table 2, entries 12–13). Furthermore, nitroalkanes other than nitroethane could also be utilized in the reaction, and the yields and enantioselectivities remained excellent. However, the neat reaction conditions had to be employed to circumvent the low reactivity of these nitroalkanes (Table 2, entries 14–16). The reaction could be run at 50 °C, and the chemical yield was improved with slightly decreased enantioselectivity (Table 2, entry 17). Currently, we were

Table 2. Reaction Scope[a]



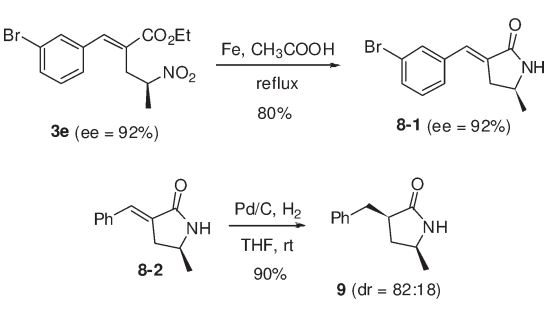
entry	R/R′, **3**	yield (%)[b]	ee (%)[c]
1	Ph/Me, **3a**	95	92
2	4-F-Ph/Me, **3b**	84	95
3	4-Cl-Ph/Me, **3c**	90	92
4	4-Br-Ph/Me, **3d**	97	90
5	3-Br-Ph/Me, **3e**	94	92
6	4-CF_3-Ph/Me, **3f**	89	92
7	3-CF_3-Ph/Me, **3g**	89	92
8	4-CH_3-Ph/Me, **3h**	85	88
9	3-CH_3-Ph/Me, **3i**	85	92
10	2-CH_3-Ph/Me, **3j**	84	79
11	4-CH_3O-Ph/Me, **3k**	87	92
12	2-Naphthyl/Me, **3l**	76	89
13	2-furyl/Me, **3m**	84	84
14[d]	Ph/*n*-Pr, **3n**	95	94
15[d]	Ph/*n*-Bu, **3o**	90	92
16[d]	Ph/*n*-Pentyl, **3p**	87	93
17[e]	Ph/*n*-Pentyl, **3p**	93	85

[a] The reactions were performed with **1** (0.025 mmol), **2** (0.25 mmol), 4 Å molecular sieves (10 mg), and **6** (0.005 mmol) in THF (0.1 mL) at room temperature. [b] Isolated yield. [c] Determined by HPLC analysis on a chiral stationary phase. [d] The reactions were performed under the neat condition with **2** (1.25 mmol) without molecular sieves. [e] The reaction was performed at 50 °C.

unable to utilize the MBH carbonates bearing an alkyl group in this substitution reaction.[18]

The chiral substitution products are highly useful molecules, and their synthetic values are illustrated in Scheme 3. Reduction of the nitro group in **3** resulted in simultaneous lactam formation, affording the substituted α-methylene-γ-butyrolactam **8**, a class of compounds with potential anticancer activities.[19] Moreover, hydrogenation of the lactam **8-2** with the exo alkylidene furnished optically enriched substituted γ-lactam **9** in excellent yield and good diastereoselectivity, which represents a molecular

Scheme 3. Synthetic Manipulations of the Substitution Product



(18) When ethyl-substituted MBH carbonate **1** was mixed with nitroethane, and **6** (20 mol %) in THF for 6 days, the conversion was below 30%.

(19) (a) Janecki, T.; Blaszczyk, E.; Studzian, K.; Janecka, A.; Krajewska, U.; Rozalski, M. *J. Med. Chem.* **2005**, *48*, 3516. (b) Choudhury, P. K.; Foubelo, F.; Yus, M. *J. Org. Chem.* **1999**, *64*, 3376. (c) Kornet, M. J.; Crider, A. M.; Magarian, E. O. *J. Med. Chem.* **1977**, *20*, 1210. (d) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed.* **1985**, *24*, 94. (e) Lee, K. Y.; Lee, Y. J.; Kim, J. N. *Bull. Korean Chem. Soc.* **2007**, *28*, 143.

(20) Basavaiah, D.; Rao, J. S. *Tetrahedron Lett.* **2004**, *45*, 1621 and references cited.

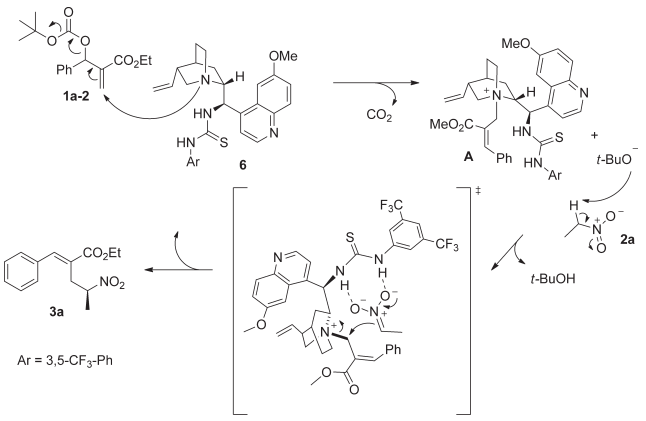


Figure 1. Plausible mechanism.

framework that is widely present in natural products and pharmaceutical agents.[20] The absolute configurations of the substitution products were assigned based on a single crystal X-ray analysis of **8-1**.

(21) No reaction was observed when the MBH acetate was used under otherwise identical reaction conditions.

A plausible reaction mechanism is depicted in Figure 1. The catalyst **6** first reacts with the MBH carbonate **1a-2** in an S_N2' fashion to yield intermediate **A**. The in situ generated *tert*-butoxide anion then deprotonates nitroethane **2a**.[21] The hydrogen bonding interactions between the thiourea moiety of the bifunctional catalyst is believed to be crucial for the observed regioselectivity and enantioselectivity of the reaction.

In conclusion, we have developed a regioselective and highly enantioselective allylic substitution of the MBH carbonates with nitroalkanes, by utilizing a quinidine-derived bifunctional catalyst. The reaction is believed to occur through an $S_N2'-S_N2$ sequence, representing a novel approach to regioselectively functionalize the MBH adducts. Extension of this strategy to other asymmetric substitution reactions are ongoing in our laboratory.

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Supporting Information Available. Representative experimental procedures, HPLC chromatogram, analytical data, NMR spectra of the products, and X-ray crystallographic data of **8-1**. This material is available free of charge via the Internet at http://pubs.acs.org.