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Alkaloids-catalyzed regio- and enantioselective allylic nucleophilic substitution of *tert*-butyl carbonate of the Morita–Baylis–Hillman products

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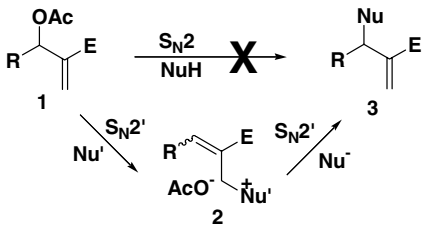
Abstract—The alkaloids-catalyzed regio- and enantioselective allylic nucleophilic substitution reactions of *tert*-butyl carbonate of the Morita–Baylis–Hillman products with pronucleophiles are reported. A number of pronucleophiles, such as nitrogen, oxygen, and active carbon pronucleophiles have been used in this facile reaction. In general, the reaction proceeded efficiently to give the substitution product in good yields with high regioselectivity and medium enantioselectivity.

The Morita–Baylis–Hillman reaction allows the direct preparation of β-methylene-α-hydroxycarbonyl compounds by organic catalyst catalyzed reaction of, α,β-unsaturated carbonyl compounds with aldehydes.[1] α-Methylene-β-hydroxy-carbonyl compounds are versatile starting materials for the synthesis of a variety of natural and non-natural target molecules.[2] Many works related to the extension of the reaction to other substrates (e.g., imines) were developed.[3] The asymmetric version of the Morita–Baylis–Hillman reaction has also become a challenge in this field.[2o,s,3a,c,4] While many works were reported related to the scope and applications of the Morita–Baylis–Hillman reaction, the direct substitution reaction of the Morita–Baylis–Hillman products were seldom reported owing to the fact that a rearranged product from a S_N2' reaction was obtained in reaction with a nucleophile. Recently, Kim's group showed interesting results on regioselective allylic nucleophilic substitution reaction of the Morita–Baylis–Hillman products or their acetates leading to the direct substitution of nucleophiles at the secondary carbon of the Baylis–Hillman products.[5] In this reaction, two successive S_N2'–S_N2' reactions of **1** occurred to give **3** as the product in one pot (Scheme 1).



Scheme 1.

Based on this reaction, a deracemization reaction of Baylis–Hillman acetates was developed yielding products with medium enantioselectivity but with low yield due to the involvement of kinetic resolution step.[5b] Very recently, Orena's group reported one DABCO-catalyzed intramolecular version of regioselective allylic amination of the Morita–Baylis–Hillman products.[6] These substitution reactions greatly broadens the scope of the application of Marita–Baylis–Hillman products. However, what are missing in these examples are the limited scope of application and/or the need of stoichiometric DABCO in most cases.

To develop a catalytic successive S_N2'–S_N2' reaction, the choice of the nucleophile, the leaving group and the catalyst are very important. If the nucleophilicity of

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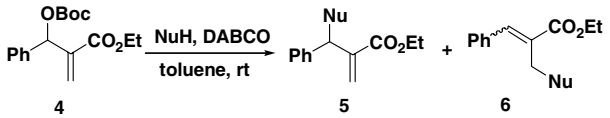
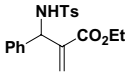
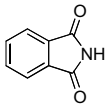
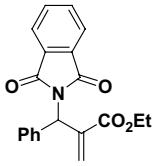
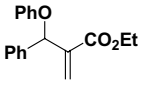
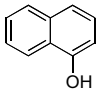
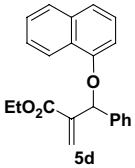
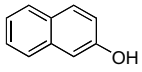
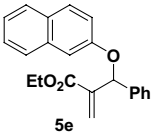
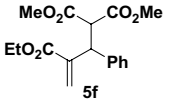
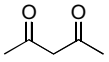
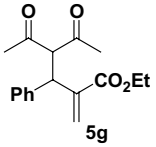
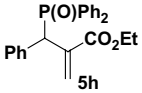
Table 1. DABCO-catalyzed allylic nucleophilic substitution of compound **4**[a]



4 5 6

Entry	NuH	Product	Yield[b,c] (%)
1	$TsNH_2$	 **5a**	74
2		 **5b**	88
3	PhOH	 **5c**	99
4		 **5d**	90
5		 **5e**	72
6		 **5f**	92
7		 **5g**	68
8	$HP(O)Ph_2$	 **5h**	84

[a] Typical reaction condition: a solution of compound **4** (0.5 mmol), pronucleophile (0.6 mmol), and DABCO (0.1 mmol) in toluene (10 mL) was stirred at ambient temperature overnight.
[b] Isolated yield.
[c] The ratio of **5/6**>97/3 as determined by ^1H NMR spectra.

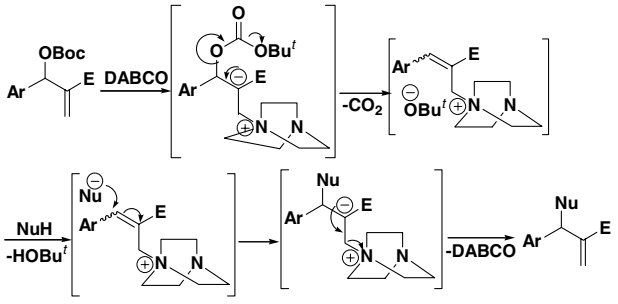
the nucleophile is too strong, a direct nucleophilic substitution will occur without the assistance of the nucleophilic catalyst. In the second step, the nucleophilicity of the nucleophile must be stronger than that of the catalyst. In view of avoiding the competition between two nucleophiles, a pronucleophile should be used in the first step and an in situ generated nucleophile is needed in the second step.

In our work of allylic phosphorus ylides,[7] we found that the *tert*-butoxycarbonyloxy group is a suitable choice, which can produce a *tert*-butoxide ion making the in situ generation of a nucleophile from the pronucleophile possible. Herein, we wish to report a DABCO-catalyzed highly regioselective allylic nucleophilic substitution of *tert*-butyl carbonate of the Morita–Baylis–Hillman products and its asymmetric version catalyzed by alkaloids.

A number of tertiary amines were chosen as the catalyst to investigate this reaction. To our delight, this reaction could proceed smoothly at room temperature using DABCO as the catalyst and tosylamine as the pronucleophile (Table 1, entry 1). Further study showed that this reaction could proceed smoothly in a high regioselective manner. Using carbonate as the substrate, a range of pronucleophiles, including oxygen, nitrogen, and carbon pronucleophiles, were examined. All of them gave satisfied yield with high regioselectivity (Table 1).

The observed results might be due to a mechanism proceeding via a tandem S_N2'–S_N2' sequence involving the initial formation of a quaternary ammonium ion, followed by elimination of the *tert*-butyl carbonate anion. After elimination of carbon dioxide, the *tert*-butoxy anion deprotonizes the pronucleophile. Then, the in situ formed nucleophilic anion attacks the olefinic bond of the cation intermediate to afford the observed products (Scheme 2).

The success of this reaction might ascribe to the fact that a pronucleophile was used in the first step making the catalyst react with the electron-deficient olefin possibly without competition. The in situ generated *tert*-butoxide anion can deprotonize a pronucleophile to produce a strong nucleophile that can add to the olefin and eliminate the catalyst.



Scheme 2.

Further studies were devoted to the asymmetric version of this novel reaction. Natural alkaloids and their derivatives are the best choice of catalysts because of their chiral nature. Quinidine was chosen as the catalyst to investigate the effect of the solvent on the reaction of **4** and $TsNH_2$. Highly polar solvents gave unsatisfied results. No optically active product was obtained when THF was used as a solvent. Disordered results were obtained when DMF, DMSO, and acetone were used as solvents. We are delighted to find that a good result (44% ee, **5a/6a**>97/3) was obtained when toluene was used as a solvent.

Focusing on the reaction of carbonate **4** with $TsNH_2$ in toluene, some alkaloids and their derivatives were investigated. Among them, 4-(3-ethyl-4-oxa-1-azatricyclo[4.4.0.0^{3,8}]dec-5-yl)quinolin-6-ol (β-isocupreidine or TQO)[8] showed the highest catalytic activity. $(DHQD)_2PYR$ showed the highest enantioselectivity, but the decreased reactivity (Table 2).

Thus, TQO was selected as the catalyst for the reaction of **4** and $TsNH_2$. The effects of the loading of the catalyst, the reaction temperature, and the concentration of compound **4** on the yield and the enantioselectivity were studied. All of them have little influence on the enantioselectivity. Certainly, the high loading of the catalyst, the high reaction temperature, or the high concentration of compound **4** led to the low enantioselectivity (Table 3).

Finally, the reactions of different pronucleophiles, including oxygen, nitrogen, and carbon pronucleophiles, were investigated under the standard condition. All of them showed a moderate enantioselectivity and high regioselectivity (Table 4). Using ketone **7** as the substrate, the reaction also gave high regioselectivity (**8/9**>97/3) and higher enantioselectivity (Scheme 3). The high yield of products implies that the kinetic resolution step as described in literature[5b] is not involved, and the highly reactive *tert*-butoxycarbonyl leaving group might play an important role in this reaction.

In conclusion, we developed an alkaloids-catalyzed regio and enantioselective nucleophilic allylic substitution reaction of *tert*-butyl carbonate of the Morita–Baylis–Hillman products with pronucleophiles. A number of pronucleophiles, such as nitrogen, oxygen, and active carbon have been used in this facile reaction. In general, the reaction proceeds efficiently to afford the successive S_N2'–S_N2' reaction product in good yields with high regio and medium enantioselectivity.

Table 2. Effect of the alkaloids catalysts on the allylic nucleophilic substitution of compound **4** with $TsNH_2$[a]

Entry	Catalyst	Time	Yield of **5a** (%)[b,c]	Ee[d] (%)
1	(+)-Quinidine	2 d	84	44 (−)
2	TQO	12 h	89	66 (−)
3	Brucine dihydrate	7 d	89	8 (+)
4	Strychnine	7 d	86	20 (+)
5	$(DHQ)_2AQN$	7 d	81	21 (−)
6	$(DHQ)_2PYR$	7 d	92	56 (+)
7	$(DHQD)_2PYR$	7 d	86	70 (−)
8	$(DHQD)_2AQN$	7 d	75	21 (+)

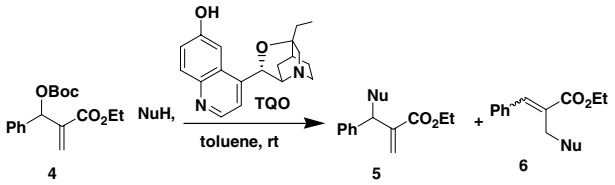
[a] Typical reaction condition: a solution of compound **4** (0.1 mmol), pronucleophile (0.12 mmol) and catalyst (0.02 mmol) in toluene (2 mL) was stirred at ambient temperature.
[b] Isolated yield.
[c] The ratio of **5a/6a**>97/3 as determined by ^1H NMR spectra.
[d] The ee value was determined by HPLC using chiralcel AS column. The sign in parenthesis represents the sign of the specific rotation.

Table 3. Effects on TQO-catalyzed allylic nucleophilic substitution of compound **4** with $TsNH_2$[a]

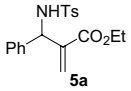
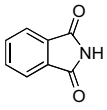
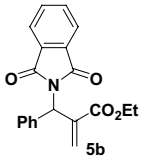
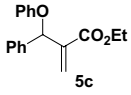
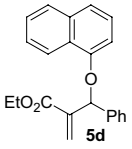
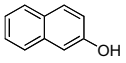
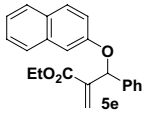
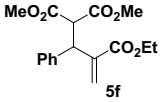
Entry	TQO (mol%)	Temperature (°C)	Time (h)	Conc. of **4** (M)	Yield[b,c] (%)	Ee[d] (%)
1	20	25	12	0.05	84	66
2	20	−20	12	0.05	36	64
3	20	50	3	0.05	86	58
4	100	25	12	0.05	42	53
5	10	25	12	0.05	61	67
6	5	25	36	0.05	72	68
7	20	25	12	0.01	83	71
8	20	25	12	0.5	86	59

[a] Typical reaction condition: a solution of compound **4** (0.1 mmol), $TsNH_2$ (0.12 mmol) and TQO in toluene was stirred at indicated temperature and time.
[b] Isolated yield.
[c] The ratio of **5a/6a**>97/3.
[d] The ee value was determined by HPLC.

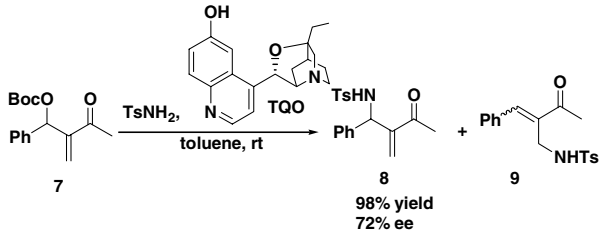
Table 4. TQO-catalyzed allylic nucleophilic substitution of compound **4**[a]



4 5 6

Entry	NuH	Product	Yield[b,c] (%)	Ee[d] (%)
1	$TsNH_2$	 5a	84	66 (−)
2		 5b	96	68 (+)
3	PhOH	 5c	85	61 (−)
4		 5d	93	72 (−)
5		 5e	84	60 (−)
6		 5f	90	51 (−)

[a] Typical reaction condition:[9] a solution of compound **4** (0.1 mmol), pronucleophile (0.12 mmol), and TQO (0.02 mmol) in toluene (2 mL) was stirred at room temperature overnight.
[b] Isolated yield.
[c] Ratio of **5**/**6**>97/3.
[d] The ee value was determined by HPLC. The sign in parenthesis represents the sign of the specific rotation.



Scheme 3.

Acknowledgements

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References and notes

1. (a) Drewes, S. E.; Roos, G. H. P. *Tetrahedron* **1988**, *44*, 4653–4670; (b) Basavaiah, D.; Dharmarao, P.; Suguna Hyma, R. *Tetrahedron* **1996**, *52*, 8001–8062; (c) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 51, pp 201–350.
2. (a) Basavaiah, D.; Sharada, D. S.; Kumaragurubaran, N.; Reddy, R. M. *J. Org. Chem.* **2002**, *67*, 7135–7137; (b) Aggarwal, V. K.; Castro, A. M. M.; Mereu, A.; Adams, H. *Tetrahedron Lett.* **2002**, *43*, 1577–1581; (c) Shi, M.; Jiang, J.-K.; Li, C.-Q. *Tetrahedron Lett.* **2002**, *43*, 127–130; (d) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am.*

Chem. Soc. **2002**, *124*, 2404–2405; (e) Basavaiah, D.; Satyanarayana, T. *Org. Lett.* **2001**, *3*, 3619–3622; (f) Kim, J. N.; Kim, H. S.; Gong, J. H.; Chung, Y. M. *Tetrahedron Lett.* **2001**, *42*, 8341–8344; (g) Lee, W.-D.; Yang, K.-S.; Chen, K. *Chem. Commun.* **2001**, 1612–1613; (h) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413–5418; (i) Räcker, R.; Döring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932–6939; (j) Ayed, T. B.; Villiéras, J.; Amri, H. *Tetrahedron* **2000**, *65*, 805–809; (k) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534–3535; (l) Kim, J. N.; Lee, K. Y.; Kim, H. S.; Kim, T. Y. *Org. Lett.* **2000**, *2*, 343–345; (m) Katoaka, T.; Kinoshita, H.; Kinoshita, S.; Iwamura, T.; Watnabe, S.-I. *Angew. Chem., Int. Ed.* **2000**, *39*, 2358–2360; (n) Li, G.; Wei, H. -X.; Gao, J. J.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1–5; (o) Yang, K.-S.; Chen, K. *Org. Lett.* **2000**, *2*, 729–731; (p) Iwabuchi, Y.; Nakatani, M.; Yokoyama, N.; Hatakeyama, S. *J. Am. Chem. Soc.* **1999**, *121*, 10219–10220; (q) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311–2312; (r) Basavaiah, D.; Kumaragurubaran, N. *J. Org. Chem.* **1999**, *64*, 1197–1200; (s) Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *J. Am. Chem. Soc.* **1997**, *119*, 4317–4318.

3. (a) Shi, M.; Xu, Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 4507–4510; (b) Shi, M.; Xu, Y. *J. Org. Chem.* **2003**, *68*, 4784–4790; (c) Kawahara, S.; Nakano, S.; Esumi, T.; Iwabuchi, Y.; Hatakeyama, S. *Org. Lett.* **2003**, *5*, 3103–3105; (d) Perlmutter, P.; Teo, C. C. *Tetrahedron Lett.* **1984**, *25*, 5951–5952; (e) Takagi, M.; Yamamoto, K. *Tetrahedron* **2000**, *56*, 4793–4797; (f) Bertenshow, S.; Kahn, M. *Tetrahedron Lett.* **1989**, *30*, 2731–2732; (g) Tian, S.-K.; Deng, L. *J. Am. Chem. Soc.* **2001**, *123*, 6195–6196.
4. (a) Langer, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 3049–3052; (b) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811–891; (c) Shi, M.; Jiang, J.-K. *Tetrahedron: Asymmetry* **2002**, *13*, 1941–1947; (d) McDaugal, N. T.; Schaus, S. E. *J. Am. Chem. Soc.* **2003**, *125*, 12094–12095; (e) Imbriglio, J. E.; Vasbinder, M. M.; Miller, S. J. *Org. Lett.* **2003**, *5*, 3741–3743; (f) Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. *J. Org. Chem.* **2003**, *68*, 915–919; (g) Aggarwal, V. K.; Mereu, A.; Tarver, G. J.; McCague, R. *J. Org. Chem.* **1998**, *63*, 7183–7189.
5. (a) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Gong, J. H. *Synlett* **2002**, 173–175; (b) Kim, J. N.; Lee, H. J.; Gong, J. H. *Tetrahedron Lett.* **2002**, *43*, 9141–9146.
6. Ciclosi, M.; Fava, C.; Galeazzi, R.; Orena, M.; Sepulveda-Arques, J. *Tetrahedron Lett.* **2002**, *43*, 2199–2202.
7. Du, Y.; Lu, X.; Zhang, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1035–1037.
8. The alkaloid derivative TQO used as the catalyst was synthesized according to the known procedure: See Ref. 2p, in which the same compound was named as QD-4. We use the name TQO as in Ref. 3a.
9. General procedure for alkaloid catalyzed allylic nucleophilic substitution of (4): To a solution of ethyl (2-methylidene-3-*tert*-butoxycarbonyloxy)phenyl-propanoate (**4**) (0.1 mmol) and pronucleophile (0.12 mmol) in dry toluene (2 mL) was added alkaloid (0.02 mmol), the reaction mixture was stirred at room temperature overnight and purified by silica gel column chromatography to obtain the product.