

A Highly α -Regioselective AgOTf-Catalyzed Nucleophilic Substitution of the Baylis–Hillman Acetates with Indoles

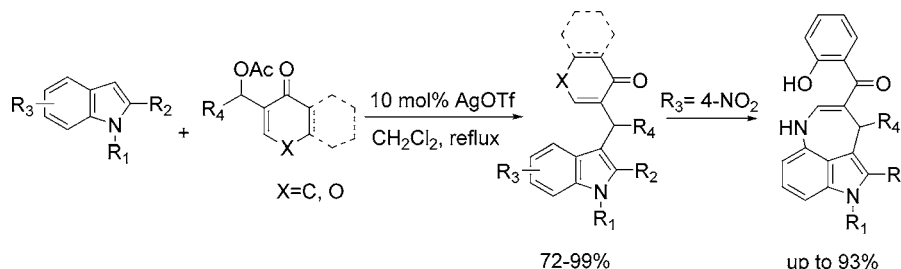
Zahid Shafiq, Li Liu,* Zhe Liu, Dong Wang, and Yong-Jun Chen*

Beijing National Laboratory for Molecular Sciences (BNLMS), Laboratory for Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China

lliu@iccas.ac.cn; yjchen@iccas.ac.cn

Received April 16, 2007

ABSTRACT



An efficient method for highly α -regioselective nucleophilic substitution of the Baylis–Hillman acetates with indoles catalyzed by AgOTf in high yields (72–99%) has been developed. Reductive cyclization of the substitution products furnished the azepinoindole derivatives in good yields (up to 93%).

The Baylis–Hillman (B–H) reaction is one of the most important C–C bond forming reactions and has received considerable attention recently.¹ The Baylis–Hillman adducts, which possess versatile functionalities bearing allylic hydroxyl and Michael acceptor units, have been illustrated as valuable synthons and starting materials for the synthesis of heterocycles and many biologically active molecules.² Regioselective introductions of nucleophiles at either the α - or γ -position of the Baylis–Hillman adduct (Figure 1) have

become powerful tools in synthetic organic chemistry.^{1,2} In most cases, a nucleophilic attack on the Baylis–Hillman adducts takes place at the γ -carbon via a S_N2' reaction.^{1–3} More recently, direct nucleophilic substitutions at the α -position of the Baylis–Hillman adduct were achieved by means of a base-promoted S_N2'–S_N2' reaction^{4,5} and through a Pd-catalyzed coupling reaction.⁶

The allylic alkylation of indoles with allylic alcohols or acetates is an important reaction in constructing indolic

(1) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Ciganek, E. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1997; Vol. 51, pp 201–350.

(2) (a) Aggarwal, V. K.; Patin, A.; Tisserand, S. *Org. Lett.* **2005**, *7*, 2555. (b) Wasnaire, P.; Wiaux, M.; Touillaux, R.; Marko', I. E. *Tetrahedron Lett.* **2006**, *47*, 985. (c) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387. (d) Luo, S.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2004**, *69*, 555. (e) Yeo, J. E.; Yang, X.; Kim, H. J.; Koo, S. *Chem. Commun.* **2004**, 236. (f) Racker, R.; Doring, K.; Reiser, O. *J. Org. Chem.* **2000**, *65*, 6932. (g) Lee, K. Y.; Gowrisankar, S.; Kim, N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481. (h) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627.

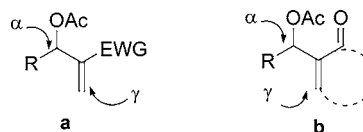


Figure 1.

alkaloids.⁷ The reaction of indoles with Baylis–Hillman acetates⁸ could be catalyzed by indium tribromide to provide the γ -allylic substitution products.⁹ However, direct substitution at the α position of Baylis–Hillman adducts is very rare.^{8a} Cyclic enones are important starting materials in the Baylis–Hillman reaction,¹⁰ and its B–H adducts could be applied in the synthesis of heterocycles such as quinolines^{10f–g} and 2*H*-indazole derivatives.^{10h} In some Pd-catalyzed reactions, cyclic B–H adducts (Figure 1, **b**) could favor α -substitution which was different with acyclic B–H adducts (Figure 1, **a**).^{6a} Recently, a silver(I)-catalyzed reaction has become an important method in organic synthesis in view of the potential dual functions of Ag(I) as both a Lewis acid¹¹ and a transition metal.¹² Herein, we wish to report a highly α -regioselective reaction of indoles with Baylis–Hillman acetates derived from cyclic enones catalyzed by AgOTf for direct nucleophilic substitution.

(3) (a) Basavaiah, D.; Satyanarayana, T. *Org. Lett.* **2001**, 3, 3619. (b) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, 5, 3803. (c) Yadav, J. S.; Gupta, M. K.; Pandey, S. K.; Reddy, B. V. S.; Sarma, A. V. S. *Tetrahedron Lett.* **2005**, 46, 2761. (d) Nag, S.; Pathak, R.; Kumar, M.; Shukla, P. K.; Batra, S. *Bioorg. Med. Chem. Lett.* **2006**, 16, 3824. (e) Basavaiah, D.; Pandiaraju, S.; Padmaja, K. *Synlett* **1996**, 393. (f) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, 5, 3803.

(4) DABCO as promoter: (a) Singh, V.; Yadav, G. P.; Maulik, P. R.; Batra, S. *Tetrahedron* **2006**, 62, 8731. (b) Lee, K. Y.; Gowrisankar, S.; Lee, Y. J.; Kim, J. N. *Tetrahedron* **2006**, 62, 8798. (c) Li, J.; Wang, X.; Zhang, Y. *Tetrahedron Lett.* **2005**, 46, 5233. (d) Du, Y.; Han, X.; Lu, X. *Tetrahedron Lett.* **2004**, 45, 4967. (e) Chung, Y. M.; Gong, J. H.; Kim, T. H.; Kim, J. N. *Tetrahedron Lett.* **2001**, 42, 9023.

(5) Phosphine catalysis: (a) Cho, C.-W.; Krische, M. J. *Angew. Chem., Int. Ed.* **2004**, 43, 6689. (b) Cho, C.-W.; Kong, J.-R.; Krische, M. J. *Org. Lett.* **2004**, 6, 1337.

(6) (a) Kabalka, G. W.; Dong, G.; Venkataiah, B.; Chen, C. *J. Org. Chem.* **2005**, 70, 9207. (b) Trost, B. M.; Tsui, H. C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, 122, 3534. (c) Roy, O.; Riahi, A.; Henin, F.; Muzart, J. *Tetrahedron* **2000**, 56, 8133. (d) Nemot, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, 9, 927.

(7) (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, 128, 6314. (b) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, 128, 1424. (c) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, 127, 4592. (d) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Org. Lett.* **2004**, 6, 3199. (e) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, 4, 2005. (f) Yasuda, M.; Somyo, T.; Baba, A. *Angew. Chem., Int. Ed.* **2006**, 45, 793. (g) Malkov, A. V.; Davis, S. L.; Baxendale, I. R.; Mitchell, W. L.; Kocovsky, P. *J. Org. Chem.* **1999**, 64, 2751–2764.

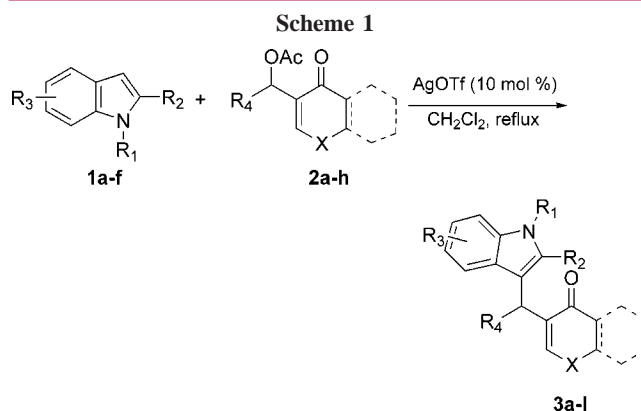
(8) (a) Ma, S.; Yu, S.; Guo, H. *J. Org. Chem.* **2006**, 71, 9865. (b) Ma, S.-M.; Yu, S.-C. *Tetrahedron Lett.* **2004**, 45, 8419. (c) Ma, S.-M.; Yu, S.-C.; Peng, Z.-H. *Org. Biomol. Chem.* **2005**, 3, 1933. (d) Ma, S.-M.; Zhang, J. *Tetrahedron* **2003**, 59, 6273. (e) Ma, S.; Zhang, J. *Tetrahedron Lett.* **2002**, 43, 3435.

(9) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2005**, 46, 639.

(10) (a) Narender, P.; Gangadasu, B.; Ravinder, M.; Srinivas, U.; Swamy, G. Y. S. K.; Ravikumar, K.; Rao, V. J. *Tetrahedron* **2006**, 5, 954. (b) Porzelle, A.; Williams, C. M.; Schwartz, B. D.; Gentle, I. R. *Synlett* **2005**, 2923. (c) Luo, S.; Mi, X. L.; Xu, H.; Wang, P. G.; Cheng, J. P. *J. Org. Chem.* **2004**, 69, 8413. (d) Luo, S. Z.; Wang, P. G.; Cheng, J. P. *J. Org. Chem.* **2004**, 69, 555. (e) Basavaiah, D.; Rao, A. J. *Chem. Commun.* **2003**, 604. (f) Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron Lett.* **2006**, 47, 73. (g) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, 69, 3739. (h) Lee, K. Y.; Gowrisankar, S.; Lee, Y. J.; Kim, J. N. *Tetrahedron Lett.* **2005**, 46, 5387.

(11) For selected examples, see: (a) Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, 126, 5360. (b) Josephohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, 126, 3734. (c) Wei, C.; Li, Z.; Li, C.-J. *Synlett* **2004**, 1472. (d) Josephohn, N. S.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, 125, 4018. (e) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, 124, 13400. (f) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, 118, 4723. (g) Yanagisawa, A. In *Lewis acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, Germany, 2000; Vol. 2, Chapter 13.

Initially, the reaction of indole **1** with 2-(acetoxycyclohex-2-en-1-yl)-cyclohex-2-en-1-one **2a** was investigated by using palladium catalysts (Scheme 1, Table 1). Under the catalysis

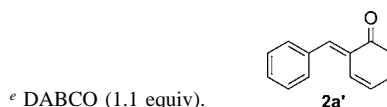


of Pd(acac)₂/PPh₃,^{8a} the reaction of *N*-methylindole (**1c**) provided substituted product 2-[(1-methylindolyl)phenyl]-

Table 1. Nucleophilic Substitution of B–H Acetate **2a** with **1a**^a

entry	catalyst	solvent	temp	time (h)	yield (%) ^b
1	PdCl ₂	CH ₂ Cl ₂	reflux	24	NR
2	Pd(OAc) ₂	CH ₂ Cl ₂	reflux	24	NR
3 ^c	Pd(acac) ₂	HOAc	80 °C	1	65/30 ^d
4	DABCO ^e	THF/H ₂ O (4:1)	rt	24	NR
5	FeCl ₃	CH ₂ Cl ₂	reflux	48	54
6	Cu (OTf) ₂	CH ₂ Cl ₂	reflux	24	48
7	Ag OTf	CH ₂ Cl ₂	rt	48	80
8	Ag OTf	CH ₂ Cl ₂	reflux	6	80
9	—	CH ₂ Cl ₂	reflux	24	NR

^a **1a**/**2a** = 1:1. Catalyst: 10 mol %. ^b Isolated yield. ^c *N*-Methyl indole (**1c**) was used, with 10 mol % of Pd (acac)₂ and 20 mol % of PPh₃. ^d **3c**/**2a**'.



^e DABCO (1.1 equiv).

methyl]-cyclohex-2-enone **3c** in 65% yield, together with an isomerized elimination product of **2a**, 2-benzylidene-cyclohex-3-enone **2a'** in 30% yield (entry 3). When DABCO was

(12) For examples, see: (a) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, 31, 12. (b) Dias, H. V. R.; Browning, R. G.; Polach, S. A.; Diyabalanage, H. V. K.; Lovely, C. J. *J. Am. Chem. Soc.* **2003**, 125, 9270. (c) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, 43, 4210. (d) Yao, X.; Li, C.-J. *J. Org. Chem.* **2005**, 70, 5752. (e) Youn, S. W.; Eom, J. I. *J. Org. Chem.* **2006**, 71, 6705.

Table 2. Reaction of Indoles **1** with BH Acetates **2** Catalyzed by AgOTf

entry	indole	BH acetate	time (h)	product	yield (%) ^a
1	1a	2a	6	3a	80
2	1b	2a	24	3b	72
3	1c	2a	12	3c	80
4	1d	2a	6	3d	87
5	1e	2a	48	3e	75
6	1a	2b	24	3f	92
7	1a	2c	6	3g	97
8	1a	2d	4	3h	90
9	1a	2e	12	3i	73
10	1f	2f	1	3j	90
11	1f	2g	1	3k	99
12	1f	2h	3	3l	89

^a Isolated yield.

used as a promoter, which was the normal method for the α -substitution of B–H adducts (via S_N2' – S_N2'), no reaction was observed after 24 h and starting materials were recovered

(entry 4). Fortunately, some Lewis acids were found to catalyze the reaction of **1a** with **2a**, and AgOTf exhibited the best catalytic ability for the nucleophilic substitution in 80% yield of **3a** with exclusive α -selection (Table 1, entry 7). No γ -product and isomerized elimination product (**2a'**) were detected in the crude reaction mixture. Increasing the temperature to reflux could shorten the reaction time (entry 7 vs 8). In the absence of the catalyst, the reaction could not proceed at all (entry 9).

To examine the effect of solvent, the reaction of **1a** with **2a** in the presence of AgOTf (10 mol %) was performed in toluene, dichloromethane (DCM), 1,2-dichloroethane, and CH₃CN, respectively. The product **3a** could be obtained in 35–80% yields. DCM was found to be the best solvent (Table 1).

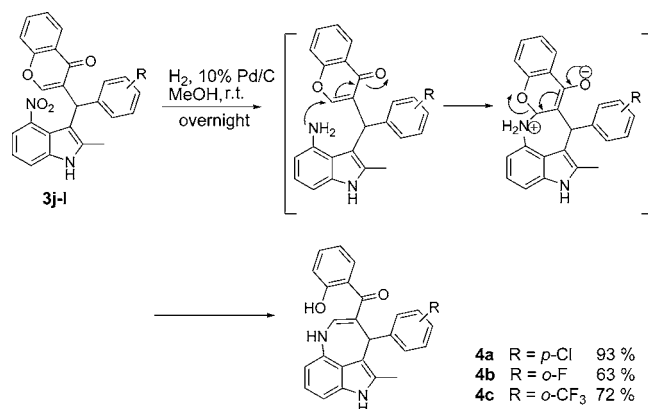
Subsequently, various indoles bearing an electron-withdrawing or electron-donating group in either the 1-, 2-, 4-, or 5-position of the indole ring (**1a–f**) were reacted with B–H acetates (**2a–h**) to provide the α -substituted products (**3a–l**) in good to excellent yields under the optimized conditions (Scheme 1, Table 2). In all cases, the α -isomer was obtained as a sole isomer, and no γ -products, isomerized elimination products, or N-alkylation products were detected in the reaction mixture. It can be found in Table 2 that when the R₄ group of the B–H acetate was a substituted phenyl group, the reaction of the B–H acetates **2c–h** with 2-methylindole **1a** or **1f** could also proceed smoothly to provide their respective products **3g–l** in excellent yields (73–99%) (Table 2, entries 7–12). If an R₄ group was a cyclohexyl group (**2b**), the yield of the reaction product (**3f**) could still be as high as 92% (entry 6). Furthermore, the B–H acetates derived from chromone (**2f–h**) reacted with 2-methyl-4-nitroindole **1f** to generate the α -products **3j–l** in excellent yields (89–99%) (entries 10–12).

Although silver complexes have been used in many organic reactions as powerful catalysts, to our knowledge, Ag-catalyzed nucleophilic substitution of allylic compounds was rare.¹³ In cyclic B–H adducts **2**, the α -position is close to the carbonyl oxygen and the coordination of Ag(I) with both carbonyl groups in the B–H adducts **2** may be responsible for the highly catalytic ability and regioselectivity for α -attack by indole nucleophiles. Meanwhile, the isomerization–elimination reaction of the starting material (B–H acetate) could be avoided.

The corresponding nucleophilic substitution products (**3j–l**) of 2-methyl-4-nitroindole (**1f**) with B–H acetates (**2f–h**) could be applied in the synthesis of novel azepinoindoles via reduction of the nitro group, followed by a cyclization (Scheme 2). The azepinoindole ring is a frequently encountered structural moiety in many alkaloids and pharmacologically relevant compounds.¹⁴ When the products **3j–l** were reduced in the presence of 10% Pd/C under a hydrogen atmosphere at room temperature, azepinoindoles **4a–c** were obtained in good yields (63–93%) (Scheme 2). The reaction is likely to proceed through the reduction of **3** and an in situ

(13) Murai, T.; Yamamoto, M.; Kondo, S.; Kato, S. *J. Org. Chem.* **1993**, *58*, 7440.

Scheme 2



aza-Michael addition, followed by the cleavage of a hemiaminal in one pot to provide the azepino-[4, 3, 2-*cd*]-indoles **4**.^{10f}

In conclusion, a mild and efficient direct nucleophilic substitution of the B–H acetates derived from cyclic enones with indoles was developed by using 10 mol % of AgOTf as a catalyst. The reaction provided highly α -regioselective

products in good to excellent yields. An inert atmosphere and strict anhydrous conditions were not required. Moreover, the reaction products of the B–H acetates with 4-NO₂-indole derivatives could be applied in the synthesis of novel azepino-[4, 3, 2-*cd*]-indoles via a one-pot reduction of a nitro group, followed by an in situ aza-Michael addition.

Acknowledgment. We thank The National Natural Science Foundation of China and The Chinese Academy of Sciences for financial support.

Supporting Information Available: Experimental procedures and characterization data of the B–H acetates (**2a–h**) and the products (**3a–l** and **4a–c**). This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL070878W

(14) (a) Matthews, J. M.; Greco, M. N.; Hecker, L. R.; Hoekstra, W. J.; Andrade-Gordon, P.; de Garavilla, L.; Demarest, K. T.; Ericson, E.; Gunnet, J. W.; Hageman, W.; Look, R.; Moore, J. B.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 753. (b) Hester, J. B. *J. Org. Chem.* **1967**, *32*, 4095. (c) Canan Koch, S. S.; Thoresen, L. H.; Tikhe, J. G.; Maegley, K. A.; Almassy, R. J.; Li, J.; Yu, X.-H.; Zook, S. E.; Kumpf, R. A.; Zhang, C.; Boritzki, T. J.; Mansour, R. N.; Zhang, K. E.; Ekker, A.; Calabrese, C. R.; Curtin, N. J.; Kyle, S.; Thomas, H. D.; Wang, L.-Z.; Calvert, A. H.; Golding, B. T.; Griffin, R. J.; Newell, D. R.; Webber, S. E.; Hostomsky, Z. *J. Med. Chem.* **2002**, *45*, 4961.