Tunable, Regioselective Control of Iodine-Catalyzed Allylic Substitution of Cyclic Baylis–Hillman Adducts with Indoles

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Abstract: Regioselective control over the nucleophilic substitution of cyclic Baylis–Hillman alcohols with indoles has been developed under the catalysis of molecular iodine. The reaction provided γ-substituted products in THF, whereas the α-products were obtained in TFE via an acid-catalyzed [1,3]-sigmatropic carbon skeleton rearrangement of allylindoles.

Key words: Baylis–Hillman adducts, indoles, molecular iodine, regioselectivities, allylic substitution

Recently, Baylis–Hillman (B–H) adducts are attracting much attentions in organic synthesis as valuable synthons and starting materials due to their ready availability and the presence of versatile allylic hydroxyl and Michael acceptor functionalities.[1] Allylic alkylation of B–H adducts has been used in an amazing number of applications in the synthesis of many bioactive molecules and natural products.[1,2]

Of great significance in allylic substitution reactions is the problem of regioselective control, especially for unsymmetrically substituted substrates.[3] In some cases, allylic alkylation for monosubstituted allylic alcohols or esters could proceed with regiocontrol by forming branched or linear products. For example, acyclic B–H adducts could provide the allylic substitution product either at the γ-position under metal catalysis and inorganic base promotion via S_N2' reaction,[4] or at the α-position under organic base catalysis via an S_N2'–S_N2' reaction.[5] However, the question of how to regioselectively introduce a nucleophile at either the α- or γ-position of unsymmetrically bis-substituted allylic electrophiles is still a challenge for synthetic chemists.

Cyclic B–H adducts derived from cyclic enones are important starting materials in the Baylis–Hillman reaction,[6] and could be used to generate fused cyclic frameworks.[7] However, a mixture of regioisomers may form from the cyclic B–H adducts due to their cyclic, unsymmetrically disubstituted allylic structures and this certainly creates some disadvantages. In some cases, cyclic B–H adducts could react with high α-regioselectivity in the presence of transition-metal catalysis,[8] however, there have been some reports on their γ-regioselectivity (Figure 1).[9] As a part of our continuing efforts to study the applications of cyclic B–H adducts in organic synthesis,[8a] herein we wish to report the highly α- and γ-regioselective reactions of cyclopent-2-enone-derived Baylis–Hillman adducts with indoles,[8a,10] in the presence of catalytic amounts of molecular iodine in different solvents. Furthermore, the application of allylic substitution products in the synthesis of azepino[4,3,2-*cd*]indoles is also demonstrated.

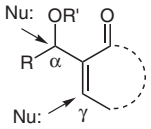

Figure 1 Regioselectivities of cyclic Baylis–Hillman adducts as unsymmetrically bis-substituted allylic electrophiles in nucleophilic substitution reactions

Initially, in the presence of various Lewis acids, 2-methylindole (**1a**) was found to react with 2-(hydroxyphenylmethyl)cyclopent-2-enone (**2a**) to provide a mixture of the allylic substitution products α-**3a** and γ-**4a** (Table 1). $InBr_3$ and AgOTf catalysis were found to favor α-selectivity (entries 1 and 3). In contrast, $FeCl_3$ generated a little more γ-product, but the conversion was still not complete even after refluxing for 12 hours in dichloromethane (entry 2). Molecular iodine showed the best catalytic efficiency and better γ-selectivity than other catalysts (entry 4). Although palladium catalyst[10a] and DABCO[5a–e] exhibited good catalytic reactivity for the reaction of acyclic B–H adducts with various nucleophiles, the Pd-catalyzed reaction of cyclic B–H adduct **2a** with 1,2-dimethylindole **1d** provided mainly the α-product (α:γ = 7:1, entry 6). DABCO lost its catalytic ability in the allylic substitution reaction of cyclic B–H adduct **1a** and only starting materials were recovered (entry 5). Molecular iodine, as a readily available, non-toxic catalyst, has been widely used in various organic transformations.[11] We and others have demonstrated that the nucleophilic substitution of allylic alcohols or esters with C-, N- or S-nucleophiles could be catalyzed by iodine.[12] Inspired by the highly efficient I_2-catalyzed allylic substitution reaction of B–H adduct **2a** with **1a**, various solvents were used in this reaction in order to optimize the regioselectivity of the reaction (Table 2). Non-protic solvents such as dichloromethane, toluene, Et_2O and THF favored γ-regioselectivity, and **4a**[13] was obtained as the major product (Table 2, entries

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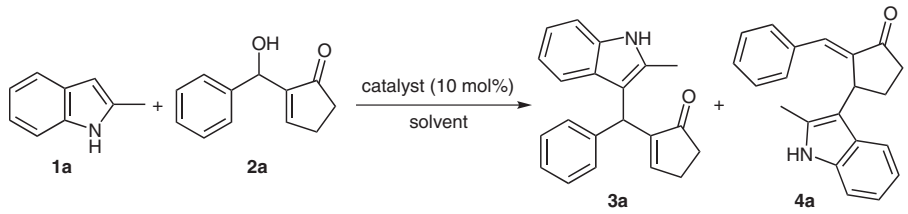
Table 1 Nucleophilic Substitution of B–H Adduct **2a** with Indole **1a** under Different Conditions



Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Conv. (%)[a]	Ratio α:γ[a]
1	$InBr_3$	CH_2Cl_2	reflux	12	100	4:1
2	$FeCl_3$	CH_2Cl_2	reflux	12	86	1:1.6
3	AgOTf	CH_2Cl_2	reflux	6	100	1.2:1
4	I_2	CH_2Cl_2	r.t.	3	100	1:2.7
5	DABCO[b]	THF–H_2O	r.t.	24	n.r.[d]	–
6[c]	$Pd(acac)_2/Ph_3P$	AcOH	80	0.5	100	7:1

[a] Determined by ^{1}H NMR.
[b] DABCO (1.1 equiv).
[c] Reaction conditions: $Pd(acac)_2$ (10 mol%), Ph_3P (20 mol%), 1,2-dimethylindole **1d** instead of **1a**.
[d] No reaction.

2–4; Table 1, entry 4); THF provided the best γ-regioselectivity (α:γ = 1:16). In protic solvents such as MeOH and EtOH, the reaction afforded an almost 1:1 mixture of α- and γ-products. However, when trifluoroethanol (TFE) under reflux was used as the solvent, the α-product **3a**[13] was formed as the major product (α:γ = 24:1). Without any catalyst, no reaction was observed in either THF or TFE (entries 9 and 10).

Under the optimized reaction conditions, the regioselectivities of the reactions of indoles with cyclic B–H adducts could be entirely controlled simply by switching the solvent. The scope of the reaction was explored with respect to various indoles and cyclic B–H adducts, and the substitution products were obtained in good to excellent yields (Table 3). In the presence of iodine (10 mol%), the reaction mainly provided γ-products **4** in THF, whereas α-products **3** were obtained in TFE in a relative longer reaction time. The substituents in the phenyl ring of cyclic B–H adducts have little effect on the reaction (entries 1–7). However, there were two exceptions: the reaction of simple indole **1b** with **2a** in THF also showed low γ-selectivity (γ:α = 2.8:1) based on isolated yields (entry 14), and the reaction of **1e** with **2a** in TFE provided low α-selectivity (γ:α = 1:2.8; entry 19).

Table 2 Solvent Effects in I_2-Catalyzed Reaction of B–H Adduct **2a** with Indole **1a**[a]

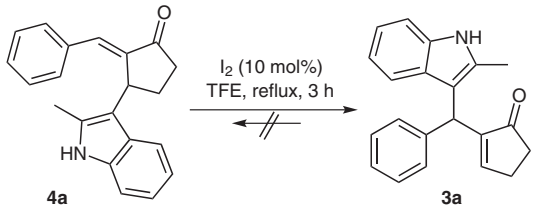
Entry	Solvent	Temp. (°C)	Time (h)	Conv. (%)[b]	Ratio α:γ[b]
1	Toluene	r.t.	2	80	1:2.2
2	Et_2O	r.t.	9	66	1:5.5
3	THF	r.t.	10	100	1:16
4	Dioxane	r.t.	1	100	1:6.1
6	MeOH	r.t.	2	100	1:1.1
7	EtOH	reflux	3	100	1:1
8	TFE	reflux	3	100	24:1
9[c]	TFE	reflux	3	–	n.r.[d]
10[c]	THF	reflux	3	–	n.r.[d]

[a] Cat: 10 mol%.
[b] Determined by ^{1}H NMR.
[c] Without catalyst.
[d] No reaction.

Interestingly, when the reactions were carried out in TFE, it was found that the ratios of α- to γ-products increased as the reaction proceeded. For example, when 2-methylindole (**1a**) was reacted with B–H adduct **2a**, in the presence of iodine in refluxing TFE, the products were obtained with an α/γ ratio of 1.2:1 after 30 minutes, and a 1.9:1 ratio after one hour. After B–H adduct **2a** was completely consumed (1.5 h), the ratio of α-**3a** to γ-**4a** increased to 9:1. When stirring of the reaction mixture was continued under the same conditions for an additional 1.5 hours (total reaction time: 3 h), the ratio of α/γ-product reached 24:1. The results demonstrated that there should be a conversion from the γ-product **4a** into the α-product **3a** during the course of the reaction of **1a** with **2a**.

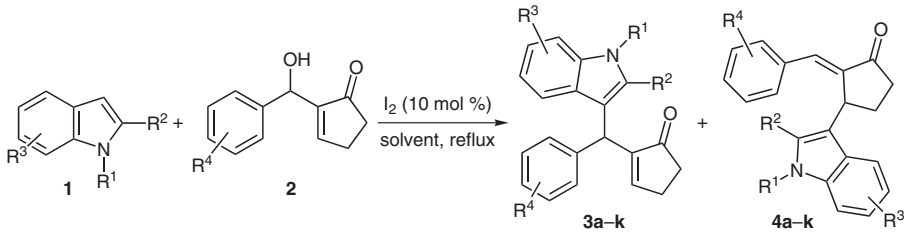
Further investigations verified the rearrangement of γ-**4a** into α-**3a** (Scheme 1). In the presence of iodine (10 mol%) in refluxing TFE, 82% of γ-**4a** was converted into α-**3a** after three hours. However, no conversion from α-**3a** into γ-**4a** could be observed under the same conditions

(Scheme 1). Since the reaction of iodine with TFE under reflux conditions could generate HI, the direct use of aqueous HI was tested and also found to result in a high conversion (90%). TFE is the best solvent and, even without any catalyst, **4a** in refluxing TFE could also be converted into **3a** in 11% yield after three hours.[14] However, in the presence of 10 mol% iodine in refluxing THF, no rearrangement was observed and **4a** was recovered after 12 hours. Based on these experimental results, it could be concluded that the excellent α-regioselectivity in the iodine-catalyzed reaction of **1a** with **2a** in TFE could be ascribed to a 1,3-shift of the indolyl group from product **4a** to **3a**.[15]



Scheme 1 [1,3]-Sigmatropic carbon rearrangement of **4a** to **3a**

Table 3 I_2-Catalyzed Regioselective Reaction of Indoles **1** with Cyclic B–H Adducts **2** in THF and TFE



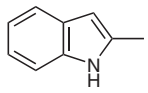
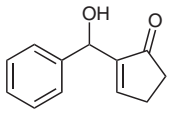
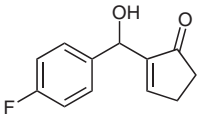
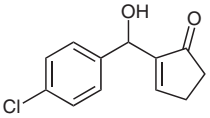
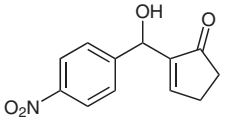
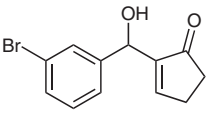
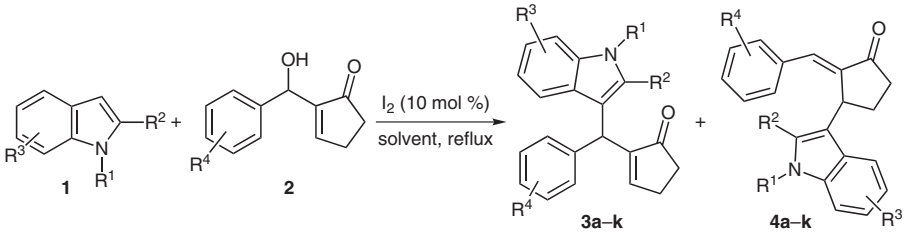
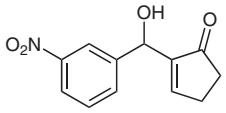
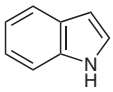
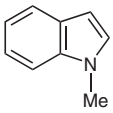
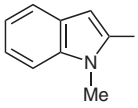
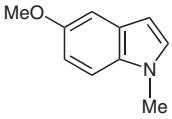
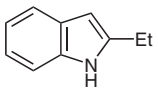
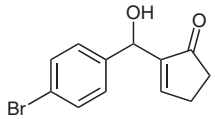
Entry	1	2	Solvent	Time (h)	Yield of **3/4** (%)[a]
1	 **1a**	 **2a**	TFE	3	78/–, **3a/4a**
2	**1a**	**2a**	THF	0.5	–/92, **3a/4a**
3	**1a**	 **2b**	TFE	2	81/–, **3b/4b**
4	**1a**	**2b**	THF	0.5	–/93, **3b/4b**
5	**1a**	 **2c**	TFE	3	76/–, **3c/4c**
6	**1a**	**2c**	THF	1	–/80, **3c/4c**
7	**1a**	 **2d**	TFE	8	82/–, **3d/4d**
8	**1a**	**2d**	THF	0.5	–/87, **3d/4d**
9	**1a**	 **2e**	TFE	4	95/–, **3e/4e**
10	**1a**	**2e**	THF	1	–/84, **3e/4e**

Table 3 I_2-Catalyzed Regioselective Reaction of Indoles **1** with Cyclic B–H Adducts **2** in THF and TFE (continued)



Entry	1	2	Solvent	Time (h)	Yield of **3/4** (%)[a]
11	**1a**	 **2f**	TFE	6	93/–, **3f/4f**
12	**1a**	**2f**	THF	1	–/78, **3f/4f**
13	 **1b**	**2a**	TFE	3	65/–, **3g/4g**
14	**1b**	**2a**	THF	2	16/60, **3g/4g**
15	 **1c**	**2a**	TFE	4	69/–, **3h/4h**
16	**1c**	**2a**	THF	0.5	–/70, **3h/4h**
17	 **1d**	**2a**	TFE	2.5	82/–, **3i/4i**
18	**1d**	**2a**	THF	10 min	–/72, **3i/4i**
19	 **1e**	**2a**	TFE	4	61/18, **3j/4j**
20	**1e**	**2a**	THF	0.5	–/71, **3j/4j**
21	 **1f**	 **2g**	TFE	2.5	71/–, **3k/4k**
22	**1f**	**2g**	THF	2	–/77, **3k/4k**

[a] Isolated yield.

We believed that hydrogen-bonding interactions could be used to explain the remarkable γ-regioselective control of the reaction in THF (Figure 2). Generally, under the catalysis of Lewis acids or Brønsted acids, both the carbonyl and the hydroxy groups in the B–H adduct could be activated, resulting in possible nucleophilic attack on both the α- and γ-positions. When iodine was used as a weak Lewis acid, the solvent could play an important role by moderating the strength of the hydrogen-bonding interactions. In a comparison of the β-values (which reflects the acceptor-ability of the forming hydrogen bond) of THF (β = 0.55), with diethyl ether (0.47), 1,4-dioxane (0.38), toluene (0.11) and dichloromethane (0), THF is found to be a better hydrogen-bond acceptor (HBA).[16] When the reaction was carried out in THF, the six-membered ring chelation between the OH and the carbonyl group in the

B–H adduct could be destroyed by solvation due to the strong hydrogen-bond acceptor ability of THF; at the same time, the carbonyl of B–H adduct should be activated by iodine to yield the γ-product via a Michael-type addition–elimination reaction (Figure 2, B). In contrast, when the reaction was carried out in protic solvent, which can be considered as a hydrogen-bond donor (HBD),[16] the hydroxy group of the B–H adduct could be activated to provide a mixture of α- and γ-products (Figure 2, A).

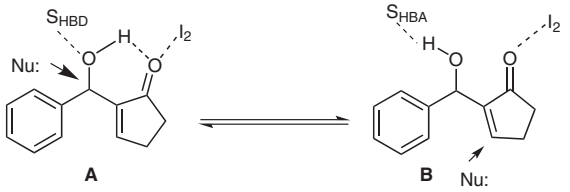
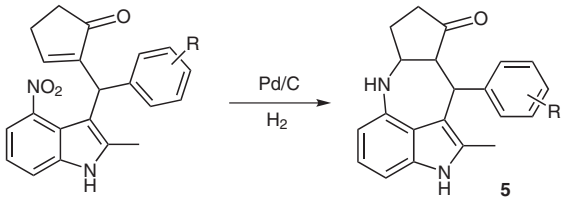


Figure 2 Solvent effects on the regioselective control of the nucleophilic substitution of B–H adduct **2a**

Further applications of allylic substitution of cyclic B–H adducts with indoles are demonstrated in Scheme 2. When α-products **3l** and **3m**, derived from 2-methyl-4-nitroindole, were treated with 10% Pd/C under a hydrogen atmosphere, azepino[4,3,2-*cd*]indoles[17] **5a** and **5b** were obtained in 80 and 51% yields, respectively, via an one-pot reduction and in situ aza-Michael addition (Scheme 2).[8a]



Scheme 2 Syntheses of azepino[4,3,2-*cd*]indoles **5**

In conclusion, we have reported a highly regioselective reaction of indoles with cyclic B–H adducts catalyzed by molecular iodine. Preliminary mechanistic investigations have revealed that the reaction provided kinetic controlled γ-products in THF, whereas α-products were obtained as thermodynamic products in TFE. The latter were generated through acid-catalyzed [1,3]-sigmatropic carbon skeleton rearrangement of allylindoles. The present method could be conveniently used in the synthesis of azepino[4,3,2-*cd*]indoles.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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References and Notes

(1) (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Basavaiah, D.; Rao, A. J.; Reddy, R. J. *Chem. Soc. Rev.* **2007**, *36*, 1581. (c) Masson, G.; Housseman, C.; Zhu, J. *Angew. Chem. Int. Ed.* **2007**, *46*, 4614. (d) Shi, Y. L.; Shi, M. *Eur. J. Org. Chem.* **2007**, 2905.

(2) For selected examples, see: (a) Trost, B. M.; Thiel, O. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2002**, *124*, 11616. (b) Trost, B. M.; Thiel, O. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2003**, *125*, 13155. (c) Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014. (d) Qi, J.; Porco, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 12682. (e) Basavaiah, D.; Aravindu, K. *Org. Lett.* **2007**, *9*, 2453.

(3) (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Cook, G. R.; Yu, H.; Sankaranarayanan, S.; Shanker, P. S. *J. Am. Chem. Soc.* **2003**, *125*, 5115. (c) Bruneau, C.; Renaud, J. L.; Demerseman, B. *Chem. Eur. J.* **2006**, *12*, 5178. (d) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, K. *Chem. Eur. J.* **2006**, *12*, 3596. (e) Plietker, B. *Angew. Chem. Int. Ed.* **2006**, *45*, 6053. (f) Yatsumonji, Y.; Ishida, Y.; Tsubouchi, A.; Takeda, T. *Org. Lett.* **2007**, *9*, 4603. (g) Nomura, N.; Komiyama, S.; Kasugai, H.; Saba, M. *J. Am. Chem. Soc.* **2008**, *130*, 812.

(4) For selected examples, see: (a) Basavaiah, D.; Satyanarayana, T. *Org. Lett.* **2001**, *3*, 3619. (b) Kabalka, G. W.; Venkataiah, B.; Dong, G. *Org. Lett.* **2003**, *5*, 3803. (c) Srihari, A.; Singh, A. P.; Basak, A. K.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 5999. (d) Chamakh, A.; M'hirsi, M.; Villieras, J.; Lebreton, J. *Synthesis* **2000**, 295. (e) Basavaiah, D.; Pandiaraju, S.; Padmaja, K. *Synlett* **1996**, 393. (f) Im, Y. J.; Lee, C. G.; Kim, H. R.; Kim, J. N. *Tetrahedron Lett.* **2003**, *44*, 2987.

(5) For selected examples see: 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. Phosphine catalysis, see: (f) Cho, C.-W.; Krische, M. J. *Angew. Chem. Int. Ed.* **2004**, *43*, 6689. (g) Jiang, Y. Q.; Shi, Y. L.; Shi, M. *J. Am. Chem. Soc.* **2008**, *130*, 7202. (h) Ma, G.-N.; Cao, S.-H.; Shi, M. *Tetrahedron: Asymmetry* **2009**, *20*, 1086.

(6) (a) He, L.; Jian, T. Y.; Ye, S. *J. Org. Chem.* **2007**, *72*, 7466. (b) Narender, P.; Gangadasu, B.; Ravinder, M.; Srinivas, U.; Swamy, G. Y. S. K.; Ravikumar, K.; Rao, V. J. *Tetrahedron* **2006**, *5*, 954. (c) Porzelle, A.; Williams, C. M.; Schwartz, B. D.; Gentle, I. R. *Synlett* **2005**, 2923. (d) Luo, S.; Mi, X. L.; Xu, H.; Wang, P. G.; Cheng, J. P. *J. Org. Chem.* **2004**, *69*, 8413. (e) Matsui, K.; Takizawa, S.; Sasai, H. *Tetrahedron Lett.* **2005**, *46*, 1943. (f) Sohtome, Y.; Tanatani, A.; Hashimoto, Y.; Nagasawa, K. *Tetrahedron Lett.* **2004**, *45*, 5589.

(7) (a) Basavaiah, D.; Rao, A. J. *Chem. Commun.* **2003**, 604. (b) Basavaiah, D.; Reddy, R. J.; Rao, J. S. *Tetrahedron Lett.* **2006**, *47*, 73. (c) Basavaiah, D.; Rao, J. S.; Reddy, R. J. *J. Org. Chem.* **2004**, *69*, 7379. (d) Schwartz, B. D.; Tilly, D. P.; Heim, R.; Wiedemann, S.; Williams, C. M.; Bernhardt, P. V. *Eur. J. Org. Chem.* **2006**, 3181. (e) Lee, K. Y.; Gowrisankar, S.; Lee, Y. J.; Kim, J. N. *Tetrahedron Lett.* **2005**, *46*, 5387. For reviews, see: (f) Kim, J. N.; Lee, K. Y. *Curr. Org. Chem.* **2002**, *6*, 627. (g) Singh, V.; Batra, S. *Tetrahedron* **2008**, *64*, 4511. (h) Shi, Y.-L.; Shi, M. *Org. Biomol. Chem.* **2007**, *5*, 1499. (i) Rezgui, F.; Amri, H.; Gaïed, M. M. E. *Tetrahedron* **2003**, *59*, 1369.

(8) (a) Shafiq, Z.; Liu, L.; Liu, Z.; Wang, D.; Chen, Y. J. *Org. Lett.* **2007**, *9*, 2525. (b) Kabalka, G. W.; Dong, G.; Venkataiah, B.; Chen, C. *J. Org. Chem.* **2005**, *70*, 9207.

(9) Suzuki, M.; Kawagishi, T.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 1809.

(10) For reaction of indoles with acyclic B–H adducts, see: (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. L. *Tetrahedron* **2003**, *59*, 6273. (e) Ma, S. M.; Zhang, J. L. *Tetrahedron Lett.* **2002**, *43*, 3435. (f) Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Narsaiah, A. V.; Prabhakar, A.; Jagadeesh, B. *Tetrahedron Lett.* **2005**, *46*, 639. (g) Yadav, J. S.; Reddy, B. V. S.; Singh, A. P.; Basak, A. K. *Tetrahedron Lett.* **2007**, *48*, 4169.

(11) For selected examples, see: (a) Alcaide, B.; Almendros, P.; Cabreroa, G.; Ruiz, M. P. *Chem. Commun.* **2008**, 615. (b) Varala, R.; Nuvula, S.; Adapa, S. R. *J. Org. Chem.* **2006**, *71*, 8283. (c) Kumar, V.; Ramesh, N. G. *Chem. Commun.* **2006**, 4952. (d) Sun, J.; Dong, Y.; Cao, L.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932. (e) Phukan, P. *J. Org. Chem.* **2004**, *69*, 4005. (f) Zhao, P. C.; Li, J.; Jia, X. S. *Synlett* **2008**, 932. (g) Wang, S. Y.; Ji, S. J.; Loh, T. P. *Synlett* **2003**, 2377. (h) Banik, B. K.; Fernandez, M.; Alvarez, C. *Tetrahedron Lett.* **2005**, *46*, 2479. (i) Lin, C. C.; Hsu, J. M.; Sastry, M. N. V.; Fang, H. L.; Tu, Z. J.; Liu, J. T.; Yao, C. F. *Tetrahedron* **2005**, *61*, 11751. (j) Periana, R. A.; Mirinov, O.; Taube, D. J.; Gamble, S. *Chem. Commun.* **2002**, 2376. (k) Togo, H.; Iida, S. *Synlett* **2006**, 2159.

(12) (a) Liu, Z.; Liu, L.; Shafiq, Z.; Wu, Y. C.; Wang, D.; Chen, Y. J. *Tetrahedron Lett.* **2007**, *48*, 3963. (b) Rao, W.; Tay, A. H. L.; Goh, P. J.; Choy, J. M. L.; Ke, J. K.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 122. (c) Wu, W. H.; Rao, W. D.; Er, Y. Q.; Loh, J. K.; Poh, C. Y.; Chan, P. W. H. *Tetrahedron Lett.* **2008**, *49*, 2620.

(13) To a solution of Baylis–Hillman adduct **2a** (0.2 mmol) and indole **1a** (0.2 mmol) in TFE (or THF) (5 mL), was added iodine (0.02 mmol). The resulting reaction mixture was heated under reflux until completion as judged by TLC, or for the time indicated. After cooling, the reaction mixture was diluted with CH_2Cl_2 and extracted into sat. $Na_2S_2O_3$ (3×5 mL). The combined organic extract was dried over anhydrous Na_2SO_4, concentrated in vacuum and purified by column chromatography over silica gel (petroleum ether–EtOAc, 8:1) to afford the desired α-product **3a** (or γ-product **4a** when THF was used as the solvent).
2-[(2-Methylindolyl)phenylmethyl]cyclopent-2-enone (**3a**): Off-white solid, mp 135–136 °C; IR (KBr): 3393, 2919, 1694, 1456, 1229, 1007, 751 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.20 (s, 3 H), 2.25–2.62 (m, 4 H), 5.29 (s, 1 H), 6.82–6.87 (m, 1 H), 6.96 (t, *J* = 7.41 Hz, 1 H), 7.06–7.18 (m, 7 H), 7.23 (s, 1 H), 7.84 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 11.0, 25.3, 33.7, 36.8, 109.3, 110.1, 118.0, 118.1, 119.6, 125.0, 126.8, 127.1, 127.2, 131.4, 134.3, 140.8, 147.5, 158.8, 207.7; EI-MS: *m*/*z* (%) = 301, 286, 284, 270, 244, 146, 130 (100); HRMS: *m*/*z* calcd. for $C_{21}H_{19}NO$: 301.1467; found: 301.1466.
(*E*)-2-Benzylidene-3-(2-methyl-1*H*-indol-3-yl)cyclopentanone (**4a**): Yellow solid; mp 184–185 °C; IR (KBr): 3397, 2925, 1704, 1615, 1456, 1223, 1179, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.13–2.22 (m, 1 H), 2.31 (s, 3 H), 2.35–2.65 (m, 3 H), 4.71 (t, *J* = 2.53 Hz, 1 H), 7.04–7.46 (m, 9 H), 7.61 (s, 1 H), 7.79 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 12.6, 30.1, 36.7, 37.9, 110.3, 112.4, 118.3, 119,4, 121.1, 127.7, 128.3, 129.2, 130.7, 130.8, 134.3, 134.7, 135.1, 138.7, 208.9; EI-MS: *m*/*z* (%) = 301 (100), 286, 272, 258, 244, 168, 130; HRMS: *m*/*z* calcd. for $C_{21}H_{19}NO$: 301.1467; found: 301.1469.

(14) Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 8421.

(15) 1,3-Isomerization of allylic alcohols or esters, selected examples: (a) Kobbelgaard, S.; Brandes, S.; Jørgensen, K. A. *Chem. Eur. J.* **2008**, *14*, 1464. (b) Shanmugam, P.; Rajasingh, P. *Tetrahedron* **2004**, *60*, 9283. (c) Kim, H. S.; Kim, T. Y.; Lee, K. Y.; Chung, Y. M.; Lee, H. J.; Kim, J. N. *Tetrahedron Lett.* **2000**, *41*, 2613. (d) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842. (e) Shekhar, S.; Trantow, B.; Leitner, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 11770.

(16) (a) Nielsen, M. F.; Ingold, K. U. *J. Am. Chem. Soc.* **2006**, *128*, 1172. (b) Kamlet, M. J.; Taft, R. W. *J. Am. Chem. Soc.* **1976**, *98*, 377.

(17) (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) Nagasaka, T.; Ohki, S. *Chem. Pharm. Bull.* **1977**, *25*, 3023.