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Stereoselective Double Friedel−Crafts Alkylation of Indoles with Divinyl Ketones

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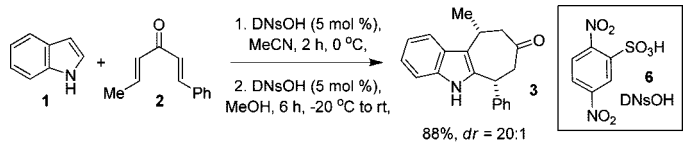
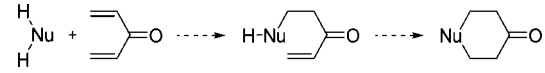
ABSTRACT



A tandem double Friedel−Crafts reaction of indoles and nonsymmetrical divinyl ketones has been achieved. The tandem reaction forms complex [6-5-7]-tricyclic indoles in excellent yields. The reaction is completely regioselective and offers high levels of *syn* diastereoselectivity. The reaction is also seen to be sensitive to substrate structure and catalyst.

Indoles are an important class of molecule because of their ubiquity in nature, their structural diversity, and the wealth of biological activity they possess.[1] Therefore, the indole nucleus has become a key component of pharmaceutical molecules and is regarded as a privileged structure.[2] As a result of the simultaneous diversity of indole structure and biology, the organic chemist continues to search for novel indole scaffolds. To answer this issue, the ability to modify simpler indoles in a rapid, diverse, and controlled manner remains an important goal.[3]

Scheme 1. Reaction of Divinyl Ketones and Double Nucleophiles



Divinyl ketones are largely associated with the Nazarov reaction for the synthesis of cyclopentenones.[4] However, divinyl ketones can also be viewed as double electrophiles, capable of participating in two conjugate addition reactions. More specifically, the use of a nucleophile with the capacity for two nucleophilic reactions allows for the formation of cyclic structures via an initial intermolecular reaction and subsequent intramolecular reaction (Scheme 1).

For example, nucleophiles such as amines,[5] water or sulfides,[6] selenides,[7] active methylenes,[8] and primary phosphines[9] have all been used in this manner. However, in the majority of cases, symmetrical divinyl ketones such as dibenzylidene acetone have been used, leading to the formation of symmetrical products of limited synthetic value.

Indoles can also be expected to fulfill the role of a double nucleophile.[10,11] It has been demonstrated that indole reacts

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(1) (a) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2003**, *20*, 216. (c) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209. (d) Angeli, M.; Bandini, M.; Garelli, A.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. *Org. Biomol. Chem.* **2006**, *4*, 3291.

(2) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(3) (a) Itoh, J.; Fuchibe, K.; Akiyama, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 4016. (b) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (c) Zaitsev, A. B.; Gruber, S.; Plüss, P. A.; Pregosin, P. S.; Veiros, L. F.; Wörle, M. *J. Am. Chem. Soc.* **2008**, *130*, 11604. (d) Phipps, R. J.; Grimster, N. P.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 8172. (e) Lebrasseur, N.; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926. (f) Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroviejo, M. P.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857. (g) Stuart, D. R.; Villemure, E.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 12072.

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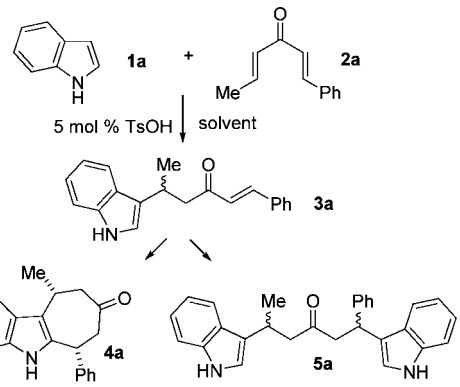
Table 1. Initial Screening of Tandem Indole Friedel−Crafts Alkylation



entry	solvent	temp (°C)	time (h)	yield (%)[a] **3**:**4**:**5**	dr[b]
1	MeCN	40	8	90:0:3	
2	MeCN	85	3	0:45:26	1:1
3	MeOH	20	6	0:57:20	11:1
4	MeOH	40	4	0:43:26	5.5:1
5	MeOH	85	1	0:40:28	4.5:1

[a] Isolated yields. [b] Measured by ^{1}H NMR analysis of crude reaction mixture.

with symmetrical divinyl ketones through the consecutive addition of two molecules of indole at the enone moieties.[12] However, there has been a single report of indole reacting with a symmetrical divinyl ketone under gold catalysis to form a fused tricyclic structure.[13] We felt that employing nonsymmetrical divinyl ketones would offer an opportunity to form diverse and biologically interesting fused-tricyclic indoles.

To explore this concept, indole **1a** was reacted under acid catalysis with divinyl ketone **2a**, a nonsymmetrical electrophile with sterically and electronically differentiated enone termini.[14]

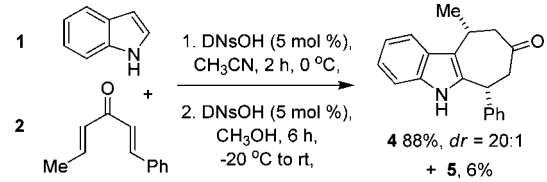
Reaction in acetonitrile at 40 °C resulted in the chemoselective formation of the mono adduct **3a** (Table 1, entry 1) with exclusive attack of the indole on the methyl-substituted enone terminus.[15] Performing the reaction at higher temperature afforded a mixture of cyclic **4a** and bis **5a** products (Table 1, entry 2). The cyclic compound was formed with complete regioselectivity (the positions of methyl and phenyl relative to indole),[16] but no diastereoselectivity was observed (the *syn*/*anti* relationship of the methyl and phenyl groups).[17]

Table 2. Solvent and Brønsted Acid Catalyst Screen[a]

entry	solvent	time (h)	acid	yield (%)[b] **3**:**4**:**5**	dr[c]
1	H_2O	168	TsOH	n.r.[d]	
2	DMSO	168	TsOH	n.r.[d]	
3	Et_2O	96	TsOH	15:0:0	
4	$PhCH_3$	168	TsOH	48:0:0	
5	$CHCl_3$	8	TsOH	80:0:4	
6	MeOH	1	TsOH	0:40:28	4.5:1
7	MeCN	3	TsOH	0:45:26	1:1
8	MeCN	2	DNsOH[e]	99:0:0	
9	MeCN	5	MsOH	74:10:6	2:1
10	MeCN	24	$(PhO)_2PO_2H$	30:26:19	1:1
11	MeCN	48	CF_3CO_2H	82:0:7	
12	MeCN	168	$PhCO_2H$	47:0:0	
13	MeCN	168	none	n.r.[d]	

[a] Reactions performed at 85 °C; 5 mol % catalyst used. [b] Isolated yields. [c] *syn*:*anti*; measured by ^{1}H NMR analysis of crude reaction mixture. [d] No reaction observed, starting material recovered. [e] DNsOH: 2,4-dinitrobenzenesulfonic acid.

Scheme 2. Improved Two-Step, Solvent Substitution Protocol



However, with methanol as solvent, the cyclic and bis compounds were formed at room temperature, with considerable diastereoselectivity in favor of the *syn* isomer (dr = 11:1, table 1, entry 3). Increasing the temperature of the reaction in methanol resulted in a drop of both cyclic compound yield and chemoselectivity (Table 1, entries 4 and 5). After this initial success, a reaction optimization was attempted with a number of variables screened (Table 2).

(4) (a) Pellissier, H. *Tetrahedron* **2005**, *61*, 6479. (b) Tius, M. A. *Eur. J. Org. Chem.* **2005**, 2193.

(5) (a) Rosiak, A.; Hoenke, C.; Christoffers, J. *Eur. J. Org. Chem.* **2007**, *2007*, 4376. (b) Radha Krishna, P.; Sreeshailam, A. *Tetrahedron Lett.* **2007**, *48*, 6924. (c) Weber, W. M.; Hunsaker, L. A.; Roybal, C. N.; Bobrovnikova-Marjon, E. V.; Abcouwer, S. F.; Royer, R. E.; Deck, L. M.; Vander Jagt, D. L. *Bioorg. Med. Chem.* **2006**, *14*, 2450. (d) Padmavathi, V.; Reddy, T. V. R.; Reddy, K. A.; Reddy, D. B. *J. Heterocycl. Chem.* **2003**, *40*, 149. (e) Snider, B. B.; Harvey, T. C. *Tetrahedron Lett.* **1995**, *36*, 4587.

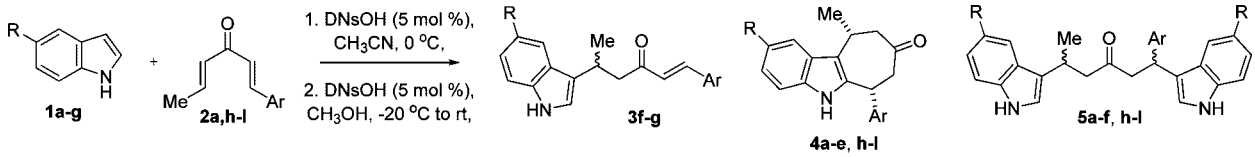
(6) (a) Rosiak, A.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2006**, *2006*, 4044. (b) Rosiak, A.; Christoffers, J. *Synlett* **2006**, 1434. Liljebris, C.; Martinsson, J.; Tedenborg, L.; Williams, M.; Barker, E.; Duffy, J. E. S.; Nygren, A.; James, S. *Bioorg. Med. Chem.* **2002**, *10*, 3197. (c) Rule, N. G.; Detty, M. R.; Kaeding, J. E.; Sinicropi, J. A. *J. Org. Chem.* **1995**, *60*, 1665. (d) Nakamura, E.; Kubota, K.; Isaka, M. *J. Org. Chem.* **1992**, *57*, 5809. (e) Powers, T. A.; Evans, S. A.; Pandiarajan, K.; Benny, J. C. N. *J. Org. Chem.* **1991**, *56*, 5589.

(7) (a) Reddy, D. B.; Reddy, A. S.; Padmavathi, V. *Synth. Commun.* **2001**, *31*, 3429. (b) Evers, M.; Christiaens, L.; Renson, M. *Tetrahedron Lett.* **1985**, *26*, 5441. (c) Nanjappan, P.; Ramalingam, K.; Satyamurthy, N.; Berlin, K. D. *J. Org. Chem.* **1981**, *46*, 2542.

(8) (a) Behera, R. K.; Behera, A. K.; Pradhan, R.; Pati, A.; Patra, M. *Synth. Commun.* **2006**, *36*, 3729. (b) Ahmed, M. G.; Ahmed, S. A.; Ahmed, S. M.; Hossain, M. M.; Hussam, A. *J. Chem. Res., Synop.* **2005**, 622. (c) Chande, M. S.; Khanwelkar, R. R. *Tetrahedron Lett.* **2005**, *46*, 7787. (d) Ahmed, M. G.; Ahmed, S. A.; Uddin, K.; Rahman, T.; Romman, U. K. R.; Fujio, M.; Tsuda, Y. *Tetrahedron Lett.* **2005**, *46*, 8217. (e) Padmavathi, V.; Basha, S. M.; Chinna, D. R.; Subbaiah, V.; Reddy, T. V. R.; Padmaja, A. *J. Heterocycl. Chem.* **2005**, *42*, 797. (f) Risitano, F.; Grassi, G.; Foti, F.; Romeo, R. *Synthesis* **2002**, 116. Takaya, H.; Murahashi, S. I. *Synlett* **2001**, 991. (g) Seifert, M.; Kuck, D. *Tetrahedron* **1996**, *52*, 13167. (h) Gomez-Bengoa, E.; Cuerva, J. M.; Mateo, C.; Echavarren, A. M. *J. Am. Chem. Soc.* **1996**, *118*, 8553. (i) Reddy, D. B.; Padmavathi, V.; Seenaiah, B.; Reddy, M. V. R. *Org. Prep. Proced. Int.* **1992**, *24*, 21. (j) Rowland, A. T.; Gill, B. C. *J. Org. Chem.* **1988**, *53*, 434.

(9) (a) Doherty, R.; Haddow, M. F.; Harrison, Z. A.; Orpen, A. G.; Pringle, P. G.; Turner, A.; Wingad, R. L. *Dalton Trans.* **2006**, 4310. (b) Brenstrum, T.; Clattenburg, J.; Britten, J.; Zavorine, S.; Dyck, J.; Robertson, A. J.; McNulty, J.; Capretta, A. *Org. Lett.* **2006**, *8*, 103. (c) Pastor, S. D.; Odorisio, P. A.; Spivack, J. D. *J. Org. Chem.* **1984**, *49*, 2906. (d) Subramanian, P. K.; Ramalingam, K.; Satyamurthy, N.; Berlin, K. D. *J. Org. Chem.* **1981**, *46*, 4376. (e) Welcher, R. P.; Day, N. E. *J. Org. Chem.* **1962**, *27*, 1824.

Table 3. Exploration of Scope between Indoles and Divinyl Ketones[a]



entry	R	Ar	time (h)[b]	yield **3** (%)	yield **4** (%)[c]	yield **5** (%)[c]	dr **4**[d]
1	H (**1a**)	Ph (**2a**)	2 + 6	0	88 (**4a**)	6	20:1
2	OMe (**1b**)	Ph (**2a**)	0.5 + 4	0	81 (**4b**)	9	10:1
3	Me (**1c**)	Ph (**2a**)	3 + 6	0	88 (**4c**)	6	11:1
4	Cl (**1d**)	Ph (**2a**)	1.5 + 5	0	86 (**4d**)	7	9:1
5	F (**1e**)	Ph (**2a**)	3 + 6	0	82 (**4e**)	9	12:1
6	CN (**1f**)	Ph (**2a**)	4.5 + 48	99[e] (**3f**)	0	0	
7	NO_2 (**1g**)	Ph (**2a**)	5 + 48	33[e] (**3g**)	0	33[e] (**5g**)	
8	H (**1a**)	4-MeO-Ph (**2h**)	2 + 7	0	84 (**4h**)	6	8:1
9	H (**1a**)	4-Me-Ph (**2i**)	2 + 7	0	89 (**4i**)	3	8:1
10	H (**1a**)	2-Me-Ph[f] (**2j**)	2 + 6	0	71 (**4j**)	13	23:1
11	H (**1a**)	4-Cl-Ph (**2k**)	2 + 6	0	93 (**4k**)	2	14:1
12	H (**1a**)	4-CF_3-Ph[f] (**2l**)	2 + 6	0	70 (**4l**)	10	17:1

[a] See Supporting Information for full experimental details. [b] Reaction times depicted as intermolecular reaction + intramolecular reaction. [c] Isolated yield. [d] Measured by ^{1}H NMR analysis relative to **4** in crude reaction mixture. [e] *syn*:*anti*; measured by ^{1}H NMR analysis of crude reaction mixture. [f] Divinyl ketones **2j** and **2l** were used as 2:1 *E*,*Z*/*E*,*E* mixtures.

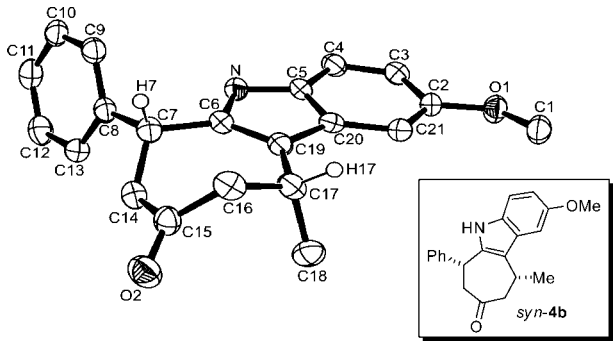
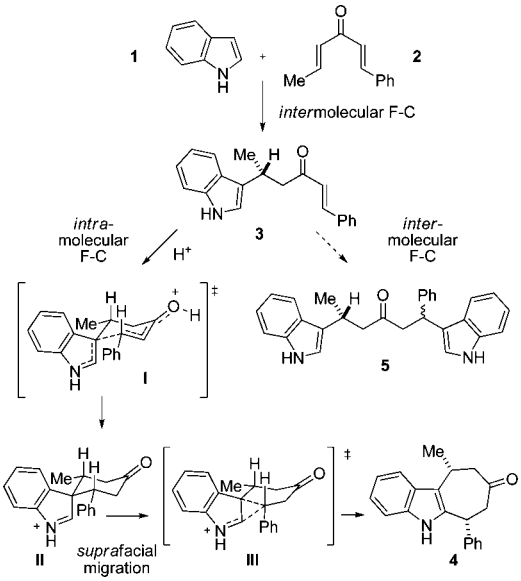


Figure 1. ORTEP plot of *syn*-**4b** (ellipsoids at 30% probability).

None of the alternative solvents improved the reaction compared to methanol or acetonitrile (Table 2, entries 1−7). A screen of Brønsted acids showed a trend between acid strength and reaction rates: the lower the pK_a the faster the reaction (Table 2, entries 7−13). Of particular note was the use of 2,4-dinitrobenzenesulfonic acid, which gave only mono adduct **3a** even at elevated temperature (Table 2, entry 8). Significantly, no Nazarov products were observed, despite the fact that the Nazarov reaction is known to be promoted by strong Brønsted acids.[18−20]

These observations were combined to give a practical two-step procedure: the first step involves reaction in acetonitrile resulting in the high-yielding formation of mono adduct **3a**. This was followed by a solvent swap to methanol and cyclization to give a further improvement in diastereoselectivity. This protocol minimizes the formation of bis adduct **5a** and ensures high yields and excellent diastereoselectivities (Scheme 2; Table 3, entry 1).

Scheme 3. Partial Mechanistic Rationale for the Formation of Fused Tricyclic Indoles from Divinyl Ketones



The *syn* diastereoisomer formed in this reaction appears to be the kinetic product, as subjection of *syn*-**4a** (dr = 10:1) to 5 mol % DNsOH in refluxing MeOH for 5 h led to a drop in dr to 1.6:1

The sense of diastereoselectivity was assigned by NOE spectroscopy with an interaction observed between the methyl group and the phenyl ring, indicating a *syn* relationship between these two moieties. This assignment was confirmed by X-ray diffraction analysis of methoxy derivative **4b** (Figure 1).

To further explore the scope of this reaction, a number of indole and divinyl ketone substrates were examined under the new two-step conditions (Table 3).

First, the effect of substitution at the C-5 position of indole was investigated (Table 3, entries 1−7). A general trend was observed, with electron-withdrawing substituents resulting in a slower intermolecular conjugate addition. Also, strongly electron-withdrawing groups prevented cyclization altogether with only mono and bis adducts observed (Table 3, entries 6 and 7). Second, the aryl substituent of the divinyl ketone was varied (Table 3, entries 8−12). In all cases, cyclization proceeded in good yield with only small amounts of bis adduct formed. The diastereoselectivity of the cyclization was seen to improve with both increasing electron-withdrawing aptitude and increasing steric bulk of the aryl substituents (Table 3, entries 10 and 12).

We postulate that **4a** forms through intramolecular cyclization to form spiroindoleninium intermediate **II** (Scheme 3). This cyclization occurs via a chair transition state and establishes the *syn* relationship between the methyl and phenyl groups. The benzylic group of spiroindoleninium intermediate **II** then undergoes a C-3 to C-2 suprafacial migration with retention of configuration,[21−23] followed by rearomatization to give the fused [6-5-7] ring system.[24] Therefore the *syn* arrangement of methyl and phenyl groups is preserved in the fused tricyclic indole product.

In conclusion, a Brønsted acid catalyzed double Friedel−Crafts reaction of indoles and nonsymmetrical divinyl ketones is reported. The reaction forms complex fused-tricyclic indole products in a highly regio- and diastereoselective manner, displaying a clear sensitivity to substrate substitution. Studies directed toward absolute stereochemistry control, mechanistic understanding, and expansion of the substrate scope are currently ongoing in our laboratories and will be reported in due course.

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Supporting Information Available: Experimental procedures, compound characterization data, and CIF file for structure **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For recent examples of stereoselective indole-enone Friedel−Crafts reactions, see: (a) Evans, D. A.; Fandrick, K. R.; Song, H. J.; Scheidt, K. A.; Xu, R. S. *J. Am. Chem. Soc.* **2007**, *129*, 10029. (b) Blay, G.; Fernandez, I.; Pedro, J. R.; Vila, C. *Org. Lett.* **2007**, *9*, 2601. (c) Yang, H.; Hong, Y. T.; Kim, S. *Org. Lett.* **2007**, *9*, 2281. (d) Yamazaki, S.; Iwata, Y. *J. Org. Chem.* **2006**, *71*, 739. (e) Evans, D. A.; Fandrick, K. R.; Song, H. J. *J. Am. Chem. Soc.* **2005**, *127*, 8942. (f) Bandini, M.; Fagioli, M.; Garavelli, M.; Melloni, A.; Trigari, V.; Umani-Ronchi, A. *J. Org. Chem.* **2004**, *69*, 7511. (g) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154. (h) Bandini, M.; Fagioli, M.; Melchiorre, P.; Melloni, A.; Umani-Ronchi, A. *Tetrahedron Lett.* **2003**, *44*, 5843. (i) Jorgensen, K. A. E. *Synthesis* **2003**, 1117. (j) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 160. (k) Chen, W.; Du, W.; Yue, L.; Li, R.; Wu, Y.; Ding, L. S.; Chen, Y. C. *Org. Biomol. Chem.* **2007**, *5*, 816. (l) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (m) Li, D. P.; Guo, Y. C.; Ding, Y.; Xiao, W. J. *Chem. Commun.* **2006**, 799. (n) Zhou, W.; Xu, L.-W.; Li, L.; Yang, L.; Xia, C.-G. *Eur. J. Org. Chem.* **2006**, 5225. (o) Li, C. F.; Liu, H.; Liao, J.; Cao, Y. J.; Liu, X. P.; Xiao, W. J. *Org. Lett.* **2007**, *9*, 1847. (p) Angeli, M.; Bandini, M.; Garelli, A.; Piccinelli, F.; Tommasi, S.; Umani-Ronchi, A. *Org. Biomol. Chem.* **2006**, *4*, 3291. (q) Rueping, M.; Nachtsheim, B. J.; Moreth, S. A.; Bolte, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 593.

(11) For a recent review covering examples of intramolecular indole Friedel−Crafts alkylations, see: Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527.

(12) (a) Mohammadpoor-Baltork, I.; Memarian, H. R.; Khosropour, A. R.; Nikoofar, K. *Heterocycles* **2006**, *68*, 1837. (b) Nayak, S. K. *Synth. Commun.* **2006**, *36*, 1307. (c) Zhan, Z. P.; Lang, K. *Synlett* **2005**, 1551. (d) Zhan, Z. P.; Yang, R. F.; Lang, K. *Tetrahedron Lett.* **2005**, *46*, 3859. (e) Reddy, A. V.; Ravinder, K.; Goud, T. V.; Krishnaiah, P.; Raju, T. V.; Venkateswarlu, Y. *Tetrahedron Lett.* **2003**, *44*, 6257. (f) Bandini, M.; Cozzi, P. G.; Giacomini, M.; Melchiorre, P.; Selva, S.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 3700.

(13) Arcadi, A.; Bianchi, G.; Chiarini, M.; D'Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944.

(14) Ketone **2a** was prepared through treatment of cinnamic acid Weinreb amide with propenylmagnesium bromide. See Supporting Information for full details.

(15) Sieber, J. D.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 2214.

(16) The regiochemistry of **4a** was determined by NMR correlation experiments.

(17) The results of this study were first presented by poster at the BOSS XI conference, Gent, Belgium, July 13−18, 2008.

(18) Amere, M.; Blanchet, J.; Lasne, M.-C.; Rouden, J. *Tetrahedron Lett.* **2008**, *49*, 2541.

(19) Rueping, M.; Ieawsuwan, W.; Antonchick, A. P.; Nachtsheim, B. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 2097.

(20) No Nazarov cyclopentenone product is observed on treating divinylketone **2** with 5% catalyst **6** in MeCN at room temperature for 60 h.

(21) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119.

(22) England, D. B.; Kuss, T. D. O.; Keddy, R. G.; Kerr, M. A. *J. Org. Chem.* **2001**, *66*, 4704.

(23) Liu, K. G.; Robichaud, A. J.; Lo, J. R.; Mattes, J. F.; Cai, Y. X. *Org. Lett.* **2006**, *8*, 5769.

(24) The possibility of a direct Friedel−Crafts cyclization at indole C-2 exists in the absence of observing the spirocycle **II**. This mechanistic matter is the focus of ongoing studies.