ORGANIC LETTERS

2005
Vol. 7, No. 22
5063−5065

# $Sc(OTf)_3$-Catalyzed Indolylation of 1,2-Allenic Ketones: Controlled Highly Selective Synthesis of β-Indolyl-α,β-unsaturetated (*E*)-Enones and β,β-Bisindolyl Ketones

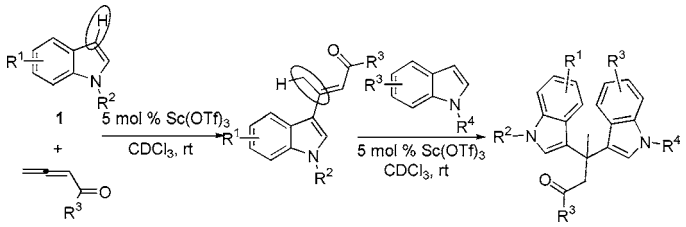
**Shengming Ma* and Shichao Yu**

*State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China*

*masm@mail.sioc.ac.cn*

**Received August 29, 2005**

## ABSTRACT




**A novel highly stereoselctive synthesis of β-indolyl-α,β-unsaturated (*E*)-enones by the hydroindolylation of the β,γ-C═C bond of 1,2-allenic ketones in the presence of 5 mol % $Sc(OTf)_3$ was developed. β,β-Bisindolyl ketones were prepared by using 2.5 equiv of indoles. A stepwise protocol for introducing different indoles was also established.**

Indoles are key structural units in many natural products and important pharmaceuticals.[1] Recently much attention has been paid to the synthesis of bisindole derivatives due to potent antitumor bioactivity.[2,3] Thus, development of efficient methodology for the synthesis of new indole derivatives has been attracting the interest of many synthetic chemists.[4] In this paper, we wish to report our recent results by applying 1,2-allenic ketones[5,6] as the receptor, providing an efficient method for the synthesis of mono-indole derivatives via the highly stereoselective (*E*)-hydroindolylation of the relatively electron-rich carbon−carbon bond of 1,2-allenic ketones, which may be followed by the second addition of indole to afford bis-indolyl derivatives with a very broad structural diversity.

Our initial investigation focused on the use of triflate salts[7] as the catalyst to catalyze the conjugate addition of indole

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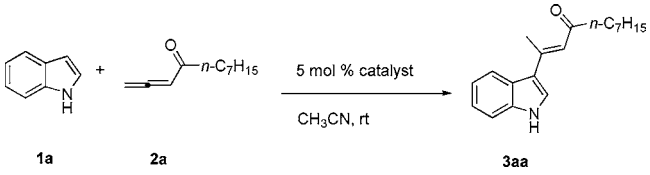
10.1021/ol052073z CCC: $30.25 
**Published on Web 10/06/2005**

(**1a**) with undeca-1,2-dien-4-one (**2a**) in acetonitrile. The data collected in Table 1 indicated that although in the presence

**Table 1.** Optimization of Reaction Conditions[a]




1a 2a 3aa

| | | | 3aa | |
|---|---|---|---|---|
| entry | catalyst | time (h) | yield (%) | *E*/*Z*[b] |
| 1 | $Mg(OTf)_2$ | 12 | NR | |
| 2 | $Yb(OTf)_3$ | 12 | NR | |
| 3 | $Sn(OTf)_2$ | 12 | 27 | >99/1 |
| 4 | $Cu(OTf)_2$ | 1.5 | 68 | 91/9[b] |
| 5[c] | $Sc(OTf)_3$ | 1.5 | 73 | >99/1 |

[a] The reaction was conducted by stirring a mixture of indole (0.2 mmol), 1,2-allenic ketone (0.3 mmol), and 5 mol % of $Sc(OTf)_3$ in $CH_3CN$ (2 mL) at room temperature for the time specified in the table. [b] The *E*/*Z* ratio of **3aa** was determined by $^1H$ NMR analysis. [c] The ratio of **1a** to **2a** is 1 to 3.

of 5 mol % $Mg(OTf)_2$ or 5 mol % $Yb(OTf)_3$ the monoindolylation reaction did not occur to significant extents within 12 h (Table 1, entries 1 and 2), 5 mol % of $Sn(OTf)_2$ gave the product **3aa** in low yield (Table 1, entry 3). Further screening led to the observation that 5 mol % $Cu(OTf)_2$ afforded **3aa** in 65% yield within 1.5 h. However, the *E*/*Z* ratio is poor (Table 1, entry 4). Further screening demonstrated that 5 mol % $Sc(OTf)_3$[8] afforded **3aa** in 75% yield with an *E*/*Z* ratio as high as >99/1 (Table 1, entry 5). The stereoselectivity was determined by $^1H-^1H$ NOESY spectra analysis. Thus, in the following cases the highly stereoselective monoindolylation reaction was conducted at room temperature in acetonitrile using 5 mol % $Sc(OTf)_3$ as the catalyst.

Similarly, various indoles such as 7-methyl-1*H*-indole, 2-methyl-1*H*-indole, and 1,2-dimethyl-1*H*-indole reacted with different 1,2-allenic ketones to afford the desired adducts in good yields (Table 2). In all cases, the reactions proceeded smoothly at ambient temperature with excellent (*E*)-stereoselectivity (>99/1).

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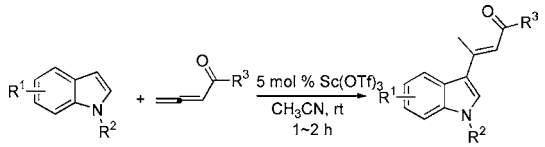
**Table 2.** $Sc(OTf)_3$-Catalyzed Synthesis of $\beta$-Indolyl-$\alpha,\beta$-unsaturated (*E*)-Enones[a]



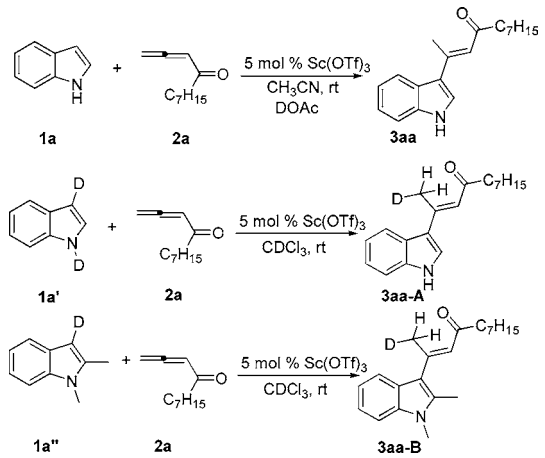

1 2 3

| | indole | | 1,2-allenic ketone | | 3 | |
|---|---|---|---|---|---|---|
| entry | $R^1$ | $R^2$ | $R^3$ | time (h) | yield (%) | *E*/*Z*[b] |
| 1 | 7-Me | H (**1b**) | *n*-$C_7H_{15}$ (**2a**) | 1 | 81 (**3ba**) | >99/1 |
| 2 | 2-Me | H (**1c**) | *n*-$C_7H_{15}$ (**2a**) | 1 | 76 (**3ca**) | >99/1 |
| 3 | 2-Me | H (**1c**) | *n*-$C_8H_{17}$ (**2b**) | 2 | 82 (**3cb**) | >99/1 |
| 4 | 2-Me | H (**1c**) | *n*-$C_6H_{13}$ (**2c**) | 2 | 77 (**3cc**) | >99/1 |
| 5 | 2-Me | H (**1c**) | *n*-$C_4H_9$ (**2d**) | 2 | 74 (**3cd**) | >99/1 |
| 6 | 2-Me | H (**1c**) | Bn (**2e**) | 2 | 80 (**3ce**) | >99/1 |
| 7 | 2-Me | Me (**1d**) | *n*-$C_7H_{15}$ (**2a**) | 1.5 | 73 (**3da**) | >99/1 |

[a] The reaction was conducted by stirring a mixture of indole (0.5 mmol), 1,2-allenic ketone (0.75 mmol), and 5 mol % of $Sc(OTf)_3$ in $CH_3CN$ (2 mL) at room temperature for the time specified in the table. [b] The *E*/*Z* ratio of **3** was determined by $^1H$ NMR analysis.

The $\beta$-indolyl-$\alpha,\beta$-unsaturated (*E*)-enone products may be formed either by isomerization of initially formed $\beta$-indolyl-$\beta,\gamma$-unsaturated (*E*)-enones or by the direct hydroindolylation of the terminal $\beta,\gamma$-C═C bond of allenic ketones. To elucidate the mechanism, the following deuterium labeling experiments were conducted (Scheme 1). When the reaction

**Scheme 1**



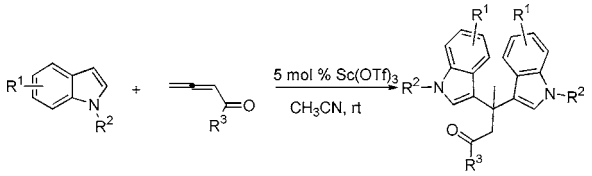

1a 2a 3aa
1a' 2a 3aa-A
1a" 2a 3aa-B

of indole **1a** with undeca-1,2-diene-4-one **2a** was carried out in the presence of DOAc, only nondeuterated product **3aa** was formed, which hints that the transferring of proton from indole is very fast. However, when deuterium-labeled indole **1a′** (92% deuteration at 3-position based on $^1H$ NMR spectra) and **1a″** (85% deuteration at 3-position based on $^1H$ NMR spectra)[9] were used, the monodeuterated product **3aa-A** (90% deuteration based on $^1H$ NMR spectra) and **3aa-B** (85% deuteration based on $^1H$ NMR spectra) were formed sepa-

rately when the reaction was conducted in $CDCl_3$, which indicates that, instead of a carbon−carbon double bond migration mechanism,[10] uniquely the products **3** may be formed by the hydroindolylation of the terminal carbon−carbon double bond of allenic ketones, at least in $CDCl_3$, although the real mechanism remains to be investigated.

Next we examined the double indolylation of 1,2-allenic ketones using the previous catalytic system simply by varying the ratio from 1:1.5 to 2.5:1 and with prolonged reaction time. As shown in Table 3, a variety of differently substituted

**Table 3.** $Sc(OTf)_3$-Catalyzed Synthesis of $\beta,\beta$-Bis(indolyl) Ketones[a]




1 2 4

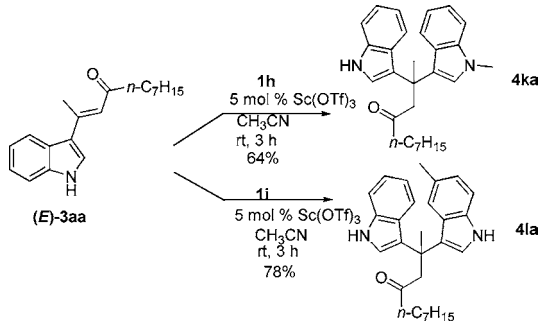
| | indole | | 1,2-allenic ketone | time | yield of |
|---|---|---|---|---|---|
| entry | $R^1$ | $R^2$ | $R^3$ | (h) | **4** (%) |
| 1 | H | H (**1a**) | *n*-$C_7H_{15}$ (**2a**) | 2 | 60 (**4aa**) |
| 2 | 5-MeO | H (**1e**) | *n*-$C_7H_{15}$ (**2a**) | 1.5 | 53 (**4ea**) |
| 3 | 5-Br | H (**1f**) | *n*-$C_7H_{15}$ (**2a**) | 2 | 56 (**4fa**) |
| 4 | 5-BnO | H (**1g**) | *n*-$C_7H_{15}$ (**2a**) | 2 | 51 (**4ga**) |
| 5 | H | Me (**1h**) | *n*-$C_7H_{15}$ (**2a**) | 2 | 61 (**4ha**) |
| 6 | H | H (**1a**) | *n*-$C_6H_{13}$ (**2c**) | 2 | 63 (**4ac**) |
| 7 | H | H (**1a**) | Bn (**2e**) | 12 | 78 (**4ae**) |

[a] The reaction was conducted by stirring a mixture of indole (1.25 mmol), 1,2-allenic ketone (0.5 mmol), and 5 mol % of $Sc(OTf)_3$ in $CH_3CN$ (2 mL) at room temperature for the time specified in the table.

indoles **1** underwent smooth double indolylations with 1,2-allenic ketones **2** to afford $\beta,\beta$-bisindolyl ketones **4** in moderate yields.

Furthermore, we have also demonstrated the stepwise double addition of indoles with 1,2-allenic ketone leading to the mixed $\beta,\beta$-bisindolyl ketones (Scheme 2). Thus, when

**Scheme 2**




(***E***)-**3aa** was subjected to 5 mol % of $Sc(OTf)_3$, and 1-methyl-1*H*-indole **1h** or 5-methyl-1*H*-indole **1i** separately, 64% and 78% of the mixed $\beta,\beta$-bisindolyl ketones **4ka** and **4la** were isolated, respectively.

In summary, we have developed a simple and efficient procedure for the highly stereoselective preparation of monoindole derivatives, i.e., $\beta$-indolyl $\alpha,\beta$-unsaturated (*E*)-enones, through the highly stereoselective (*E*)-hydroindolylation reactions of the $\beta,\gamma$-C═C bond of 1,2-allenic ketones in the presence of 5 mol % $Sc(OTf)_3$. Double indolylation of 1,2-allenic ketones afforded $\beta,\beta$-bisindolyl ketones. A stepwise protocol for introducing different indoles was also established. Because of the potentials of these compounds, this methodology will be useful in indole-related science. Further study in this area is being carried out in our laboratory.

**Acknowledgment.** Financial support from the National Natural Science Foundation of China and the Major State Basic Research Development Program (Grant G2000077500) and Shanghai Municipal Community of Science and Technology are greatly appreciated.

**Supporting Information Available:** Analytical data for compounds **3** and **4** and $^1H$ NMR and $^{13}C$ NMR spectra of those compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052073Z

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