Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron Letters 47 (2006) 487–492

Tetrahedron Letters

CAN and iodine-catalyzed reaction of indole or 1-methylindole with α,β-unsaturated ketone or aldehyde

Shengkai Ko, Chunchi Lin, Zhijay Tu, Yi-Fu Wang, Chieh-Chieh Wang and Ching-Fa Yao*

Department of Chemistry, National Taiwan Normal University 88, Sec. 4, Tingchow Road, Taipei 116, Taiwan, ROC

Received 13 October 2005; revised 9 November 2005; accepted 11 November 2005
Available online 6 December 2005

Abstract—CAN (cerium ammonium nitrate) and iodine can catalyze the reactions of indole or 1-methylindole with α,β-unsaturated ketone or aldehyde in DMSO/H_2O (5:1) or ether solution at room temperature to obtain moderate to high yields of different products.

Indole and their derivatives are well known as biologically active substances.[1] Organic chemists are paying attention to synthesize different kinds of indole compounds, including bis(indolyl)methanes,[2] β-indolylnitro,[3] β-indolylketone,[4] and β-indolylalcohol[5] compounds, etc. It has been reported in the literature that 1 equiv of *trans*-cinnamaldehyde can react with 2 equiv of indole to yield bis(indolyl)methane in high yield[2g,i,j,o,p] or 1 equiv of 2-cyclohexen-1-one can react with 1 equiv of indole to obtain high yields of β-indolylcyclohexanone.[4g] However, our recent study about the same reactions found that different results were observed and trisindolylalkane was also isolated when *trans*-cinnamaldehyde or 2-cyclohexen-1-one reacted with the same amount of indole, which was reported in the literature under the same conditions. Until now, only two literatures have been reported about the preparation of the above compounds.[6] For example, it has also been reported by Harrington and Keer that trisindolylcyclohexane was given in 6% yield under ultra high pressure condition[6a] and Shi et al. have also reported that these compounds can be prepared by using metal triflate as catalyst.[6b] However, both methods have some disadvantages, such as harsh reaction condition (13 kbar), long reaction time (1–3 days), and the use of expensive metal catalysts.[6]

Based on these observations and reports, we wish to improve the same reactions to obtain high yields of different products as described above using other proper reagents under simple conditions. It has been reported that cerium ammonium nitrate (CAN) is well known and has been used as a oxidation reagent or catalyst in many organic reactions recently.[4b,7] The advantages of this catalyst are cheap, environmentally benign, and commercially available. To observe the catalytic effect of CAN, 1 equiv of 2-cyclohexen-1-one **1a** was used to react with 4 equiv of indole **2a** in the presence of different amounts of CAN in DMSO/H_2O (5:1) solution at room temperature (Eq. 1 and Table 1). First, neither 1,4-addition product **4aa** nor 1,4- and then 1,2-addition product **5aa** was observed when the reaction was performed in the absence of any reagent for 20 h (entry 1). However, the reaction was improved dramatically and 14% of **4aa** and 85% of **5aa** were generated when the same reaction was carried out in the presence of 0.1 equiv of CAN for 12 h (entry 2). Surprisingly, only 93% of **5aa** was obtained when the same reaction was carried out for 20 h (entry 3).

To improve the optimized yield of **5aa**, the amount of CAN was increased to 0.3 equiv and, as expected, the yield of **4aa** was decreased to 8% only but **5aa** was increased to 92% for 6 h (entry 4). Fortunately, only 99% of the single product **5aa** was generated when the same reaction was carried out for 13 h (entry 5).[9] Although the increase of CAN to 0.5 equiv can accelerate the reaction dramatically, however, the yields of **4aa** and **5aa** were decreased to 11% and 77% for 2 h and

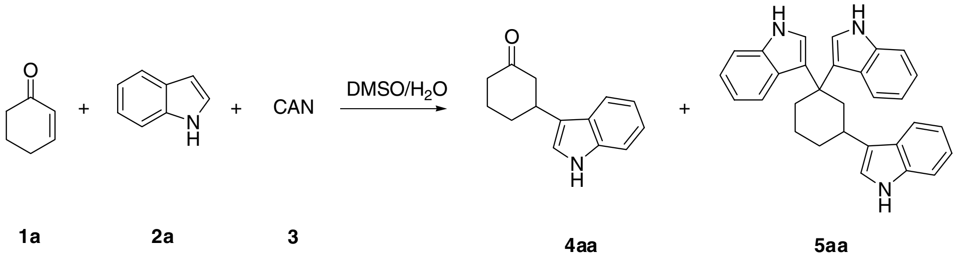
---

Keywords: Catalyzed; CAN; Indole; Iodine; Trisindolylalkane.

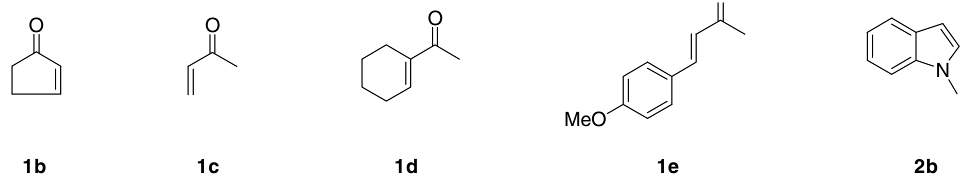
* Corresponding author. Tel./fax: +886 2 29309092; e-mail: cheyaocf@scc.ntnu.edu.tw

0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.11.058

Table 1. Reaction of α,β-unsaturated ketone **1** and indole **2a** in the presence of cerium ammonium nitrate



(1)



Entry	**1** (1 equiv)	**2** (4 equiv)	**3** (equiv)	Time (h)	$\mathbf{4}^{a}$ (%)	$\mathbf{5}^{a}$ (%)
1	**1a**	**2a**	—	20	**4aa** (—)	**5aa** (—)
2	**1a**	**2a**	0.1	12	**4aa** (14)	**5aa** (85)
3	**1a**	**2a**	0.1	20	**4aa** (—)	**5aa** (93)
4	**1a**	**2a**	0.3	6	**4aa** (8)	**5aa** (92)
5	**1a**	**2a**	0.3	13	**4aa** (—)	**5aa** (99)
6	**1a**	**2a**	0.5	2	**4aa** (11)	**5aa** (77)
7	**1a**	**2a**	0.5	4	**4aa** (—)	**5aa** (85)
8	**1b**	**2a**	0.3	1	**4ba** (99)	**5ba** (—)
9	**1c**	**2a**	0.3	1/6	**4ca** (90)	**5ca** (—)
10	**1d**	**2a**	0.3	72	**4da** (62)	**5da** (—)
11	**1e**	**2a**	0.3	4	**4ea** (60)	**5ea** (—)

[a] NMR yields.

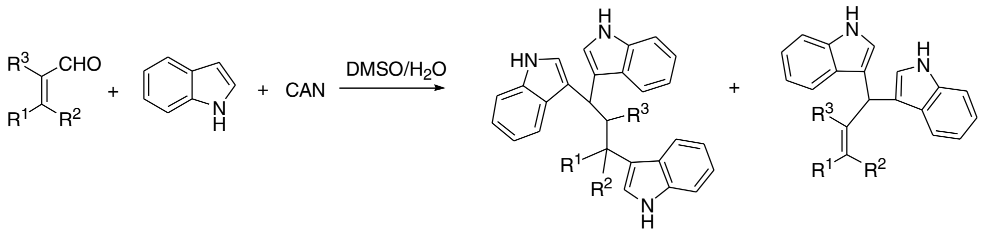
only 85% of **5aa** was observed for 4 h (entries 6 and 7). Possible explanation is that the starting material or product may be destroyed during reaction if the exothermic reactions occur too fast when excess amount of CAN was added. According to the above results we can conclude that CAN actually can catalyze the reaction efficiently to obtain high yields of **5aa** and the best amount of CAN to be used in this reaction is 0.3 equiv. In addition to **1a**, similar reactions were also conducted by using **1b**–**e**, respectively, under similar conditions and the results were shown as entries of 8–11.

Based on the data of Table 1, we found different and interesting results were observed between **1a** and **1b**–**e**. Only **1a** can undergo the 1,4-addition to yield **4aa** first and then the intermediate **4aa** can react with indole **2a** to undergo 1,2-addition to obtain **5aa** finally. However, **1b**–**e** only can undergo 1,4-addition to yield medium to high yields of **4ba**–**ea**, respectively. About the generation of the different products from **1a** and **1b**, we proposed that the torsional strain effect plays an important and major role to the product or intermediate during reaction. The addition of the first equivalent of **2a** to **1a** or to **1b** forms 3-indolylcyclohexanone **4aa** or 3-indolylcyclopentanone **4ba**. When further reaction occurs, the conversion of the sp^2 carbon atom of the carbonyl functional group of **4aa** to a sp^3 of six-membered ring of **5aa** leads to a completely staggered (chair) arrangement and reduces the torsional strain. On the contrary, the torsional strain is increased because of the increase in the number of eclipsing interaction which was generated from the further reaction product of **5ba**.[11]

Next, reactions of α,β-unsaturated aldehyde **6** and **2a** were investigated and interesting results were shown as Eq. 2 and Table 2. For example, when crotonaldehyde **6a** was used to react with **2a** in the presence of 0.1 equiv of CAN at room temperature for 1 h, only 99% of **7aa** was generated but no bis(indolyl)methane **8aa** was observed when the mixture was checked by NMR or GCMS (entry 1). However, not only 64% of **7ba** but also 29% of **8ba** was also generated when β-methylcrotonaldehyde **6b** was used (entry 2). Compared to **6a** or **6b**, the results of the use of **6c** or **6d** were slightly different and only 32% of **7ca** and 66% of **8ca** or 20% of **7da** and 80% of **8da** were generated (entries 3 and 4). We were surprised to find that only 99% of **8ea** was generated when **6e** was used (entry 5).

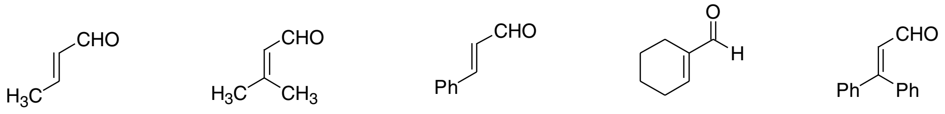
Based on Tables 1 and 2, we can conclude that the use of α,β-unsaturated ketone **1** can generate **4** and/or **5** and the use of α,β-unsaturated aldehyde **6** yield **7** and/or **8**. The reaction mechanisms for the generation of **7** and **5** are all proposed to proceed through the 1,4-addition first and then to undergo the 1,2-addition but **8** is proposed to proceed through the 1,2-addition only which is different from the generation of **4** by proceeding through the 1,4-addition only. These different results possibly could be explained by the different steric hindrances between aldehyde and ketone. Aldehyde is

Table 2. CAN-catalyzed reaction of α,β-unsaturated aldehyde **6** with indole **2a**



6 **2a** **3** **7** **8**

(2)



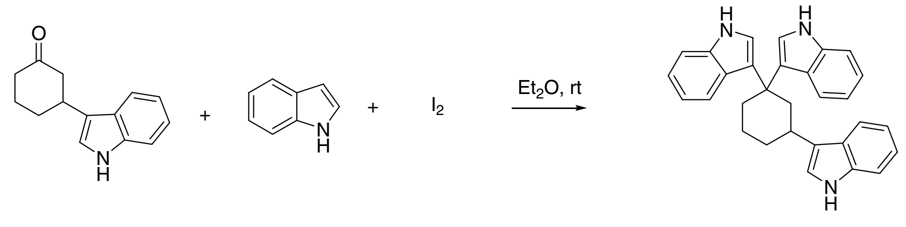
6a **6b** **6c** **6d** **6e**

Entry	**1**	**3** (equiv)	Time (h or min)	**7**[a] (%)	**8**[a] (%)
1	**6a**	0.1	1 h	**7aa** (99)	**8aa** (—)
2	**6b**	0.1	10 min	**7ba** (64)	**8ba** (29)
3	**6c**	0.1	1 h	**7ca** (32)	**8ca** (66)
4	**6d**	0.1	5 min	**7da** (20)	**8da** (80)
5	**6e**	0.1	15 min	**7ea** (—)	**8ea** (99)

[a] NMR yields.

always more reactive than ketone because the formyl group is much smaller than the acyl group. This assumption could also be proved by the fact that only 0.1 equiv of CAN is required for the aldehyde but at least 0.3 equiv of CAN is required for ketone under similar condition. In addition to the above description, the generation of the different products **7** and **8** from aldehydes such as **7aa** from **6a** and **8ea** from **6e** could also be explained by the presence of the different steric effects which were generated from the presence of the different groups at α and/or β carbon in these two substrates.

Because indole derivatives are important biologically active compounds which have profound medical applications, development of a reaction that uses catalytic amount of mild toxic and readily available iodine should greatly contribute to the creation of environmentally benign processes. It has been reported by Banik et al. that iodine can catalyze the Michael reaction of indole with α,β-unsaturated ketone to undergo conjugate addition to offer high yields of **4** under solvent-free condition efficiently[4g] and by Shi et al. that both **4** and **5** were or only **5** was generated when similar reactions were carried out by using $Yb(OTf)_3$ or $Zr(OTf)_4$ as catalyst.[6b]



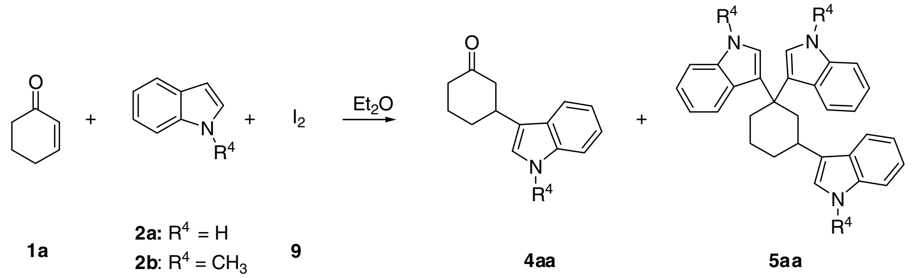
4aa **2a** **9** **5aa**

(4)

Recently, the use of molecular iodine has received considerable attention as an inexpensive, nontoxic, and readily available catalyst for various organic transformations to afford the corresponding products in excellent yields with high selectivity. The mild Lewis acidity associated with iodine enhanced its usage in organic synthesis to realize several organic transformations using stoichiometric levels to catalytic amounts. Owing to numerous advantages associated with this eco-friendly element, iodine has been explored as a powerful catalyst for various organic transformations.[2i,4c,g,8]

Based on the above study and those viewpoints of iodine, we then changed CAN to iodine as a catalyst. Similar to the results of Table 1, both **4aa** and **5aa** or only **5aa** were observed when 1 equiv of **1a** reacted with 4 equiv of **2a** in the presence of different amounts of I_2 in 1 mL of diethyl ether (Et_2O) solution (Eq. 3 and Table 3). When only 0.15 equiv of I_2 was used, not only **4aa** but also **5aa** was isolated (entry 1). The most significant and interesting results were that only 93% or 99% of **5aa** was obtained when 0.3 or 0.5 equiv of **9** I_2 (iodine) was used for 2 or 1 h under similar conditions (entries 3 and

Table 3. Reaction of α,β-unsaturated ketone **1** and indole **2a/2b** in the presence of molecular iodine



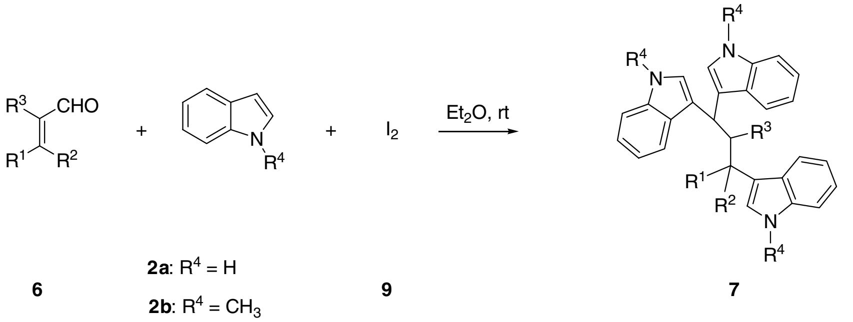
(3)

Entry	**1** (1 equiv)	**2** (4 equiv)	I_2 (equiv)	Time (h)	**4**[a] (%)	**5**[a] (%)
1	**1a**	**2a**	0.15	1.5	**4aa** (28)	**5aa** (49)
2	**1a**	**2a**	0.3	1	**4aa** (5)	**5aa** (68)
3	**1a**	**2a**	0.3	2	**4aa** (—)	**5aa** (93)
4	**1a**	**2a**	0.5	1	**4aa** (—)	**5aa** (99)
5	**1a**	**2a**	1	1	**4aa** (—)	**5aa** (62)
6	**1a**	**2b**	0.3	5/12	**4ab** (—)	**5ab** (99)
7	**1b**	**2a**	0.3	2/3	**4ba** (92)	**5ba** (—)
8	**1c**	**2a**	0.3	1/6	**4ca** (91)	**5ca** (—)
9	**1d**	**2a**	0.3	72	**4da** (43)	**5da** (—)
10	**1e**	**2a**	0.3	5	**4ea** (79)	**5ea** (—)

[a] NMR yields.

4).[10] Unfortunately, only 62% of **5aa** was observed when I_2 was increased to 1 equiv (entry 5). These results indicate that the use of 0.3 equiv of I_2 is good enough for this reaction. Based on the above condition, similar reactions were conducted by using **1a–d** and **2a** or **2b** to obtain different yields of **4** and the results were shown as entries of 6–10. Compared to the results of Table 1 by using CAN, most of the substrates except **1d** could produce moderate to high yields of **4** when the reaction was conducted in the presence of I_2. To substrate **1d**, only 49% of **4da** was generated compared to the use of CAN whose yield was 62%. The only difference is that all reactions were conducted in DMSO–H_2O solution by using CAN and in ether solution by using I_2.

Table 4. Reaction of α,β-unsaturated aldehyde **6** and indole **2** in the presence of molecular iodine



(5)

Entry	**6**	**2**	I_2 (equiv)	Time	**7**[a] (%)
1	**6a**	**2a**	0.1	15 min	**7aa** (95)
2	**6a**	**2b**	0.1	10 min	**7ab** (86)
3	**6b**	**2a**	0.1	10 min	**7ba** (99)
4	**6b**	**2b**	0.1	10 min	**7bb** (76)
5	**6c**	**2a**	0.1	3 h	**7ca** (93)
6	**6c**	**2b**	0.1	30 min	**7cb** (95)
7	**6d**	**2a**	0.1	5 min	**7da** (28)[b]
8	**6e**	**2a**	0.1	10 min	**7ea** (—)[c]
9	R^1 = *p*-$MeOC_6H_4$, R_2 = H, R_3 = H **6f**	**2a**	0.1	10 min	**7fa** (79)
10		**2b**	0.1	10 min	**7fb** (82)
11	R^1 = *o*-$MeOC_6H_4$, R_2 = H, R_3 = H **6g**	**2a**	0.1	10 min	**7ga** (87)
12		**2b**	0.1	10 min	**7gb** (95)

[a] NMR yield.

[b] 46% of bis(indolyl)methane **8da** was also generated.

[c] 99% of bis(indolyl)methane **8ea** was generated.

About the generation of **4aa** and **5aa**, the mechanism was proposed to proceed through the 1,4-addition first to obtain **4aa** and then **4aa** can react with **2a** continuously to undergo the 1,2-addition to generate **5aa**. In order to prove this assumption, 1 equiv of **4aa** was used to react with 3 equiv of **2a** in the presence of 0.3 equiv of iodine in 1 mL of ether for 1 h and 87% **5aa** was isolated (Eq. 4). This result is good enough to explain why both **4** and **5** were generated when the same reaction was quenched or workup for shorter reaction time and only **5** was generated for longer reaction time.

Based on Tables 1–3, similar reactions of **6** and **2** in the presence 0.1 equiv of I_2 were also studied and the results were shown as Eq. 5 and Table 4. Compared to the results of Table 2, slight results were observed. To substrates **6a**–**c** and **6f**–**g**, only products **7aa**–**ca** and **7fa**–**ga** were generated but no products **8** were observed. Possible explanation for the different results may be assumed due to that CAN belongs to hard acid but I_2 belongs to soft acid under similar reactions, so that most of the starting material **6a**–**c** and **6f**–**g** can undergo the 1,4-addition and then 1,2-addition predominately in the presence of I_2. However, to **6d**, **8da** is the major products and to **6e**, **8ea** is the only product and both products were all proposed to be generated from the 1,2-addition only and these results were also similar to the results of the use of CAN. These special results can also be explained by the steric hinderance which was generated from the presence of different groups at β-carbon of aldehyde. This is the reason why these two substrates prefer to proceed thorough 1,2-addition to undergo the 1,4-addition and then 1,2-addition.

In conclusion, we have observed different results compared to the literature report by using CAN or iodine as catalyst when **1** or **6** with excess amount of indole or 1-methylindole. The generation of the different products can be explained by the presence of the different steric hindrances of starting material and the different Lewis acidities of the catalyst. The advantages of the use of CAN and iodine as catalysts for the reactions are efficiency, easy to handle, and under mild condition and these catalyst are also cheap and commercially available.

Acknowledgements

Financial support of this work by the National Science Council of the Republic of China and National Taiwan Normal University (ORD93-C) is gratefully acknowledged.

References and notes

1. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.
2. (a) Bergman, J.; Hoegberg, S.; Lindstroem, J. *Tetrahedron* **1970**, *26*, 3347; (b) Banerjee, A.; Mukhopadhyay, A. K. *Indian J. Chem.* **1982**, *21B*, 239; (c) Chen, D.; Yu, L.; Wang, P. G. *Tetrahedron Lett.* **1996**, *37*, 4467; (d) Denis, J.; Mauger, H.; Vallee, Y. *Tetrahedron Lett.* **1997**, *38*, 8518; (e) Babu, G.; Sridhar, N.; Perumal, P. T. *Synth. Commun.* **2000**, *30*, 1609; (f) Chalaye-Mauger, H.; Denis, J.; Averbuch-Pouchot, M.; Vallee, Y. *Tetrahedron* **2000**, *56*, 791; (g) Yadav, J. S.; Readdy, B. V. S.; Murthy, Ch. V. S. R.; Kumar, M.; Madan, Ch. *Synthesis* **2001**, 783; (h) Chakrabarty, M.; Ghosh, N.; Basak, R.; Harigaya, Y. *Tetrahedron Lett.* **2002**, *43*, 4075; (i) Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett.* **2003**, *44*, 1959; (j) Yadav, J. S.; Reddy, B. V. S.; Sunitha, S. *Adv. Synth. Catal.* **2003**, 349; (k) Ji, S.-J.; Zhou, M.-F.; Gu, D.-G.; Wang, S.-Y.; Loh, T.-P. *Synlett.* **2003**, 2077; (l) Ji, S.-J.; Zhou, M.-F.; Gu, D.-G.; Wang, S.-Y.; Loh, T.-P. *Eur. J. Org. Chem.* **2004**, 1584; (m) Bartoli, G.; Bosco, M.; Foglia, G.; Giuliani, A.; Marcantoni, E.; Sambri, L. *Synthesis* **2004**, *6*, 895; (n) Mi, X.; Luo, S.; He, J.; Cheng, J.-P. *Tetrahedron Lett.* **2004**, *45*, 4567; (o) Sharma, G. V. M.; Reddy, J. J.; Lakshmi, P. S.; Krishna, P. R. *Tetrahedron Lett.* **2004**, *45*, 7729; (p) Wang, L.; Han, J.; Tian, H.; Sheng, J.; Fan, Z.; Tang, X. *Synlett* **2005**, 337.
3. (a) Noland, W. E.; Hartman, P. J. *J. Chem. Soc.* **1954**, *76*, 3227; (b) Noland, W. E.; Christensen, G. M.; Sauer, G. L.; Dutton, G. G. S. *J. Chem. Soc.* **1955**, *77*, 456; (c) Lloyd, D. H.; Nichols, D. E. *J. Org. Chem.* **1986**, *51*, 4294; (d) Chakrabarty, M.; Basak, R.; Ghosh, N. *Tetrahedron Lett.* **2001**, *41*, 3913; (e) Komoto, I.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 1115; (f) Chakrabarty, M.; Basak, R.; Ghosh, N.; Harigaya, Y. *Tetrahedron* **2004**, *60*, 1941.
4. (a) Yadav, J. S.; Abraham, S.; Reddy, B. V. S.; Sabitha, G. *Synthesis* **2001**, 2165; (b) Ji, S.-J. *Synlett.* **2003**, 2074; (c) Wang, S.-Y.; Ji, S.-J.; Loh, T.-P. *Synlett* **2003**, 2377; (d) Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115; (e) Srivastava, N.; Banik, B. K. *J. Org. Chem.* **2003**, *68*, 2109; (f) Arcadi, A.; Bianchi, G.; Chiarini, M.; D' Anniballe, G.; Marinelli, F. *Synlett* **2004**, 944; (g) Banik, B. K.; Fernandez, M.; Alvarez, C. *Tetrahedron Lett.* **2005**, *46*, 2479.
5. (a) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *J. Org. Chem.* **2002**, *67*, 5386; (b) Bandini, M.; Fagioli, M.; Melloni, A.; Umani-Ronchi, A. *Adv. Synth. Catal.* **2004**, 573; (c) Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 84.
6. (a) Harrington, P.; Keer, M. A. *Can. J. Chem.* **1998**, *76*, 1256; (b) Shi, M.; Cui, S.-C.; Li, Q.-J. *Tetrahedron* **2004**, *60*, 6679.
7. (a) Hwu, J. R.; King, K. Y. *Curr. Sci.* **2001**, *81*, 1043; (b) Nair, V.; Panicker, S. B.; Nair, L. G.; George, T. G.; Augustine, A. *Synlett.* **2003**, 156; (c) Sommermann, T. *Synlett* **2003**, 834.
8. (a) Kim, K. M.; Ryu, E. K. *Tetrahedron Lett.* **1996**, *37*, 1441; (b) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem.* **2001**, *66*, 7527; (c) Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Tetrahedron Lett.* **2002**, *43*, 879; (d) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett.* **2002**, *43*, 3653; (e) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2002**, *43*, 9703; (f) Das, B.; Banerjee, J.; Ramu, R.; Pal, R.; Ravindranath, N.; Ramesh, C. *Tetrahedron Lett.* **2003**, *44*, 5465; (g) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett.* **2003**, *44*, 6211; (h) Ji, S.-J.; Wang, S.-Y.; Zhang, Y.; Loh, T.-P. *Tetrahedron* **2004**, *60*, 2051; (i) Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* **2004**, *45*, 2951; (j) Phukan, P. *J. Org. Chem.* **2004**, *69*, 4005; (k) Phukan, P. *Tetrahedron Lett.* **2004**, *45*, 4785; (l) Sun, J.; Dong, Y.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem.* **2004**, *69*, 8932; (m) Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett.* **2004**, *45*, 9111; (n) Ke,

B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett.* **2005**, *46*, 1751; (o) Chu, C.-M.; Gao, S.; Sastry, M. N. V.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 4971; (p) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 5771; (q) More, S. V.; Sastry, M. N. V.; Wang, C.-C.; Yao, C.-F. *Tetrahedron Lett.* **2005**, *46*, 6345.

9. A typical experimental procedure for the preparation of **5aa**: A 10 mL of round-bottomed flask was charged with 2-cyclohexen-1-one **1a** (0.096 g, 1.0 mmol), indole **2a** (0.468 g, 4.0 mmol), and CAN (0.164 g, 0.3 mmol) in 1 mL of the polar solvent $DMSO/H_2O$ (5:1). The mixture was then stirred at room temperature until the reaction was completed (6 h, monitored by TLC). The reaction mixture was treated with dilute HCl solution, extracted with ethyl acetate (2 × 5 mL). The solvent was removed under reduced pressure and the residue was purified by column chromatography by using hexane/EA (5:1) to give **4aa** and **5aa**. Compound **4aa**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.75–2.04 (m, 3H), 2.20 (m, 1H), 2.35–2.55 (m, 2H), 2.61 (m, 1H), 2.77 (m, 1H), 3.42 (m, 1H), 6.92 (d, 1H, $J = 2.0$ Hz), 7.08–7.61 (m, 4H), 8.17 (br s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.9, 31.8, 36.0, 41.6, 48.1, 111.4, 119.1, 119.4, 119.6, 120.5, 122.2, 126.2, 136.5, 212.2; HRMS calculated for $C_{14}H_{15}NO$ 213.1154 (M^+), found 213.1148. Compound **5aa**: ^1H NMR (400 MHz, $CDCl_3$): δ 1.50–1.58 (m, 1H), 1.70–1.90 (m, 2H), 2.10–2.34 (m, 3H), 2.90 (m, 1H), 3.10–3.19 (m, 2H), 6.46 (d, 1H, $J = 2.4$ Hz), 6.59 (d, 1H, $J = 2.0$ Hz), 6.80–7.62 (m, 16H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 31.0, 34.0, 36.5, 40.3, 43.8, 111.1, 111.2, 118.5, 118.6, 118.8, 119.3, 119.6, 120.8, 121.0, 121.1, 121.3, 121.7, 121.8, 122.5, 123.3, 126.5, 126.6, 136.2, 137.0; HRMS calculated for $C_{30}H_{27}N_3$ 429.2205 (M^+), found 429.2196.
10. A typical experimental procedure for the preparation of **5aa**: A 10 mL of round-bottomed flask was charged with 2-cyclohexen-1-one **1a** (0.096 g, 1.0 mmol), indole **2a** (0.468 g, 4.0 mmol), and iodine **9** (0.076 g, 0.3 mmol) in 1 mL of diethyl ether. The mixture was then stirred at room temperature for 2 h until the reaction was completed, which can be checked by TLC. The reaction mixture was treated with ice cold saturated $Na_2S_2O_3$ solution, extracted with ethyl acetate (2 × 5 mL). The solvent was removed under reduced pressure and the residue was checked by NMR to indicate the mixture contained 93% of **5aa** and then the mixture was purified by column chromatography by using hexane/EA = 5:1 to give pure **5aa**.

11. (a) Brown, H. C.; Ham, G. *J. Am. Chem. Soc.* **1956**, *78*, 2735; (b) Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, 221; (c) Schneider, H.-J.; Thomas, F. *J. Am. Chem. Soc.* **1980**, *102*, 1424; (d) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry. Part A: Structure and Mechanisms*, 4th ed.; Kluwer Academic/Plenum Publishers: New York, 2000, p 171.