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An expedient synthesis of 3-alkylideneoxindoles by Ti(O^iPr)$_4$/pyridine-mediated Knoevenagel condensation

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ABSTRACT

3-Alkylideneoxindoles have been prepared in excellent yields from oxindole and carbonyl compounds via an in situ generated titanium enolate of oxindole. (*Z*)-3-Alkylideneoxindoles could be synthesized selectively as major products from unsymmetrical ketones.

3-Alkylideneoxindole derivatives have been received much attention due to their diverse biological activities and synthetic applicability.[1,2] For example, 3-alkylideneoxindoles are important synthetic intermediates of natural products such as TMC-95[2a] or Gelsemine,[2b] and numerous biologically interesting spirooxindoles.[2c–i]

The synthesis of 3-alkylideneoxindoles has been carried out most frequently by the Knoevenagel condensation between oxindole and carbonyl compounds catalyzed by secondary amines such as piperidine or pyrrolidine.[3] However, the synthesis of these compounds suffers from low yields of products and/or harsh reaction conditions in some cases.[3b,e,g] The condensation of oxindole and aldehydes usually provided the corresponding 3-(mono-substituted)alkylideneoxindoles in good yields under mild conditions. However, the reactions with ketones suffer from the use of a long reaction time, elevated temperature, and low to moderate yield of product, 3-(disubstituted)alkylidene derivative.[3a,b,e] In addition, thermodynamically more stable *E*-isomer was obtained as a major product with unsymmetrical ketones.[1c,3d] Thus, 3-(disubstituted)alkylideneoxindoles have been prepared most frequently by a metal-catalyzed cyclization of acyclic precursors including *N*-cinnamoylanilines or *N*-arylpropiolamides.[4] Transition metal-catalyzed synthesis of 3-alkylideneoxindoles can afford the *Z*-isomer in some cases.[4g,h,5]

In 2011, Robichaud and Liu have reported Ti(O^iPr)$_4$/pyridine-mediated Knoevenagel condensation between aromatic ketones and cyanoacetamides.[6a] An example of condensation between acetophenone and oxindole has been included, and they obtained the corresponding *Z*-isomer as a major product in good yield although they did not suggest the reason for the selective formation of *Z*-isomer.[6a] The result prompted us to investigate a facile and stereoselective synthesis of 3-alkylideneoxindole derivatives via a titanium-mediated Knoevenagel condensation.[6,7]

At the outset of our experiment, the reaction of oxindole (**1a**) and acetone was examined in the presence of Ti(O^iPr)$_4$ (3.0 equiv) and pyridine (2.0 equiv) in THF at room temperature, as shown in Table 1. The reaction afforded **2a** in high yield (95%) in short time (entry 1). When we reduced the amount of Ti/pyridine (entry 2), the yield of **2a** was not changed. However, the reaction was not completed with lesser amount of Ti/pyridine (entries 3 and 4) even at elevated temperature. Although the yield was satisfactory in the case of acetone, we examined the optimum conditions for three representative carbonyl compounds, benzophenone (entries 5–7), acetophenone (entries 8–11), and benzaldehyde (entries 12–18).

The reaction of sterically hindered benzophenone was not effective even in the presence of an excess amount of Ti/pyridine and a long reaction time (entries 5 and 6), while the reaction at 60 °C afforded the product **2d** in high yield in short time (entry 7). The reaction of acetophenone afforded good yield of **2e** in THF or toluene (entries 8–10), while the use of $TiCl_4$ was not effective (entry 11). It is interesting to note that *Z*-isomer was formed selectively (**2e**-*Z*:**2e**-*E* = 5:1), as compared to the selective formation of *E*-isomer by the amine-catalyzed Knoevenagel condensation method.[1c,3d] The structures of **2e**-*Z* and **2e**-*E* were confirmed by comparison their ^{1}H NMR data with the reported.[4g,6a] The methyl proton of **2e**-*E* appeared downfield (δ = 2.80 ppm) than the *Z*-form (δ = 2.63 ppm) due to deshielding anisotropic effect of the carbonyl

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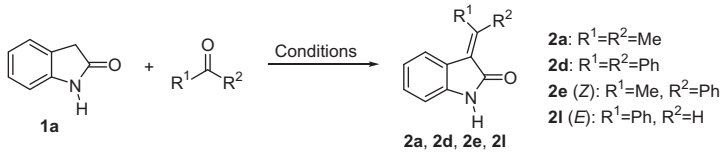
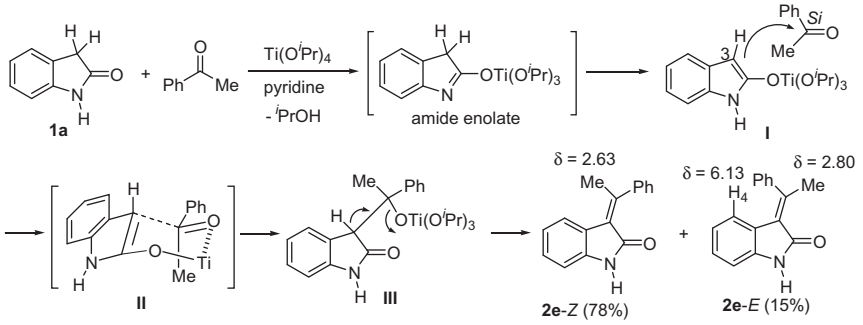
Table 1
Optimization of reaction conditions with oxindole **1a**[a]



Entry	Carbonyls	Conditions[b]	Product[c] (%)
1	Acetone	$Ti(O^iPr)_4$ (3.0), pyridine (2.0), THF, rt, 1 h	**2a**, 95
2	Acetone	$Ti(O^iPr)_4$ (1.5), pyridine (1.0), THF, rt, 1 h	**2a**, 95
3	Acetone	$Ti(O^iPr)_4$ (0.8), pyridine (0.4), THF, rt, 10 h	**2a**, 66[d]
4	Acetone	$Ti(O^iPr)_4$ (0.8), pyridine (0.4), THF, reflux, 10 h	**2a**, 83[d]
5	Benzophenone	$Ti(O^iPr)_4$ (3.0), pyridine (2.0), THF, rt, 24 h	**2d**, 40[d]
6	Benzophenone	$Ti(O^iPr)_4$ (5.0), pyridine (3.5), THF, rt, 20 h	**2d**, 80[d]
7	Benzophenone	$Ti(O^iPr)_4$ (3.0), pyridine (2.0), THF, 60 °C, 5 h	**2d**, 89
8	Acetophenone	$Ti(O^iPr)_4$ (1.5), pyridine (1.0), THF, rt, 5 h	**2e**, 88 (1:5)[d]
9	Acetophenone	$Ti(O^iPr)_4$ (2.0), pyridine (1.5), THF, rt, 5 h	**2e**, 91 (1:5)
10	Acetophenone	$Ti(O^iPr)_4$ (1.5), pyridine (1.0), toluene, rt, 5 h	**2e**, 87 (1:5)[d]
11	Acetophenone	$TiCl_4$ (2.0), pyridine (1.5), THF, rt, 5 h	**2e**, 25[e]
12	Benzaldehyde	$Ti(O^iPr)_4$ (1.5), pyridine (1.0), THF, rt, 1 h	**2l**, 50 (5:1)
13	Benzaldehyde	$Ti(O^iPr)_4$ (0.8), pyridine (0.4), THF, rt, 3 h	**2l**, 92 (6:1)
14	Benzaldehyde	$Ti(O^iPr)_4$ (0.2), pyridine (0.1), THF, rt, 15 h	**2l**, 76[d,e]
15	Benzaldehyde	$Ti(O^iPr)_4$ (0.8), THF, rt, 5 h	**2l**, 70[e]
16	Benzaldehyde	$Ti(O^iPr)_4$ (0.8), Et_3N (0.4), THF, rt, 5 h	**2l**, 60[e]
17	Benzaldehyde	$Ti(O^iPr)_4$ (0.8), 2,6-lutidine (0.4), THF, rt, 5 h	**2l**, 90 (7:1)
18	Benzaldehyde	$Ti(O^iPr)_4$ (0.8), pyridine (0.4), THF, −20 °C, 5 h	**2l**, 60[e]

[a] Oxindole (0.3 mmol) and carbonyl compounds (1.2 equiv) were used except for acetone (2.0 equiv).
[b] Equivalents in parenthesis.
[c] Isolated yield and the ratio of *E*/*Z* in parenthesis based on ^1H NMR.
[d] Oxindole **1a** was remained in variable amounts.
[e] *E*/*Z* ratio was not determined.



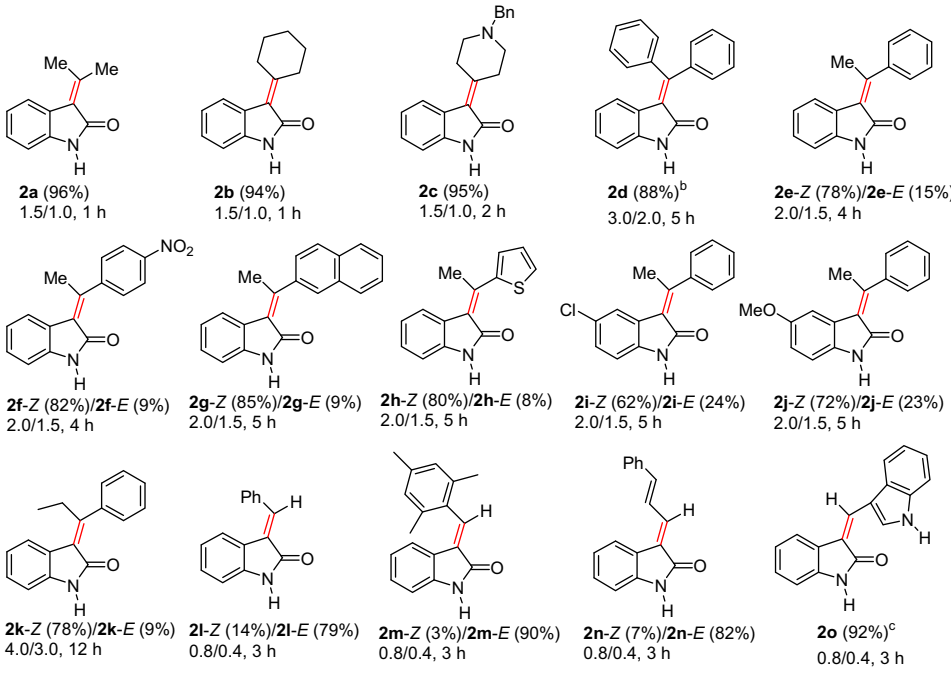
Scheme 1.

group of oxindole moiety (vide infra, Scheme 1). In addition, the proton at the C-4 position of **2e**-*E* appeared quite upfield (δ = 6.13 ppm) due to shielding effect of the phenyl ring.

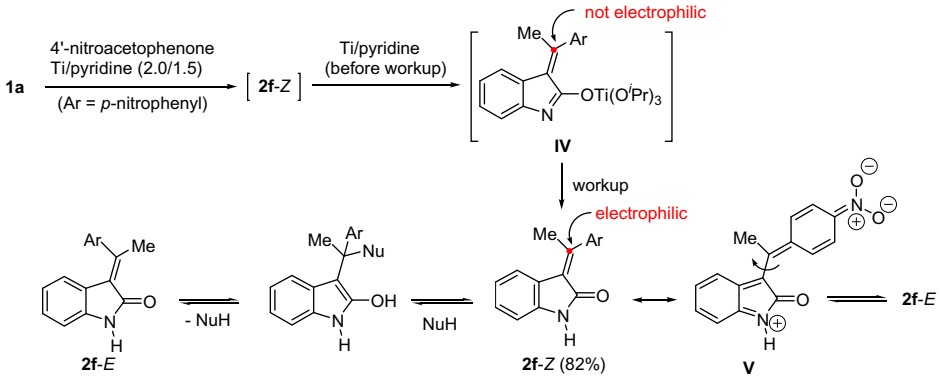
The reaction of benzaldehyde in the presence of 1.5 equiv of Ti catalyst (entry 12) gave moderate yield of product **2l**, to our surprise, due to the formation of some intractable side products. When we reduced the amount of catalyst (entry 13) the reaction produced **2l** in high yield (92%). However, more stable *E*-isomer[4a,g] was isolated as a major product presumably due to rapid isomerization of the initially formed **2l**-*Z* under the reaction conditions (vide infra). The reaction with lesser amount of catalyst (entry 14) was not completed. In order to reduce the isomerization, we carried out the reaction in the absence of pyridine (entry 15), in the presence of other base such as Et_3N and 2,6-lutidine (entries 16 and 17), or at low temperature (entry 18). However, **2l**-*E* was obtained as a major product in all entries.

According to the brief optimization results we examined the reactions of various carbonyl compounds, and the results are summarized in Table 2.[8] The reactions of **1a** and cyclohexanone and *N*-benzylpiperidone afforded **2b** and **2c**, respectively, in high yields. The reaction of benzophenone afforded **2d** in high yield (88%) by using Ti/pyridine (3:2) system at 60 °C. As for the reaction of acetophenone, the reactions with 4′-nitroacetophenone, 2′-acetonaphthone, 2-acetylthiophene afforded **2f**–**h** in good yields (88–94%). The reactions of 5-chlorooxindole (**1b**) and 5-methoxyoxindole (**1c**) with acetophenone gave the corresponding products **2i** and **2j** in good yields (86–95%) with a similar *E*/*Z* selectivity. The reaction of propiophenone also showed a similar reactivity to give **2k** (87%). In all cases, *Z*-isomer was isolated as a major product. The selective formation of *Z*-isomer could be explained, as shown in Scheme 1. Oxindole might be converted to the titanium enolate **I** via the initially formed amide enolate, and the nucleophilic attack

Table 2
Synthesis of 3-alkylideneoxindoles[a]



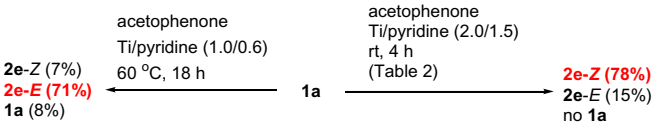
[a] Oxindoles (0.5 mmol), carbonyl compounds (1.2 equiv), dry THF, and rt are common. Isolated yield and the equivalents of Ti/pyridine and reaction time are indicated below.
[b] At 60 °C.
[c] *E*/*Z* (ca. 1:9 by ^{1}H NMR) mixture.



Scheme 2.

of **I** toward the *Si* face of acetophenone via a six-membered transition state **II**, bearing a larger phenyl group at the equatorial position, would produce the *Z*-isomer as a major product.[6f,9]

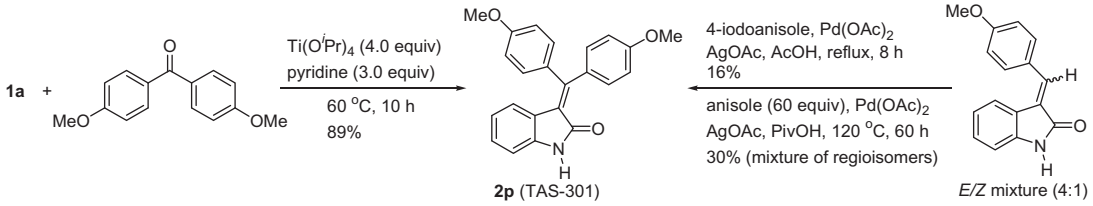
It is interesting to note that the isolated **2f**-*Z* of 4′-nitroacetophenone was isomerized slowly to **2f**-*E* to some extent at room temperature in $CDCl_3$,[10,11] although **2f**-*Z* was not isomerized during the reaction progress. Actually, the ratio of *E*/*Z* (ca. 1:9) was not changed when we let the reaction mixture for a long time (20 h). The initially formed **2f**-*Z* might be present in its enolate form **IV** in the reaction mixture before acidic workup, as shown in Scheme 2. The indicated carbon atom of **IV** is not electrophilic. Thus a plausible isomerization, caused by some nucleophilic species such as water or pyridine, would not occur during the reaction progress. In contrast to the carbon atom of **IV**, the indicated carbon atom of **2f**-*Z* is electrophilic and the isomerization would proceed slowly via an addition/elimination of a nucleophile.[10,11]



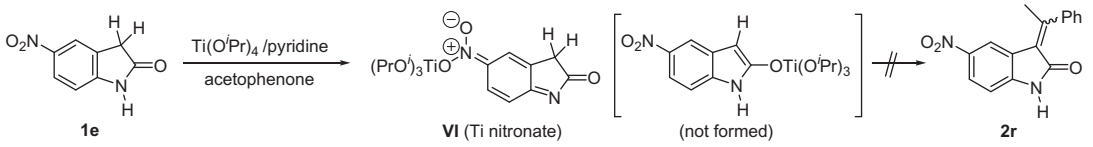
Scheme 3.

The isomerization via rotation around the C–C single bond of the canonical structure **V** might contribute to some extent for the isomerization process.[10b]

The reactions of mesitaldehyde and cinnamaldehyde provided the corresponding products **2m** and **2n** in good yields (89–93%), and the ratio of *E*/*Z* was similar to that of benzaldehyde. Initially formed *Z*-isomer, via the chelation-controlled transition state, could be isomerized into more stable *E*-isomer[4a,g,10a] via the same



Scheme 4.



Scheme 5.

pathway in Scheme 2. The reaction of indole-3-carboxaldehyde gave **2o** in good yield (92%); however, the *E*/*Z* ratio was converted and the reason might be ascribed to an intramolecular hydrogen-bond interaction between the carbonyl of oxindole and NH of indole moiety.[1c]

As observed for the seven examples of unsymmetrical ketones in Table 2, *Z*-isomers (**2e**–**k**) were obtained as major products. As a next experiment, we examined the feasibility for the synthesis of *E*-isomer as a major product. We carried out the reaction of **1a** and acetophenone in the presence of a limited amount of Ti catalyst (1.0 equiv) in order to obtain **2e**-*E* as a major product, as shown in Scheme 3. According to our hypothesis in Scheme 2, we presumed that the initially formed **2e**-*Z* would not be converted to its amide enolate intermediate (such as **IV**) without an excess Ti catalyst. Accordingly, an isomerization of **2e**-*Z* would proceed to form **2e**-*E* as a major product. As expected, **2e**-*E* was formed selectively and could be isolated in good yield (71%) although the reaction was not completed even after 18 h at 60 °C.

TAS-301 (3-bis-(4-methoxyphenyl)methylene-2-indolinone) has been synthesized in refluxing THF in the presence of an excess amount of NaH (2.5 equiv) for a long time (5 days) in moderate yield (55%).[3e] However, we could prepare TAS-301 in high yield (89%), as shown in Scheme 4. We also examined a palladium-catalyzed arylation of easily available *p*-methoxybenzylidene oxindole (*E*/*Z*, 4:1) with 4-iodoanisole or anisole according to our previous paper;[5] however, the result was quite disappointing, as also shown in Scheme 4.

The reaction of *N*-methyloxindole (**1d**) and acetophenone was not completed under the standard condition (Ti/pyridine, 2.0/1.5). Thus the reaction was carried out in the presence of Ti/pyridine (4.0/3.0) for 7 h at room temperature, and the corresponding products **2q**-*Z* (*N*-methyl **2e**-*Z*, 70%) and **2q**-*E* (*N*-methyl **2e**-*E*, 13%) were obtained in reasonable yields. The sluggish reactivity of *N*-methyl derivative **1d** as compared to **1a** is not clear at this stage.[12] More stable **2q**-*E* could be prepared as a major product by carrying out the reaction at 60 °C, as in the case of **2e**-*E* in Scheme 3 (vide supra). Actually, the reaction of **1d** in the presence of Ti/pyridine (4.0/3.0) for 7 h at 60 °C produced **2q**-*E* (72%) along with **2q**-*Z* (15%).

As a limitation of this protocol, the reaction of 5-nitrooxindole (**1e**) and acetophenone failed completely to obtain the product **2r**, as shown in Scheme 5. The reaction of **1e** and Ti/pyridine might produce a nitronate **VI** instead of the Ti enolate. The fate of **VI** is not clear at this stage; however, many intractable polar side spots were observed on TLC.

In summary, we prepared various 3-alkylideneoxindoles in high yields using in situ generated titanium enolate of oxindole. (*Z*)-3-Alkylideneoxindoles, which could not be synthesized by a traditional Knoevenagel condensation, could be obtained selectively as a major product from unsymmetrical ketones such as acetophenone.[13]

Acknowledgments

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8. *Typical procedure for the synthesis of* ***2e****:* To a stirred solution of oxindole (**1a**, 67 mg, 0.5 mmol), acetophenone (72 mg, 0.6 mmol), and pyridine (59 mg, 0.75 mmol) in dry THF (0.5 mL) was added dropwise a solution of $Ti(O^iPr)_4$ (284 mg, 1.0 mmol) in THF (0.3 mmL), and the reaction mixture was stirred at room temperature for 4 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/ether, 2:1) **2e**-*Z* (92 mg, 78%) and **2e**-*E* (18 mg, 15%) were obtained. Other compounds were synthesized similarly, and the structures of known compounds **2a**–**e** and **2k**–**p** were characterized by comparing their melting points and ^{1}H NMR spectrum with the reported.[3,4] The selected spectroscopic data of unknown compounds **2f**–**j** and **2q** are as follows.
Compound **2f**-*Z*: yellow solid, mp 211–212 °C; IR (KBr) 3446, 1687, 1590, 1508, 1338 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.63 (s, 3H), 6.80 (d, J = 7.8 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.65 (d, J = 7.8 Hz, 1H), 7.98 (br s, 1H), 8.27 (d, J = 8.7 Hz, 2H); ESIMS m/z 281 [M+H]$^+$. Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.78; H, 4.64; N, 9.75.
Compound **2f**-*E*: yellow solid, mp 239–240 °C; IR (KBr) 3446, 1695, 1616, 1592, 1515, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.80 (s, 3H), 6.08 (d, J = 7.8 Hz, 1H), 6.66 (t, J = 7.8 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.51 (dd, J = 6.9 and 1.8 Hz, 2H), 7.81 (br s, 1H), 8.38 (dd, J = 6.9 and 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ 21.65, 109.49, 120.67, 122.05, 122.41, 124.27, 124.72, 127.65, 128.54, 147.22, 149.33, 149.83, 149.85, 169.05; ESIMS m/z 281 [M+H]$^+$.
Compound **2g**-*Z*: yellow solid, mp 203–204 °C; IR (KBr) 3236, 1698, 1615, 1502, 1264 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.70 (s, 3H), 6.60 (d, J = 7.5 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.40–7.52 (m, 3H), 7.63 (d, J = 7.5 Hz, 1H), 7.74–7.89 (m, 4H), 8.24 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.75, 109.62, 121.52, 124.11, 124.22, 124.25, 125.94, 126.21, 126.37, 126.58, 127.27, 127.72, 128.33, 128.39, 133.11, 133.15, 139.86, 140.72, 153.12, 167.84; ESIMS m/z 286 [M+H]$^+$. Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.26; H, 5.61; N, 4.77.
Compound **2g**-*E*: yellow solid, mp 175–176 °C; IR (KBr) 3193, 1691, 1613, 1502, 1366 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.89 (s, 3H), 6.18 (d, J = 7.8 Hz, 1H), 6.52 (t, J = 7.8 Hz, 1H), 6.84 (d, J = 7.8 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 7.42 (d, J = 8.7 Hz, 1H), 7.47–7.62 (m, 2H), 7.80 (s, 1H), 7.82–8.00 (m, 3H), 8.83 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.98, 109.36, 121.30, 123.16, 123.34, 123.98, 124.77, 125.56, 126.56, 126.60, 127.87, 128.15, 128.27, 128.99, 133.01, 133.46, 139.68, 140.22, 155.29, 170.24; ESIMS m/z 286 [M+H]$^+$.
Compound **2h**-*Z*: yellow solid, mp 181–182 °C; IR (KBr) 3446, 1686, 1616, 1578, 1464, 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.73 (s, 3H), 6.79 (d, J = 7.8 Hz, 1H), 7.01 (t, J = 7.8 Hz, 1H), 7.10 (dd, J = 5.1 and 3.6 Hz, 1H), 7.19 (t, J = 7.8 Hz, 1H), 7.49 (dd, J = 5.1 and 1.2 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.61 (dd, J = 3.6 and 1.2 Hz, 1H), 8.31 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.58, 109.49, 121.57, 124.08, 124.40, 124.71, 127.16, 128.33, 128.36, 130.52, 140.14, 142.13, 144.98, 167.60; ESIMS m/z 242 [M+H]$^+$. Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.68; H, 4.59; N, 5.80. Found: C, 69.82; H, 4.52; N, 5.64.
Compound **2h**-*E*: yellow solid, mp 193–194 °C; IR (KBr) 3452, 1692, 1612, 1464, 1251 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.83 (s, 3H), 6.66–6.80 (m, 2H), 6.83 (d, J = 7.8 Hz, 1H), 7.06–7.16 (m, 2H), 7.18 (dd, J = 3.6 and 0.9 Hz, 1H), 7.50 (dd, J = 5.1 and 0.9 Hz, 1H), 8.56 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.92, 109.42, 121.36, 122.92, 123.17, 125.37, 126.60, 127.34, 127.50, 128.57, 139.67, 143.72, 147.40, 169.72; ESIMS m/z 242 [M+H]$^+$.
Compound **2i**-*Z*: yellow solid, mp 191–192 °C; IR (KBr) 3474, 1697, 1606, 1444, 1259 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.62 (s, 3H), 6.64 (d, J = 8.1 Hz, 1H), 7.17 (dd, J = 8.1 and 1.8 Hz, 1H), 7.30-7.36 (m, 2H), 7.37–7.45 (m, 3H), 7.58 (d, J = 1.8 Hz, 1H), 8.16 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.75, 110.32, 123.27, 124.31, 125.64, 126.89, 127.53, 128.04, 128.06, 128.46, 138.95, 141.79, 155.42, 167.40; ESIMS m/z 270 [M+H]$^+$, 272 [M+H+2]$^+$. Anal. Calcd for $C_{16}H_{12}ClNO$: C, 71.25; H, 4.48; N, 5.19. Found: C, 71.53; H, 4.71; N, 5.32.
Compound **2i**-*E*: yellow solid, mp 209–210 °C; IR (KBr) 3445, 1693, 1614, 1468, 1303 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.81 (s, 3H), 6.05 (d, J = 1.8 Hz, 1H), 6.76 (d, J = 8.4 Hz, 1H), 7.04 (dd, J = 8.4 and 1.8 Hz, 1H), 7.22–7.32 (m, 2H), 7.44–7.58 (m, 3H), 8.93 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.95, 110.20, 123.18, 123.31, 124.72, 126.19, 126.56, 127.78, 128.82, 129.33, 138.02, 142.19, 157.61, 169.92; ESIMS m/z 270 [M+H]$^+$, 272 [M+H+2]$^+$.
Compound **2j**-*Z*: yellow solid, mp 163–164 °C; IR (KBr) 3231, 1699, 1596, 1483, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.62 (s, 3H), 3.84 (s, 3H), 6.64 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 8.4 Hz, 1H), 7.24 (s, 1H), 7.28–7.50 (m, 5H), 8.34 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.59, 56.00, 109.71, 112.00, 112.68, 124.26, 125.21, 127.57, 127.98, 128.17, 134.45, 142.15, 154.16, 155.05, 167.98; ESIMS m/z 266 [M+H]$^+$. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.12; H, 5.67; N, 5.36.
Compound **2j**-*E*: yellow solid, mp 195–196 °C (dec.); IR (KBr) 3448, 1690, 1594, 1475, 1205 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.82 (s, 3H), 3.41 (s, 3H), 5.71 (d, J = 2.4 Hz, 1H), 6.65 (dd, J = 8.4 and 2.4 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 7.24–7.40 (m, 2H), 7.41–7.60 (m, 3H), 8.67 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.74, 55.18, 109.10, 109.71, 114.09, 124.12, 124.21, 126.40, 128.41, 129.20, 133.42, 142.70, 154.52, 155.90, 170.24; ESIMS m/z 266 [M+H]$^+$.
Compound **2q**-*Z*: yellow solid, mp 131–132 °C; IR (KBr) 1704, 1606, 1488, 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.56 (s, 3H), 3.06 (s, 3H), 6.74 (d, J = 7.8 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 7.15–7.42 (m, 6H), 7.58 (d, J = 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.45, 25.61, 107.68, 121.66, 123.47, 123.56, 123.85, 127.24, 127.98, 128.02, 128.39, 142.49, 143.25, 153.02, 166.22; ESIMS m/z 250 [M+H]$^+$. Anal. Calcd for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.72; H, 6.18; N, 5.39.
Compound **2q**-*E*: yellow solid, mp 123–124 °C; IR (KBr) 1695, 1604, 1485, 1469 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (s, 3H), 3.20 (s, 3H), 6.06 (d, J = 7.8 Hz, 1H), 6.56 (t, J = 7.8 Hz, 1H), 6.68 (d, J = 7.8 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.16–7.26 (m, 2H), 7.32–7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.81, 25.70, 107.41, 121.31, 122.61, 122.77, 123.40, 126.45, 128.03, 128.28, 129.13, 142.21, 142.98, 154.84, 168.23; ESIMS m/z 250 [M+H]$^+$.
9. The proton at the C-3 position of oxindole is more acidic (pK_a = 18.2) than the protons of the carbonyl compounds in this work such as acetone or acetophenone (pK_a = 24–26). For the pK_a data of oxindole derivatives, see: (a) Ding, M.; Zhou, F.; Qian, Z.-Q.; Zhou, J. *Org. Biomol. Chem.* **2010**, *8*, 2912–2914; (b) Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, *56*, 4218–4223.
10. For the isomerization of 3-alkylideneoxindoles, see: (a) Jiang, T.-S.; Tang, R.-Y.; Zhang, X.-G.; Li, X.-H.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 8834–8837; (b) Ankati, H.; Akubathini, S. K.; Kamila, S.; Mukherjee, C.; D'Mello, S. R.; Biehl, E. R. *Open Org. Chem. J.* **2009**, *3*, 1–10; For the photoisomerization of 3-alkylideneoxindole, see: (c) Milanesio, M.; Viterbo, D.; Albini, A.; Fasani, E.; Bianchi, R.; Barzaghi, M. *J. Org. Chem.* **2000**, *65*, 3416–3425.
11. The major isomer **2e**-*Z* obtained from acetophenone was not isomerized during the separation, and it can be stored at room temperature. However, **2e**-*Z* was isomerized slowly to **2e**-*E* in solution state even at room temperature, and the isomerization was accelerated at 60 °C in the presence of pyridine. Actually, an isolated pure **2e**-*Z* was converted to a mixture (*E*/*Z*, 7:1) when we let the THF solution at 60 °C in the presence of pyridine (1.0 equiv) for 24 h. The three Z-isomers of **2f**, **2j** and **2q** were isomerized to their *E*-isomers more rapidly than other compounds in solution state. The contribution for the isomerization via the canonical structure **V** (Scheme 2) might be increased for the *p*-nitrophenyl and *N*-methyl derivatives.
12. The generation of a titanium enolate of oxindole (**1a**) would be facile as compared to *N*-methyloxindole (**1d**). The formation of a titanium enolate **I** in the case of **1a** could be facilitated by an initial formation of an amide enolate (Scheme 1).
13. During the evaluation process, one of the referees asked to show an example of unsymmetrical aliphatic ketone. Thus we examined the reaction of **1a** and 2-butanone under the typical conditions, $Ti(O^iPr)_4$/pyridine (1.5/1.0), at room temperature for 1 h. The corresponding Knoevenagel condensation product was obtained in high yield (95%) as an inseparable *E*/*Z* mixture (1:5 based on ^{1}H NMR). ^{1}H NMR ($CDCl_3$, 300 MHz) δ *Z*-isomer (major): 1.19 (t, J = 7.5 Hz, 3H), 2.37 (s, 3H), 3.11 (q, J = 7.5 Hz, 2H), 6.85 (d, J = 7.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 8.26 (br s, 1H), *E*-isomer (minor): 1.26 (t, J = 7.5 Hz, 3H), 2.59 (s, 3H), 2.70 (q, J = 7.5 Hz, 2H), 6.87 (d, J = 7.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 7.5 Hz, 1H), 8.29 (br s, 1H).