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Multicomponent reactions studies: Yonemitsu-type trimolecular condensations promoted by Ti(IV) derivatives

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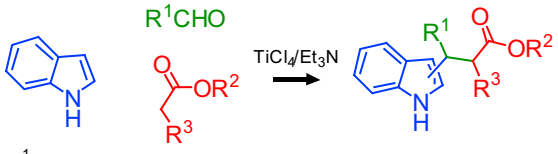
ABSTRACT

We have developed a Ti(IV)/Et_3N-promoted trimolecular condensation of aromatic heterocycles (furan, pyrrole, imidazole, indole) with aldehydes and active methylene compounds. In the case of indole and methyl acetoacetate the reaction afforded three-component products or tricyclic cyclopenta[*b*]indole derivative, depending on the reaction conditions. In both cases, NMR analysis evidenced that titanium enolate is the reactive species involved in the reaction.

1. Introduction

Multicomponent reactions (MCRs) are one-pot reactions where three or more molecules react in the same reaction vessel affording a single product without isolation of any intermediate.[1] This approach combines multiple advantages like operationally simple and easily automatable procedure, requiring readily available starting materials and final work-up only. Moreover, as this methodology is also characterized by high atom economy and exploratory power, it became a method of choice especially in drug discovery.[2] Even if titanium(IV) reagents are widely used in organic synthesis for C–C bond formation or functional group transformations,[3] their utilization as promoters in multicomponent approach has been rarely investigated.[4,5]

The Yonemitsu condensation of indole with Meldrum's acid and an aldehyde is an example of multicomponent reaction.[6] This reaction combined with simple functional group transformations can be used to synthesize various β-substituted tryptophans, β-carbolines, and carbazoles of biological interest.[7,8] We have recently reported its $TiCl_4/Et_3N$-promoted version using aldehydes, aromatic heterocycles, and various active methylene compounds (Scheme 1).[9] By this way the Yonemitsu condensation has been extended to active methylene derivatives, e.g., malonesters, nitroacetates or triethylphosphonoacetate, non-reactive species under classical conditions (D,L-proline, CH_3CN). To further explore the scope and limitations of this methodology for the preparation of new heterocyclic scaffolds, we tested some aldehydes, heterocycles, and activated carbonyl compounds in the presence of two Ti(IV) derivatives.



R^1= Alkyl, aryl, ...
R^2 = Me, Et, ...
R^3 = CO_2Et, COMe, NO_2, $P(O)(OEt)_2$

Scheme 1. $TiCl_4/Et_3N$-promoted trimolecular condensation.

2. Results and discussion

The $TiCl_4/Et_3N$ system promotes the trimolecular condensation of furan, isobutyraldehyde, and diisopropyl malonate or methyl acetoacetate in 65% and 71% yield, respectively (Table 1, entries 1 and 2). With these encouraging results in hand we were keen to investigate whether pyrrole derivatives were compatible with such conditions. Even if pyrrole is more reactive than furan toward electrophiles, the yield of condensation products **3c** and **3d** (Table 1, entries 3 and 4) is much lower (13%) probably due to the polymerization of pyrrole derivatives in the presence of strong Lewis acid.[10] For this reason, we decided to decrease the acidity of the titanium promoter by replacing chlorine atoms with more hindered and less electronegative isopropoxide groups. Titanium(IV) isopropoxide was discarded owing to its very low activity observed in a previous study.[9] Consequently, we turned to $TiCl_2(O\text{-}^iPr)_2$,

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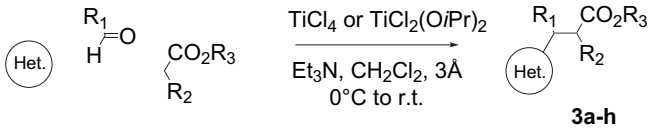
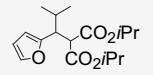
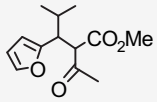
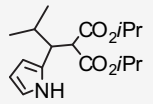
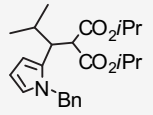
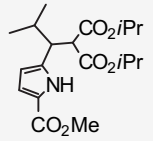
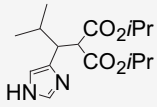
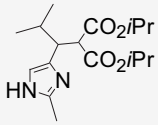
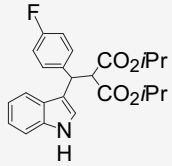
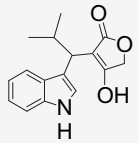
Table 1
Trimolecular condensation of heterocycles, aldehydes, and active methylene compounds promoted by Ti(IV) derivatives



3a-h

Entry	Condensation product		Yield[a] (%) $TiCl_4$	$TiCl_2(O\text{-}^iPr)_2$
1	**3a**		65	Knoev.
2	**3b**		71	—
3	**3c**		13	88
4	**3d**		Traces	90
5	**3e**		34	Knoev.
6	**3f**		Traces	33
7	**3g**		—	52
8	**3h**		14	72
9	**3i**		—	85

[a] Yield refers to chromatographically purified product. Knoev.: Knoevenagel adduct; (—) no condensation product observed.

directly prepared in the reaction medium by mixing equal amount of $TiCl_4$ and $Ti(O\text{-}^iPr)_4$. We were pleased to find that the trimolecular condensation between pyrrole, isobutyraldehyde, and diisopropyl malonate occurred in good yield (88%) in the presence of 1.0 equiv of $TiCl_2(O\text{-}^iPr)_2$ and 1.0 equiv of Et_3N (Table 1, entry 3). Similarly, high yield was observed with *N*-benzylpyrrole (Table 1, entry 4). However, we found that $TiCl_2(O\text{-}^iPr)_2$ was weak to promote the three-component reaction with less reactive partners like furans or methyl-2-pyrrolecarboxylate (Table 1, entries 1, 2, and 5). We found that imidazole and 2-methylimidazole in the presence of $TiCl_2(O\text{-}^iPr)_2$ smoothly afforded three-component products (**3f** and **3g**) thus opening the way to the preparation of histidine derivatives or imidazole condensed heterocycles (Table 1, entries 6 and 7). Similarly, switching from $TiCl_4$ to $TiCl_2(O\text{-}^iPr)_2$ to promote the condensation reaction with 4-fluorobenzaldehyde or tetronic acid allowed to improve the chemical yields of the corresponding trimolecular adducts **3h** and **3i** to 72% and 85% yield, respectively (Table 1, entries 8 and 9).

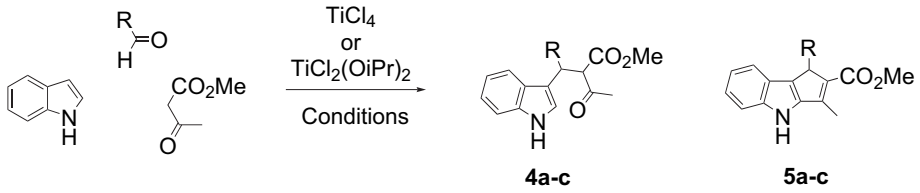
Considering the synthetic utility of β-ketoesters,[11] their reactivity with indole and various aldehydes has also been investigated (Table 2). Thus, the reaction of methyl acetoacetate with indole and isobutyraldehyde in the presence of 1 equiv of $TiCl_4$ at room temperature afforded the corresponding trimolecular adduct **4a** in 45% yield after 30 min stirring (Table 2, entry 1).[9] These experimental conditions could successfully be extended to benzaldehyde and 2-nitrobenzaldehyde giving trimolecular adducts **4b** and **4c** with satisfactory yields (Table 2, entries 1, 5, and 8). Surprisingly, a longer (about 3 h) reaction time led to an unexpected new condensation product that we unambiguously identified as a tricyclic derivative **5a** (Table 2, entry 2). Tricyclic compounds **5b** and **5c** could also be selectively obtained under the same experimental conditions with aromatic aldehydes (Table 2, entries 6 and 9). Three-component derivative **5c** may be versatile for the synthesis of new pentacyclic ring systems by subsequent nitro group reduction and cyclization. However, the $TiCl_2(O\text{-}^iPr)_2$-promoted version of this approach afforded only trimolecular derivatives **4a–c**, even if the reactions were carried out overnight (Table 2, entries 3, 4, 7, and 10). The fact that such polyfunctionalized 2,3-cyclopentene-annulated indole core was accessible only by laborious manner[12] our trimolecular methodology may offer new perspectives in heterocyclic chemistry.

From mechanistic point of view, $TiCl_4$-promoted trimolecular condensation is likely to take place in three steps, namely (i) enolate formation; (ii) Knoevenagel condensation between this reactive species and the aldehyde; (iii) Michael addition of indole to the Knoevenagel adduct. The proposed mechanism is the same that we have recently studied in an analogous reaction[13] and could confirm the formation of the diastereomerically pure bicyclic product **4a** bearing isopropyl and methoxycarbonyl groups in *anti* position after equilibration in the reaction mixture.[14] In the case of aromatic aldehydes, additional steric constraints could explain the observed low diastereoselectivity for compounds **4b** and **4c** (unseparable mixture of the two diastereomers in 80/20 and 50/50 ratio, respectively).

The mechanism of the $TiCl_2(O\text{-}^iPr)_2$-promoted condensation seemed to be analogous to that observed in the presence of $TiCl_4$ involving the generation of the reactive enolate ion. This hypothesis is supported by NMR analysis. Indeed, when 1.0 equiv of diisopropyl malonate was added to a solution of $TiCl_2(O\text{-}^iPr)_2$ in $CDCl_3$, both $TiCl_2(O\text{-}^iPr)_2$ and diester signals shifted to lower fields (from δ 4.92 to 5.00 ppm and δ 3.26 to 3.72 ppm, respectively) in accord with the formation of a complex of lower electron density.[15] Addition of 1.0 equiv of triethylamine provoked the formation of an orange solution of enolate. The signal corresponding to the enolate α hydrogen (at around δ 4.30 ppm) disappeared after quenching with DCl. ^{13}C NMR spectra were in agreement with proton spectra: complexation with Ti resulted in the deshielding of methylene signal (from δ 38.8 to 42.4 ppm), whereas a second shift from δ 42.4 to 69.4 ppm corresponded to the formation of the enolate.

Tricyclic derivatives **5a–c** probably arise from an intramolecular cyclization of the corresponding bicyclic derivatives **4a–c**. A plausible mechanism for their formation is depicted in Scheme 2. The trimolecular condensation involves the conversion of $TiCl_4$ into $TiOCl_2$[13] that forms a complex (**I**) with the condensation product.

Table 2
Trimolecular condensation of indole, methyl acetoacetate, and various aldehydes

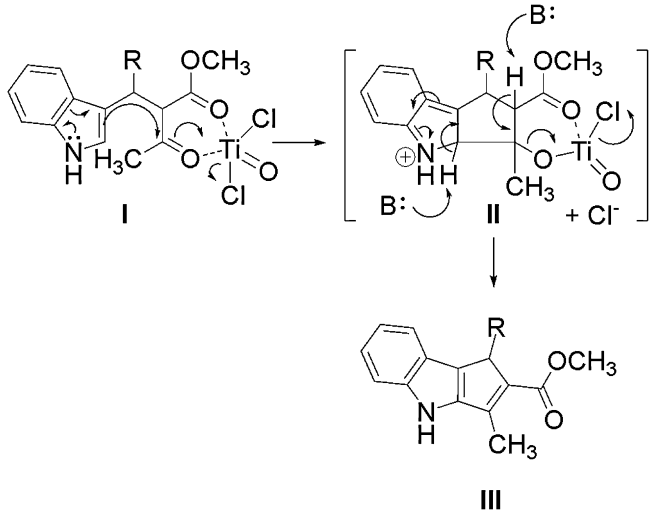


4a-c **5a-c**

Entry	R	Conditions	Yield[a] (%)	
			Compd **4**[b]	Compd **5**[b]
1	**a** : 	$TiCl_4$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 30 min	45	—
2		$TiCl_4$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 3 h	Traces	48
3		$TiCl_2(O\text{-}^iPr)_2$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 3 h	40	—
4		$TiCl_2(O\text{-}^iPr)_2$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, overnight	45	—
5	**b** : 	$TiCl_4$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 30 min	49	Traces
6		$TiCl_4$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 2 h 30 min	5	34
7		$TiCl_2(O\text{-}^iPr)_2$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, overnight	37	Traces
8	**c** : 	$TiCl_4$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 30 min	41	—
9		$TiCl_4$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, 3 h	15	77
10		$TiCl_2(O\text{-}^iPr)_2$, Et_3N, CH_2Cl_2, 3 Å, 0 °C to rt, overnight	50	—

[a] Isolated yield after purification by silica gel chromatography.
[b] All new compounds gave satisfactory ^1H and ^{13}C NMR, IR, and HRMS or elemental analysis data; (—) no condensation product observed.

Complexation increases the electrophilicity of the carbonyl groups favoring the intramolecular attack of indole to the ketone carbonyl and the formation of the intermediate **II**. Finally, a deprotonation restores the full aromaticity of indole and a β-like elimination leads to the tricyclic adduct **III**. There are some experimental evidences showing that **I** is not a complex of $TiCl_4$. When isolated **4a** was treated with 1 equiv of $TiCl_4$ in CH_2Cl_2, the solution changed color, suggesting the formation of a complex **4a**–$TiCl_4$. However, this complex did not furnish the tricyclic product **5a**, even after 24 h of stirring. Therefore, **4a**–$TiCl_4$ is not the intermediate in the formation of the tricyclic compound.



Scheme 2. Proposed mechanism for the formation of the tricyclic compounds **5a–c**.

3. Conclusion

Continuing our investigations on Ti(IV)-promoted three-component reactions between various heterocycles, aldehydes, and active methylene compounds we evidenced $TiCl_2(O\text{-}^iPr)_2/Et_3N$ system as an alternative to $TiCl_4$ in the case of incompatibility with reaction partners. Thus, heteroaromatic derivatives like pyrroles or imidazoles and active methylene compounds (malonates, acetoacetates or tetronic acid) were successfully incorporated in trimolecular condensation product. $TiCl_4/Et_3N$-promoted reaction of indole, methyl acetoacetate, and aldehydes with longer reaction time afforded tricyclic cyclopenta[*b*]indole derivatives paving the way to the synthesis of functionalized indole heterocycles of biological interest. NMR spectral measurements gave a better insight into the elementary steps of this three-component reaction. The feasibility of an asymmetric version using chiral Ti(IV) ligands is currently under investigation.

4. Experimental section

4.1. General

All solvents were dried and purified by standard literature methods prior to use. Melting points were determined on a Reichert Thermovar hot-stage apparatus and are uncorrected. Reactions were monitored with Merck TLC aluminum sheets (Kieselgel $60F_{254}$) and preparative chromatographies were carried out on silica gel 60 (70–230 mesh ASTM) supplied by Merck. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were acquired on a Bruker AC 300 spectrometer in $CDCl_3$, with TMS as internal standard. IR spectra (film or KBr) were measured with a PERKIN ELMER SPECTRUM BX FTIR instrument. Mass spectra were either recorded with a VG Autospec apparatus or with a GCT Micromass Waters apparatus. Elemental analyses were carried out by the Microanalysis Service of the University of Reims.

4.2. General procedure for the trimolecular condensation promoted by Ti(IV) derivatives

In a typical procedure, the 1,3-dicarbonyl derivative (1.0 equiv) is added to a solution of $TiCl_4$ (1.0 equiv) in dry dichloromethane (20 mL/10 mmol) or a mixture of $TiCl_4$ (0.5 equiv) and $Ti(O\text{-}^iPr)_4$ (0.5 equiv) in dry dichloromethane (20 mL/10 mmol), at 0 °C under nitrogen using 3 Å molecular sieves. After 20 min, Et_3N (1.0 equiv) was added and the solution became orange. A few minutes later, the aldehyde (1.0 equiv) was added dropwise and the mixture was

stirred at 0 °C until its disappearance. Finally, the heterocycle (1.0 equiv) was added and the mixture was allowed to warm up to room temperature until the reaction was complete (monitored by TLC). After quenching with an aqueous 1 M HCl solution, the organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product. Purification by column chromatography on silica gel or by recrystallization furnished the corresponding trimolecular adduct.

4.2.1. Isopropyl 2-isopropoxycarbonyl-3-(2-furyl)-3-(2-propyl)propanoate ***3a***. Pale yellow oil (0.88 g, 65%); ^{1}H NMR ($CDCl_3$) δ 0.84 (d, J=6.6 Hz, 3H), 0.87 (d, J=6.6 Hz, 3H), 1.12–1.27 (m, 12H), 2.09 (m, 1H), 3.51 (dd, J=10.2, 4.5 Hz, 1H), 3.98 (d, J=10.2 Hz, 1H), 4.85 (s, 3H), 5.11 (s, 3H), 6.09 (m, 1H), 6.23 (m, 1H), 7.32 (d, J=2.1 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 17.4, 21.1, 21.4, 21.7, 30.1, 44.6, 55.1, 68.7, 68.9, 107.7, 108.1, 141.5, 153.1, 168.2, 168.8 ppm; IR (KBr) ν 2990, 1765, 1733, 1023 cm^{-1}; MS (CI): m/z 311 [M+H], 267, 223, 174, 136. $C_{17}H_{26}O_5$ (310.39): calcd C 65.78, H 8.44; found C 66.04, H 8.56.

4.2.2. Methyl 2-(acetyl)-3-(2-furyl)-3-(2-propyl)propanoate ***3b***. White solid (0.74 g, 71%); mp 90–92 °C; ^{1}H NMR ($CDCl_3$) δ 0.82 (d, J=6.7 Hz, 3H), 0.88 (d, J=6.7 Hz, 3H), 1.84 (m, 1H), 2.30 (s, 3H), 3.56 (m, 4H), 4.12 (dd, J=13.5, 11.7 Hz, 1H), 6.08 (d, J=3.2 Hz, 1H), 6.30 (m, 1H), 7.34 (d, J=1.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 17.5, 21.6, 29.2, 44.3, 52.3, 61.7, 107.7, 109.9, 141.3, 152.3, 168.5, 201.7 ppm; IR (KBr) ν 2960, 1744, 1714, 1458, 1352, 1260, 1159 cm^{-1}; MS (CI): m/z 238, 195, 178, 153, 121; HRMS calcd for $C_{13}H_{18}O_4$ (M^+) 238.1205, found: 238.1295.

4.2.3. Isopropyl 2-isopropoxycarbonyl-3-(pyrrol-2-yl)-3-(2-propyl)-propanoate ***3c***. Colorless oil (2.38 g, 88%); ^{1}H NMR (300 MHz, $CDCl_3$) 0.78 (d, J=6.6 Hz, 3H), 0.93 (d, J=6.7 Hz, 3H), 1.03 (d, J=6.3 Hz, 3H), 1.08–1.20 (m, 9H), 2.02 (m, 1H), 3.05 (t, J=7.6 Hz, 1H), 3.82 (d, J=7.5 Hz, 1H), 4.89 (m, 1H), 5.04 (m, 1H), 5.86 (m, 1H), 6.01 (m, 1H), 6.65 (m, 1H), 9.16 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 21.1, 21.2, 21.4, 21.6, 30.1, 45.9, 54.7, 68.6, 68.7, 106.7, 108.2, 116.6, 129.0, 168.1, 168.8 ppm; IR (KBr) ν 3056, 2983, 1745, 1320, 1111, 710 cm^{-1}; MS (CI) m/z 310 [M+H], 268, 243, 141, 122. $C_{17}H_{27}NO_4$ (309.40) calcd C 65.99, H 8.80, N 4.53; found C 65.81, H 8.66, N 4.78.

4.2.4. Isopropyl 2-isopropoxycarbonyl-3-(N-benzylpyrrol-2-yl)-3-(2-propyl)propanoate ***3d***. Pale yellow oil (3.5 g, 90%); ^{1}H NMR (300 MHz, $CDCl_3$) 0.64 (d, J=7.0 Hz, 3H), 0.76 (d, J=7.0 Hz, 3H), 1.01 (d, J=8.5 Hz, 3H), 1.07 (d, J=8.5 Hz, 3H), 1.24 (d, J=6.3 Hz, 3H), 1.26 (d, J=6.3 Hz, 3H), 1.85 (m, 1H), 3.55 (dd, J=10.8, 5.2 Hz, 1H), 3.69 (d, J=10.8 Hz, 1H), 4.78 (m, 1H), 5.08 (m, 1H), 5.12 (AB, J=15.4 Hz, 2H), 5.92 (m, 1H), 6.06 (m, 1H), 6.46 (m, 1H), 7.22–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5, 21.1, 21.7, 21.8, 21.9, 31.4, 41.3, 50.7, 57.6, 68.8, 69.1, 107.2, 107.6, 120.9, 127.7, 128.2, 128.8, 131.2, 138.4, 168.1, 168.6 ppm; IR (KBr) ν 2976, 1749, 1473, 1259, 1101, 708 cm^{-1}; MS (EI) m/z 399 [$M^{\bullet+}$], 356, 228, 212, 210, 168; HRMS calcd for $C_{24}H_{33}NO_4$ 399.2410, found: 399.2381.

4.2.5. Methyl 2-methoxycarbonyl-3-(5-methoxycarbonyl-pyrrol-2-yl)-3-(2-propyl)propanoate ***3e***. Orange solid (0.93 g, 34%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82 (m, 6H), 0.88 (m, 1H), 3.33 (dd, J=11.0, 4.5 Hz, 1H), 3.52 (s, 3H), 3.75 (s, 3H), 3.83 (s, 3H), 3.84 (d, J=11.0 Hz, 1H), 6.74 (m, 1H), 6.79 (m, 1H), 9.60 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 21.5, 29.4, 43.9, 51.3, 52.2, 52.5, 55.7, 115.6, 121.6, 121.7, 122.7, 161.7, 168.5, 169.0 ppm; IR (KBr) ν 3322, 2955, 1702, 1437, 1210, 1135, 768 cm^{-1}; MS (EI) m/z 311 [$M^{\bullet+}$], 268, 180, 168; HRMS calcd for $C_{15}H_{21}NO_6$ (M^+) 311.1369, found: 311.1411.

4.2.6. Isopropyl 2-isopropoxycarbonyl-3-(imidazol-3-yl)-3-(2-propyl)propanoate ***3f***. Colorless oil (0.90 g, 33%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 (d, J=6.8 Hz, 3H), 0.91 (d, J=6.8 Hz, 3H), 1.03 (d, J=6.3 Hz, 6H), 1.13 (d, J=6.3 Hz, 3H), 1.26 (d, J=6.3 Hz, 3H), 2.22 (m, 1H), 3.86 (d, J=9.6 Hz, 1H), 4.53 (dd, J=9.6, 6.0 Hz, 1H), 4.82 (m, 1H), 4.99 (m, 1H), 6.91 (s, 1H), 7.44 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.5, 19.8, 21.0, 21.1, 21.2, 21.3, 30.8, 55.4, 62.3, 69.7, 70.0, 121.6, 128.0, 135.0, 165.8, 166.1 ppm; IR (KBr) ν 3219, 2940, 1639, 1326, 1064, 829, 752 cm^{-1}; MS (EI) m/z 310 [$M^{\bullet+}$], 181, 140, 139, 123, 122; HRMS calcd for $C_{16}H_{26}N_2O_4$ (M^+) 310.1893, found: 310.1893.

4.2.7. Isopropyl 2-isopropoxycarbonyl-3-((5′-methyl)imidazol-3-yl)-3-(2-propyl)propanoate ***3g***. Colorless oil (0.74 g, 52%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, J=6.9 Hz, 3H), 0.86 (d, J=6.9 Hz, 3H), 1.05 (d, J=6.5 Hz, 6H), 1.20 (d, J=6.3 Hz, 3H), 1.25 (d, J=6.3 Hz, 3H), 2.17 (m, 1H), 2.40 (s, 3H), 3.85 (d, J=10.1 Hz, 1H), 4.56 (dd, J=10.1, 6.3 Hz, 1H), 4.81 (m, 1H), 5.05 (m, 1H), 6.85 (s, 1H), 6.93 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 17.8, 19.7, 21.2, 21.3, 21.4, 21.5, 32.2, 56.4, 59.5, 69.7, 69.9, 127.2, 153.9, 165.8, 166.4 ppm; IR (KBr) ν 3452, 3043, 2987, 1746, 1723, 1274, 1101, 765 cm^{-1}; MS (EI) m/z 324 [$M^{\bullet+}$], 218, 158, 140, 122; HRMS calcd for $C_{17}H_{28}N_2O_4$ (M^+) 324.2049, found: 324.2043.

4.2.8. Isopropyl 2-isopropoxycarbonyl-3-(indol-3-yl)-3-(4-fluorophenyl)propanoate ***3h***. Pink solid (2.67 g, 74%); mp 154–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (d, J=6.2 Hz, 6H), 1.01 (d, J=6.2 Hz, 3H), 1.11 (d, J=6.2 Hz, 3H), 4.19 (d, J=11.7 Hz, 1H), 4.86 (m, 2H), 5.04 (d, J=11.7 Hz, 1H), 6.91–7.52 (m, 9H), 8.14 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 21.4, 41.9, 58.6, 68.9, 69.0, 111.0, 114.9, 115.2, 116.9, 119.2, 119.5, 120.7, 122.2, 126.5, 129.8, 136.2, 137.2, 161.5, 167.3, 167.4 ppm; IR (KBr) ν 3396, 2970, 1738, 1505, 1335, 1213, 1153, 1099, 735 cm^{-1}; MS (CI) m/z 411 [M+H], 225, 224, 147, 105; HRMS calcd for $C_{24}H_{26}NO_4F$ (M^+) 411.1846, found: 411.1833.

4.2.9. 2-(Indol-3-yl)-2-(2-propyl)tetronic acid ***3i***. Pale yellow oil (1.01 g, 85%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (d, J=6.6 Hz, 3H), 1.05 (d, J=6.6 Hz, 3H), 2.64 (m, 1H), 3.79 (d, J=9.2 Hz, 1H), 4.42 (AB, J=16.1 Hz, 2H), 7.05–7.34 (m, 4H), 7.62 (d, J=7.6 Hz, 1H), 8.06 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.4, 21.7, 29.7, 38.0, 66.9, 104.1, 111.1, 116.4, 119.1, 119.4, 122.2, 127.1, 135.9, 173.2, 177.4 ppm; IR (KBr) ν 3457, 3149, 2981, 1734, 1661, 1415, 1044 cm^{-1}; MS (EI) m/z 271 [$M^{\bullet+}$], 228, 171, 156, 130, 116; HRMS calcd for $C_{16}H_{17}NO_3$ (M^+) 271.1208, found: 271.1203.

4.2.10. (2S, 3R*)-Methyl 2-(acetyl)-3-(indol-3-yl)-3-(2-propyl)propanoate* ***4a***. White solid (0.97 g, 45%); mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, J=5.6 Hz, 6H), 1.90 (s, 3H), 2.05 (m, 1H), 3.78 (s, 3H), 3.88 (dd, J=12.2, 3.8 Hz, 1H), 4.05 (d, J=12.2 Hz, 1H), 6.89 (d, J=2.4 Hz, 1H), 7.12 (m, 2H), 7.32 (d, J=4.8 Hz, 1H), 7.67 (d, J=7.5 Hz, 1H), 8.14 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.2, 21.9, 30.7, 41.9, 52.6, 64.8, 111.1, 111.9, 119.2, 119.6, 122.2, 128.2, 135.6, 169.8, 203.4 ppm; IR (KBr) ν 3277, 3048, 2977, 2951, 1727, 1696, 1423, 1253 cm^{-1}; MS (EI) m/z 287 [$M^{\bullet+}$], 202, 170, 156, 130, 115; HRMS calcd for $C_{17}H_{21}NO_3Na$ 310.1419, found 310.1414.

4.2.11. (2S,3R*)-Methyl 2-(acetyl)-3-(indol-3-yl)-3-(phenyl)propanoate* ***4b***. Diastereomeric mixture (80/20); colorless oil (0.69 g; 49%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 (s, 3H), 3.54 (s, 3H) (3.51), 4.51 (d, J=11.8 Hz, 1H) (4.38), 5.10 (d, J=11.8 Hz, 1H) (5.05), 7.02 (t, J=7.9 Hz, 1H), 7.08–7.32 (m, 8H), 7.50 (d, J=7.7 Hz, 1H), 8.08 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.7, 42.8 (42.9), 52.6 (52.4), 65.6 (66.5), 111.2 (111.0), 117.2, 119.1, 122.3 (122.5), 126.5, 126.8, 127.9, 128.3, 128.4, 128.6, 136.2, 141.1, 168.5, 202.2 ppm; IR (KBr) ν 3348, 3048, 2977, 2669, 1740, 1634, 1418 cm^{-1}; MS (EI) m/z 321 [$M^{\bullet+}$], 279, 265, 204, 173, 122; HRMS calcd for $C_{20}H_{19}NO_3$ 321.1365, found 321.1356.

4.2.12. (2S, 3R*)-Methyl 2-(acetyl)-3-(indol-3-yl)-3-(2-nitrophenyl)-propanoate* ***4c***. Diastereomeric mixture (50/50); pale yellow oil (0.66 g, 41%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (s, 3H) (2.15), 3.52

(s, 3H) (3.56), 4.40 (d, J=12.1 Hz, 1H) (4.61), 5.91 (d, J=12.1 Hz, 1H) (5.98), 7.05–7.80 (m, 9H), 8.09 (s, 1H) (8.12) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2 (29.2), 36.1 (36.4), 52.2 (52.7), 65.6 (66.2), 111.1 (111.2), 114.1 (114.2), 119.2 (119.3), 119.7 (119.8), 122.3 (122.5), 122.6 (122.7), 124.3 (124.5), 124.7 (125.0), 127.2 (127.3), 129.7 (129.9), 132.5 (132.6), 136.5 (136.6), 149.9 (150.0), 167.8 (168.2), 201.4 (201.9) ppm; IR (KBr) ν 3365, 3048, 2977, 2916, 1638, 1419 cm^{-1}; MS (EI) m/z 366 [M$^{\bullet+}$], 316, 218, 167, 149; HRMS calcd for $C_{20}H_{18}N_2O_5$ 366.1216, found 366.1217.

4.2.13. Methyl 1-isopropyl-3-methyl-1,4-dihydrocyclo penta[b]indole-2-carboxylate ***5a***. Pale yellow oil (0.56 g, 48%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.37 (d, J=6.8 Hz, 3H), 1.48 (d, J=6.8 Hz, 3H), 2.53 (s, 3H), 2.82 (m, 1H), 3.78 (m, 1H), 3.85 (s, 3H), 7.16 (m, 2H), 7.41 (d, J=8.5 Hz, 1H), 7.70 (d, J=7.2 Hz, 1H), 8.29 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.1, 15.8, 23.1, 28.4, 50.9, 52.6, 112.2, 120.4, 121.1, 122.2, 124.7, 126.2, 135.2, 141.1, 143.8, 146.7, 165.9 ppm; IR (KBr) ν 3356, 3048, 2986, 1652, 1264 cm^{-1}; MS (EI) m/z 269 [M$^{\bullet+}$], 254, 238, 210, 194, 167; HRMS calcd for $C_{17}H_{19}NO_2$ 269.1416, found 269.1412.

4.2.14. Methyl 1-phenyl-3-methyl-1,4-dihydrocyclopenta[b]indole-2-carboxylate ***5b***. Yellow oil (0.11 g, 34%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.84 (s, 3H), 6.72 (s, 1H), 7.18–7.55 (m, 5H), 7.61–7.88 (m, 4H), 7.95 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 50.8, 52.9, 111.5, 113.9, 118.1, 119.9, 122.5, 122.6, 122.8, 123.0, 123.7, 124.7, 127.5, 129.1, 132.5, 136.4, 167.1 ppm; MS (EI) m/z 303 [M$^{\bullet+}$], 288, 229, 226; HRMS calcd for $C_{20}H_{17}NO_2$ 303.1259, found 303.1266.

4.2.15. Methyl 1-(2-nitrophenyl)-3-methyl-1,4-dihydro cyclopenta[b] indole-2-carboxylate ***5c***. Pale yellow oil (0.27 g, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.50 (s, 3H), 3.66 (s, 3H), 6.68 (s, 1H), 7.25–7.43 (m, 5H), 7.51–7.75 (m, 2H), 7.84 (m, 1H), 8.05 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 51.2, 52.4, 111.3, 114.5, 118.3, 119.7, 122.5, 122.6, 123.7, 124.7, 127.5, 129.1, 132.6, 136.3, 148.9, 166.9 ppm; IR (KBr) ν 3048, 2977, 2951, 1696, 1415, 1252 cm^{-1}; MS (EI) m/z 348 [M^{+}], 333, 302, 289, 226, 122; HRMS calcd for $C_{20}H_{16}N_2O_4$ 348.1110, found 348.1121.

4.3. Procedure for the enolate formation test

To a solution of Ti(O-^{i}Pr)$_4$ (0.5 equiv) in $CDCl_3$ (700 μL) were added subsequently $TiCl_4$ (0.5 equiv), diisopropyl malonate (1.0 equiv), Et_3N (1.0 equiv), and DCl/D_2O 35% (3.0 equiv). After each addition ^{1}H NMR and ^{13}C NMR spectra were recorded. The concentration of Ti(Oi-Pr)$_4$ in $CDCl_3$ was 2.19×10^{-2} M.

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