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Cyclopropane Intermediates from Insertion Reactions of Platinum–Carbenes: A Route to Heterospiranes

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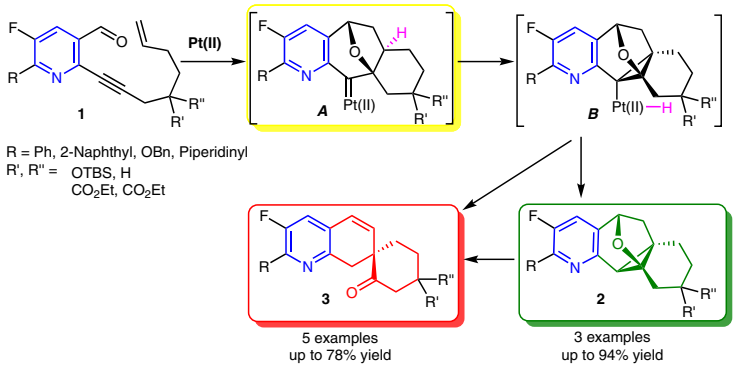

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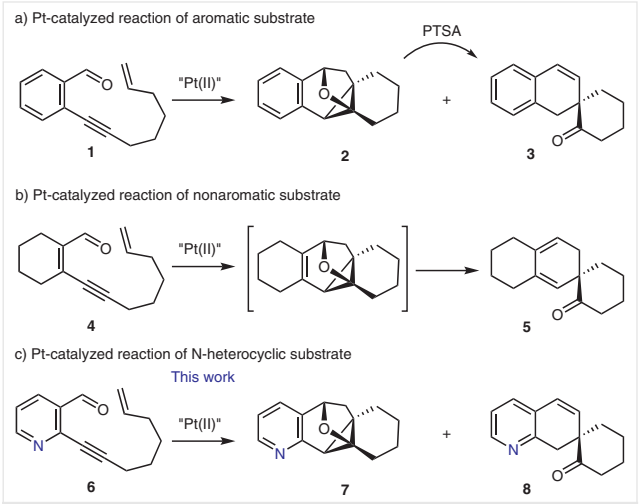
Abstract Heteroaromatic-anchored enynals with a pendent alkene group were successfully cyclized through a Huisgen-type [3+2] cycloaddition to give a tetracyclic Pt–carbene complex that underwent insertion into the C–H bond in the β-position to give fused cyclopropanes that are otherwise inaccessible. On heating, the cyclopropanes smoothly rearranged to form the corresponding heterospiranes with excellent levels of stereoselectivity and high yields.

Key words cyclization, platinum catalysis, pyrylium ions, carbenes, heterospiranes

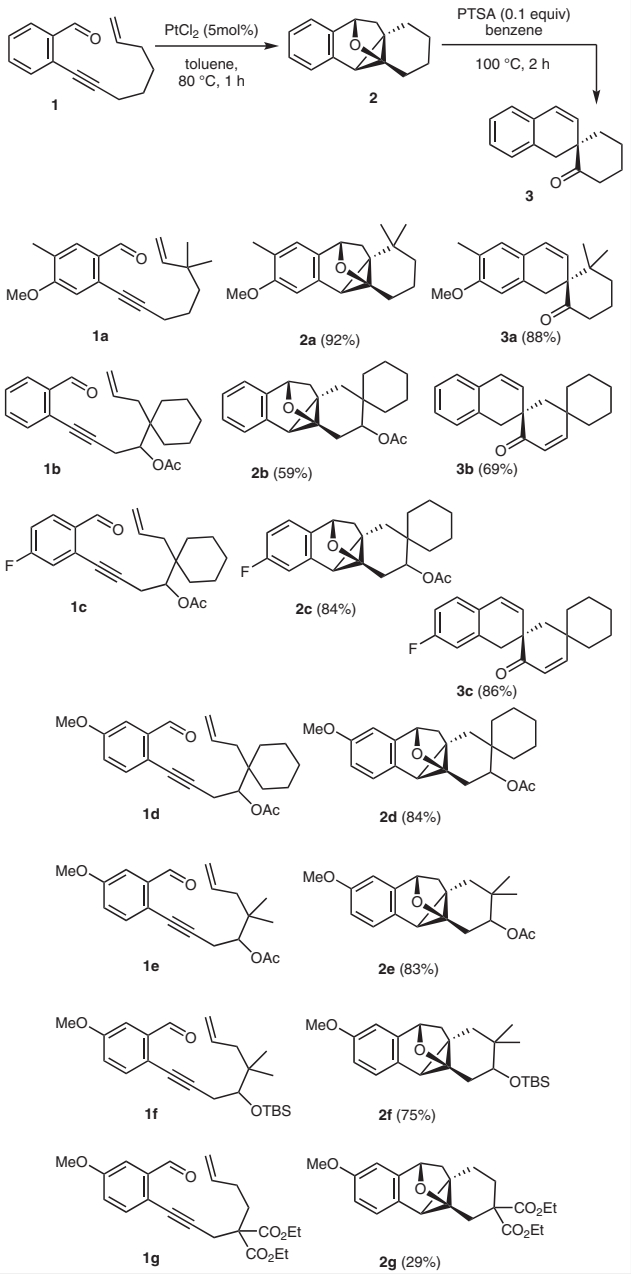
Spirocyclic compounds have garnered a considerable amount of recent attention due to their biological importance and their widespread occurrence in nature.[1] Spirocyclic compounds consist of two or more cyclic rings linked together by a common carbon.[2] The importance of spirocycles has also been illustrated by their use as valuable synthetic intermediates in total syntheses of natural products.[3] Spirocycles are also widely used in materials science.[4] Despite the utility of spirocycles, the efficient formation of the spiro quaternary carbon remains an important challenge in organic synthesis.[5] Heterospiranes are spiro compounds from biological sources that contain heteroatoms (N, O, or S) in the spirane rings or elsewhere.[6]

We have long been interested in developing methods for synthesizing a variety of polycyclic compounds by using rhodium,[7] gold,[8] or platinum catalysts.[9] The aromatic-anchored enynals **1** have been shown to generate Pt–carbene intermediates via a platinum-bound pyrylium and through a Huisgen-type [3+2] cyclization [Scheme 1(a)].[9] The Pt–carbene intermediate was expected to furnish a [6,7,6]-tricyclic (±)-faveline derivative under our initial conditions.[9c,9d] However, the Pt–carbene intermediate generated the cyclopropanes **2**, which rearranged to form spiranes **3**.[9c] Next, we extended the Pt-catalyzed cyclization to the cycloalkane-anchored enynals **4**. The cycloalkane-based enynals were catalytically converted into the corresponding tricyclic spiranes **5** in good to excellent yields [Scheme 1(b)].[9f] With this successful result, we extended our protocol to the intramolecular Pt-catalyzed spirocyclization of N-fused enynal systems to synthesize biologically interesting carbo- and heterospiranes.[5,6] Furthermore, we designed an enynal system that contained a cyclohexyl group on a pendent alkene, which we used to obtain polycyclic spiranes.



Scheme 1 Platinum-catalyzed cyclizations to form spiranes

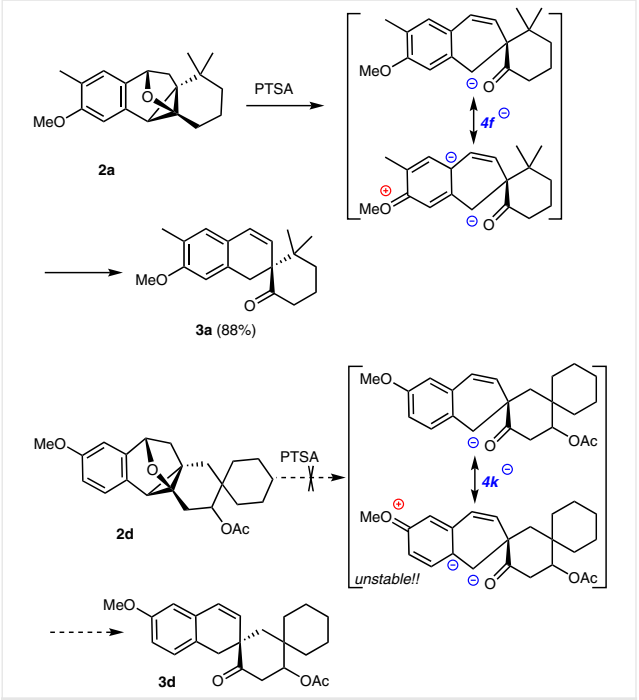
On the basis of these previous reaction trends, spirocycles **3** should be obtained via the cyclopropanes **2** (Scheme 2). We therefore examined the cyclization of enynal **1a** in the presence of a platinum catalyst under our previous reaction conditions,[9c] and we isolated cyclopropane **2a** in 91%



Scheme 2 Platinum-catalyzed cyclization to give products **2** and **3**

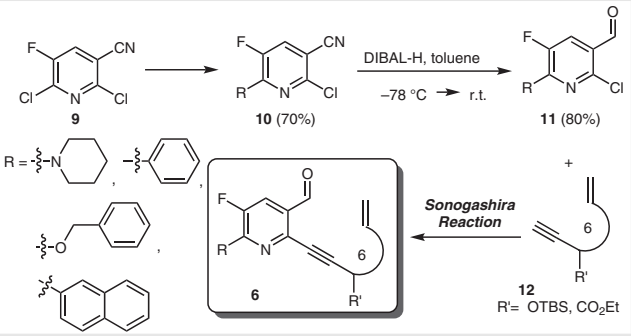
yield and, subsequently, spiro compound **3a** in 88% yield through rearrangement with a catalytic amount of 4-toluenesulfonic acid (PTSA) in refluxing benzene. To extend the substrate scope, we selected substrates **1b–d**, which contained a spirocycle-like cyclohexyl group and an oxygen-containing functional group (OAc) on the pendent alkene. The 4-fluoro-substituted substrate **1c** and 4-methoxy-substituted substrate **1d**, containing an electron-withdrawing and an electron-donating group, respectively, afforded the corresponding cyclopropanes **2c** and **2d** in 84% yield. When the products **2b** and **2c** were refluxed in benzene in the presence of PTSA, the corresponding spiro compounds **3b** and **3c** were obtained in good to excellent yields with retention of stereochemistry. The oxygen-containing OAc functional groups did not interfere with the reaction, but was eliminated during PTSA-catalyzed rearrangement. Note that products **2a–c** and **3a–c** were isolated with high levels of stereoselectivity, although these reactions generated multiple stereogenic centers that led to the formation of the several isomeric products.

Unfortunately, the rearrangement reaction of the 5-methoxy-substituted substrate **2d** was messy, and we could not establish optimal condition for this reaction. Consequently, we further studied the formation of 5-methoxy spiranes. We attempted to accomplish isomerization of cyclopropanes **2d–g**, because we suspected that the OAc and OMe groups might interact. The present method worked for **1d–g** and gave the corresponding cyclopropanes **2d–g** without any problems, but longer reaction times at the given temperature led to decomposition in all cases. These phenomena might be understood in terms of an electron-donating effect of the methoxy group, where the electron-rich methoxy group mismatched with the electron-rich carbon generated during rearrangement to the spirocycle **3d** (Scheme 3). The cyclopropanes **2e–g** showed similar phenomena. Note that **1a**, which has a methoxy substituent in the *meta*-position to the benzylic hydrogen in **2a** rearranged to the corresponding spiro compound **3a**.



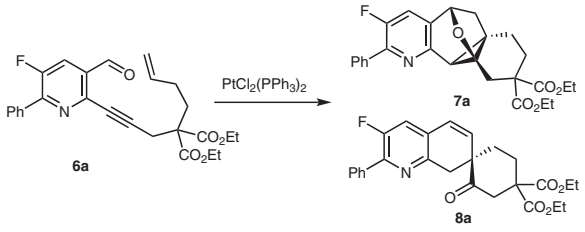
Scheme 3 Possible mechanism for the formation of spiranes **3**

Finally, we applied our previous work to a typical N-heterocyclic system, 2,6-dichloro-5-fluoronicotinonitrile (**9**; CFN). First, we prepared pyridines **6** in three steps as starting materials for the CFN system. The advantage of this method was that we could freely change the R^1 group to give various N-containing compounds substituted with piperidin-1-yl, phenyl, 2-naphthyl, or benzyloxy groups (Scheme 4).



Scheme 4 Synthesis of starting material for the CFN system

Table 1 Optimization of the Platinum-Catalyzed Reaction of Enynal **6a**[a]

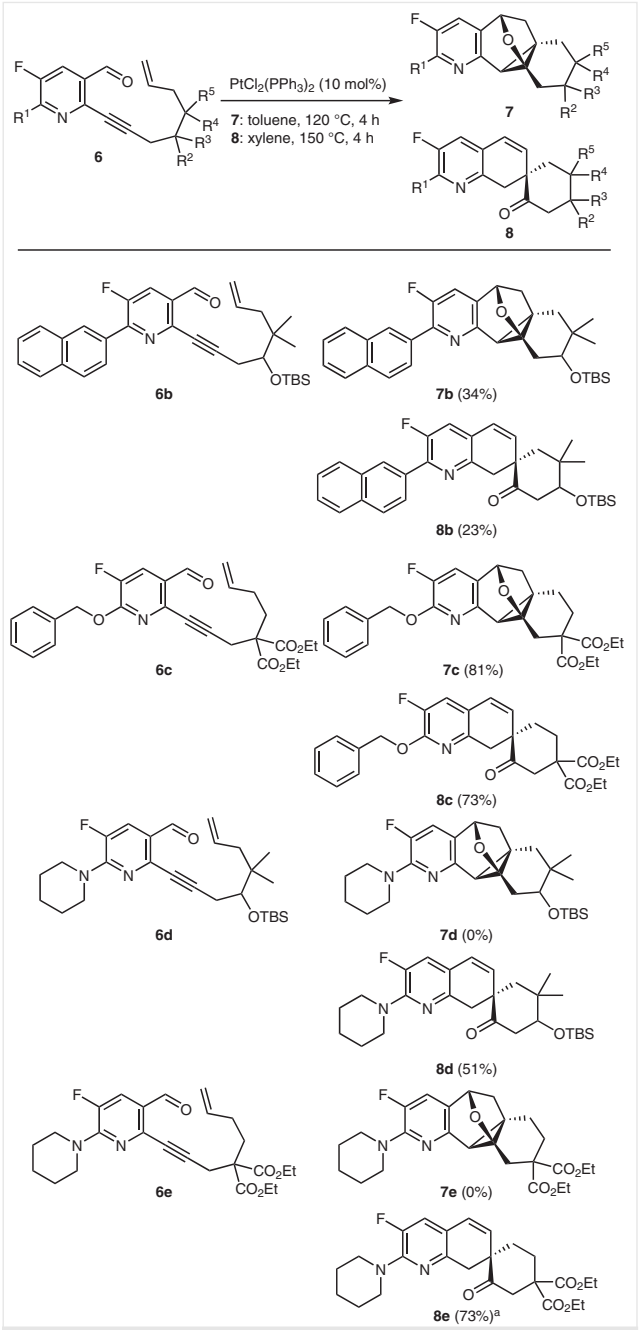


Entry	Solvent	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	toluene	120	4	**7a**	94
2	toluene	120	20	**7a** **8a**	35 8
3	DCE	80	12	**7a**	43
4	1,4-dioxane	120	8	**7a**	63
5	xylene	150	4	**8a**	78

[a] Reaction conditions: **6a** (0.40 mmol), $PtCl_2(PPh_3)_2$ (10 mol%) , under Ar.
[b] Isolated yield.

We then examined the reaction of substrate **6a** in the presence of a Pt catalyst under a variety of conditions (Table 1). First, the reaction of **6a** with $PtCl_2(PPh_3)_2$ as the catalyst proceeded smoothly in refluxing toluene to furnish product **7a** in 94% yield (Table 1, entry 1). A longer reaction time under the same conditions gave cyclopropane **7a** and spiro compound **8a** in 35 and 38% yield, respectively (entry 2). DCE, and 1,4-dioxane, could also be used as solvents for the reaction (entries 3–4). Surprisingly, when **6a** was treated with $PtCl_2(PPh_3)_2$ at 150 °C for four hours in xylene, the reaction gave spiro compound **8a** in 78% yield (entry 5).

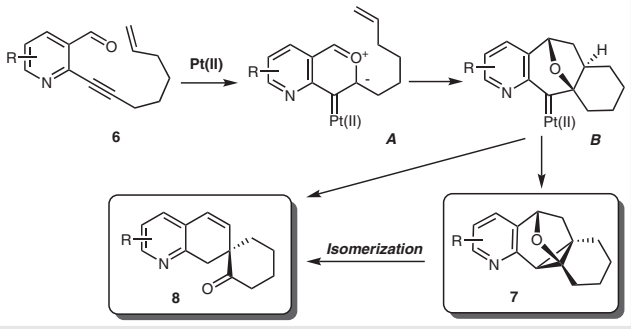
We then used a variety of substrates to explore the scope and limitations of this reaction. Most of the substrates gave the corresponding products **7**[10] and **8**[11] in good to excellent yields, but compound **6b**, which contained a 2-naphthyl group, gave products **7b** and **8b** in reduced yields (Scheme 5). On the other hand, when substrate **6c** was



Scheme 5 Platinum-catalyzed cyclization of CFN systems. *Reaction conditions*: **6** (0.40 mmol) $PtCl_2(PPh_3)$ (10 mol%); (for product **7**): toluene, 120 °C, 4 h, under Ar; or (for product **8**) xylene, 150 °C, 4 h, under Ar. Isolated yields are reported.
[a] Hexane was used instead of xylene.

treated under the same condition, product **7c** was obtained in an excellent yield. When substrate **6c** was treated with $PtCl_2(PPh_3)_2$ in refluxing xylene (150 °C) for four hours, the spiro compound **8c** was obtained in 73% yield. Unfortunately, substrates **6d** and **6e**, which contain a piperidin-1-yl group, did not form the corresponding cyclopropane compound; instead, the spiranes **8d** and **8e** were obtained in 51 and 73% yield, respectively. Interestingly, the OTBS group of substrate **8d** was not eliminated during the Pt-catalyzed isomerization. The product **8e** was formed in a high yield on changing the solvent to hexane (Scheme 5).

In our proposed mechanism, intermediate ***A*** undergoes [3+2] cycloaddition to the pendent double bond to form the Pt–carbene complex ***B***. The Pt–carbene complex ***B*** inserts into the tertiary C–H bond to form the cyclopropane intermediate **7**, which then isomerizes to the corresponding spirane **8** on heating or under PTSA-catalyzed conditions (Scheme 6).[9c,9f]



Scheme 6 Proposed mechanism for the formation of **7** and **8**

The Pt-catalyzed cycloisomerization of aromatic and N-heterocyclic aldehydes substituted with a enynyl group at the 2-position gave the corresponding spirocycles isolated in high to excellent yields via cyclopropane intermediates. This reaction is a valuable choice for the synthesis of certain spirocyclic compounds.

Funding Information

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Supporting Information

Supporting information for this article (copies of ^1H and ^{13}C NMR spectra for compounds **2b–g**, **3b–c**, **7a–c**, **8a–e**) is available online at https://doi.org/10.1055/s-0036-1591489.

References and Notes

(1) (a) Müller, G.; Berkenbosch, T.; Benningshof, J. C. J.; Stumpfe, D.; Bajorath, J. *Chem. Eur. J.* **2017**, *23*, 703. (b) Zheng, Y.; Tice, C. M.; Singh, S. B. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3673. (c) Blunt, J. W.; Copp, B. R.; Keyzers, R. A.; Munro, M. H. G.; Prinsep, M. R. *Nat. Prod. Rep.* **2014**, *31*, 160. (d) Carreira, E. M.; Fessard, T. C. *Chem. Rev.* **2014**, *114*, 8257.

(2) (a) Mihiş, A.; Golban, L. B.; Raţ, C. I.; Bogdan, E.; Terec, A.; Grosu, I. *Struct. Chem.* **2012**, *23*, 61. (b) Terec, A.; Grosu, I.; Condamine, E.; Breau, L.; Plé, G.; Ramondenc, Y.; Rochon, F. D.; Peulon-Agasse, V.; Opris, D. *Tetrahedron* **2004**, *60*, 3173. (c) Grosu, I.; Bogdan, E.; Plé, G.; Toupet, L.; Ramondenc, Y.; Condamine, E.; Peulon-Agasse, V.; Balog, M. *Eur. J. Org. Chem.* **2003**, 3153. (d) Balog, M.; Grosu, I.; Plé, G.; Ramondenc, Y.; Toupet, L.; Condamine, E.; Lange, C.; Loutelier-Bourhis, C.; Peulon-Agasse, V.; Bogdan, E. *Tetrahedron* **2004**, *60*, 4789. (e) Grosu, I.; Plé, G.; Mager, S.; Martinez, R.; Mesaros, C.; del Carmen Camacho, B. *Tetrahedron* **1997**, *53*, 6215.

(3) (a) Kong, K.; Moussa, Z.; Lee, C.; Romo, D. *J. Am. Chem. Soc.* **2011**, *133*, 19844. (b) Fuse, S.; Inaba, K.; Takagi, M.; Tanaka, M.; Hirokawa, T.; Johmoto, K.; Uekusa, H.; Shin-ya, K.; Takahashi, T.; Doi, T. *Eur. J. Med. Chem.* **2013**, *66*, 180. (c) Smith, L. K.; Baxendale, I. R. *Org. Biomol. Chem.* **2015**, *13*, 9907.

(4) (a) Kang, F.-A.; Sui, Z. *Tetrahedron Lett.* **2011**, *52*, 4204. (b) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.

(5) (a) Rios, R. *Chem. Soc. Rev.* **2012**, *41*, 1060. (b) Hsu, D.-S.; Chen, C.-H.; Hsu, C.-W. *Eur. J. Org. Chem.* **2016**, 589. (c) Kotha, S.; Deb, A. C.; Lahiri, K.; Manivannan, E. *Synthesis* **2009**, 165. (d) Brimble, M. A.; Stubbing, L. A. *Top. Heterocycl. Chem.* **2014**, *35*, 189. (e) Chabaud, L.; Raynal, Q.; Barre, E.; Guilloua, C. *Adv. Synth. Catal.* **2015**, *357*, 3880. (f) Mostinski, Y.; Lankri, D.; Tsvelikhovsky, D. *Synthesis* **2017**, *49*, 2361.

(6) (a) Undheim, K. *Synthesis* **2014**, *46*, 1957. (b) Undheim, K. *Synthesis* **2015**, *47*, 2497. (c) Undheim, K. *Synthesis* **2017**, *49*, 705. (d) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213.

(7) (a) Shin, S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429. (b) Oh, C. H.; Reddy, K. V. *Bull. Korean Chem. Soc.* **2007**, *28*, 1927.

(8) (a) Gupta, A. K.; Rhim, C. Y.; Oh, C. H.; Mane, R. S.; Han, S.-H. *Green Chem.* **2006**, *8*, 25. (b) Oh, C. H.; Kim, A.; Park, W.; Park, D. I.; Kim, N. *Synlett* **2006**, *17*, 2781. (c) Oh, C. H.; Kim, A. *New J. Chem.* **2007**, *31*, 1719. (d) Oh, C. H.; Kim, A. *Synlett* **2008**, 777. (e) Oh, C. H.; Lee, S. J.; Lee, J. H.; Na, Y. J. *Chem. Commun.* **2008**, 5794. (f) Oh, C. H.; Karmakar, S. *J. Org. Chem.* **2009**, *74*, 370. (g) Karmakar, S.; Kim, A.; Oh, C. H. *Synthesis* **2009**, 194. (h) Oh, C. H.; Karmakar, S.; Park, H. S.; Ahn, Y. C.; Kim, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 1792. (i) Oh, C. H.; Piao, L.; Kim, J. H. *Synthesis* **2013**, *45*, 174. (j) Oh, C. H.; Kim, J. H.; Oh, B. K.; Park, J. R.; Lee, J. H. *Chem. Eur. J.* **2013**, *19*, 2592. (k) Oh, C. H.; Kim, J. H.; Piao, L.; Yu, J.; Kim, S. Y. *Chem. Eur. J.* **2013**, *19*, 10501. (l) Lee, Y. J.; Heo, H. G.; Oh, C. H. *Tetrahedron* **2016**, *72*, 6113.

(9) (a) Oh, C. H.; Reddy, V. R.; Kim, A.; Rhim, C. Y. *Tetrahedron Lett.* **2006**, *47*, 5307. (b) Oh, C. H.; Lee, J. H.; Lee, S. J.; Kim, J. I.; Hong, C. S. *Angew. Chem. Int. Ed.* **2008**, *47*, 7505. (c) Oh, C. H.; Lee, J. H.; Lee, S. M.; Yi, H. J.; Hong, C. S. *Chem. Eur. J.* **2009**, *15*, 71. (d) Oh, C. H.; Lee, S. M.; Hong, C. S. *Org. Lett.* **2010**, *12*, 1308. (e) Oh, C. H.; Yi, H. J.; Lee, J. H.; Lim, D. H. *Chem. Commun.* **2010**, *46*, 3007. (f) Oh, C. H.; Tak, S. Y.; Lee, J. H.; Piao, L. *Bull. Korean Chem. Soc.* **2011**, *32*, 2978. (g) Kim, J. H.; Ray, D.; Hong, C. S.; Han, J. W.; Oh, C. H. *Chem. Commun.* **2013**, *49*, 5690. (h) Han, J. W.; Lee, J. H.; Oh, C. H. *Synlett* **2013**, *24*, 1433.

(10) **Heterocyclopropane 7a; Typical Procedure**
A new 5 mL test tube was charged with the 2-alkynylnicotinaldehyde **6a** (0.40 mmol), $PtCl_2(PPh_3)_2$ (11 mg, 0.04 mmol), and anhyd toluene (1.5 mL) at 0 °C under argon. The mixture was stirred for 4 h in a preheated oil bath (120 °C). When the reac-

tion was complete (TLC), the solvent was removed under vacuum, and the crude product was purified by flash column chromatography (silica gel, hexane–EtOAc) to give a yellow oil; yield: 169 mg (94%); R_f = 0.41 (EtOAc–hexane, 1:4). IR (NaCl): 2980, 1732, 1440, 1244 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.0 Hz, 2 H), 7.49–7.46 (m, 2 H), 7.42 (d, *J* = 7.2 Hz, 1 H), 7.24 (d, *J* = 10.0 Hz, 1 H), 5.13 (d, *J* = 5.6 Hz, 1 H), 4.30–4.16 (m, 4 H), 3.12 (d, *J* = 15.2 Hz, 1 H), 2.45 (s, 1 H), 2.30 (d, *J* = 14.4 Hz, 2 H), 2.18–2.11 (m, 1 H), 1.93–1.78 (m, 3 H), 1.42 (d, *J* = 11.6 Hz, 1 H), 1.30 (t, *J* = 7.2 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 170.8, 157.2, 154.6, 148.8, 148.7, 144.8, 144.7, 135.7, 135.6, 128.9, 128.8, 128.8, 128.5, 118.3, 118.1, 73.8, 61.9, 61.7, 61.7, 53.3, 33.7, 31.4, 30.7, 26.5, 22.8, 21.6, 14.2, 14.1. HRMS (ESI): *m/z* [M + Na]$^+$ calcd for $C_{26}H_{26}FNNaO_5$: 474.1688; found: 474.1691.

(11) **Spiro(cyclohexane-1,7′-quinoline) 8a; Typical Procedure**

A new 5 mL test tube was charged with the 2-alkynylnicotinaldehyde **6a** (0.40 mmol), $PtCl_2(PPh_3)_2$ (11 mg, 0.04 mmol), and anhyd xylene (1.5 mL) at 0 °C under argon. The mixture was stirred for 1 h in a preheated oil bath (150 °C) until the reaction was complete (TLC). The solvent was removed under vacuum, and the crude product was purified by flash column chromatography (silica gel, hexane–EtOAc) to give a yellow oil; yield: 140 mg (78%); R_f = 0.33 (EtOAc–hexane, 1:4). IR (NaCl): 2981, 1731, 1441, 1249, 1249 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.96 (d, *J* = 8.4 Hz, 2 H), 7.49–7.39 (m, 3 H), 7.13 (d, *J* = 11.2 Hz, 1 H), 6.52 (d, *J* = 9.2 Hz, 1 H) , 6.15 (d, *J* = 9.6 Hz, 1 H), 4.27–4.19 (m, 4 H), 3.36 (d, *J* = 16.0 Hz, 1 H), 3.10 (d, *J* = 16.0 Hz, 1 H), 2.92 (ABq, Δδ = 38.8 Hz, *J* = 15.2 Hz, 2 H), 2.44–2.28 (m, 2 H), 1.91–1.85 (m, 2 H), 1.26 (t, *J* = 7.2 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.0, 170.4, 170.1, 158.0, 155.4, 149.6, 149.5, 143.8, 143.7, 135.4, 135.4, 132.7, 132.6, 129.2, 129.1, 128.9, 128.9, 128.8, 128.8, 128.6, 127.9, 127.8, 126.3, 121.1, 120.9, 62.2, 62.2, 57.5, 50.6, 42.5, 38.4, 32.0, 26.0, 14.1. HRMS (ESI): *m/z* [M + Na]$^+$calcd for $C_{26}H_{26}FNNaO_5$: 474.1688; found: 474.1695.