Organic LETTERS

Letter

pubs.acs.org/OrgLett

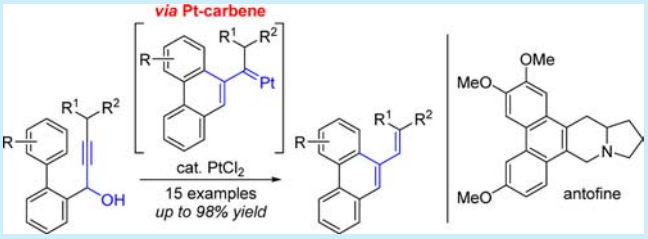
Platinum-Catalyzed Synthesis of Substituted Phenanthrenes from Biphenyl Propargyl Alcohols via a Carbene Intermediate

Yongseok Kwon, Illan Kim, and Sanghee Kim*

College of Pharmacy, Seoul National University, Seoul 151-742, Korea

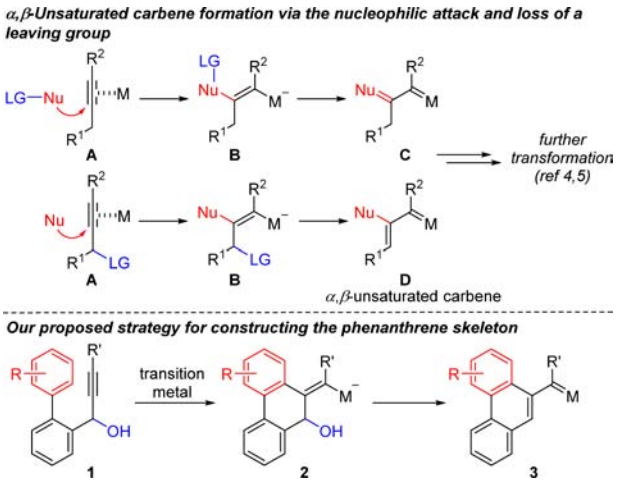
Supporting Information

ABSTRACT: An efficient synthesis for phenanthrenes via a Pt−carbene intermediate is described. Using Pt as a catalyst, the readily accessible biphenyl propargyl alcohol substrate can be transformed to the vinylphenanthrene system through a cascade involving electrophilic cyclization, dehydration, and 1,2-H migration. The synthetic utility and efficiency of this protocol were demonstrated via the concise total synthesis of antofine.



Recent advances in transition-metal catalysis have provided facile access to various types of metal carbenes from the alkyne functional group.[1] Among metal carbenes, the α,β-unsaturated carbene has attracted considerable interest in recent years because it offers the potential for a substantial increase in molecular complexity.[2−5] As shown in Scheme 1, the transition-metal-assisted formation of α,β-unsaturated carbene from alkyne is achieved through an initial nucleophilic attack on the π-coordinated alkyne **A** to afford the vinylmetal species **B** followed by loss of the leaving group. Depending on the position of the leaving group, different types of carbene complexes (**C** or **D**) can be formed.[4,5] A variety of functional groups, such as hydroxy,[4a,b] hydroxylamine,[4c] phenylamine,[4d−g] urea,[4h] *N*-oxide,[4i] and azide groups,[4j,k] can serve as the nucleophile in this reaction. A carbon−carbon double bond or aromatic ring can also function as a nucleophile. However, only a few such examples have been reported in the literature,[4g,5] despite the great potential for the construction of a wide range of carbocyclic compounds.

Scheme 1. Proposed Strategy for the Construction of Phenanthrenes via Nucleophilic Attack and Loss of a Leaving Group



During the course of our research on the synthesis of polyaromatic natural products and their analogues, we required new and facile synthetic methods for phenanthrene rings. We envisioned that a phenanthrene carbon skeleton could be derived from the 2-propargylbiphenyl derivative **1** (Scheme 1) via transition-metal-assisted intramolecular cyclization. The subsequent loss of a hydroxy group would afford the α,β-unsaturated carbene functional group, thereby completing the formation of the phenanthrene system. The carbene functional unit in the anticipated intermediate **3** might participate in various reactions, thus providing considerable opportunities for preparing a variety of phenanthrene-based compounds.

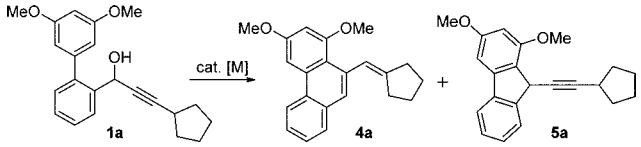
For this transformation to be successful, the regioselectivity issue would need to be overcome, i.e., the competition between the formation of 5-, 6-, and 7-membered rings. We hypothesized that this issue could be solved through the careful choice of metal catalysts based on our and others' reports of a cyclization process toward the formation of polyaromatic compounds such as phenanthrene[6] and naphthothiophene.[5a,b] Herein, we report our results regarding the formation of phenanthrene via platinum−carbene intermediates and the concise total synthesis of a phenanthroindolizidine alkaloid through the use of this efficient synthetic protocol.

The feasibility of our proposed approach for obtaining phenanthrene rings was examined using easily accessible biaryl propargyl alcohol **1a**[7] (Table 1). In this model substrate, a simple cyclopentyl group was attached to the alkyne terminus to avoid complications during the cyclization process, particularly those resulting from the presence of the carbene functional group. To achieve the envisioned cyclization process, various alkynophilic metal catalysts (10 mol %) were screened in toluene (0.05 M) at 80 °C (oil bath). Several metal catalysts, including $Pd(OAc)_2$ and

Received: August 20, 2014
Published: September 11, 2014

dx.doi.org/10.1021/ol502465e | *Org. Lett.* 2014, 16, 4936−4939

Table 1. Optimization of the Reaction Conditions[a]



					yield[b] (%)	
entry	catalyst (10 mol %)	solvent	temp (°C)	time (h)	4a	5a
1	$Pd(OAc)_2$	toluene	80	20	0	0
2	$Cp(PPh_3)_2RuCl$	toluene	80	20	0	0
3	$InCl_3$	toluene	80	2	0	80 (78)[c]
4	AgOTf	toluene	80	1	0	62
5	AuCl	toluene	80	20	16	33
6	$AuCl_3$	toluene	80	2	21	39
7	$PtCl_2$	toluene	80	1	98 (96)[c]	0
8	$PtCl_4$	toluene	80	1	88	5
9	$PtBr_2$	toluene	80	1	76	16
10	$PtCl_2$	$ClCH_2CH_2Cl$	80	10	76	9
11	$PtCl_2$	THF	80	1	89	6

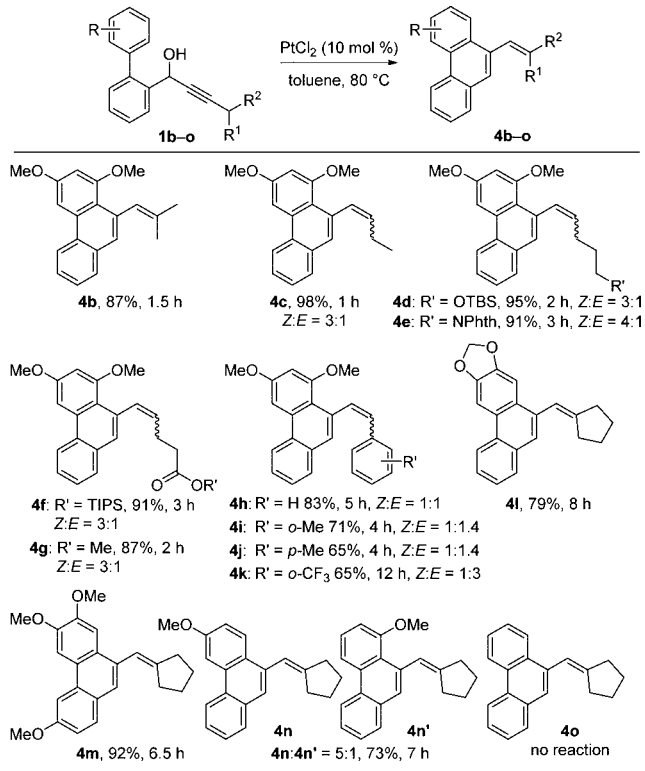
[a]Reaction conditions: **1a** (0.1 mmol) and metal catalyst (0.01 mmol, 10 mol %) in solvent (2 mL). [b]Yield determined by ^1H NMR using 1,1,2,2-tetrachloroethane as the internal standard. [c]The value in parentheses indicates the isolated yield.

a Ru complex, were found to be ineffective at promoting the reaction, and recovery of the starting material or decomposition was observed (entries 1 and 2). The reactions using $InCl_3$ and AgOTf as the catalyst resulted in good conversions of the starting material, but they only afforded the undesired product fluorene **5a** (entries 3 and 4).[8] When more carbophilic Au salts were employed, such as AuCl and $AuCl_3$, the desired phenanthrene **4a** was formed, but in low yield. Substantial amounts of fluorene **5a** were also formed (entries 5 and 6).

Among the tested metal species, Pt salts induced the desired cyclization most efficiently. Under the screening conditions, the use of $PtCl_2$ resulted in the formation of phenanthrene **4a** in 1 h in excellent yield (98%) without noticeable formation of any side products (entry 7). Other Pt salts, such as $PtCl_4$ and $PtBr_2$, afforded the desired product with satisfactory results. However, these salts were found to be less effective than $PtCl_2$ with respect to reaction yield and selectivity (entries 8 and 9). The reaction with $PtCl_2$ also proceeded in $ClCH_2CH_2Cl$ and THF, but the yield and selectivity were slightly lower (entries 10 and 11).

With the optimal conditions in hand, we examined the substrate scope of this reaction. We first investigated alkyne substrates with various attached groups (Scheme 2). All of the examined substrates showed exclusive preference for cyclization to phenanthrene over the competing cyclization pathways. The reaction of alkyne **1b** bearing an isopropyl group afforded the disubstituted vinylphenanthrene **4b** in 87% yield. The *n*-propyl-substituted alkyne **1c** also underwent smooth cyclization to yield the monosubstituted vinylphenanthrene **4c** in excellent yield. The reaction of this substrate afforded a mixture of *Z* and *E* isomers in a 3:1 ratio. Other primary alkyl group substituted alkynes **1d**–**g** readily produced the corresponding products in high yields and with similar *Z*/*E* ratios.[9] The successful results obtained with substrates **1d**–**g** illustrated the good functional group tolerance and the potential usefulness of the reaction, as these substrates possessed synthetically valuable functional groups such as a silyl-protected alcohol, *N*-phthalimide-protected amine, and ester groups. The benzyl substrate **1h** (R^1 = Ph, R^2 = H, Scheme 2) also successfully yielded phenanthrene **4h**, but the *Z*/*E* ratio of the isomers was only 1:1. When an electron-donating methyl group was present on the

Scheme 2. Substrate Scope of Biaryl Propargyl Alcohols[a]



[a]Reaction conditions: **1** (0.1 mmol) and $PtCl_2$ (0.01 mmol, 10 mol %) in toluene (2 mL)

benzene ring, the *Z*/*E* ratio of the product (**4i** and **4j**) was not significantly changed.[10] However, with an electron-withdrawing trifluoromethyl group in the ortho position (substrate **1k**), the *Z*/*E* ratio of the product (**4k**) changed to 1:3.

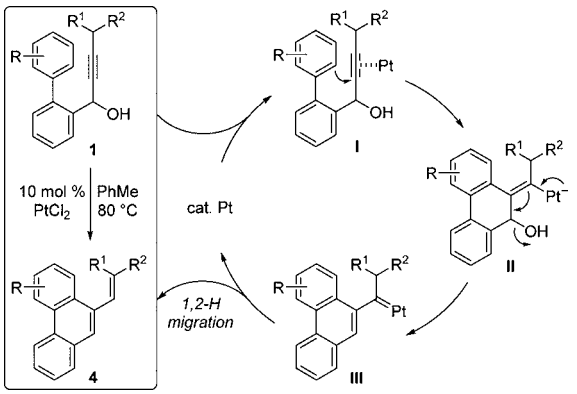
To explore the substrate scope further, the reaction was extended to other biphenyl systems (Scheme 2). The substrates bearing electron-donating groups, such as 3,4-methylenedioxy or 3,4-dimethoxy groups, on the upper ring of the biphenyl backbone underwent smooth cyclization to afford phenanthrene

dx.doi.org/10.1021/ol502465e | Org. Lett. 2014, 16, 4936–4939

products **4l** and **4m** in high yield. The reaction of the 3-methoxy-functionalized substrate afforded a 5:1 regiochemical mixture of phenanthrene products **4n** and **4n′**, favoring cyclization on the less hindered position. Substrate **1o** with an unfunctionalized biphenyl backbone failed to give the desired phenanthrene product **4o**, even under prolonged high temperature conditions, due to the lower nucleophilicity of its aryl ring.

Scheme 3 illustrates the proposed mechanism for the production of substituted vinyl phenanthrenes **4**. First, the triple

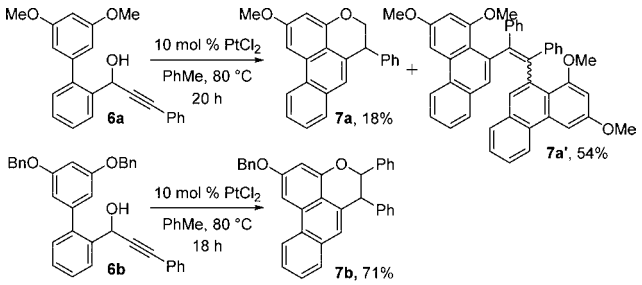
Scheme 3. Plausible Mechanistic Pathway for the Formation of Vinylphenanthrenes



bond coordinates to platinum to render it susceptible to nucleophilic attack by the aromatic ring. Intramolecular cyclization of the metal-activated alkyne complex **I** produces the phenanthrene carbon skeleton **II** with a vinylmetal functional unit. Subsequent loss of a hydroxy group with the assistance of the metal would give Pt-carbene intermediate **III**. Although various characteristic reactions of the carbene complex could have occurred, this carbene intermediate underwent 1,2-H migration[11] to afford vinylphenanthrene product **4**.

To demonstrate the involvement of a carbene intermediate in this reaction, we prepared substrate **6a**, in which a 1,2-H migration is not possible (Scheme 4). Treatment of **6a** with $PtCl_2$

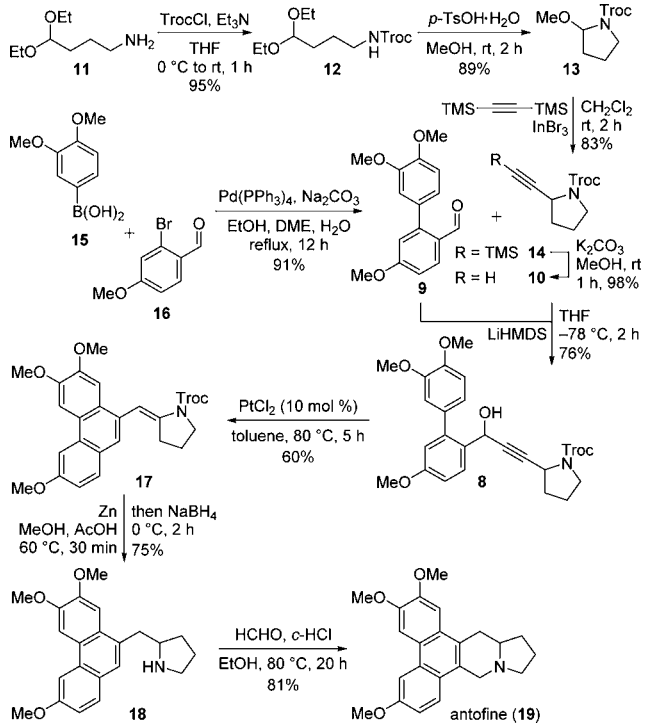
Scheme 4. C−H Insertion and Dimerization of Pt−Carbene Complexes



in toluene at 80 °C under a N_2 atmosphere resulted in formation of a mixture of phenanthrene products **7a** and **7a′**, which might arise from C−H insertion[3d,12] and dimerization[13] of the carbene intermediate, respectively. When the methoxy group of **6b** was replaced with a benzyloxy group, which has more acidic C−H bonds, tandem cyclization occurred in good yield (71%) to afford the polycyclic C−H insertion product **7b**.[14] These results strongly suggested that a Pt−carbene is a key intermediate in this cascade and encouraged further exploration of this transformation for the synthesis of more sophisticated polycyclic compounds by taking advantage of the high versatility of carbene species.

To illustrate the synthetic utility of our method, a concise synthetic route was developed for the synthesis of a representative phenanthroindolizidine alkaloid, antofine,[15] which possesses significant antiproliferative activity (Scheme 5). Our key synthetic intermediate was biaryl propargyl alcohol **8**.

Scheme 5. Total Synthesis of Antofine



This intermediate was readily synthesized through the reaction of aldehyde **9** with the acetylide derived from **10**. Intermediate **10** was obtained in four steps from commercially available 4-aminobutyraldehyde acetal **11**. The amine group of **11** was protected as a Troc carbamate. The Troc-protected acetal **12** was treated with TsOH in MeOH to afford cyclic hemiaminal ether **13** in good yield.[16] Terminal alkyne **10** was produced in good overall yield by treating *N,O*-acetal **13** with bis(trimethylsilyl)-acetylene in the presence of $InBr_3$ in CH_2Cl_2[17] followed by desilylation using K_2CO_3 in methanol. Another precursor for key intermediate, aldehyde **9**, was easily prepared in high yield through Suzuki coupling of arylboronic acid **15** with aryl bromide **16**, both of which are commercially available.

Propargyl alcohol **8** was treated with $PtCl_2$ to induce an intramolecular cyclization. This reaction afforded phenanthrene **17** in 60% yield. In this case, only the *E* isomer was produced.[18] Reductive removal of the Troc group of **17** with Zn/AcOH in MeOH, followed by the sequential addition of $NaBH_4$, led to the formation of known pyrrolidine **18**[19] in 75% yield. Finally, Pictet−Spengler annulation of pyrrolidine **18**, using the previously reported reaction conditions, furnished antofine (**19**) in 81% yield; the spectroscopic data were in good agreement with those reported in the literature.[19] Thus, we completed the synthesis of antofine in nine total steps starting from commercially available materials, with the longest linear sequence being eight steps. Our efficient synthetic strategy could

dx.doi.org/10.1021/ol502465e | Org. Lett. 2014, 16, 4936−4939

be applied to the divergent synthesis of phenanthroindolizidines by preparing a series of polysubstituted biaryl aldehydes.

In conclusion, we have developed a Pt(II)-catalyzed synthesis of phenanthrenes from readily accessible biaryl propargyl alcohol substrates. In the presence of a catalytic amount of $PtCl_2$, intramolecular cyclization and subsequent dehydration are utilized to obtain a phenanthrene with a carbene functional group. The resulting carbene rapidly undergoes 1,2-H migration to afford a vinylphenanthrene system. The reaction proceeds under mild conditions and tolerates important functional groups, thus allowing the synthesis of functionalized phenanthrene compounds. This efficient synthetic protocol has potential for the rapid synthesis of various biologically intriguing phenanthrene alkaloids, as demonstrated by the concise synthesis of antofine.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of all new compounds and preparation of starting materials. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: pennkim@snu.ac.kr.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Mid-Career Researcher Program (No. 2013R1A2A1A01015998) of the National Research Foundation of Korea (NRF) grant funded by the Korean government (MSIP). This work was also supported by NRF (National Research Foundation of Korea) Grant funded by the Korean Government (NRF-2012-Fostering Core Leaders of the Future Basic Science Program).

■ REFERENCES

(1) For selected reviews, see: (a) Furstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (d) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (e) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (f) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (g) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410.

(2) For reviews on the transition metal-catalyzed acyloxy migration of propargyl esters, see: (a) Shu, X.-Z.; Shu, D.; Schienebeck, C. M.; Tang, W. *Chem. Soc. Rev.* **2012**, *41*, 7698. (b) Xiao, J.; Li, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 7226. (c) Wang, S.; Zhang, G.; Zhang, L. *Synlett* **2010**, 692. (d) Marion, N.; Nolan, S. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 2750. (e) Marco-Contelles, J.; Soriano, E. *Chem.—Eur. J.* **2007**, *13*, 1350.

(3) For recent examples of reactions via α,β-unsaturated metal carbene, see: (a) Xia, Y.; Qu, S.; Xiao, Q.; Wang, Z.-X.; Qu, P.; Chen, L.; Liu, Z.; Tian, L.; Huang, Z.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2013**, *135*, 13502. (b) Sanz, R.; Miguel, D.; Gohain, M.; García-García, P.; Fernández-Rodríguez, M. A.; González-Pérez, A.; Nieto-Faza, O.; de Lera, Á. R.; Rodríguez, F. *Chem.—Eur. J.* **2010**, *16*, 9818. (c) Dudnik, A. S.; Xia, Y.; Li, Y.; Gevorgyan, V. *J. Am. Chem. Soc.* **2010**, *132*, 7645. (d) Oh, C. H.; Lee, J. H.; Lee, S. J.; Kim, J. I.; Hong, C. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 7505. (e) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598. (f) Lin, G.-Y.; Li, C.-W.; Hung, S.-H.; Liu, R.-S. *Org. Lett.* **2008**, *10*, 5059. (g) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160. (h) Peng, L.; Zhang, X.; Zhang, S.; Wang, J. *J. Org. Chem.* **2007**, *72*, 1192.

(4) For select examples of the heteroatom-based nucleophilic attack and loss of a leaving group, see: (a) Allegretti, P. A.; Ferreira, E. M. *J. Am. Chem. Soc.* **2013**, *135*, 17266. (b) Allegretti, P. A.; Ferreira, E. M. *Org. Lett.* **2011**, *13*, 5924. (c) Allegretti, P. A.; Ferreira, E. M. *Chem. Sci.* **2013**, *4*, 1053. (d) Yang, W.; Wang, T.; Yu, Y.; Shi, S.; Zhang, T.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2013**, *355*, 1523. (e) Shu, D.; Song, W.; Li, X.; Tang, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3237. (f) Shu, D.; Winston-McPherson, G. N.; Song, W.; Tang, W. *Org. Lett.* **2013**, *15*, 4162. (g) Saito, K.; Sogou, H.; Suga, T.; Kusama, H.; Iwasawa, N. *J. Am. Chem. Soc.* **2010**, *133*, 689. (h) Nakamura, I.; Sato, Y.; Terada, M. *J. Am. Chem. Soc.* **2009**, *131*, 4198. (i) Ye, L.; Cui, L.; Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 3258. (j) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349. (k) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260.

(5) For select examples of the carbon-based nucleophilic attack and loss of a leaving group, see: (a) Tsai, F.-Y.; Lo, J.-X.; Hsu, H.-T.; Lin, Y.-C.; Huang, S.-L.; Wang, J.-C.; Liu, Y.-H. *Chem.—Asian J.* **2013**, *8*, 2833. (b) Tsai, F.-Y.; Ma, H.-W.; Huang, S.-L.; Lin, Y.-C.; Wang, Y.; Liu, Y.-H. *Chem.—Eur. J.* **2012**, *18*, 3399. (c) Chung, C.-P.; Chen, C.-C.; Lin, Y.-C.; Liu, Y.-H.; Wang, Y. *J. Am. Chem. Soc.* **2009**, *131*, 18366. (d) Taduri, B. P.; Sohel, S. M. A.; Cheng, H.-M.; Lin, G.-Y.; Liu, R.-S. *Chem. Commun.* **2007**, 2530.

(6) Kwon, Y.; Cho, H.; Kim, S. *Org. Lett.* **2013**, *15*, 920.

(7) See the Supporting Information for synthetic details.

(8) For the Lewis acid-catalyzed Friedel—Crafts cyclization reactions of biaryl alcohols, see: Li, G.; Wang, E.; Chen, H.; Li, H.; Liu, Y.; Wang, P. G. *Tetrahedron* **2008**, *64*, 9033.

(9) The ratio of *Z*/*E* isomer was not significantly changed when the catalyst, solvents, and reaction time were varied.

(10) Prolonged reaction time did not change the *Z*/*E* ratio of the products.

(11) For select 1,2-H shifts of metal carbenes, see: (a) Cho, E. J.; Lee, D. *Adv. Synth. Catal.* **2008**, *350*, 2719. (b) Zhang, G.; Catalano, V. J.; Zhang, L. *J. Am. Chem. Soc.* **2007**, *129*, 11358. (c) Kusama, H.; Yamabe, H.; Onizawa, Y.; Hoshino, T.; Iwasawa, N. *Angew. Chem., Int. Ed.* **2005**, *44*, 468. (d) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908. (e) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4163. See also ref 4a and references cited therein.

(12) (a) Cambeiro, F.; López, S.; Varela, J. A.; Saá, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 723. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (c) For a recent review of catalytic carbene insertion into C—H bonds, see: Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704.

(13) (a) Chu, G. M.; Fernández, I.; Sierra, M. A. *J. Org. Chem.* **2013**, *78*, 865. (b) Barluenga, J.; de Sáa, D.; Gómez, A.; Ballesteros, A.; Santamaría, J.; de Prado, A.; Tomás, M.; Suárez-Sobrino, A. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6225. (c) Bertani, R.; Biasiolo, M.; Darini, K.; Michelin, R. A.; Mozzon, M.; Visentin, F.; Zanotto, L. *J. Organomet. Chem.* **2002**, *642*, 32.

(14) Structure of **7b** was further confirmed after being converted to the fully aromatized compound.

(15) For a recent total synthesis of antofine, see: (a) Yi, M.; Gu, P.; Kang, X.-Y.; Sun, J.; Li, R.; Li, X.-Q. *Tetrahedron Lett.* **2014**, *55*, 105. (b) Ying, W.; Herndon, J. W. *Eur. J. Org. Chem.* **2013**, 3112. (c) Niphakis, M. J.; Georg, G. I. *Org. Lett.* **2011**, *13*, 196. (d) Pansare, S. V.; Lingampally, R.; Dyapa, R. *Eur. J. Org. Chem.* **2011**, 2235.

(16) (a) King, F. D. *Tetrahedron* **2007**, *63*, 2053. (b) Pichon, M.; Figadère, B.; Cavé, A. *Tetrahedron Lett.* **1996**, *37*, 7963.

(17) Lundkvist, J. R. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1989**, *32*, 863.

(18) The geometry of the double bond was determined on the basis of NOESY correlations. For more details, see the Supporting Information.

(19) (a) Lebrun, S.; Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1999**, *55*, 2659. (b) Kim, S.; Lee, J.; Lee, T.; Park, H.-g.; Kim, D. *Org. Lett.* **2003**, *5*, 2703.