JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

# Enantioselective Total Synthesis of (−)-Incarviatone A

Benke Hong,[†,‡,∥] Chao Li,[†,∥] Zhen Wang,[§] Jie Chen,[‡] Houhua Li,[*,§] and Xiaoguang Lei[*,†,§]

[†]Beijing National Laboratory for Molecular Sciences, Department of Chemical Biology, College of Chemistry and Molecular Engineering, Synthetic and Functional Biomolecules Center, and Peking-Tsinghua Center for Life Sciences, Peking University, Beijing 100871, China

[‡]School of Pharmaceutical Science and Technology, Tianjin University, Tianjin 300072, China

[§]National Institute of Biological Sciences (NIBS), Beijing 102206, China

Supporting Information

**ABSTRACT:** We report herein the first total synthesis of (−)-incarviatone A (**1**) in 14 steps starting from commercially available inexpensive phenylacetic acid (**9**). Our early stage synthesis relies on the scalable and sequential C−H functionalization to rapidly assemble the indanyl dialdehyde framework. Further biomimetic cascade strategy allows us to obtain the natural product in a one-pot operation. We also conduct detailed mechanistic studies and disclose all the possible intermediates and isomers formed during the biomimetic cascade process.

(−)-Incarviatone A was first isolated as a unique natural product hybrid by Zhang group in 2012 (Figure 1).[1] Preliminary

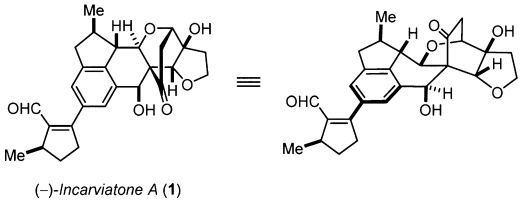
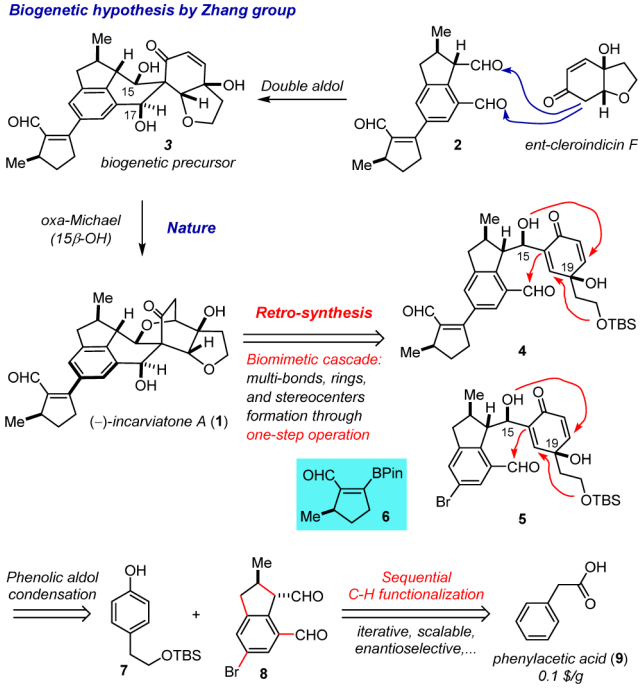



**Figure 1.** Naturally occurring hybrid (−)-incarviatone A (**1**).

biological tests disclosed that **1** showed notable potential as a novel monoamine oxidase (MAO) inhibitor ($IC_{50}$ 29 nM against monoamine oxidase A), which represented a great potential for the treatment of depression, Alzheimer's disease, and other neurological disorders.[2] However, the poor accessibility (4.1 mg out of 17 kg dried plants) prevents its continued biological studies. From a synthetic point of view, (−)-incarviatone A (**1**) is also exceedingly attractive due to the unprecedented polycyclic framework with eight contiguous stereogenic centers. We report herein our synthetic endeavors, which ultimately accumulate into the total synthesis of (−)-**1** in 14 steps.

As hypothesized by Zhang and co-workers, (−)-**1** is biogenetically derived from a dehyroiridodial dimer and benzofuranone analogue (Scheme 1). In detail, Diels−Alder cycloaddition of two dehydroiridodial molecules followed by functional group interconversions provides dialdehyde **2**, which undergoes double aldol reactions with *ent*-cleroindicin F to furnish **3** as the key biosynthetic intermediate. Subsequent oxa-Michael addition through 15*β*-hydroxyl group attack provides (−)-**1**.

**Scheme 1. Synthetic Analysis of (−)-1**




It is widely recognized that nature in many cases rapidly assembles polycyclic molecules (i.e., triterpenes and steroids)[3] with the desired architectural complexity and diversity using cascade stereoselective reactions.[4] Not surprisingly, this biomimetic cascade strategy has continuously inspired synthetic chemists to invent many landmark syntheses for decades.[5,6] In our synthetic plan, we envisaged that (−)-**1** could be synthetically derived from the advanced precursors **4** or **5** by utilizing the biomimetic cascade strategy. While **4** could be installed by Suzuki coupling of **5** with vinyl boronic ester **6**. Phenolic aldol condensation was considered for the assembly of **5** by coupling of phenol **7** with indanyl dialdehyde **8**.[7,8] Finally, sequential C−H functionalization has emerged as an ideal tool for complex total synthesis in recent years.[9,10] Successful examples have been reported with indole,[11] pyrrole,[12] and dihydrobenzofuran frameworks.[13] In our case, four sequential and different C−H

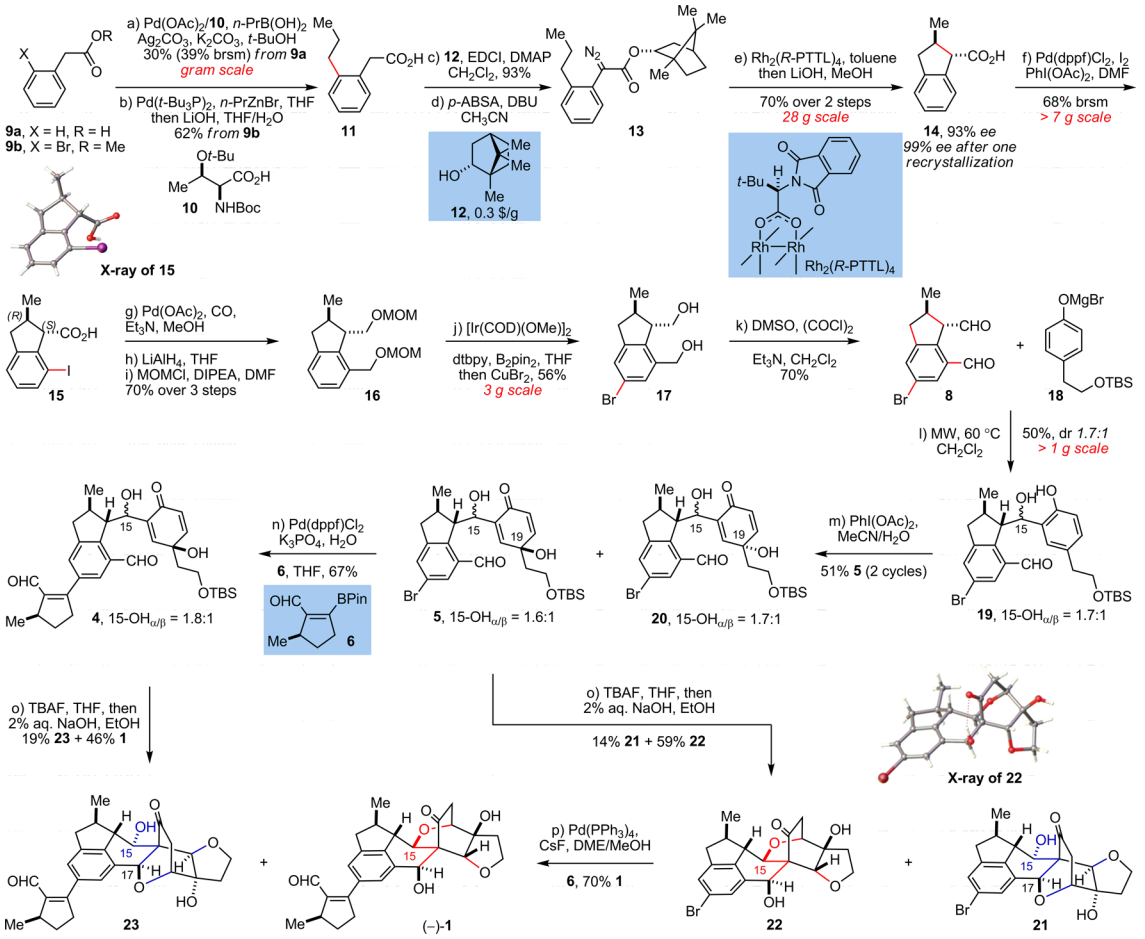
**Received:** August 13, 2015
**Published:** September 15, 2015





DOI: 10.1021/jacs.5b08551
J. Am. Chem. Soc. 2015, 137, 11946−11949

**Scheme 2. Fourteen-Step Total Synthesis of (−)-1**




functionalization including a scalable and diastereoselective intramolecular C−H insertion step would be responsible for the rapid assembly of the highly functionalized indane skeleton of precursor **8**, starting from inexpensive phenylacetic acid **9**.

Our synthesis commenced with *ortho*-C−H alkylation of **9a** using Yu's protocol (Scheme 2).[14] The desired *ortho*-propyl phenyl acetic acid **11** was obtained in 30% yield (brsm 39%) on a gram scale, along with di-*ortho*-propyl product in 10% yield. An alternative Negishi coupling was also proceeded well from bromo-methyl ester **9b** and provided **11** in 62% yield after *in situ* hydrolysis. The subsequent catalytic enantioselective synthesis of indane carboxylic acid via intramolecular C−H insertion in the presence of chiral rhodium catalysts proved to be crucial for our synthetic sequence. Although a series of intramolecular C−H insertions have been reported by Hashimoto and Davies for the enantioselective synthesis of dihydrobenzofurans,[15,16] previous attempts to access indanes have met with only limited success to date.[16b,17] Indeed, we also observed nonsuperior results with a $\alpha$-diazo methyl ester substrate.[18] Chiral auxiliaries turned out to be the next reasonable move.[13a,16c] After extensive screening of different chiral auxiliaries, we were delighted to observe that the desired *trans*-indane acid **14** could be obtained in 93% *ee* (up to 99% *ee* after one recrystallization) after a 3-step sequence using inexpensive (−)-borneol **12** as a chiral auxiliary. The highly diastereoselective C−H insertion of **13** was performed on 28 g scale in 70% yield, which lays a firm basis for catalytic asymmetric synthesis of indane via intramolecular C−H insertion for the first time. Yu's Pd(II)-catalyzed *ortho*-C−H iodination of **14** with a modification using $Pd(dppf)Cl_2$ as an optimal catalyst afforded iodo-acid **15** in a scalable manner.[19,20] The absolute configurations of the two vicinal stereogenic centers were also assigned at this stage by single crystal X-ray diffraction analysis.[18] Sequential carbonylation, carbonyl reduction, and alcohol MOM (methoxymethyl) protection of iodide **15** yielded **16** in 70% overall yield. The one-pot procedure for Hartwig's *meta*-borylation, bromination, and MOM deprotection proceeded efficiently with substrate **16** to furnish diol **17** in 56% yield on 3 g scale.[21−23] Subsequent Swern oxidation delivered the enantiopure indanyl dialdehyde **8**.

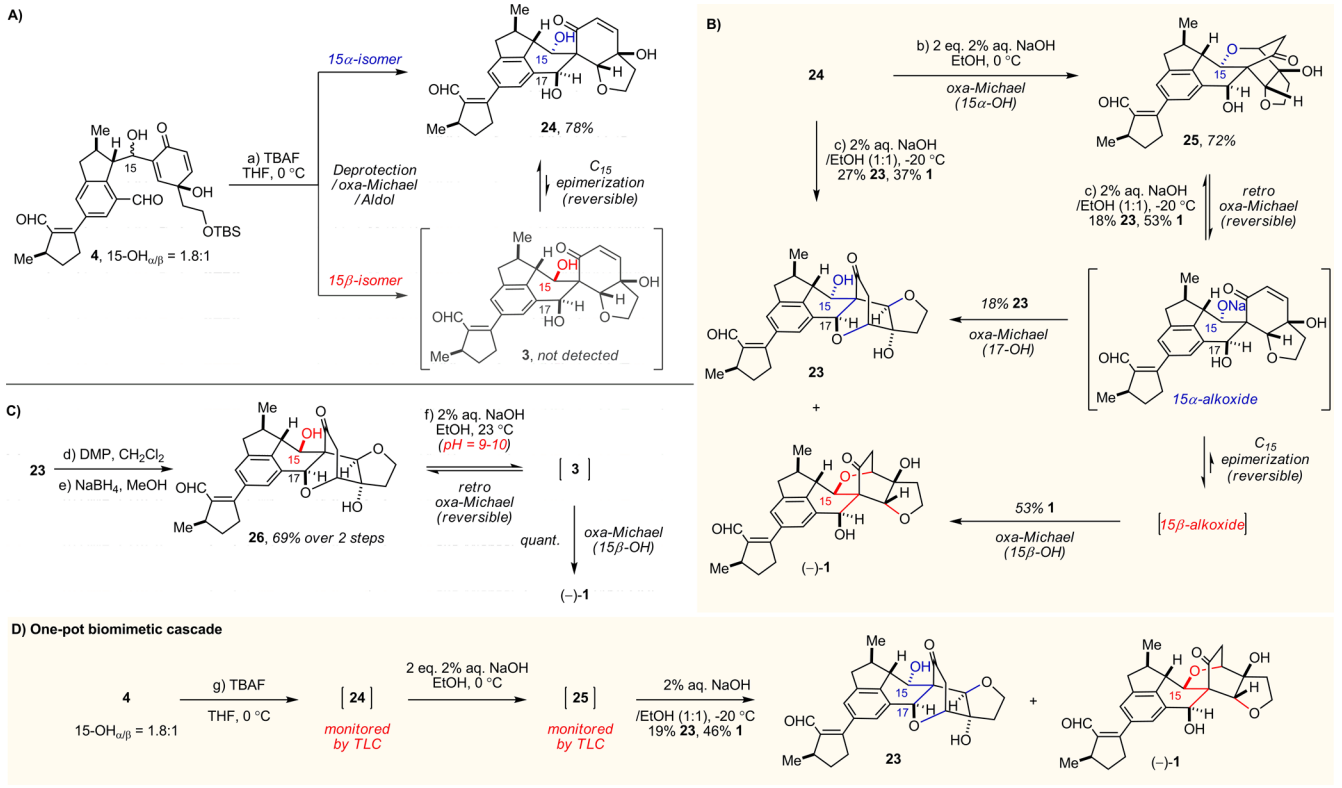
As shown in Scheme 2, dialdehyde **8** was found to undergo phenolic aldol condensation with magnesium phenolate **18** under the optimized microwave conditions to provide **19** as an inseparable diastereomeric mixture (15-$OH_{\alpha/\beta}$ = 1.7:1).[7,18] Subsequent dearomatization of the phenol afforded dienone **5** as inseparable diastereoisomers in 40% yield,[24] along with the undesired C19-epimer **20** in 37% yield, which could be reduced to starting material **19** in the presence of zinc and then re-engage into the previous dearomatization. Compound **5** was finally obtained in 51% yield after two cycles. Suzuki coupling of **5** with vinyl boronic ester (*R*)-**6** yielded another precursor **4**.[25,26]

With precursors **5** and **4** in hand, we started our investigation into the biomimetic cascade process. After careful examination, we found that starting from the inseparable diastereoisomers **5**, the desired diol **22** could be obtained in 59% yield along with another isomer **21** in 14% yield under the optimal conditions. Both structures were initially determined by 2D-NMR spectros-



DOI: 10.1021/jacs.5b08551
J. Am. Chem. Soc. 2015, 137, 11946−11949

**Scheme 3. Late-Stage Biomimetic Cascade of 4**




copy and later confirmed by single crystal X-ray diffraction analysis.[18] The end-game Suzuki coupling of **22** with (*R*)-**6** provided natural product (−)-**1** smoothly in 70% yield.[27] Finally, applying the inseparable diastereoisomers **4** pregenerated from Suzuki coupling of **5** with (*R*)-**6** into the same one-pot conditions resulted in the one-step facile formation of (−)-**1** in 46% yield along with the minor isomer **23** in 19% yield. The spectroscopic data of synthetic (−)-**1** fully matched with the natural isolate. Thus, we achieved the total synthesis of (−)-**1** in 14 steps and established the absolute configuration of (−)-**1**.

Based on a thorough and stepwise exploration, we were able to identify the relevant intermediates and isomers formed during this striking biomimetic cascade process, which allowed us to illuminate the mechanisms involved (Scheme 3). Specifically, both diastereoisomers of **4** were initially converted into intermediate **24** upon treatment with tetrabutylammonium fluoride (TBAF) in THF at 0 °C: the product **24** was isolated in 78% yield after quenching with 0.5 N hydrochloric acid at 0 °C (Scheme 3A). Although, both 15*α* and 15*β*-**4** presumably undergo the TBAF-mediated TBS deprotection, oxa-Michael addition, and intramolecular aldol reaction cascade in parallel to afford **24** and **3**, respectively. However, **3** could not be detected due to the facile epimerization of $C_{15}$ via retro-aldol/aldol condensation to furnish **24** (Scheme 3A). The intermediate **24** could be easily transformed into the first regioisomer **25** with 2% NaOH (2 equiv) in EtOH at 0 °C via oxa-Michael addition through 15*α*-hydroxyl group attack (Scheme 3B). Upon the treatment of **25** with 2% NaOH in EtOH (v/v = 1:1) at −20 °C, the natural product (−)-**1** was isolated in 53% yield as well as another C17-regioisomer **23** in 18% yield.

During this reaction, (−)-**1** was formed preferentially, presumably because the initial retro-oxa-Michael addition of **25** generates the sodium 15*α*-alkoxide active species, which kinetically favors sequential, reversible $C_{15}$ epimerization and 15*β*-oxa-Michael addition processes to furnish (−)-**1** at −20 °C rather than direct oxa-Michael addition through the 17-hydroxyl group attack to afford **23**. This hypothesis was later supported by the inferior results (37% (−)-**1** and 27% **23**) obtained upon the treatment of **24** under the same reaction conditions (Scheme 3B). Compound **23** failed to be converted directly into (−)-**1** by any means (Scheme 3C); a two-step oxidation/reduction sequence was performed to furnish isomer **26**, the C15 epimer of **23**. Upon treatment with 2% NaOH in EtOH (pH = 9−10) at ambient temperature, **26** could be exclusively transformed into (−)-**1** presumably via sequential, reversible retro-oxa-Michael addition and oxa-Michael addition through 15*β*-hydroxyl group attack. Finally, we maneuvered to operate a one-step biomimetic cascade of **4** in a one-pot fashion (Scheme 3D), starting from **4** and through in situ sequential formations of **24** and **25**, the desired product (−)-**1** and isomer **23** were isolated in 46% and 19% yields, respectively. Further studies of the inseparable diastereoisomers **5** showed that it behaved similarly in all cases. All the structures of the intermediates and isomers described above were determined based on 2D-NMR spectroscopy.[18]

Inspired by the initial biogenetic hypothesis, we also conducted extensive biomimetic studies in our laboratory using dialdehyde **8** and *ent*-cleroindicin F. Unfortunately, all attempts led to either racemization of *ent*-cleroindicin F (E1CB and 1,4-addition)[28] or decomposition of **8** under various basic conditions. However, under acidic conditions we merely isolated side product.[18]

To conclude, we have accomplished the first total synthesis of (−)-incarviatone A (**1**) in 14 steps starting from inexpensive phenylacetic acid. In the course of our synthetic studies, we have developed a scalable and sequential C−H functionalization process for the rapid assembly of the highly functionalized indane


DOI: 10.1021/jacs.5b08551
J. Am. Chem. Soc. 2015, 137, 11946−11949

skeleton. More interestingly, we have also identified a striking biomimetic cascade reaction to furnish the desired natural product in one step. In addition, the route is flexible and should be amenable to the synthesis of natural product analogues or derivatives to facilitate the follow-up chemical biology studies, which are currently underway and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08551.

Experimental procedures and spectroscopic data for all compounds (PDF)

X-ray crystallographic data for **15** (CCDC 1414007) (CIF)

X-ray crystallographic data for **22** (CCDC 1414008) (CIF)

X-ray crystallographic data for **27** (CCDC 1414009) (CIF)

## ■ AUTHOR INFORMATION


### Corresponding Authors

*xglei@pku.edu.cn.

*lihouhua@gmail.com

### Author Contributions

‖These authors contributed equally to this work.


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We thank Prof. Noah Z. Burns (Stanford University), Prof. Thomas J. Maimone (University of California, Berkeley), and Dr. Alex Jones for helpful discussions. We also thank Prof. Weidong Zhang (Second Military Medical University) for providing us the original NMR spectra of (−)-incarviatone A, and Prof. Wenxiong Zhang and Prof. Nengdong Wang (Peking University) for the assistance with X-ray analyses and crystallographic data collection and refinement. Financial support from the National High Technology Projects 973 (2015CB856200) and NNSFC (21222209, 91313303, and 21472010) is gratefully acknowledged.

## ■ REFERENCES


(1) Shen, Y.-H.; Ding, Y.; Lu, T.; Li, X.-C.; Tian, J.-M.; Li, H.-L.; Shan, L.; Ferreira, D.; Khan, I. A.; Zhang, W.-D. *RSC Adv.* **2012**, *2*, 4175−4180.

(2) Carradori, S.; Petzer, J. P. *Expert Opin. Ther. Patents* **2015**, *25*, 91−110.

(3) (a) Wendt, K. U.; Poralla, K.; Schulz, G. E. *Science* **1997**, *277*, 1811−1815. (b) Thoma, R.; Schulz-Gasch, T.; D'Arcy, B.; Benz, J.; Aebi, J.; Dehmlow, H.; Hennig, M.; Stihle, M.; Ruf, A. *Nature* **2004**, *432*, 118−122. (c) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730−4756.

(4) Dewick, P. M., Ed. *Medicinal Natural Products: A Biosynthetic Approach*, 2nd ed.; John Wiley & Sons: Chichester, U.K., 2002.

(5) For reviews, see: (a) Sorensen, E. J. *Bioorg. Med. Chem.* **2003**, *11*, 3225−3228. (b) Gravel, E.; Poupon, E. *Eur. J. Org. Chem.* **2008**, *2008*, 27−42.

(6) For selected landmark total syntheses using biomimetic cascade strategy, see: (a) Piettre, S.; Heathcock, C. H. *Science* **1990**, *248*, 1532−1534. (b) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328−9329. (c) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552−4553. (d) Stark, L. M.; Pekari, K.; Sorensen, E. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 12064−12066. (e) Gravel, E.; Poupon, E.; Hocquemiller, R. *Org. Lett.* **2005**, *7*, 2497−2499.

(7) Casiraghi, G.; Cornia, M.; Rassu, G. *J. Org. Chem.* **1988**, *53*, 4919−4922.

(8) Compound **7** was prepared in one step from the commercially available 2-(4-hydroxyphenyl)ethanol, see: Brown, P. D.; Willis, A. C.; Sherburn, M. S.; Lawrence, A. L. *Org. Lett.* **2012**, *14*, 4537−4539.

(9) For selected recent reviews, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67−72. (b) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885−1898. (c) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976−1991. (d) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960−9009.

(10) For selected recent examples, see: (a) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824−828. (b) Lu, P.; Gu, Z.; Zakarian, A. *J. Am. Chem. Soc.* **2013**, *135*, 14552−14555. (c) Dailler, D.; Danoun, G.; Baudoin, O. *Angew. Chem., Int. Ed.* **2015**, *54*, 4919−4922.

(11) (a) Mandal, D.; Yamaguchi, A. D.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2011**, *133*, 19660−19663. (b) Pitts, A. K.; O'Hara, F.; Snell, R. H.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 5451−5455.

(12) (a) Beck, E. M.; Hatley, R.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3004−3007. (b) Ueda, K.; Amaike, K.; Maceiczyk, R. M.; Itami, K.; Yamaguchi, J. *J. Am. Chem. Soc.* **2014**, *136*, 13226−13232. (c) Yamaguchi, A. D.; Chepiga, K. M.; Yamaguchi, J.; Itami, K.; Davies, H. M. L. *J. Am. Chem. Soc.* **2015**, *137*, 644−647.

(13) (a) Wang, D.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 5767−5769. (b) Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6774−6777.

(14) Thuy-Boun, P. S.; Villa, G.; Dang, D.; Richardson, P.; Su, S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 17508−17513.

(15) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417−424.

(16) (a) Davies, H. M. L.; Grazini, M. V. A.; Aouad, E. *Org. Lett.* **2001**, *3*, 1475−1477. (b) Saito, H.; Oishi, H.; Kitagaki, S.; Nakamura, S.; Anada, M.; Hashimoto, S. *Org. Lett.* **2002**, *4*, 3887−3890. (c) Lu, P.; Mailyan, A.; Gu, Z.; Guptill, D. M.; Wang, H.; Davies, H. M. L.; Zakarian, A. *J. Am. Chem. Soc.* **2014**, *136*, 17738−17749.

(17) Shaw group developed an asymmetric intramolecular C−H insertion of donor−donor carbenoids and also presented one example in the preparation of 1,2-*cis*-diphenylindane instead of indanyl carbonyl compounds (76% *ee*, >97:3 dr), see: Soldi, C.; Lamb, K. N.; Squitieri, R. A.; González-López, M.; Di Maso, M. J.; Shaw, J. T. *J. Am. Chem. Soc.* **2014**, *136*, 15142−15145.

(18) See Supporting Information for details.

(19) Mei, T.-S.; Wang, D.-H.; Yu, J.-Q. *Org. Lett.* **2010**, *12*, 3140−3143.

(20) We have also conducted *ortho*-C−H bromination of methyl ester derivative of **14**. Whereas the bromination reaction afforded 83% isolated yield on 20 mg scale, the reaction on 200 mg scale gave poor yield (5−20%). See: Sun, X.; Shan, G.; Sun, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4440−4444.

(21) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434−15435.

(22) For reviews, see: (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890−931. (b) Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864−873.

(23) For selected examples of iridium-catalyzed *meta*-borylation in complex total synthesis, see: (a) Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926−5927. (b) Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088−2091.

(24) You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2009**, *48*, 547−550.

(25) Sridhar, T.; Berrée, F.; Sharma, G. V. M; Carboni, B. *J. Org. Chem.* **2014**, *79*, 783−789.

(26) Compound (*R*)-**6** was prepared in two steps from commercially available (*R*)-(+)-3-methylcyclopentanone; see Supporting Information for details.

(27) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095−6097.

(28) Wenderski, T. A.; Huang, S.; Pettus, T. R. R. *J. Org. Chem.* **2009**, *74*, 4104−4109.




DOI: 10.1021/jacs.5b08551
*J. Am. Chem. Soc.* 2015, 137, 11946−11949