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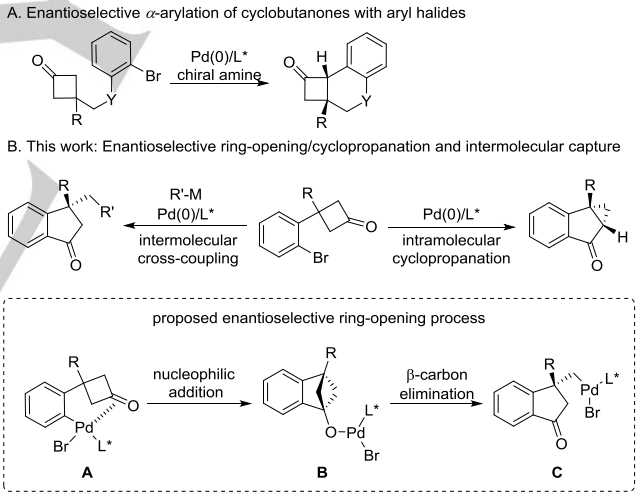
Pd-Catalyzed Enantioselective Ring-Opening/Cross-Coupling and Cyclopropanation of Cyclobutanones

Jian Cao, Ling Chen[+], Feng-Na Sun[+], Yu-Li Sun, Ke-Zhi Jiang, Ke-Fang Yang, Zheng Xu, and Li-Wen Xu**

Abstract: *A palladium-catalyzed enantioselective sequential ring-opening/cross-coupling of cyclobutanones is disclosed, providing chiral indanones bearing C3-quaternary stereocenters. The reaction process involves palladium-catalyzed nucleophilic addition of cyclobutanones and aryl halides, enantioselective β-carbon elimination and intermolecular trapping of a transient σ-alkylpalladium complex with boronic acids. Alternatively, an intramolecular cyclopropanation is realized via C-H bond functionalization in the absence of external coupling reagents, affording chiral cyclopropane-fused-indanones in good yields and enantioselectivity.*

Quaternary carbon stereocenters, bonded by four different carbon substituents, are omnipresent in natural products and pharmaceuticals. Catalytic enantioselective creation of quaternary stereocenters is a long-term challenge.[1] In this respect, enantioselective desymmetrization of prochiral small-ring compounds has emerged as a powerful tool for creating quaternary carbon stereocenters.[2] For example, enantioselective desymmetrization of prochiral cyclobutanones via Rh- and Ni-catalyzed ring-opening and ring-expansion has been achieved by the groups of Murakami,[3] Cramer,[4] and Dong.[5] In addition, Pd-catalyzed racemic ring-opening and ring-expansion reaction patterns of cyclobutanones were established by Murakami with achiral catalyst systems.[6] Recently, Lu reported a Pd-catalyzed asymmetric intramolecular α-arylation of prochiral cyclobutanones and aryl halides, forming chiral cyclobutanones containing quaternary carbon stereocenters (Scheme 1A).[7] Herein, we disclose an enantioselective Pd-catalyzed tandem ring-opening/carbon-carbon bond forming reaction pattern between prochiral cyclobutanones and aryl halides (Scheme 1B). Our strategy is based on the proposed enantioselective ring-opening process: arylpalladium species **A** generated via oxidative addition of symmetrical cyclobutanones with palladium catalysts would undergo nucleophilic addition toward carbonyl group to form alkoxypalladium intermediate **B**.[8] With appropriate chiral ligands, enantioselective β-carbon elimination[9] can be expected to lead to σ-alkylpalladium species **C** containing all-carbon quaternary stereocenters. σ-Alkylpalladium species, usually formed via enantioselective intramolecular carbopalladation of alkenes, have become versatile intermediates for creating quaternary stereocenters owing to the endeavor of the groups of Zhu,[10] Jia,[11] Diaz,[12] and Zhang.[13] We anticipate the σ-alkylpalladium species generated through ring-opening of cyclobutanones would be trapped by various nucleophiles to produce indanones bearing C3-quaternary stereocenters. Alternatively, a C(sp^3)−C(sp^3) bond could be forged via intramolecular C-H functionalization in the absence of external nucleophiles, thus leading to chiral cyclopropane-fused-indanones.[14] Chiral indanones and cyclopropane-fused-cyclopentane skeletons are important structural units in many natural products and pharmaceuticals.[15]



Scheme 1. Pd-catalyzed enantioselective desymmetrization of prochiral cyclobutanones with aryl halides.

To achieve this proposal, the following issues need to be addressed: (1) The critical step nucleophilic addition (**A** to **B**) requires effective carbonyl-palladium coordination to avoid direct cross-coupling, therefore judicious choices of bulky monodentate phosphine ligands capable of leaving a vacant orbital of palladium is a prerequisite. (2) At the chirality-determining step (**B** to **C**), appropriate chiral, and at the same time bulky monodentate phosphine ligands are required to achieve both high enantioselectivity and good chemoselectivity. (3) It is nontrivial to identify two sets of reaction conditions to achieve competitive intermolecular capture and intramolecular C-H functionalization respectively.

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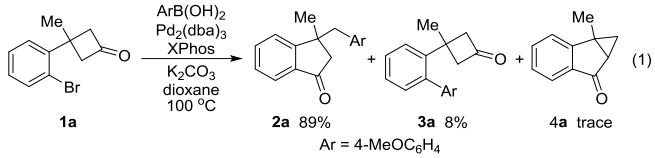
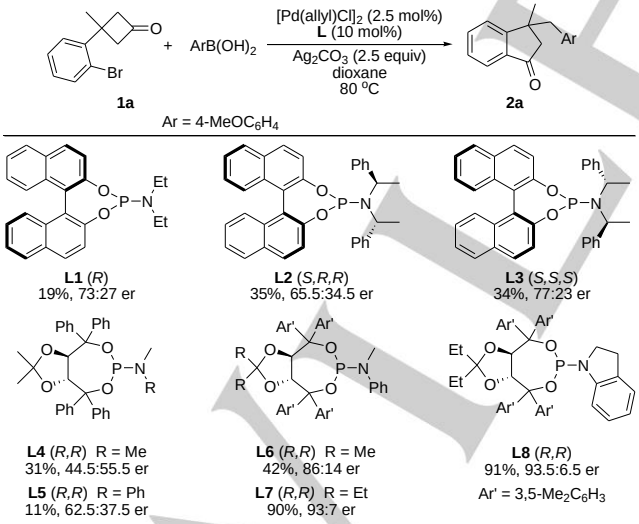
Initially, aryl boronic acids were selected as the nucleophiles to examine the feasibility of ring-opening/cross-coupling sequence since Suzuki-Miyaura coupling has become one of the most robust methods for the construction of carbon-carbon bonds. 3-(2-Bromophenyl)-3-methylcyclobutanone **1a** and 4-methoxyphenyl-boronic acid were used as the model substrates. After a systematic survey of reaction parameters (Table S1 in supporting information), the following optimum conditions were identified: $Pd_2(dba)_3$ (0.05 equiv), XPhos (0.1 equiv), K_2CO_3 (2.5 equiv), 1,4-dioxane, 100 °C, affording the desired 1-indanone **2a** in 89% yield and direct cross-coupling product **3a** [Eq. (1)]. It should be noted that the cyclopropanation product **4a** was also observed albeit in trace amounts.



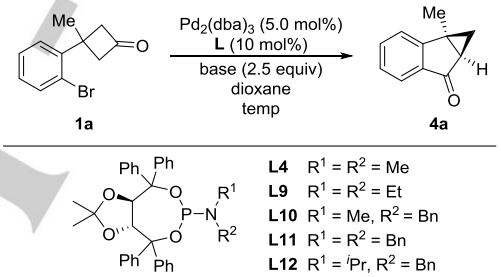
Subsequently, a range of chiral monodentate phosphine ligands were examined to realize the enantioselective sequential reaction. Among the screened phosphine ligands, BINOL- and TADDOL-derived phosphoramidites[16] showed promising level of enantioselectivity and selected examples were shown in Scheme 2 (for screening of other parameters, see Table S2 in supporting information). While BINOL-derived phosphoramidites **L1**-**L3** resulted in only moderate enantioselectivity, new TADDOL-derived phosphoramidites **L7** and **L8** proved to be suitable, giving good yield and enantioselectivity. Thus **L8** was chosen as the optimized chiral ligand for subsequent evaluation of the generality of this enantioselective reaction.



Scheme 2. Selected screening of chiral ligands for tandem ring-opening/cross-coupling reaction.

At the same time, the highly strained cyclopropanation product **4a** attracted our interest. Thus we next examined this tandem ring-opening/cyclopropanation using cyclobutanone **1a** as the model substrate. Under the optimum conditions for ring-opening/Suzuki-Miyaura reaction in the absence of boronic acid, the desired cyclopropanantion product **4a** was obtained in only 9% yield and significant amount of substrate **1a** remained intact, suggesting the difficulty of formation of three-membered ring (Table 1, entry 1). After extensive screening of reaction parameters, we found that addition of one equivalent of Brønsted acids (e.g. TsOH, entry 2) greatly increased the yield. Further screening led to the finding that simply replacing the base K_2CO_3 with $KHCO_3$ without additional acids resulted in excellent yield (entry 3). Subsequently, a set of chiral ligands were screened for achieving enantioselective cyclopropanation. Among the screened phosphine ligands, TADDOL-derived phosphoramidites showed promising level of enantioselectivity and **L12** proved to be most effective (entries 4-8). Lowering the reaction temperature to 90 °C increased the yield to 94% and enantiomer ratio to 97.5:2.5 (entry 9, for detailed screening of other parameters, see Table S3 in supporting information).

Table 1. Optimization of the enantioselective ring-opening/cyclopropanation.[a]

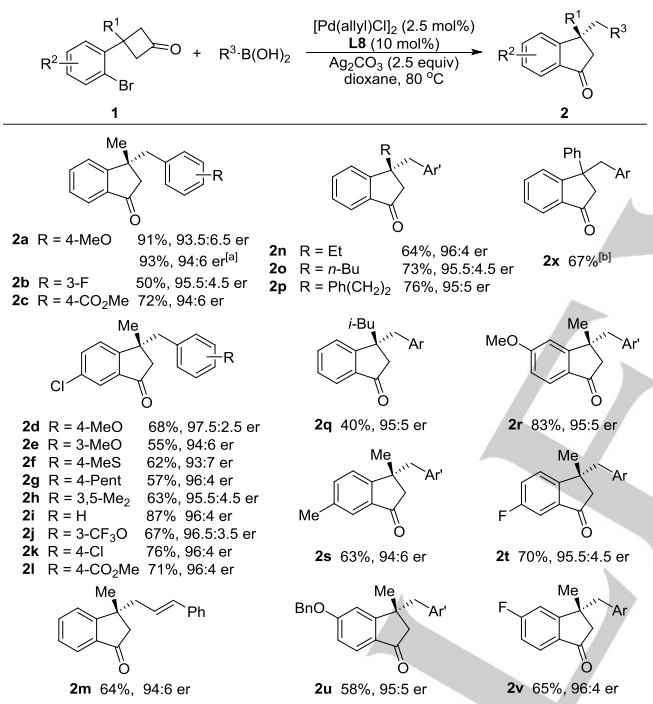


Entry	Ligand	Base	Yield [%]	er
1	XPhos	K_2CO_3	9	/
2	XPhos	K_2CO_3 + TsOH	49	/
3	XPhos	$KHCO_3$	96	/
4	**L4**	$KHCO_3$	94	66:34
5	**L9**	$KHCO_3$	92	90:10
6	**L10**	$KHCO_3$	96	89:11
7	**L11**	$KHCO_3$	94	87.5:12.5
8	**L12**	$KHCO_3$	91	96.5:3.5
9[b]	**L12**	$KHCO_3$	94	97.5:2.5

[a] Unless otherwise specified, the reactions were run on 0.2 mmol scale in 2 mL solvents at 100 °C for 24 h. [b] The reaction was run at 90 °C

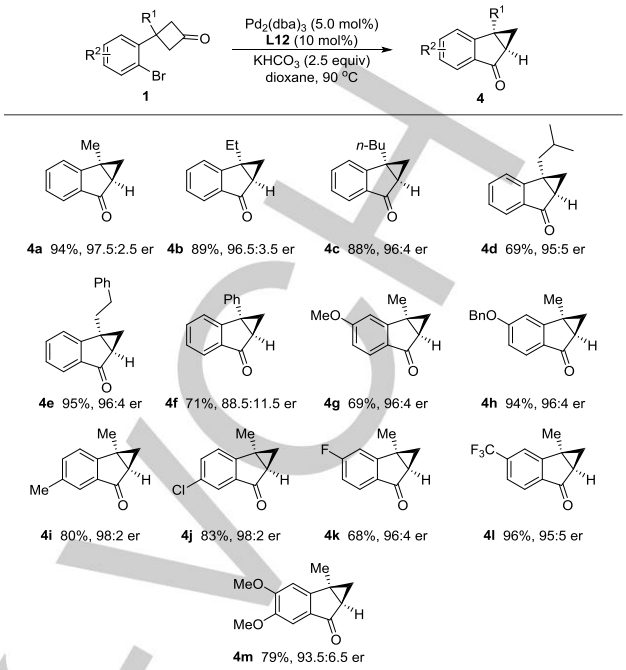
With the two sets of optimum conditions in hand, the scope and limitation of these enantioselective ring-opening/carbon-carbon bond forming reactions was examined. As depicted in Scheme 3, a wide variety of boronic acids proved to be amenable to this transformation. Aryl boronic acids bearing both electron-donating and -withdrawing groups regardless of their positions participated efficiently to afford the desired products **2a**-**2l**. Functional groups including methoxy, methylthio, fluorine,

chlorine, trifluoromethoxy, and ester were well tolerated. In addition, an alkenyl group could also be easily incorporated in the product **2m**. On the other hand, the scope of cyclobutanones was also screened. Cyclobutanones bearing various alkyl groups at the R^1 position are compatible (**2n**-**2q**). Although the product **2x** with a phenyl group at R^1 position can be obtained in 67% yield under racemic conditions, enantioselective reaction only gave the desired product in trace amount. When R^1 was H, the desired product was not found and only direct Suzuki-Miyaura coupling product was obtained. Substituents on the phenyl moiety of cyclobutanones, including halogen and methoxy, were well tolerated, leaving ample room for further functionalization (**2d**, **2r**-**2v**). Generally, enantiomeric ratio ranged from 93:7 to 97.5:2.5. The absolute configurations of **2f** and **2v** were disclosed by X-ray diffraction analysis.[17] To demonstrate the practicability of our protocol, a gram-scale experiment (8 mmol) was conducted and **2a** was obtained in excellent yield and good enantioselectivity.



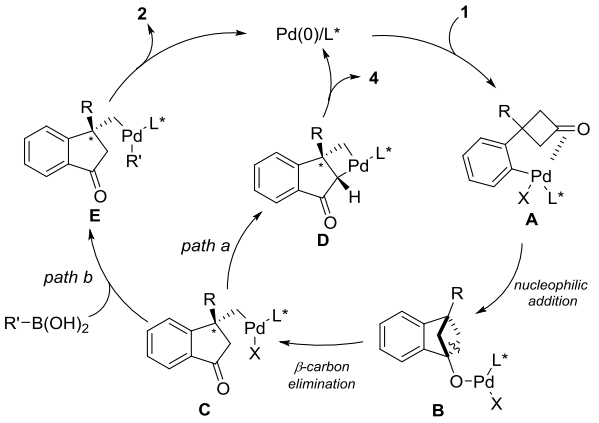
Scheme 3. Reaction scope of the enantioselective ring-opening/cross-coupling. [a] 8 mmol scale. Ar = 4-MeOC$_6$H$_4$, Ar' = 4-(MeOCO)C$_6$H$_4$. [b] Under racemic conditions in Eq 1.

Next, the scope and limitation of the enantioselective ring-opening/cyclopropanation was examined with a variety of cyclobutanones. As shown in Scheme 4, alkyl groups were well tolerated at R^1 position, delivering the expected products **4a**-**4e**. Phenyl was also amenable albeit with lower enantioselectivity (**4f**). Unfortunately, no reaction occurred when R^1 was H. Cyclobutanones with functional groups on the phenyl moiety, such as Cl, F, and MeO, afforded the desired products **4g**-**4m** in good yields and enantioselectivity. The absolute configuration of **4m** was disclosed by X-ray diffraction analysis.[17]



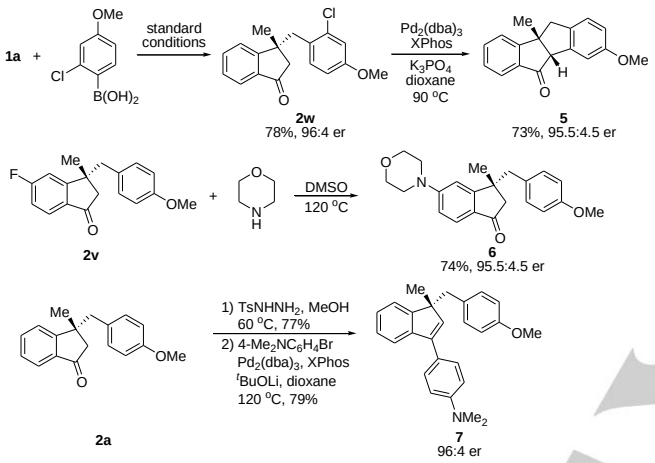
Scheme 4. Reaction scope of the enantioselective tandem ring-opening/cyclopropanation.

A plausible mechanism was proposed for these enantioselective tandem ring-opening/carbon-carbon bond forming reactions.[18] As outlined in Scheme 5, symmetrical cyclobutanones **1** undergo oxidative addition to form arylpalladium species **A**. Subsequent nucleophilic addition of arylpalladium toward carbonyl group in cyclobutanones generates highly strained alkoxypalladium intermediate **B**. With appropriate chiral ligands, enantioselective β-carbon elimination leads to σ-alkylpalladium species **C**. Intramolecular C-H bond functionalization affords the cyclopropanation product **4** via palladacyclobutane intermediate **D** (path a). Alternatively, σ-alkylpalladium species **C** is captured by boronic acids to form intermediate **E** (path b), which gives 1-indanone **2** through reductive elimination.



Scheme 5. Proposed mechanism.

Since halogens Cl and F were well tolerated, various cross-coupling technologies can be considered for downstream derivatization. For example, **2w** obtained from **1a** under standard conditions smoothly underwent Pd-catalyzed *α*-arylation to afford polycyclic product **5** as the sole diastereoisomer (Scheme 6). The relative configuration of **5** was deduced by NOESY spectrum (see supporting information). The fluorine atom in **2v** could be easily replaced by an amine via nucleophilic aromatic substitution to form **6**. In addition, the versatile carbonyl group was transferred to carbon-carbon double bond, delivering chiral indene **7** through 2 steps. It should be noted that all the derivatives were obtained without racemization.



Scheme 6. Synthetic applications.

In conclusion, we developed a tandem nucleophilic addition/β-carbon elimination paradigm between cyclobutanones and intramolecular aryl halides, generating σ-alkylpalladium species bearing β-quaternary carbon stereocenters. Using boronic acids as external nucleophilic trapping reagents, the enantioselective domino ring-opening/cross-coupling reaction was achieved for the construction of 1-indanones bearing C3-quaternary stereocenters. In addition, a ring-opening/cyclopropanation sequence was realized in the absence of external nucleophiles, affording chiral cyclopropane-fused-indanones in good yields and enantioselectivity.

Acknowledgements

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Keywords: Cyclobutanone • C-C activation • quaternary stereocenter • asymmetric catalysis • palladium-catalysis

[1] For recent reviews, see: a) K. W. Quasdorf, L. E. Overman, *Nature* **2014**, *516*, 181; b) Y. Liu, S.-J. Han, W.-B. Liu, B. M. Stoltz, *Acc. Chem. Res.* **2015**, *48*, 740.

[2] X.-P. Zeng, Z.-Y. Cao, Y.-H. Wang, F. Zhou, J. Zhou, *Chem. Rev.* **2016**, *116*, 7330.

[3] a) T. Matsuda, M. Shigeno, M. Makino, M. Murakami, *Org. Lett.* **2006**, *8*, 3379; b) T. Matsuda, M. Shigeno, M. Murakami, *J. Am. Chem. Soc.* **2007**, *129*, 12086; c) L. Liu, N. Ishida, M. Murakami, *Angew. Chem. Int. Ed.* **2012**, *51*, 2485; *Angew. Chem.* **2012**, *124*, 2535.

[4] a) E. Parker, N. Cramer, *Organometallics* **2014**, *33*, 780; b) L. Souillart, E. Parker, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 3001; *Angew. Chem.* **2014**, *126*, 3045; c) L. Souillart, N. Cramer, *Angew. Chem. Int. Ed.* **2014**, *53*, 9640; *Angew. Chem.* **2014**, *126*, 9794.

[5] a) X. Zhou, G. Dong, *Angew. Chem. Int. Ed.* **2016**, *55*, 15091; *Angew. Chem.* **2016**, *128*, 15315; b) X. Zhou, G. Dong, *J. Am. Chem. Soc.* **2015**, *137*, 13715; c) H. M. Ko, G. Dong, *Nature Chemistry* **2014**, *6*, 739.

[6] a) T. Matsuda, M. Shigeno, M. Murakami, *Org. Lett.* **2008**, *10*, 5219. For other racemic Pd-catalyzed ring-opening and ring-expansion of cyclobutanones, see: b) N. Ishida, W. Ikemoto, M. Murakami, *Org. Lett.* **2012**, *14*, 3230; c) N. Ishida, W. Ikemoto, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 5912.

[7] M. Wang, J. Chen, Z. Chen, C. Zhong, P. Lu, *Angew. Chem. Int. Ed.* **2018**, *57*, 2707; *Angew. Chem.* **2018**, *130*, 2737.

[8] For Pd-catalyzed nucleophilic addition of aryl halides to ketones, see: a) L. G. Quan, V. Gevorgyan, Y. Yamamoto, *J. Am. Chem. Soc.* **1999**, *121*, 3545; b) V. Gevorgyan, L. G. Quan, Y. Yamamoto, *Tetrahedron Lett.* **1999**, *40*, 4089; c) L. G. Quan, M. Lamrani, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 4827; d) J. Vicente, J.-A. Abad, B. López-Peláez, E. Martínez-Viviente, *Organometallics* **2002**, *21*, 58; e) D. Solé, L. Vallverdú, X. Solans, M. Font-Bardía, J. Bonjoch, *J. Am. Chem. Soc.* **2003**, *125*, 1587; f) Y. B. Zhao, B. Mariampillai, D. A. Candito, B. Laleu, M. Z. Li, M. Lautens, *Angew. Chem. Int. Ed.* **2009**, *48*, 1849; *Angew. Chem.* **2009**, *121*, 1881.

[9] For enantioselective β-carbon elimination of palladium(II)-alcoholate species, see: a) T. Nishimura, S. Matsumura, Y. Maeda, S. Uemura, *Chem. Commun.* **2002**, 50; b) S. Maysumura, Y. Maeda, T. Nishimura, S. Uemura, *J. Am. Chem. Soc.* **2003**, *125*, 8862; c) A. Ziadi, A. Correa, R. Martin, *Chem. Commun.* **2013**, *49*, 4286.

[10] a) A. Pinto, Y. Jia, L. Neuville, J. Zhu, *Chem. Eur. J.* **2007**, *13*, 961; b) W. Kong, Q. Wang, J. Zhu, *J. Am. Chem. Soc.* **2015**, *137*, 16028; c) W. Kong, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2016**, *55*, 9714; *Angew. Chem.* **2016**, *128*, 9866; d) W. Kong, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 3987; *Angew. Chem.* **2017**, *129*, 4045; e) X. Bao, Q. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 9577; *Angew. Chem.* **2017**, *129*, 9705; f) S. Tong, A. Limouni, Q. Wang, M.-X. Wang, J. Zhu, *Angew. Chem. Int. Ed.* **2017**, *56*, 14192; *Angew. Chem.* **2017**, *129*, 14380.

[11] a) C. Shen, R.-R. Liu, R.-J. Fan, Y.-L. Li, T.-F. Xu, J.-R. Gao, Y.-X. Jia, *J. Am. Chem. Soc.* **2015**, *137*, 4936; b) R.-R. Liu, Y.-G. Wang, Y.-L. Li, B.-B. Huang, R.-X. Liang, Y.-X. Jia, *Angew. Chem. Int. Ed.* **2017**, *56*, 7475; *Angew. Chem.* **2017**, *129*, 7583.

[12] P. Diaz, F. Gendre, L. Stella, B. Charpentier, *Tetrahedron* **1998**, *54*, 4579.

[13] Z.-M. Zhang, B. Xu, Y. Qian, L. Wu, Y. Wu, L. Zhou, Y. Liu, J. Zhang, *Angew. Chem. Int. Ed.* **2018**, *57*, 10373; *Angew. Chem.* **2018**, *130*, 10530.

[14] For examples of racemic Pd-catalyzed cyclopropanation via C-H functionalization, see: W. Du, Q. Gu, Z. Li, D. Yang, *J. Am. Chem. Soc.* **2015**, *137*, 1130.

[15] a) T. Lomberget, E. Bentz, D. Bouyssi, G. Balme, *Org. Lett.* **2003**, *5*, 2055; b) T. Ito, T. Tanaka, M. Iinuma, K. Nakaya, Y. Takahashi, R. Sawa, J. Murata, D. Darnaedi, *J. Nat. Prod.* **2004**, *67*, 932; c) E. Fillion, D. Fishlock, A. Wilsily, J. M. Goll, *J. Org. Chem.* **2005**, *70*, 1316; d) G. Yue, L. Yang, C. Yuan, X. Jiang, B. Liu, *Org. Lett.* **2011**, *13*, 5406.

[16] For selected reviews on TADDOL-derived phosphoramidites ligands, see: a) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346; b) J. F. Teichert, B. L. Feringa, *Angew. Chem. Int. Ed.* **2010**, *49*, 2486; *Angew. Chem.* **2010**, *122*, 2538; c) J. Pedroni, N. Cramer, *Chem. Commun.* **2015**, *51*, 17647.

[17] CCDC 1816797, 1816798 and 1840312 contain the supplementary crystallographic data for this paper (**2f**, **2v** and **4m**). These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[18] The ring-opening/cyclopropanation reaction was monitored by in-situ IR, NMR, GC-MS and HRMS. See supporting information.

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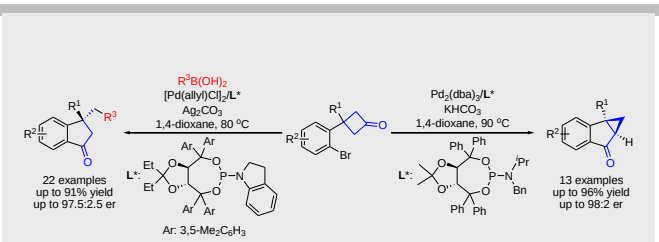

Enantioselective desymmetrization of prochiral cyclobutanones is realized via tandem palladium-catalyzed ring-opening/cyclopropanation, providing chiral cyclopropane-fused-indanones. With external coupling reagents, the transient σ-alkylpalladium intermediate can be captured to afford an array of chiral indanones bearing C3-quaternary stereocenters.

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