Communication

# Enantioselective Palladium-Catalyzed Intramolecular #-Arylative Desymmetrization of 1,3-Diketones

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# Enantioselective Palladium-Catalyzed Intramolecular α-Arylative Desymmetrization of 1,3-Diketones

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**ABSTRACT:** An efficient enantioselective protocol has been reported to build highly oxygenated and densely substituted bicyclo[m.n.1] skeletons through intramolecular asymmetric α-arylative desymmetrization of 1,3-diketones. Employing Pd catalyst and FOXAP ligand, various bicyclo[m.n.1] skeleton with different size can be accessed with high enantio- and diastereoselectivities. Utilizing the present method as a key step, formal asymmetric total synthesis of the (-)-parvifoline has been demonstrated.

Highly oxygenated and densely substituted bicyclo[*m.n.*1] framework is highly important building blocks in basic structural motifs of many natural products and bioactive compounds.[1] Most of these compounds contain quaternary carbon centers adjacent to a bridged ketone.[2] Owing to the promising biological properties and challenging structures of these molecules, considerable efforts have been devoted to develop efficient methods to construct such skeletons.[3] Among them, Pd-catalyzed intramolecular α-arylation of carbonyl compounds represents an attractive strategy, which has been applied successfully in total synthesis of many nature products including dysidavarone A[4], welwitindolinones[5] and so on (Figure 1a).[6] However, it's necessary to carry out a high regio-, diastereo- and enantio-controlled alkylation at α methylene group for the subsequent α-arylation and cyclization to produce the desired enantiomeric pure products in the case of this strategy. Inspired by the frequent occurrence of bicyclo[*m.n.*1] skeleton in natural products, we offer a concise and scalable asymmetric catalytic strategy to access these chiral products directly.

Desymmetrization of symmetric 1,3-diketone[7] is attractive for reaction design due to the acidic α methylene group that can easily be functionalized by deprotonation with various types substituents.[8] Most of known processes so far have focused on the desymmetrization of two carbonyl groups to deliver chiral bicyclo[*m.n.*0] products.[9] In view of the precedent work on asymmetric α-arylation of ketones with aryl (pseudo)halides,[10] we wondered a related process to build bicyclo[*m.n.*1] skeleton involving the combined α-arylation reaction and enantioselective desymmetrization of 1,3-diketones with aryl halides in an intramolecular fashion. Herein, we report the first enantioselective Pd-catalyzed desymmetrization of 1,3-diketones to afford a range of chiral bicyclo[*m.n.*1] compounds (Figure 1b). The advantage of this method is that various bicyclo[*m.n.*1] skeleton bearing more than two stereocenters can be readily prepared with excellent stereoselectivity using a modular operation. Compared to the intermolecular asymmetric α-arylation only limited to construct α-carbonyl quaternary stereogenic center, the generated tertiary center in our method can be prevented to be racemized by this rigid structural property under basic conditions.

To begin our studies, we have chosen 2-(2-bromobenzyl)-2-methylcyclohexane-1,3-dione (**1a**) bearing a *β*-quaternary carbon

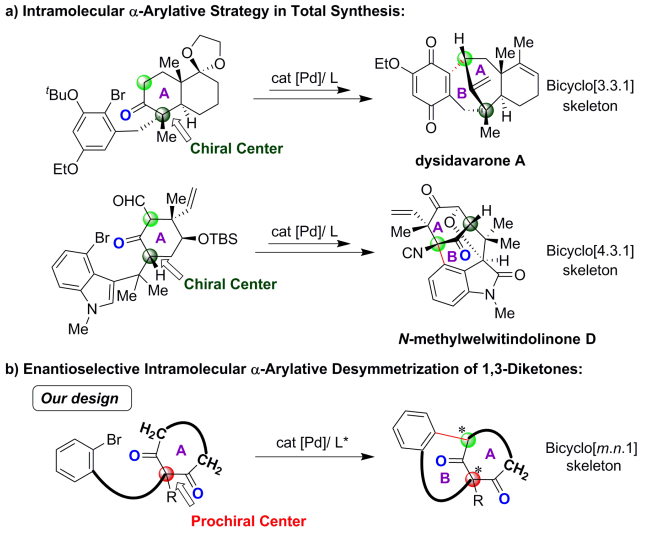
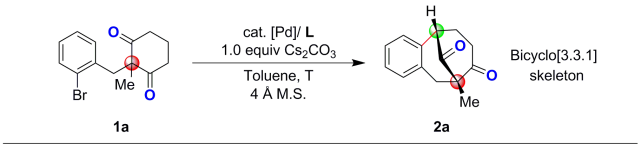


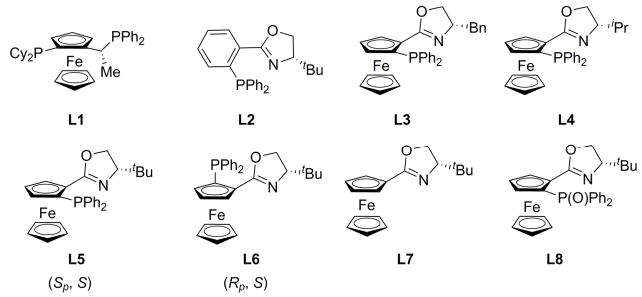

**Figure 1.** Inspiration for enantioselective desymmetrization of symmetric 1,3-diketone to build bicyclo[m.n.1] skeleton.

center as the model substrate (Table 1). In presence of 10 mol% $Pd(OAc)_2$, 11 mol % (*R*)-Binap (**L1**), 1.0 equiv $Cs_2CO_3$, and 100 mg 4 ÅM.S., at 80 °C under an argon atmosphere in toluene, we indeed observed the cyclization product **2a** after 12 h in 93% yield albeit with 18% ee (entry 1). To improve the result, we evaluated various chiral bidentate ligands including JOSIPHOS, PHOX, and FOXAP families (entries 2-6). ($S_p$, *S*)-$^t$Bu-FOXAP (**L5**) ligand was proved to be the best in terms of reactivity and enantioselectivity (67% yield, 92% ee, entry 6). Extending the reaction time to 48 h the product **2a** yield was improved to 98% yield without sacrificing the enantioselectivity (entry 7). Interestingly, the diastereoisomeric ligand ($R_p$, *S*)-$^t$Bu-FOXAP (**L6**) also gave **2a** in 93% yield with 92% ee which indicated that the chirality of the product is mainly determined by chiral oxazoline skeleton (entry 8).[11] In addition, application of monodentate ligand **L7** (entry 9) or chiral phosphine oxide ligand **L8** (entry 10) resulted inferior results and demonstrated that the tertiary phosphine group in ligand **L5** had a great influence on the reaction outcome. Decreasing the catalyst loading or lowering of the reaction temperature resulted in a much lower yield, but slightly higher ee values were observed (entries 11-12). Moreover, other palladium source like $Pd_2(dba)_3$ exhibited significantly worse reactivity (entry 13). Finally, control experiments revealed that the absence of molecular sieves dramatically reduced the yield (entry 14) and the reaction was unsuccessful without $Cs_2CO_3$ (entry 15).

With the set of optimized reaction conditions in hand, we first examined the scope of this desymmetrization reaction (Table 2). Substrates with a broad range of substitution at C4-C6 on the benzene ring were first examined. Electron- neutral, donating and withdrawing substituents were generally well-tolerated, affording

**Table 1.** Screening of Representative Ligands and Different Conditions.[a]



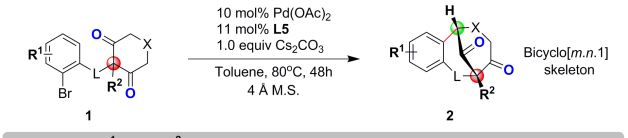




| entry | [Pd] (mol%) | L (mol%) | T (°C) | time (h) | ee (%)[b] | yield (%)[c] |
|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ (10) | **(*R*)-Binap** (11) | 80 | 12 | 18 | 93 |
| 2 | $Pd(OAc)_2$ (10) | **L1** (11) | 80 | 12 | 54 | 69 |
| 3 | $Pd(OAc)_2$ (10) | **L2** (11) | 80 | 12 | - | trace |
| 4 | $Pd(OAc)_2$ (10) | **L3** (11) | 80 | 12 | 74 | 52 |
| 5 | $Pd(OAc)_2$ (10) | **L4** (11) | 80 | 12 | 83 | 55 |
| 6 | $Pd(OAc)_2$ (10) | **L5** (11) | 80 | 12 | 92 | 67 |
| **7** | **$Pd(OAc)_2$ (10)** | **L5 (11)** | **80** | **48** | **92** | **98 (83)[d]** |
| 8 | $Pd(OAc)_2$ (10) | **L6** (11) | 80 | 48 | 92 | 93 |
| 9 | $Pd(OAc)_2$ (10) | **L7** (11) | 80 | 48 | -15 | 14 |
| 10 | $Pd(OAc)_2$ (10) | **L8** (11) | 80 | 48 | 0 | trace |
| 11 | $Pd(OAc)_2$ (5) | **L5** (5.5) | 80 | 48 | 93 | 47 |
| 12 | $Pd(OAc)_2$ (10) | **L5** (11) | 60 | 48 | 95 | 81 |
| 13 | $Pd_2(dba)_3$ (5) | **L5** (11) | 80 | 48 | 87 | 46 |
| 14[e] | $Pd(OAc)_2$ (10) | **L5** (11) | 80 | 48 | 92 | 44 |
| 15[f] | $Pd(OAc)_2$ (10) | **L5** (11) | 80 | 48 | - | trace |

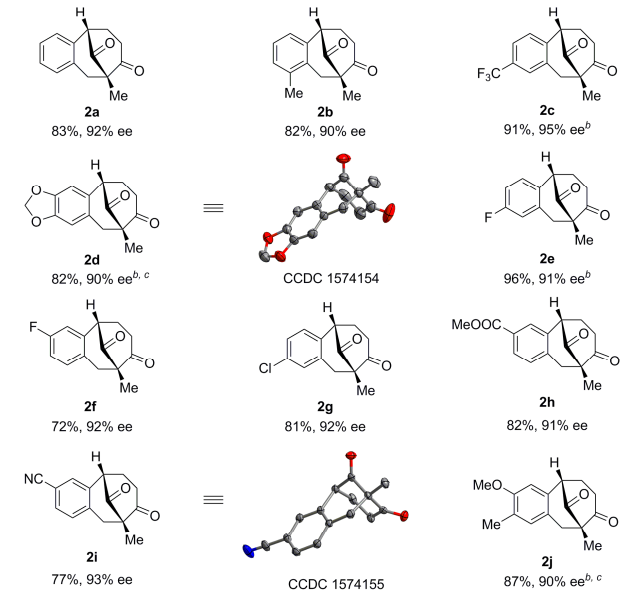
[a]Reaction conditions: **1a** (0.10 mmol), 5-10 mol% [Pd], 5.5-11 mol% ligand, $Cs_2CO_3$ (0.10 mmol), 100 mg 4 Å M.S. in 1 mL toluene for 12-48 hours under argon. [b]Enantiomeric excess values were determined by chiral HPLC analysis. [c]Yields were determined by GC. [d]Isolated yield after chromatography. [e]Without molecular sieves. [f]Without $Cs_2CO_3$.

the desired products **2b-2i** bearing methyl (**2b**), $CF_3$ (**2c**), methoxy (**2d**), F (**2e-f**), Cl (**2g**), ester (**2h**), and cyano (**2i**) functionalities in good yields with excellent enantioselectivities. Moreover, substrate **1j** with multiple substituents at benzene ring also led to excellent yield and enantioselectivity (87%, 90% ee). We found that substrates with various $R^2$ group at α methylene position also gave chiral diketones **2k-p** in 64-95% yields (87-94% ee). Particularly the substrate **1o** with a substituent derived from (*S*)-(-)-citronellal, the desired product **2o** was observed in 83% yield with an excellent diastereoselectivity (>14:1 dr). The scope of this enantioselective desymmetrization could also be extended to prepare products with different ring sizes (**2q-2u**). Among them, indole substrates **2t** and **2u** showed high reactivity generating [5.3.1]-, and [6.3.1]-bicyclic ring systems in good yields and high levels of enantioinduction. Notably, this process is not only limited to cyclohexane-1,3-dione as the electrophilic trap, cyclic 1,3-diketones with different size are also effective to build [3.2.1]-, [3.3.1]-, and [3.4.1]- bicyclic ring systems (**2v-x**). To determine the absolute configuration of these products, we were fortunate to get crystals of the products **2d**, **2i** and **2t** and subjected to X-ray crystallographic analysis.

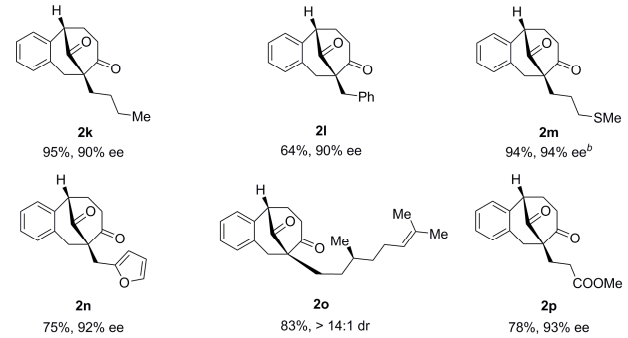
**Table 2.** Substrate Scope.[a]



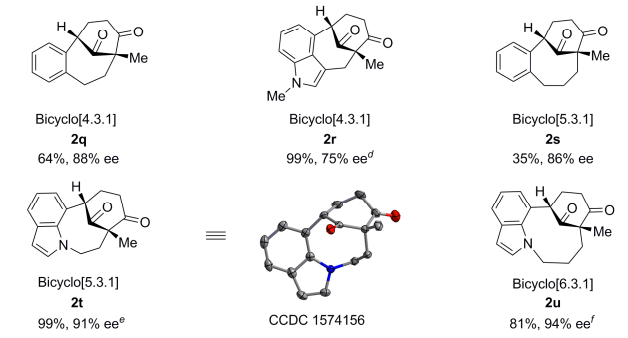

**a) Variation of $R^1$ group ($R^2$ = Me, X = $CH_2$, L = $CH_2$), Bicyclo[3.3.1]:**



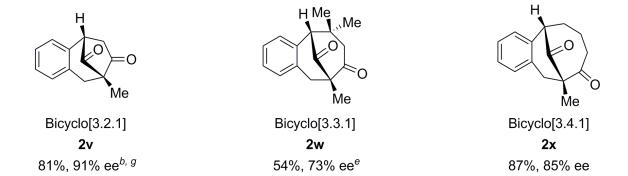

**b) Variation of $R^2$ group ($R^1$ = H, X = $CH_2$, L = $CH_2$), Bicyclo[3.3.1]:**




**c) Variation of linker L ($R^1$ = H, $R^2$ = Me, X = $CH_2$):**

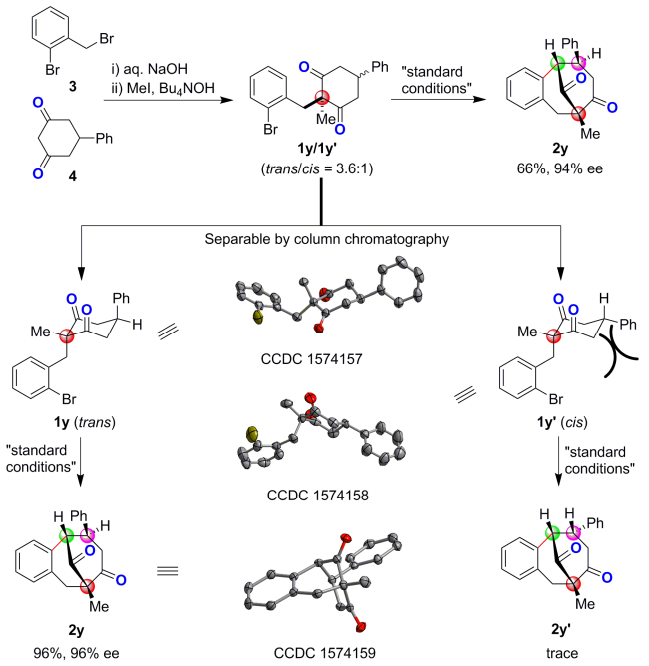



**d) Variation of X ($R^1$ = H, $R^2$ = Me, L = $CH_2$):**



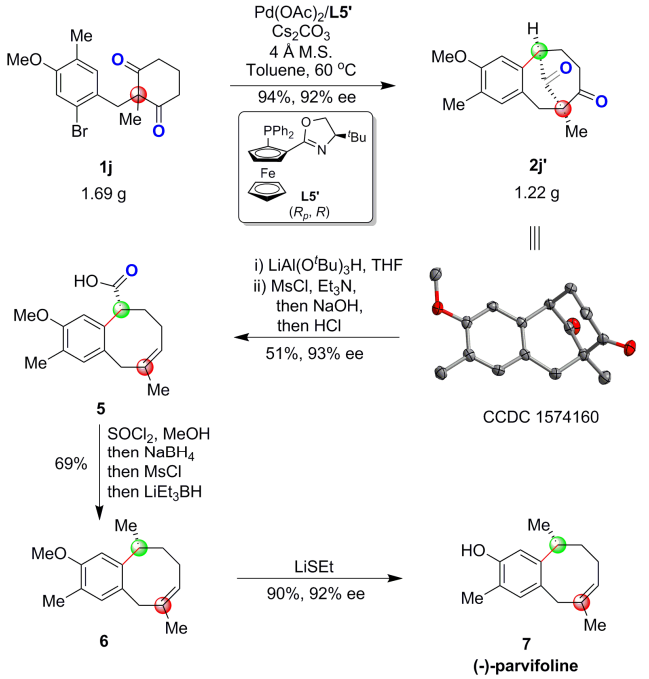

[a]Reaction conditions: **1** (0.10 mmol), 10 mol% $Pd(OAc)_2$, 11 mol% **L5**, $Cs_2CO_3$ (0.10 mmol), 100 mg 4 Å M.S. in 1 mL toluene, 80 °C, 48 hours, under argon; Isolated yields with ee values determined by chiral HPLC. [b]96 h. [c]60 °C. [d]90 °C. [e]100 °C. [f]120 °C. [g]20 mol% $Pd(OAc)_2$, 22 mol% **L5**.

**Scheme 1.** Asymmetric Synthesis of Bicyclo[3.3.1] Skeleton Bearing Three Stereocenters.




We next investigated whether this strategy could be applied to 5-substituted cyclohexane-1,3-diones that would provide products containing three stereocenters. Interstingly, the catalytic desymmetrization and asymmetric cyclization of the diasteromeric mixture, **1y**/**1y'** (*trans*/*cis* = 3.6:1) derived from commercially available material **3** and **4** provided the product **2y** as single diastereomer in 66% yield with 96% ee. To gain insight into this high diastereoselectivity, we isolated the mixture of **1y** and **1y'** by column chromatography. Both relative configurations of the products were confirmed by X-ray crystallographic analysis. Catalytic desymmetrization of the **1y** provided the product **2y** in 96% yield with 96% ee. In contrast, only trace amount of product **2y'** was obtained probably due to steric hindrance between 5-phenyl group and two α methylene groups in this *cis*-configuration.

**Scheme 2.** Enantioselective Total Synthesis of (-)-Parvifoline.




The formed bicyclo[*m*.*n*.1] products can be used as precursors for the preparation of chiral medium-sized cyclic compounds. This utility can be exemplified by a short synthesis of (−)-parvifoline,[12] a sesquiterpene isolated from the species Coreopsis with a special trimethyl benzocyclooctene structural unit.[13] On the basis of the above experimental results and the absolute configuration of (−)-parvifoline, we used ($R_p$, *R*)-$^t$Bu-FOXAP (**L5'**) as the ligand in catalytic desymmetrization, providing the key bicyclo[3.3.1] skeleton **2j'** on gram-scale in 94% yield and 92% ee under the developed conditions. The absolute configuration of this key intermediate was also confirmed by X-ray crystallography. Then one-pot regio- and stereoselective reduction of the least hindered carbonyl group of **2j'**, mesylatation and followed by a Grob fragmentation[14] afforded the benzocyclooctene carboxylic acid **5** in 51% overall yield with 93% ee. It was then subjected to esterification, reduction, and mesylation followed by a reduction of the crude mesylate with $LiEt_3BH$ to provide chiral product **6** in 69% overall yield. Finally, cleavage of the methyl ether in **6** with EtSLi in dry DMF gave final product (-)-parvifoline (**7**) in 90% yield with 92% ee, whose spectroscopic properties were identical with the litearture.[12b]

The observation of the stereoselectivities in **L5**-**L6** and a linear relationship of enantiomeric purity between ligand and product (see SI),[15] coupled with our knowledge of the absolute palladium stereochemistry,[16] suggests the model for stereochemical induction proposed in Figure 2. During oxidative addition, the bigger aryl group coordinated to palladium center is *trans* to $PPh_2$ group in **L5**-**L6**, and the smaller Br group on *cis* position. The diketone skeleton like a tail of the aryl ring, occupies the opposite side of the sterically $^t$Bu group on the ligand. The same stereoselectivity resulted from the diastereoisomers **L5** and **L6** is reasonable when the favored site of α methylene groups attack palladium center from the back side because of the bulk $PPh_2$ group.

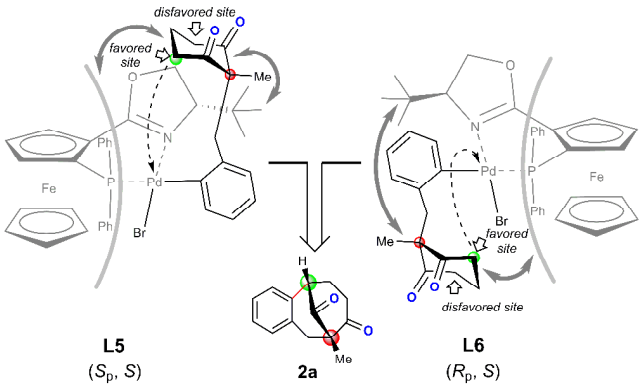



**Figure 2.** Model Explaining the Observed Stereochemistry.

In summary, we have described a highly enantioselective Pd-catalyzed intramolecular α-arylative desymmetrization of 1,3-diketones providing various functionalized bicyclo[*m*.*n*.1] architectures with several stereocenters. As the key step, the utility of this method has been highlighted by enantioselective total synthesis of (-)-parvifoline. We expect broad utility of this simple protocol for the synthesis of many other natural products.

## ASSOCIATED CONTENT

Experimental procedures, characterization data and spectra of new compounds, and X-ray crystal structures of **2d**, **2i**, **2t**, **1y**, **1y'**, **2y**, **2j'**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## REFERENCES

(1) Ciochina, R.; Grossman, R. B. *Chem. Rev.* **2006**, *106*, 3963.
(2) (a) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *Helv. Chim. Acta* **2001**, *84*, 3380. (b) Barriault, L.; Ang, P. A. J.; Lavigne, R. M. A. *Org. Lett.* **2004**, *6*, 1317. (c) Nicolaou, K. C.; Carenzi, G. E. A.; Jeso, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 3895.
(3) (a) Spiegel, D. A.; Njardason, J. T.; McDonald, I. M.; Wood, J. L. *Chem. Rev.* **2003**, *103*, 2691. (b) Boa, A. N.; Jenkins, P. R.; Lawrence, N. J. Contemp. *Org. Synth.* **1994**, *1*, 47. (c) Sheehan, S. M.; Lalic, G.; Chen, J. S.; Shair, M. D. *Angew. Chem., Int. Ed.* **2000**, *39*, 2714. (d) Butkus, E. *Synlett* **2001**, 1827. (e) Lavigne, R. M. A.; Riou, M.; Girardin, M.; Morency, L.; Barriault, L. *Org. Lett.* **2005**, *7*, 5921. (f) Barabé, F.; Bétournay, G.; Bellavance, G.; Barriault, L. *Org. Lett.* **2009**, *11*, 4236.
(4) (a) Schmalzbauer, B.; Herrmann, J.; Müller, R.; Menche, D. *Org. Lett.* **2013**, *15*, 964. (b) Yu, C.; Zhang, X.; Zhang, J.; Shen, Z. *Tetrahedron* **2016**, *72*, 4337.
(5) (a) Bhat, V.; Allan, K. M.; Rawal. V. H. *J. Am. Chem. Soc.* **2011**, *133*, 5798. (b) MacKay, J. A.; Bishop, R. L.; Rawal. V. H. *Org. Lett.* **2005**, *7*, 3421. (c) Heidebrecht, Jr. R. W.; Gulledge, B.; Martin, S. F. *Org. Lett.* **2010**, *12*, 2492. (d) Fu, T.; McElroy, W. T.; Shamszad, M.; Martin, S. F. *Org. Lett.* **2012**, *14*, 3834. (e) Komine, K.; Nomura, Y.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2015**, *17*, 3918.
(6) Liu, D.; Chen, J.; Ai, L.; Zhang, H.; Liu, J. *Org. Lett.* **2013**, *15*, 410.
(7) (a) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev*. **2005**, *105*, 313. (b) Zeng. X.-P.; Cao. Z.-Y.; Wang. Y.-H.; Zhou, F.; Zhou. J. *Chem. Rev*. **2016**, *116*, 7330.
(8) For a recent work on enantioselective palladium/L-proline-catalyzed α-arylative desymmetrization of cyclohexanones, see: Liu, R.-R.; Li, B.-L.; Lu,J.; Shen, C.; Gao, J.-R.; Jia, Y.-X. *J. Am. Chem. Soc.* **2016**, *138*, 5198. Jackson, K. E.; Stegbauer, L.; Paton, R. S.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2015**, *54*, 4899.
(9) For some recent examples, see: (a) Wu, X.; Chen, Z.; Bai, Y.-B.; Dong, V. M. *J. Am. Chem. Soc.* **2016**, *138*, 12013. (b) Clarke, C.; Incerti-Pradillos, C. A.; Lam, H. W. *J. Am. Chem. Soc.* **2016**, *138*, 8068. (c) Burns, A. R.; Solana González, J.; Lam, H. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 10827.
(10) For reviews on α-arylation, see: (a) Culkin, D. A.; Hartwig, J. F. *Acc. Chem. Res.* **2003**, *36*, 234. (b) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (c) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 676. For examples on enantioselective α-arylation, see: (d) Jiao, Z.; Beiger, J. J.; Jin, Y.; Ge, S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2016**, *138*, 15980. (e) Cornella, J.; Jackson, E. P.; Martin, R. *Angew. Chem., Int. Ed.* **2015**, *54*, 4075. (f) Ge, S.; Chaładaj, W.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4149. (g) Ge, S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 16630. (h) Z Liao, X.; Weng, Z.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 195. (i) Chen, G.; Kwong, F. Y.; Chan, H. O.; Yu, W.-Y.; Chan, A. S. C. *Chem. Commun.* **2006**, 1413. (j) Xie, X.; Chen, Y.; Ma, D. *J. Am. Chem. Soc.* **2006**, *128*, 16050. (k) Hamada, T.; Chieffi, A.; Åhman, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1261. (l) Åhman, J.; Wolfe, J. P.; Troutman, M. V.; Palucki, M.;. Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 1918.
(11) (a) Dai, L.-X.; Hou, L.-X.; Deng, W.-P.; You, S.-L.; Zhou. Y.-G. *Pure Appl. Chem.* **1999**, *77*, 1401. (b) Bolm, C.; Muñiz-Fernández, K.; Seger, A.; Raabe, G.; Günther, K. *J. Org. Chem.* **1998**, *63*, 7860.
(12) (a) Covarrubias-Zúñiga, A.; Cantú, F.; Maldonado, L. A. *J. Org. Chem.* **1998**, *63*, 2918. (b) Chavan, S. P.; Thakkar, M.; Jogdand, G. F.; Kalkote, U. R. *J. Org. Chem.* **2006**, *71*, 8986. (c) Villaomez-Ibarra, R.; Alvarez-Cisneros, C.; Joseph-Nathan, P. *Tetrahedron* **1995**, 51, 9285.
(13) Joseph-Nathan, P.; Hernandez-Medel, M.; Martinez, E.; Rojas-Gardida, M.; Cerda, C. M. *J. Nat. Prod.* **1988**, *51*, 675.
(14) (a) Boeckman, R. K.; Arvanitis, A.; Voss, M. E. *J. Am. Chem. Soc.* **1989**, *111*, 2737. (b) Bhowmik, D. R.; Venkateswaran, R. V. *Tetrahedron Lett.* **1999**, *40*, 7431.
(15) Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2017**, *139*, 4225.
(16) (a) Bolm, C.; Hildebrand, J. P.; Muñiz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284. (b) Linton, E. C.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 16162. (c) Zhao, G.; Xu, G.; Qian, C.; Tang, W. *J. Am. Chem. Soc.* **2017**, *139*, 3360.

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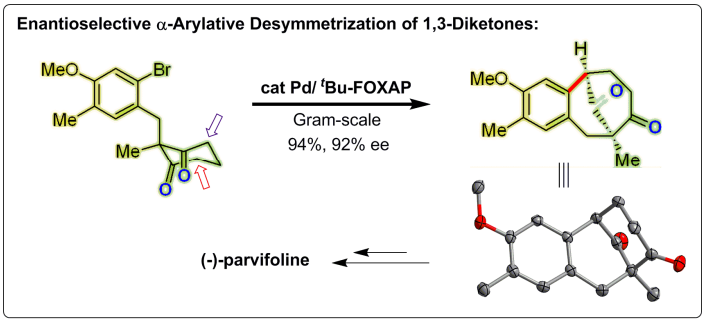
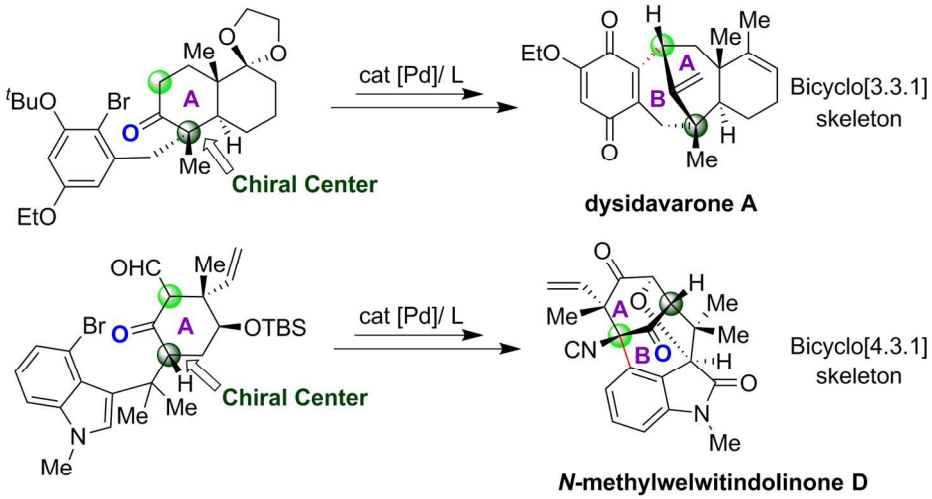
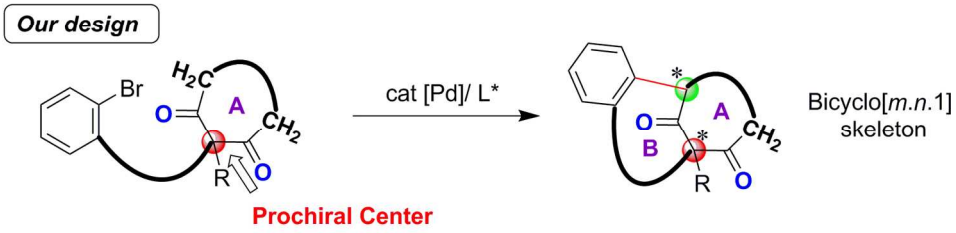

Enantioselective α-Arylative Desymmetrization of 1,3-Diketones:
MeO
Br
Me
Me
O
O
cat Pd/ tBu-FOXAP
Gram-scale
94%, 92% ee
H
MeO
Me
O
O
Me
(-)-parvifoline

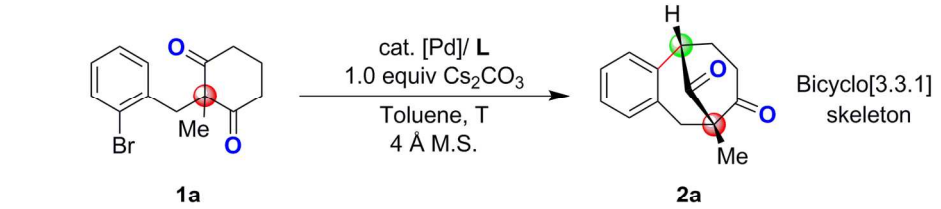
**a) Intramolecular α-Arylative Strategy in Total Synthesis:**

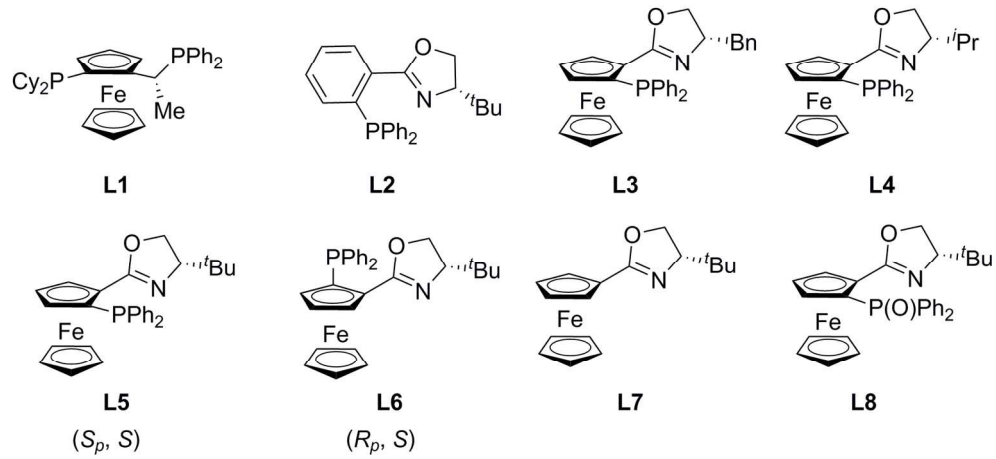



**b) Enantioselective Intramolecular α-Arylative Desymmetrization of 1,3-Diketones:**

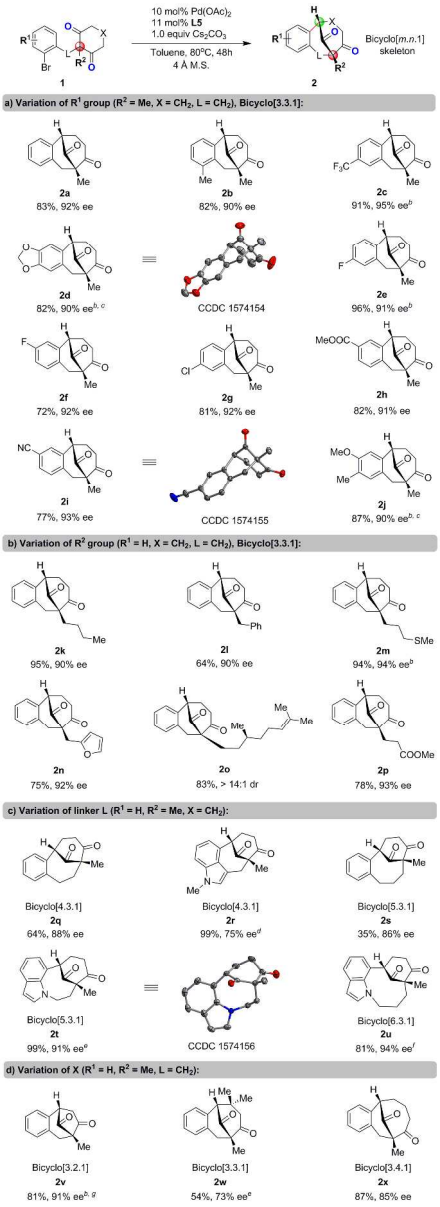



152x127mm (300 x 300 DPI)

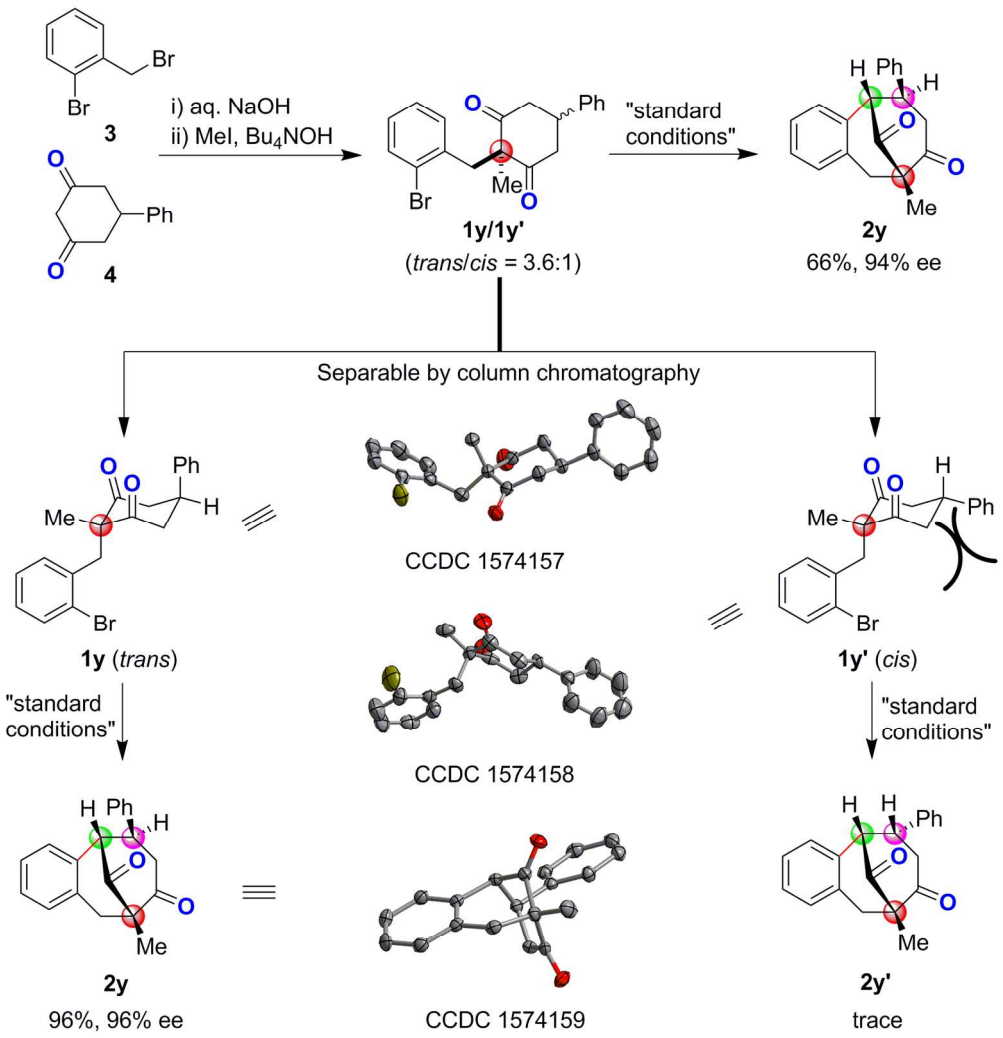


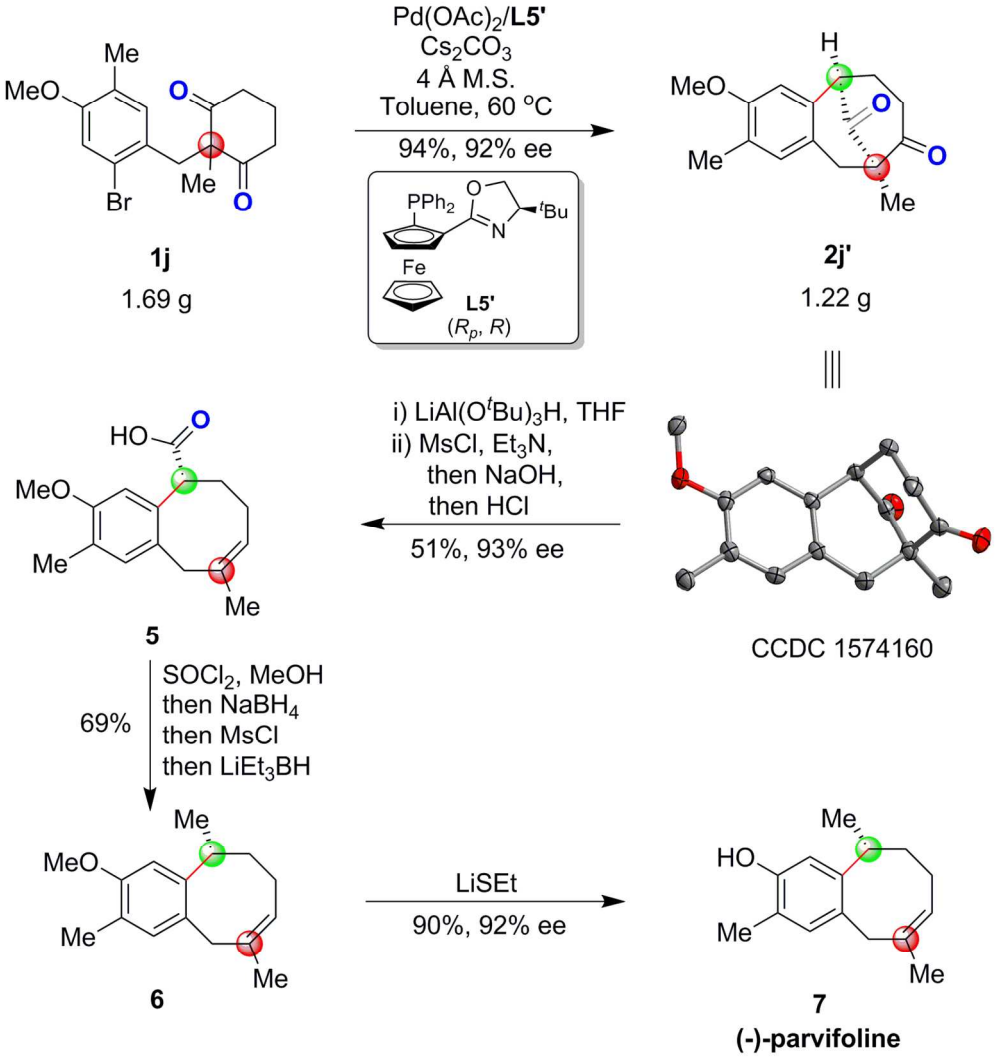

154x107mm (300 x 300 DPI)



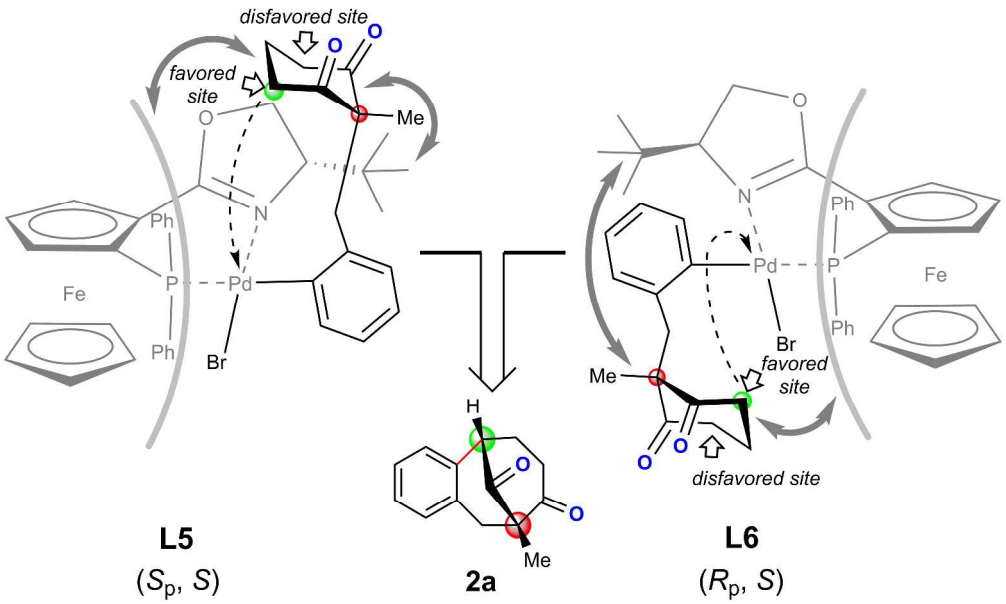

163x447mm (300 x 300 DPI)



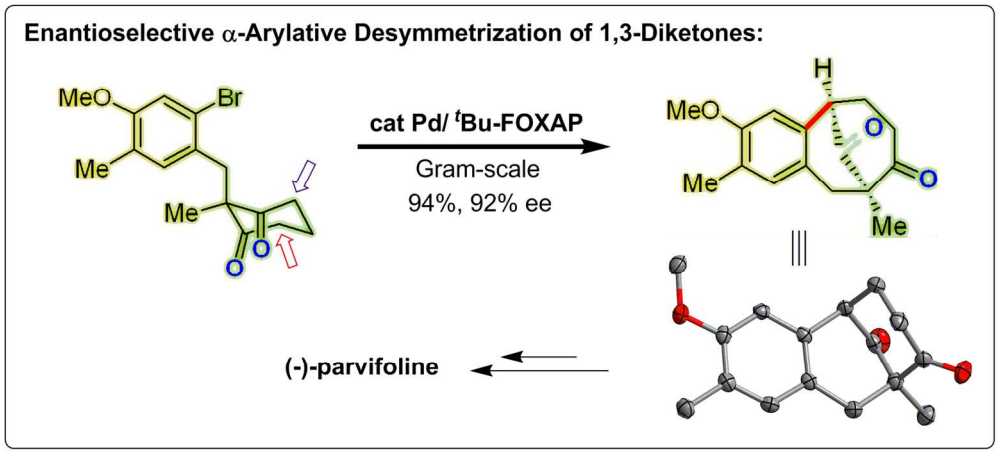

155x161mm (300 x 300 DPI)




136x145mm (300 x 300 DPI)




425x254mm (300 x 300 DPI)




146x66mm (300 x 300 DPI)