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Asymmetric Synthesis of Chiral 9,10-Dihydrophenanthrenes Using Pd-Catalyzed Asymmetric Intramolecular Friedel–Crafts Allylic Alkylation of Phenols

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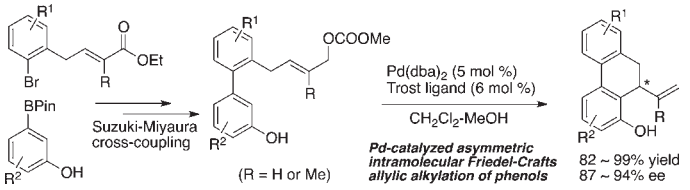
ABSTRACT



We developed a novel asymmetric synthetic method for multisubstituted 9,10-dihydrophenanthrenes based on the Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols, which produces 10-vinyl or 10-isopropenyl chiral 9,10-dihydrophenanthrene derivatives in high yield with up to 94% ee.

Highly oxygenated 9,10-dihydrophenanthrenes are ubiquitous structural motifs in biologically active natural products, such as cedrelins, which are cytotoxic against *Staphylococcus aureus* (209P), *Bacillus subtilis* (IAM1213), and paralycolines, which exhibit cytotoxic activity against KB and P388 cells (Figure 1).[1] In addition to the multiple oxygen functionalities on the aromatic rings, these natural products commonly possess an isopropenyl group at the 10-position of the 9,10-dihydrophenanthrene skeleton. The potential for diverse biological activities, as well as their various substitution patterns of this class of natural products, make this structural motif an interesting synthetic target. Therefore, the development of an efficient and flexible synthetic method for multisubstituted 9,10-dihydrophenanthrenes has attracted attention in synthetic organic chemistry and medicinal chemistry.[2]

Transition-metal-catalyzed asymmetric allylic alkylation is one of the most important synthetic transformations in organic synthesis.[3] Various stabilized carbon nucleophiles, and nitrogen, oxygen, and sulfur nucleophiles, are applicable to this reaction process. Phenols are generally utilized as oxygen nucleophiles in this catalytic transformation, with very few exceptions of *C*-allylation.[4] In contrast to the general reactivity, we recently reported that Pd-catalyzed intramolecular allylic alkylation of *para*-substituted phenol derivatives occurs on the aromatic carbons, affording the corresponding spirocyclohexadienones

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(2) For recent selected examples of the synthesis of functionalized 9,10-dihydrophenanthrenes, see: (a) Pratap, R.; Ram, V. J. *J. Org. Chem.* **2007**, *72*, 7402. (b) Zhu, C.; Shi, Y.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1243. (c) Jana, R.; Chatterjee, I.; Samanta, S.; Ray, J. K. *Org. Lett.* **2008**, *10*, 4795. (d) Saito, N.; Shiotani, K.; Kinbara, A.; Sato, Y. *Chem. Commun.* **2009**, 4284. (e) Sustac Roman, D.; Takahashi, Y.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3242. (f) Ueno, S.; Komiya, S.; Tanaka, T.; Kuwano, R. *Org. Lett.* **2012**, *14*, 338.

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through an *ipso*-Friedel–Crafts-type reaction.[5,6] This reaction could be extended to a catalytic asymmetric process by selecting a suitable chiral ligand. This background led us to hypothesize that 10-isopropenyl-9,10-dihydrophenantherene-1-ol **I**, the core structure of cedrelins and paralycolines, could be synthesized in an optically active form using a Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of *m*-hydroxy biaryl compounds **II**, which in turn, could be prepared using catalytic biaryl coupling reactions (Scheme 1). Herein, we report a novel method for synthesizing 10-vinyl or 10-isopropenyl chiral dihydrophenanthrenes using a Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols.[7]

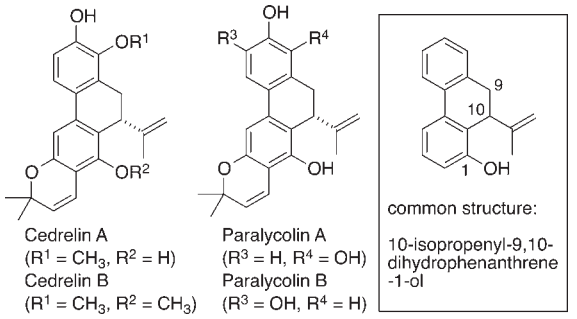
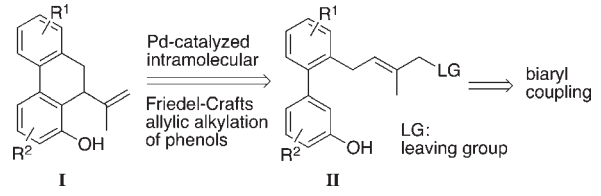


Figure 1. Natural products with a 10-isopropenyl 9,10-dihydrophenanthren-1-ol skeleton.

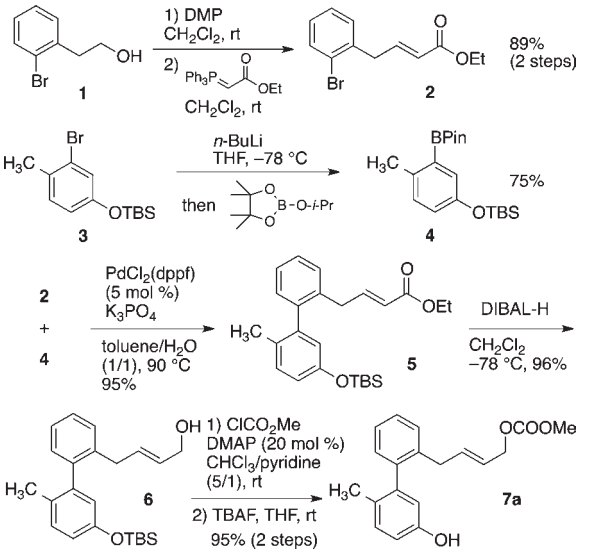
Scheme 1. Synthetic Plan



We first prepared a model substrate for the target reaction based on a biaryl coupling reaction (Scheme 2).

After oxidation of commercially available **1** using Dess–Martin periodinane (DMP), the obtained crude residue was reacted with a Wittig reagent to give the northern fragment **2** in 89% yield. On the other hand, the southern fragment was prepared from compound **3** through a one-pot process involving a bromine–lithium exchange, followed by entrapment with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and compound **4** was obtained in 75% yield. Suzuki–Miyaura cross-coupling[8] of **2** with **4** proceeded smoothly using 5 mol % of $PdCl_2$(dppf) and K_3PO_4 as a base, affording biaryl derivative **5** in 95% yield. After reduction of the ester unit with DIBAL-H (96% yield), the obtained alcohol **6** was transformed into **7a** in 95% yield over two steps.

Scheme 2. Synthesis of a Model Substrate



The reaction conditions were optimized using **7a** as the substrate (Table 1). We first examined the reaction using 5 mol % of $Pd(dba)_2$ and 12 mol % of PPh_3 in CH_2Cl_2 at room temperature, which were the optimum conditions for the previously reported Pd-catalyzed intramolecular *ipso*-Friedel–Crafts allylic alkylation of phenols. Desired product **8a** was obtained in only 12% yield but was, however, accompanied by the formation of some oligomeric byproduct through intermolecular allylic etherification.[9] The use of other common solvents failed to improve the yield (entries 1–4). In this reaction system, deprotonation of the phenol occurs by the endogenous methoxide anion to increase the nucleophilicity of the aromatic carbon, as well as the phenol oxygen.[5] Therefore, solvation of the

(6) For other examples of transition-metal-catalyzed ncleophilic dearomatization of phenols, see: (a) Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4455. (b) Rousseaux, S.; García-Fortanet, J.; Del Aguila Sanchez, M. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 9282.

(7) For representative examples of transition metal-catalyzed asymmetric Friedel–Crafts allylic alkylation of indoles or other heterocycles, see: (a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (b) Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani–Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424. (c) Cheung, H. Y.; Yu, W.-Y.; Lam, F.-L.; Au-Yeung, T. T.-L.; Zhou, Z.; Chan, T. H.; Chen, A. S. C. *Org. Lett.* **2007**, *9*, 4295. (d) Liu, W.-B.; He, H.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2008**, *10*, 1815. (e) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9533. (f) Wu., Q.-F.; He, H.; Liu, W.-B.; You, S.-L. *J. Am. Chem. Soc.* **2010**, *132*, 11418. (g) Hoshi, T.; Sasaki, K.; Sato, S.; Ishii, Y.; Suzuki, T.; Hagiwara, H. *Org. Lett.* **2011**, *13*, 932. (h) Cao, Z.; Liu, Y.; Liu, Z.; Feng, X.; Zhuang, M.; Du, H. *Org. Lett.* **2011**, *13*, 2164. (i) Zhuo, C.-X.; Liu, W.-B.; Wu, Q.-F.; You, S.-L. *Chem. Sci* **2012**, *3*, 205. (j) Wu, Q.-F.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 1680.

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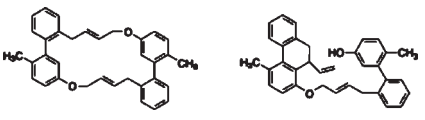
(9) *O*-allylated adducts shown below were obtained as the major byproduct in this reaction.

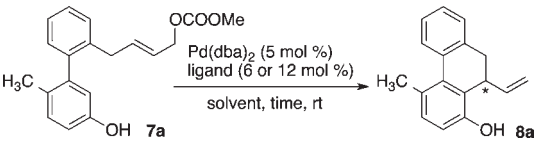


phenoxide anions by the addition of a protic solvent was expected to prevent the undesired intermolecular *O*-alkylation selectively. Thus, we examined the reaction using a protic solvent as the cosolvent. The yield was significantly improved to 71% when the reaction was performed in a CH_2Cl_2−MeOH mixed solvent system (entry 6). The satisfactory results using PPh_3 led us to focus on the asymmetric version of this transformation. First, we examined the reaction using chiral monodentate phosphorus ligands. 9-NapBN,[10] MOP,[11] and phosphoramidite ligands[12] like Monophos are effective chiral monodentate phosphorus ligands in transition-metal-catalyzed allylic substitution reactions. Trials using these chiral ligands, however, gave unsatisfactory results (entries 10−13). We next examined the reaction using privileged bidentate ligands for the transition metal-catalyzed asymmetric allylic substitution reactions. Although the reaction rarely occurred using a PHOX-type ligand (entry 14),[13] the desired transformation proceeded smoothly when Trost ligands were used (entries 15−17). Among the Trost ligands examined, (*R*,*R*)-ANDEN-phenyl Trost ligand **H** was best for asymmetric induction, and chiral dihydrophenanthrene derivative **8a** was obtained in 97% yield and 91% ee (entry 17).[14]

The stereochemistry of the product **8a** was determined using X-ray analysis (Scheme 3). Reduction of the double bond of **8a** (91% ee), followed by bromination of the phenolic ring, afforded **9** in 86% yield in two steps. After esterification of the phenol with a *p*-nitrobenzoyl chloride (99% yield), single recrystallization of the product from hexane-ethyl acetate gave compound **10** with 99% ee. X-ray analysis of the obtained crystal revealed that the absolute stereochemistry of the benzylic position of **8a** was (*S*).[15]

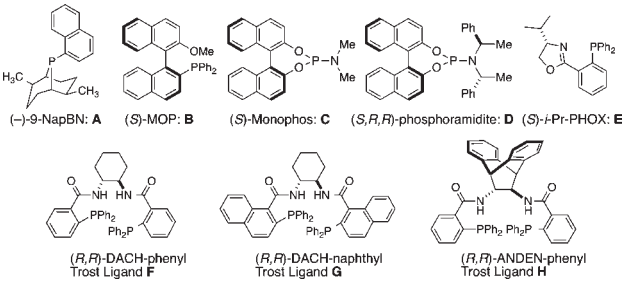
We next examined the scope and limitations of various substrates under the optimized reaction conditions. All reactions were performed using 5 mol % of $Pd(dba)_2$ and

Table 1. Optimization of the Reaction Conditions Using **7a**

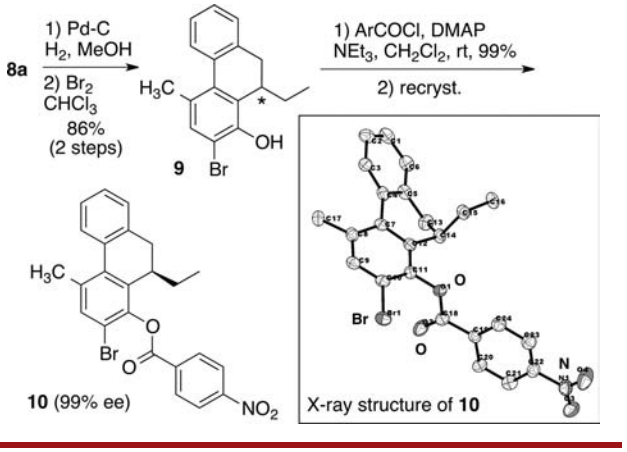


entry	ligand (mol %)	solvent	time (h)	yield[a] (%)	ee[b] (%)
1	PPh_3 (12)	CH_2Cl_2	5	12	
2	PPh_3 (12)	CH_3CN	16	trace	
3	PPh_3 (12)	toluene	5	11	
4	PPh_3 (12)	THF	3	trace	
5	PPh_3 (12)	THF/MeOH (4/1)	6	63	
6	PPh_3 (12)	CH_2Cl_2/MeOH (4/1)	16	71	
7	PPh_3 (12)	CH_2Cl_2/MeOH (1/1)	16	12	
8	PPh_3 (12)	CH_2Cl_2/MeOH (9/1)	16	46	
9	PPh_3(12)	CH_2Cl_2/*t*-BuOH (4/1)	16	30	
10	**A** (12)	CH_2Cl_2/MeOH (4/1)	10	trace	
11	**B** (12)	CH_2Cl_2/MeOH (4/1)	16	62	−7
12	**C** (12)	CH_2Cl_2/MeOH (4/1)	6	56	4
13	**D** (12)	CH_2Cl_2/MeOH (4/1)	18	76	−32
14	**E** (6)	CH_2Cl_2/MeOH (4/1)	16	trace	
15	**F** (6)	CH_2Cl_2/MeOH (4/1)	16	66	−65
16	**G** (6)	CH_2Cl_2/MeOH (4/1)	6	88	−10
17	**H** (6)	CH_2Cl_2/MeOH (4/1)	6	97	91

[a] Isolated yield. [b] Determined by chiral HPLC analysis. Negative value means the opposite enantiomer.



Scheme 3. Determination of the Absolute Configuration of **8a**



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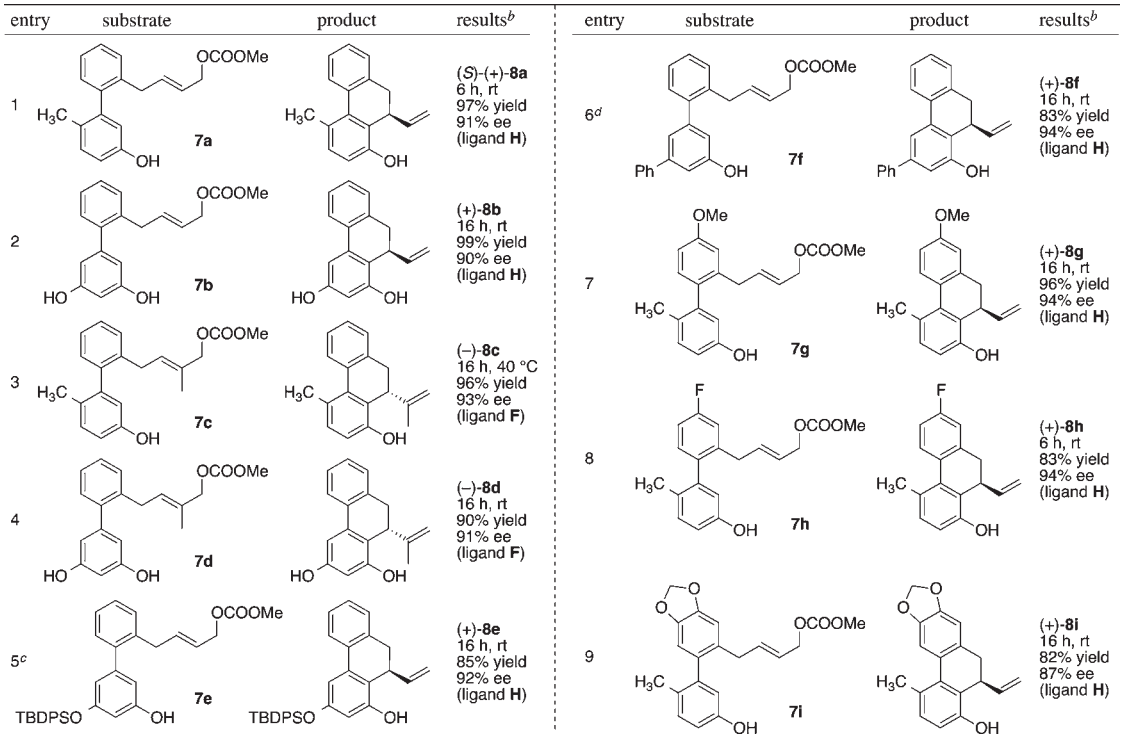
(12) For a review on the chiral phosphoramidite ligands, see: Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486.

(13) For a review on the PHOX ligands, see:Helmuchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336.

(14) For recent selected examples of catalytic asymmetric reactions using the ANDEN-phenyl Trost ligand **H**, see: (a) Trost, B. M.; Tsui, H.-C.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 3534. (b) Trost, B. M.; Tang, W. *J. Am. Chem. Soc.* **2003**, *125*, 8744. (c) Trost, B. M.; Frederiksen, M. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 308. (d) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846. (e) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 17180. (f) Trost, B. M.; Xu, J.; Reichle, M. *J. Am. Chem. Soc.* **2007**, *129*, 282. (g) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2008**, *130*, 14092. (h) Trost, B. M.; Thaisrivongs, D. A. *J. Am. Chem. Soc.* **2009**, *131*, 12056. (i) Trost, B. M.; Lehr, K.; Michaelis, D. J.; Xu, J.; Buckl, A. K. *J. Am. Chem. Soc.* **2010**, *132*, 8915. (j) Trost, B. M.; Czabaniuk, L. C. *J. Am. Chem. Soc.* **2010**, *132*, 15534. (k) Trost, B. M.; Thaisrivongs, D. A.; Hartwig, J. *J. Am. Chem. Soc.* **2011**, *133*, 12439. (l) Trost, B. M.; Schäffner, B.; Osipov, M.; Wilton, D. A. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 3548.

(15) See the Supporting Information for details.

Table 2. Scope and Limitations[a]



[a] Reaction conditions: $Pd(dba)_2$ (5 mol %), (*R*,*R*)-Trost ligand (6 mo l%), CH_2Cl_2–MeOH (4/1) (0.05 M). [b] Isolated yield. Enantiomeric excesses were determined by chiral HPLC analysis. Absolute configuration of the reaction products other than (*S*)-(+)-**8a** was tentatively assigned based on the sign of optical rotation. [c] 10% of *para*-substituted adduct was also obtained. [d] 13% of *para*-substituted adduct was also obtained.

6 mol % of (*R*,*R*)-Trost ligand in a CH_2Cl_2–MeOH mixed solvent system. Similar to the case of model substrate **7a**, asymmetric intramolecular Friedel–Crafts allylic alkylation of substrate **7b**, bearing a symmetric 3,5-dihydroxyphenyl ring, proceeded smoothly at room temperature and produced the corresponding products **8b** in 99% yield with 90% ee (Table 2, entry 2). Substrates with a trisubstituted olefin **7c** and **7d** were also applicable to this reaction. Using (*R*,*R*)-DACH-phenyl Trost ligand **F**, 10-isopropenyldihydrophenanthrene derivatives **8c** and **8d** were obtained in excellent yield with 93% ee and 91% ee, respectively. When phenol derivatives bearing asymmetric substituent patterns on the southern ring, such as **7e** and **7f**, were used as substrates, the Friedel–Crafts allylic alkylation preferentially occurred on the *ortho*-position, providing 10-vinyl-9,10-dihydrophenantherene-1-ols **8e** and **8f** in 85% yield with 92% ee and 83% yield with 94% ee, respectively. In addition, compounds **7g**–**i**, bearing electron-donating and electron-withdrawing functionalities on the northern aromatic ring, were tolerant to this reaction, giving the corresponding products **8g**–**i** in high yield with 87–94% ee.

In conclusion, we achieved a Pd-catalyzed asymmetric intramolecular Friedel–Crafts allylic alkylation of phenols that provided a series of 10-vinyl- or 10-isopropenyldihydrophenanthren-1-ol derivatives in high yield with high enantiomeric excess. Application of the developed method to asymmetric synthesis of natural products is ongoing.

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Supporting Information Available. Experimental procedures, compound characterization, crystallographic information file (CIF) of **10**, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.