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Advanced Synthesis & Catalysis

Palladium-Catalyzed Tandem γ-Arylation/Aromatization of Cyclohex-2-En-1-One Derivatives: A Route to 3,4-Dihydroanthracen-1(2*H*)-Ones

Yi-Kang Song,[a] Si-Yu Xu,[a] Shu-Sheng Zhang,[a] Jian-Guo Fu,[a,*] Guo-Qiang Lin,[a, b] and Chen-Guo Feng[a, b, c,*]

[a] The Research Center of Chiral Drugs, Innovation Research Institute of Traditional Chinese Medicine Shanghai, University of Traditional Chinese Medicine, 1200 Cailun Road, Shanghai 201203, People's Republic of China
Fax: (+86) 21-5132-2416;
phone: (+86) 21-5132-2416
E-mail: fujg@shutcm.edu.cn; fengcg@shutcm.edu.cn
[b] CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Science, 345 Lingling Road, Shanghai 200032, People's Republic of China
[c] Shanghai Key Laboratory for Molecular Engineering of Chiral Drugs, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, People's Republic of China

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Abstract: An intramolecular palladium-catalyzed tandem γ-arylation/aromatization reaction of cyclohex-2-en-1-one derivatives was developed. This work provides a simple and efficient approach for the construction of substituted 3,4-dihydroanthracen-1(2*H*)-ones in good yields with a broad substrate scope.

Keywords: palladium; γ-arylation; tandem reactions; cyclization; dihydroanthracen-1(2*H*)-ones

Transition metal-catalyzed α-arylation of carbonyl derivatives via enolates has become a powerful tool for the construction of carbon-carbon bonds.[1] In contrast, the corresponding vinylogous γ-arylation of α,β-unsaturated carbonyl compounds via dienolates has received less attention, which may be ascribed to several obvious challenges, including the difficulty in controlling the regioselectivity between α-, β-, and γ-arylation, the reduced nucleophilicity of dienolates compared with enolates, and the side reactions through self-condensation or Heck process.[2–4]

In 1998, Miura and co-workers described a palladium-catalyzed γ-arylation of α,β-unsaturated aldehydes with aryl bromides.[5] Since then, a number of α,β-unsaturated aldehydes,[6] ketones,[3b,7] amides[8] and esters[9] were applied in such transformations (Scheme 1a). In the meantime, a few cascade reactions were also developed. Maier and co-workers reported a palladium-catalyzed γ-arylation/aromatization sequence of enones (Scheme 1b).[10] Imahori employed a similar γ-arylation/aromatization strategy for the synthesis of substituted phenols (Scheme 1b).[11] Recently, Liu and co-workers described an efficient palladium-catalyzed γ-arylation/aza-Michael addition cascade (Scheme 1c).[12] Despite the achievement in intermolecular γ-arylation, the corresponding intramolecular process, which is potentially quite useful in the construction of complex ring systems, has not been reported yet.

3,4-Dihydroanthracen-1(2*H*)-one is an important tricyclic skeleton in many bioactive natural products, like mithramycin,[13] aloesaponol I[14] and peroxisomicine A1 (Figure 1).[15] Although a few synthetic methods have been presented for this core structure, they often suffered from limited substrate scope,

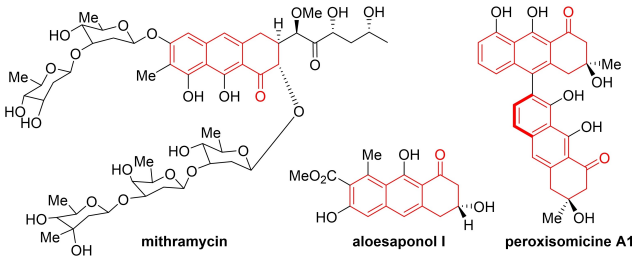
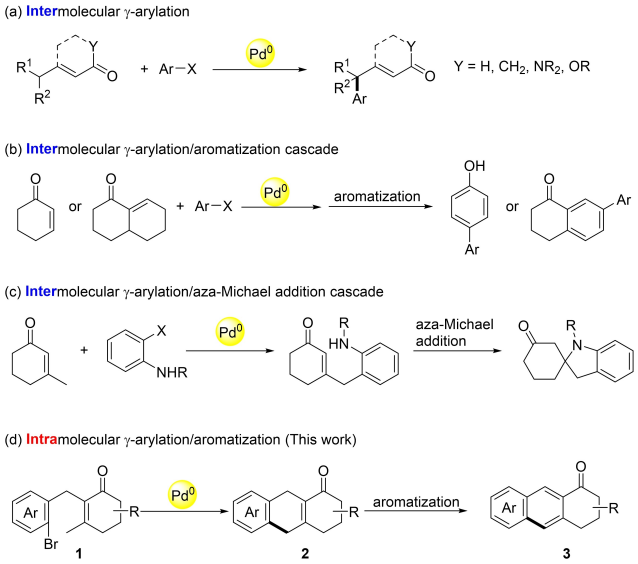


Figure 1. Selected examples of bioactive natural products containing 3,4-dihydroanthracen-1(2*H*)-one units.

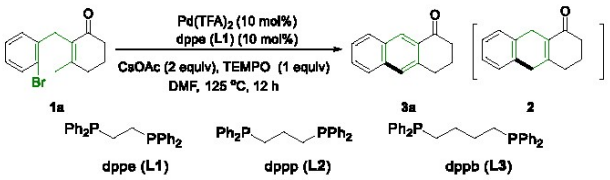


Scheme 1. γ-Arylation of α,β-unsaturated carbonyl compounds.

tedious reaction procedure and poor regioselectivity.[16] Therefore, more efficient synthetic methods are highly desirable. We envision that an intramolecular γ-arylation of cyclohex-2-en-1-one derivatives **1** can afford tricyclic skeleton **2**, which may subsequently undergo a Pd-catalyzed dehydrogenation to produce the desired 3,4-dihydroanthracen-1(2*H*)-ones **3** (Scheme 1d).[17]

With the above consideration in mind, we began our investigation of this cascade process using aryl bromide **1a** as the model substrate (Table 1). In the presence of palladium catalyst, the desired 3,4-dihydroanthracen-1(2*H*)-one **3a** was generated and the intermediate enone **2** was not observed. The structure of **3a** was unambiguously confirmed by X-ray crystallographic analysis.[18] Notably, the possible side product from Heck pathway was also not observed, and the most common and identifiable side reaction was the debromination of **1a**. Extensive screening of reaction conditions led to the best isolated yield of 72% for the desired product **3a** (entry 1). The reaction could be promoted by both bisphosphine and monophosphine ligands, however the electron-deficient triarylphosphine ligand **L6** resulted in a significant decrease in reaction yield (entry 6). As expected, base was crucial for this transformation, and no desired product was generated without adding CsOAc (entry 7). Other bases, CsOPiv and KOAc, were also workable, but less effective (entries 8 and 9). Solvent effects were also surveyed, and it was found that amide-group-containing polar solvents were essential for the efficient reaction (entries 10-12). Comparable results were obtained when precatalyst $Pd(TFA)_2$ was replaced by $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ or $Pd_2(dba)_3$ (entries 13-15). 2,2,6,6-Tetramethyl-1-piperidinyloxy

Table 1. Optimization of the reaction conditions.[a]



Entry	Deviation from standard conditions	Yield of **3a** (%)[b]
1	**none**	74
2	dppp (**L2**) instead of dppe	65
3	dppb (**L3**) instead of dppe	56
4	PPh_3 (**L4**) instead of dppe	60
5	$P(4\text{-}MeOPh)_3$ (**L5**) instead of dppe	65
6	$P(4\text{-}CF_3Ph)_3$ (**L6**) instead of dppe	8
7	without CsOAc	0
8	CsOPiv instead of CsOAc	66
9	KOAc instead of CsOAc	66
10	toluene instead of DMF	21
11	dioxane instead of DMF	14
12	NMP instead of DMF	61
13	$Pd(OAc)_2$ instead of $Pd(TFA)_2$	70
14	$Pd(PPh_3)_2Cl_2$ instead of $Pd(TFA)_2$	64
15	$Pd_2(dba)_3$ instead of $Pd(TFA)_2$	71
16	without TEMPO	50
17	BQ instead of TEMPO	66
18	115 °C instead of 125 °C	64
19	135 °C instead of 125 °C	70
20	20 mol% **L1** instead of 10 mol%	57

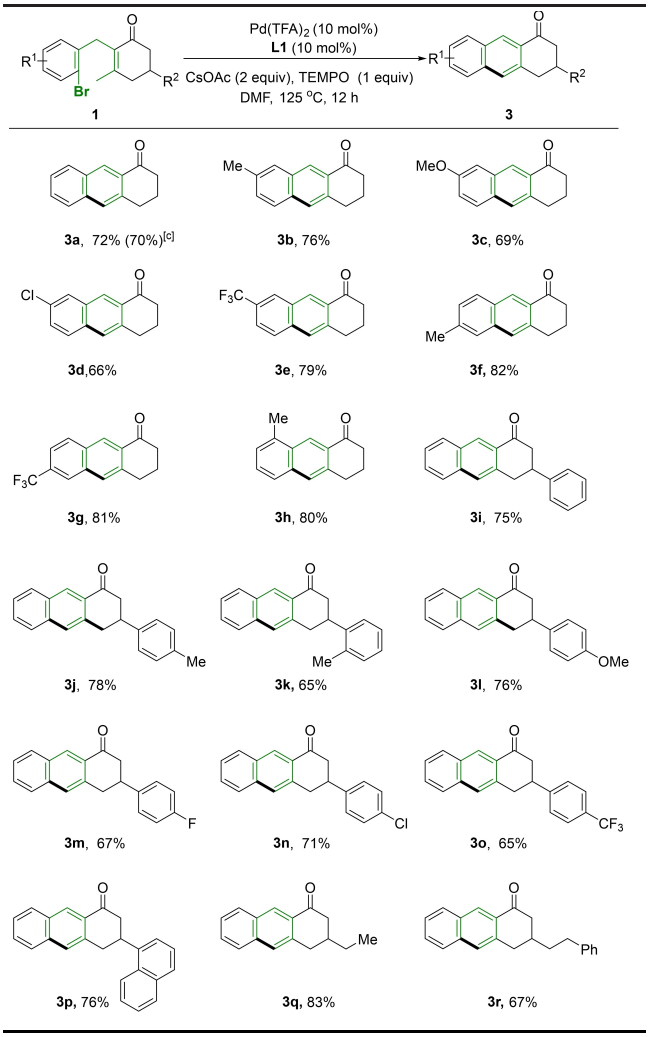
[a] Reaction conditions: **1a** (0.20 mmol), $Pd(TFA)_2$ (0.02 mmol), **L1** (0.02 mmol), CsOAc (0.40 mmol), TEMPO (0.20 mmol) in DMF (2 mL) under N_2 at 125 °C for 12 h unless otherwise noted.

[b] Determined by ^1H NMR spectroscopy analysis using CH_2Br_2 as an internal standard.

(TEMPO) was not indispensable for this transformation, but it had a strong beneficial effect on the reaction yield (entry 16). Although the exact role of TEMPO was unclear at this moment, we speculate that it may act as a promoter in the dehydrogenative aromatization step. Further attempts to improve the yield by temperature variation proved to be fruitless (entries 18 and 19).

With the optimized reaction conditions in hand, the substrate scope was explored for this γ-arylation/aromatization cascade process (Table 2). Small fluctuations in yield were observed when various substituents were introduced to different positions of the phenyl ring (**3a**–**3h**), and the yields did not show a clear relationship with the electronic or steric profiles of the

Table 2. Palladium-catalyzed tandem γ-arylation/aromatization of cyclohex-2-en-1-one derivatives.[a,b]



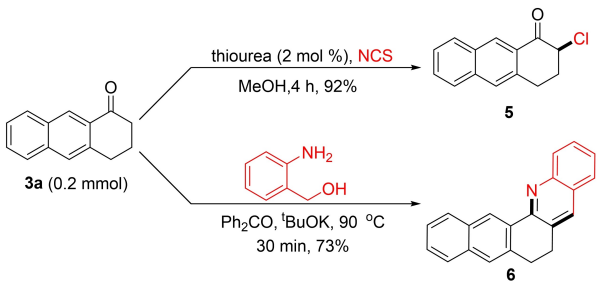
[a] Reaction conditions: **1a** (0.20 mmol), $Pd(TFA)_2$ (0.02 mmol), **L1** (0.02 mmol), CsOAc (0.40 mmol), TEMPO (0.20 mmol) in DMF (2 mL) under N_2 at 125 °C for 12 h.
[b] Isolated yields.
[c] A gram-scale reaction with **1a** (1.112 g, 4.00 mmol) was carried out.

substituents. Next, substituents at the β-position of carbonyl group were also examined. For aryl substituents, the introduction of electron-withdrawing groups or the steric hindrance (like *ortho*-methyl group) to the phenyl ring showed detrimental effect on the reaction yields (**3i**–**3o**). The replacement of phenyl ring with naphthyl group was well tolerated (**3p**), giving the desired product in 76% yield. As for aliphatic substituents, an ethyl group at this position resulted in some improvement in reaction yield (**3q**), but the longer phenethyl chain brought the yield back to 67% (**3r**). Notably, a comparable result was achieved for the gram-scale synthesis of **3a**. While the β-methyl substitution in cyclohex-2-en-1-one **1a** was replaced by a ethyl group, the cascade process proceeded rather sluggishly, and the generation of an inseparative polysubstituted phenol was accompanied (see supporting information for details).

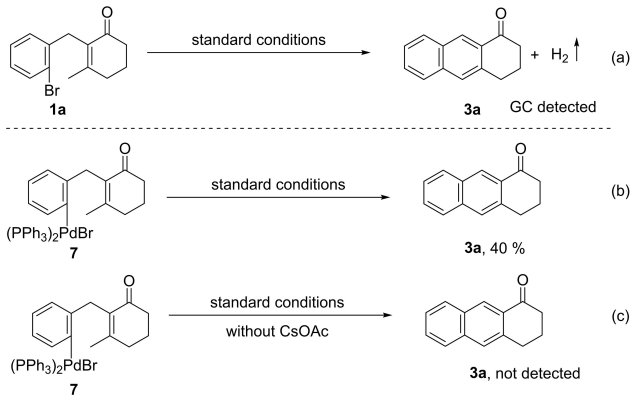
To demonstrate the utility of the cyclization products, transformations of the product **3a** were conducted (Scheme 2). Chlorine atom could be installed at the α-position of carbonyl group by treatment with *N*-chlorosuccinimide (NCS), providing a good handle for further derivatization.[19] Friedländer condensation with 2-aminobenzyl alcohol furnished a polycyclic compound **6**.[20]

To gain insights into the reaction mechanism, several control experiments were carried out. Upon completion, hydrogen evolution was detected according to GC analysis of the gas in the sealed reaction tube (Scheme 3a). When palladium complex **7** was prepared and subjected to the standard conditions, the desired cyclization product could be obtained in 40% yield (Scheme 3b). However, in the absence of CsOAc, the product **3a** was not generated at all (Scheme 3c).

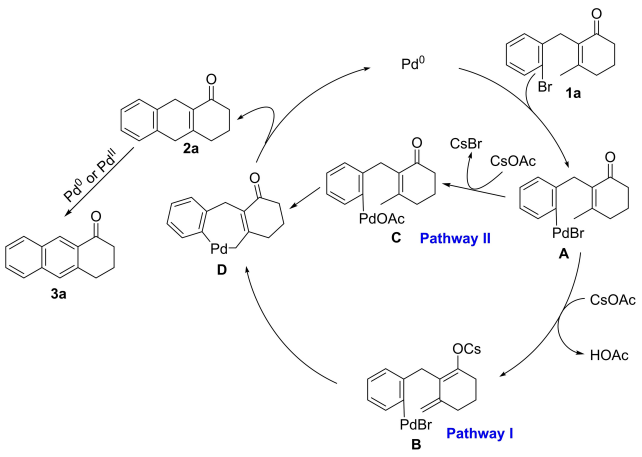
Based on the above experimental observation, a postulated mechanism is outlined in Scheme 4. First, oxidative addition of aryl bromide to palladium(0) generates the intermediate **A**, which can be deprotonated by CsOAc to provide dienolate **B**. Then, an intramolecular nucleophilic substitution of the bromide by enolate takes place, forming a seven-membered



Scheme 2. Conversion of the obtained product **3a**.



Scheme 3. Mechanistic experiments.



Scheme 4. Proposed catalytic cycle (ligands are omitted for clarity).

palladacycle **D**. Finally, reductive elimination of **D** and the subsequent dehydrogenative aromatization in the presence of either palladium(0)[21] or palladium (II) catalyst afford the desired product **3 a**.[22] However, another pathway cannot be totally excluded at current stage. Instead of forming dienolate **B** in pathway I, intermediate **A** exchanges its halide with an acetate anion to give **C**, which can further yield the palladacycle **D** through an allylic C–H activation (Pathway II).[23]

In summary, an intramolecular palladium-catalyzed γ-arylation of cyclohex-2-en-1-one derivatives was realized, which was followed by a tandem dehydrogenative aromatization. This work provides an efficient and reliable approach to prepare 3,4-dihydroanthracen-1(2*H*)-ones in very good reaction yields. Mechanistic studies revealed the existence of a hydrogen evolution process, and the crucial role of CsOAc.

Experimental Section

General Procedures for the Synthesis of 3,4-Dihydroanthracen-1(2*H*)-Ones

Under nitrogen atmosphere, a mixture of **1 a–r** (0.2 mmol), $Pd(TFA)_2$ (6.6 mg, 0.02 mmol), dppe (8.0 mg, 0.02 mmol), CsOAc (76.8 mg, 0.40 mmol) and TEMPO (31.2 mg, 0.20 mmol) in DMF (2 mL) was stirred at 125 °C for 12 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (15 mL) and washed with brine. The organic phase was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel chromatography to afford corresponding products **3 a–r**.

Acknowledgements

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References

[1] For selected reviews, see: a) C. C. C. Johansson, T. J. Colacot, *Angew. Chem.* **2010**, *122*, 686; *Angew. Chem. Int. Ed.* **2010**, *49*, 676; b) F. Bellina, R. Rossi, *Chem. Rev.* **2010**, *110*, 1082; c) Y.-J. Hao, X.-S. Hu, Y. Zhou, J. Zhou, J.-S. Yu, *ACS Catal.* **2020**, *10*, 955.

[2] For selected reviews, see: a) I. Franzoni, C. Mazet, *Org. Biomol. Chem.* **2014**, *12*, 233; b) J. Chen, D. Chang, F. Xiao, G. Deng, *Prog. Chem.* **2018**, *30*, 564; c) G. Saini, M. Kapur, *Chem. Commun.* **2021**, *57*, 1693.

[3] For similar γ-arylation with prepared silyl-dienol ethers, see: a) D. S. Huang, J. F. Hartwig, *Angew. Chem.* **2010**, *122*, 5893; *Angew. Chem. Int. Ed.* **2010**, *49*, 5757; b) G. Saini, A. Mondal, M. Kapur, *Org. Lett.* **2019**, *21*, 9071.

[4] For similar γ-arylation with β,γ-uansaturated carbonyl compounds, see: a) A. M. Hyde, S. L. Buchwald, *Angew. Chem.* **2008**, *120*, 183; *Angew. Chem. Int. Ed.* **2008**, *47*, 177; b) A. M. Hyde, S. L. Buchwald, *Org. Lett.* **2009**, *11*, 2663; c) M. Grigalunas, P.-O. Norrby, O. Wiest, P. Helquist, *Angew. Chem.* **2015**, *127*, 11988; *Angew. Chem. Int. Ed.* **2015**, *54*, 11822.

[5] Y. Terao, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **1998**, *39*, 6203.

[6] a) I. Franzoni, L. Guénée, C. Mazet, *Chem. Sci.* **2013**, *4*, 2619; b) I. Franzoni, A. I. Poblador-Bahamonde, *Organometallics* **2016**, *35*, 2955.

[7] a) Y.-C. Yang, Y.-C. Lin, Y.-K. Wu, *Org. Lett.* **2019**, *21*, 9286; b) O. Y. Yuen, C. M. So, *Angew. Chem. Int. Ed.* **2020**, *59*, 23438; *Angew. Chem.* **2020**, *132*, 23644.

[8] M. Yu, Y. Xie, J. Li, Y. Zhang, *Adv. Synth. Catal.* **2011**, *353*, 2933.

[9] M. E. Sexton, A. Okazaki, Z. Yu, A. van Venrooy, J. R. Schmink, W. P. Malachowski, *Tetrahedron Lett.* **2019**, *60*, 151057.

[10] G. N. Varseev, M. E. Maier, *Org. Lett.* **2005**, *7*, 3881.

[11] T. Imahori, T. Tokuda, T. Taguchi, H. Takahata, *Org. Lett.* **2012**, *14*, 1172.

[12] X.-W. Zhang, H. Zhang, H.-C. Wang, M.-H. Zhu, H. Cong, W.-B. Liu, *Chem. Commun.* **2020**, *56*, 12013.

[13] a) S. Mansilla, I. Garcia-Ferrer, C. Mendez, J. A. Salas, J. Portugal, *Biochem. Pharmacol.* **2010**, *79*, 1418; b) M. A. Bosserman, T. Downey, N. Noinaj, S. K. Buchanan, J. Rohr, *ACS Chem. Biol.* **2013**, *8*, 2466.

[14] A. Yenesew, J. A. Ogur, H. Duddeck, *Phytochemistry* **1993**, *34*, 1442.

[15] J. M. Wanjohi, A. Yenesew, J. O. Midiwo, M. Heydenreich, M. G. Peter, M. Dreyer, M. Reichert, G. Bringmann, *Tetrahedron* **2005**, *61*, 2667.

[16] a) D. N. Hickman, K. J. Hodgetts, P. S. Mackman, T. W. Wallace, J. M. Wardleworth, *Tetrahedron* **1996**, *52*, 2235; b) V. Premasagar, V. A. Palaniswamy, E. J. Eisenbraun, *J. Org. Chem.* **1981**, *46*, 2974; c) D. L. Boger, J. Zhou, *J. Org. Chem.* **1993**, *58*, 3018; d) M. Yokota, D. Fujita, J. Ichikawa, *Org. Lett.* **2007**, *9*, 4639.
[17] For intramolecular γ-alkenylation of α,β-unsaturated carbonyl compounds, see: T. Wang, J. M. Cook, *Org. Lett.* **2000**, *2*, 2057.
[18] CCDC-2031753 (**3 a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[19] Y. Mei, P. A. Bentley, J. Du, *Tetrahedron Lett.* **2008**, *49*, 3802.
[20] R. Martínez, D. J. Ramón, M. Yus, *J. Org. Chem.* **2008**, *73*, 9778.
[21] N. Yasukawa, H. Yokoyama, M. Masuda, Y. Monguchi, H. Sajiki, Y. Sawama, *Green Chem.* **2018**, *20*, 1213.
[22] T. Diao, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 14566.
[23] a) G. Liu, Y. Wu, *Top. Curr. Chem.* **2009**, *292*, 195; b) F. Liron, J. Oble, M. M. Lorion, G. Poli, *Eur. J. Org. Chem.* **2014**, *27*, 5863.

COMMUNICATIONS

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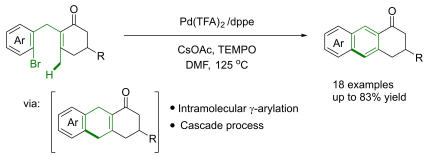

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