Chinese Chemical Letters 34 (2023) 108297

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Pd-catalyzed cascade cyclization of allenylethylene carbonates and indandiones: Synthesis of tetracyclic dihydrocyclopentaindenofuranone derivatives☆

Yujie Dong[a], Jun Liu[a], Xing Gao[a], Ting Pan[a], Biming Mao[a], Songcheng Yu[b], Yongjun Wu[b], Cheng Zhang[a,*], Hongchao Guo[a,*]

[a] *Department of Chemistry and Innovation Center of Pesticide Research, China Agricultural University, Beijing 100193, China*
[b] *College of Public Health, Zhengzhou University, Zhengzhou 450001, China*

A R T I C L E I N F O

Article history:
Received 5 December 2022
Revised 24 February 2023
Accepted 1 March 2023
Available online 6 March 2023

Keywords:
Palladium
Allenylethylene carbonates
Indandiones
Cascade cyclization
Decarboxylation

A B S T R A C T

A palladium-catalyzed cascade cyclization of allenylethylene carbonates with 1,3-indandiones was developed, providing biologically interesting tetracyclic dihydrocyclopentaindenofuranone derivatives having three contiguous quaternary carbon centers in moderate to high yields with excellent diastereoselectivities. In this reaction, the allene moiety was fully fused into the cyclopentene ring.

Terpenoids such as Ginkgolides and Bilobalide (Fig. 1) are unique components of the Ginkgo biloba tree, which displayed diverse bioactivities such as antioxidant, anti-aging, blood pressure lowering, blood circulation promotion and anti-platelet activating factors [1–4]. Therefore, synthesis of Ginkgolides, Bilobalide and their derivatives having multicyclic skeleton are very significant and have attracted much attention [5]. However, assembly of contiguous quaternary carbons in these terpenoid natural products remains a big challenge. New synthetic methods for these structures are highly desirable.

Pd-catalyzed decarboxylative cycloadditions are one of the most powerful tools for synthesis of carbo- and hetero-cyclic compounds from readily available starting material [6–20]. Generally, these $(m+n)$ cycloadditions were furnished through stepwise reactions of in situ generated zwitterionic π-allyl palladium intermediates from decarboxylation of precursors with electron-deficient reaction partner [6–20]. Obviously, the type and reactivity of the precursors for formation of π-allyl palladium intermediate played a key role in Pd-catalyzed decarboxylative cycloadditions. In 2021, we designed and synthesized the allenylethylene carbonates (AECs) as the precursor of π-allyl palladium intermediates, which may act as 1,3 or 1,5-dipoles undergoing cycloadditions with dipolarophiles [21]. In our early exploration, we studied the cycloaddition reactions of AECs with electron-deficient reaction partner and successfully developed a palladium-catalyzed (3 + 3) annulation of AECs with nitrile oxides, producing 3,6-disubstituted-5-hydro-1,4,2-dioxazines in high yields (Scheme 1a) [21]. In this example, AECs worked as three-membered synthons and the allene moiety in AECs did not participate in the construction of six-membered ring. As continuous efforts in the exploration on the application of AECs in Pd-catalyzed cycloadditions, we anticipated to achieve formation of ring system involving the allenyl moiety. In 2019, Shao reported an elegant Pd-catalyzed (4 + 1) cycloaddition of allenyl acetates and pyrazolones, in which allenic esters worked as C4 synthons to be fused in cyclopentene rings (Scheme 1b) [22]. This inspired us to think about transformations of allene moiety of AECs for construction of cyclic framework. The 1,3-indandiones were often used in cascade/domino reactions to construct various cyclic compounds because the protons of methylene group are very acidic and prone to isomerize into their enol forms [23,24]. Considering the high reactivity of 1,3-indandiones, we explored their reaction with AECs under palladium catalysis. Herein we report palladium-catalyzed cascade cyclization of AECs with 1,3-indandiones, giving tetracyclic dihydrocyclopentaindeno-

---

☆ Dedication to Prof. Lixin Dai on the Occasion of His Centenary Birthday.

* Corresponding authors.

E-mail addresses: zhangc9711@cau.edu.cn (C. Zhang), hchguo@cau.edu.cn (H. Guo).

https://doi.org/10.1016/j.cclet.2023.108297

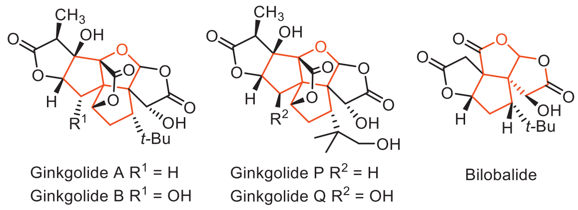


Fig. 1. Terpenoid natural products.

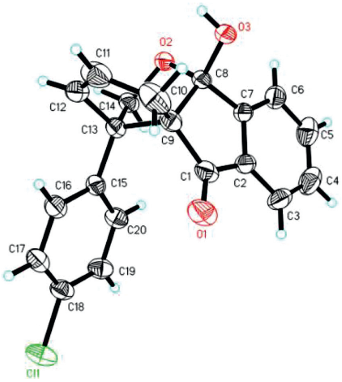
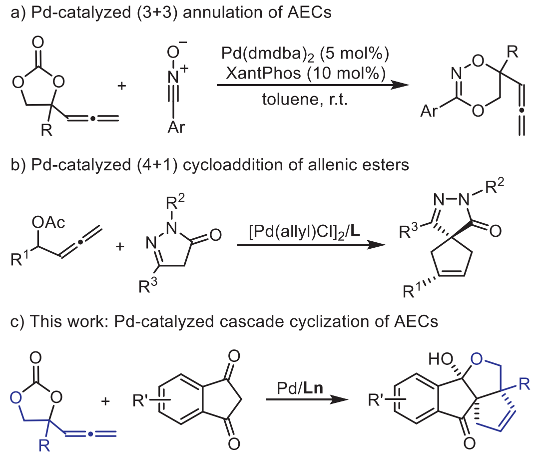


Fig. 2. X-ray crystal structure of the product **3af**.

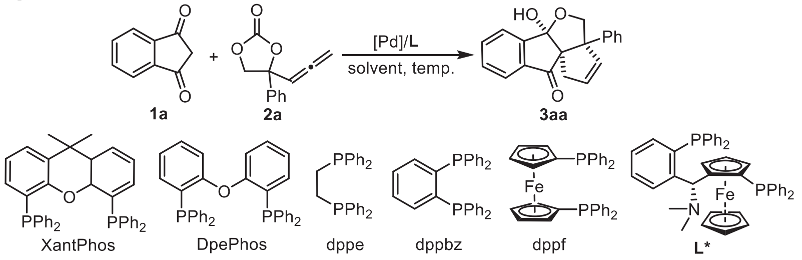


Scheme 1. Pd-catalyzed decarboxylative annulations of AECs.

furanone derivatives having three contiguous quaternary carbon centers (Scheme 1c).

We chose the reaction of 1,3-indandione **1a** and AEC **2a** to begin the investigation (Table 1), which was performed in CH_2Cl_2 at 25 °C. When the combination of $Pd_2dba_3{\cdot}CHCl_3$ with PPh_3 was used, no product was observed (Table 1, entry 1). We then screened a series of ligands (entries 2–6) and found that when XantPhos was used as the ligand, and the desired product **3aa** was isolated in the highest 35% yield (entry 2). Subsequently, with XantPhos as the ligand, different palladium catalysts were tested and no bet-

Table 1
Optimization of reaction conditions.[a]



Entry	[Pd]	Ligand	Solvent	T (°C)	t (h)	Yield (%)[b]	dr[c]
1	$Pd_2dba_3{\cdot}CHCl_3$	PPh_3	CH_2Cl_2	25	48	trace	ND
2	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	CH_2Cl_2	25	48	35	>20:1
3	$Pd_2dba_3{\cdot}CHCl_3$	DpePhos	CH_2Cl_2	25	48	23	>20:1
4	$Pd_2dba_3{\cdot}CHCl_3$	Dppe	CH_2Cl_2	25	48	NR	ND
5	$Pd_2dba_3{\cdot}CHCl_3$	Dppbz	CH_2Cl_2	25	48	NR	ND
6	$Pd_2dba_3{\cdot}CHCl_3$	Dppf	CH_2Cl_2	25	48	trace	ND
7	$Pd(dba)_2$	XantPhos	CH_2Cl_2	25	48	26	>20:1
8	$Pd(dmdba)_2$	XantPhos	CH_2Cl_2	25	48	26	>20:1
9	$Pd(PPh_3)_4$	XantPhos	CH_2Cl_2	25	18	trace	ND
10	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	$Cl(CH_2)_2Cl$	25	26	22	>20:1
11	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	$CHCl_3$	25	26	44	>20:1
12	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	toluene	25	26	trace	ND
13	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	THF	25	26	32	>20:1
14	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	CCl_4	25	48	NR	ND
15	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	$CHCl_3$	40	6	39	>20:1
16	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	$CHCl_3$	60	6	55	>20:1
17	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	$CHCl_3$	80	6	17	>20:1
18[d]	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	$CHCl_3$	60	6	64	>20:1
19[d,e]	$Pd_2dba_3{\cdot}CHCl_3$	XantPhos	$CHCl_3$	60	6	77	>20:1
20[f]	$Pd_2dba_3{\cdot}CHCl_3$	**L***	$CHCl_3$	25	56	60	>20:1 (0% *ee*)

[a] Unless noted otherwise, the reactions of **1a** (0.1 mmol), **2a** (0.15 mmol), [Pd] (5 mol%), and ligand (20 mol% for Ph_3P, 10 mol% for diphosphines) were performed in 1 mL of solvent. NR: no reaction; ND: not detected; dba: dibenzylidene acetone; dmdba: 3,5,3′,5′-dimethoxydibenzylidene acetone.

[b] Isolated yield.

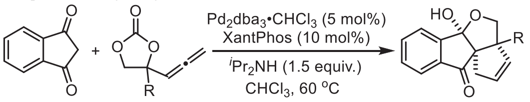
[c] Determined by ^1H NMR.

[d] With 0.2 mmol of **2a**.

[e] With 0.15 mmol of $^iPr_2NH$.

[f] See details of reaction conditions in Supporting information.

Table 2
Scope of allenylethylene carbonates.[a]



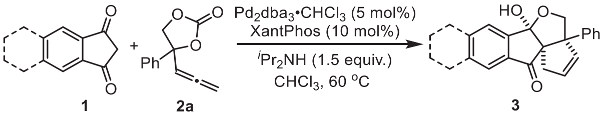
1a **2** **3**

Entry	R	3	t (h)	Yield (%)[b]
1	C$_6$H$_5$	**3aa**	6	77
2	3-FC$_6$H$_4$	**3ab**	12	45
3	3-ClC$_6$H$_4$	**3ac**	6	68
4	3-BrC$_6$H$_4$	**3ad**	6	50
5	4-FC$_6$H$_4$	**3ae**	6	54
6	4-ClC$_6$H$_4$	**3af**	6	74
7	4-BrC$_6$H$_4$	**3ag**	6	69
8	3,5-F$_2$C$_6$H$_3$	**3ah**	12	43
9	3-OMeC$_6$H$_4$	**3ai**	6	70
10	4-OMeC$_6$H$_4$	**3aj**	6	69
11	4-MeC$_6$H$_4$	**3ak**	6	85
12	4-CNC$_6$H$_4$	**3al**	6	52
13	4-CF$_3$C$_6$H$_4$	**3am**	6	56
14	4-PhC$_6$H$_4$	**3an**	6	70
15	2-naphthyl	**3ao**	6	81
16	3-thienyl	**3ap**	6	66
17	Me	**3aq**	12	17
18	Et	**3ar**	12	22

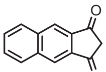
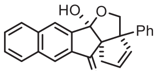
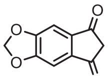
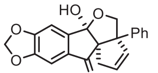
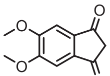
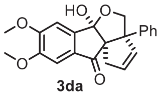
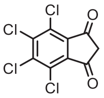
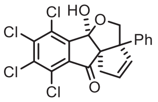
[a] All reactions were carried out with **1a** (0.1 mmol), **2** (0.2 mmol), Pd$_2$dba$_3$·CHCl$_3$ (5 mol%), XantPhos (10 mol%) and ^{i}Pr$_2$NH (0.15 mmol) in 1 mL of CHCl$_3$ at 60 °C.

[b] Isolated yield. >20:1 *dr*, determined by ^{1}H NMR.

Table 3
Scope of indandiones.[a]



1 **2a** **3**

Entry	1	3	t (h)	Yield (%)[b]
1	 **1b**	 **3ba**	6	51
2	 **1c**	 **3ca**	6	43
3	 **1d**	 **3da**	6	48
4	 **1e**	 **3ea**	24	0

[a] All reactions were carried out with **1** (0.1 mmol), **2a** (0.2 mmol), Pd$_2$dba$_3$·CHCl$_3$ (5 mol%), XantPhos (10 mol%) and ^{i}Pr$_2$NH (0.15 mmol) in 1 mL of CHCl$_3$ at 60 °C.

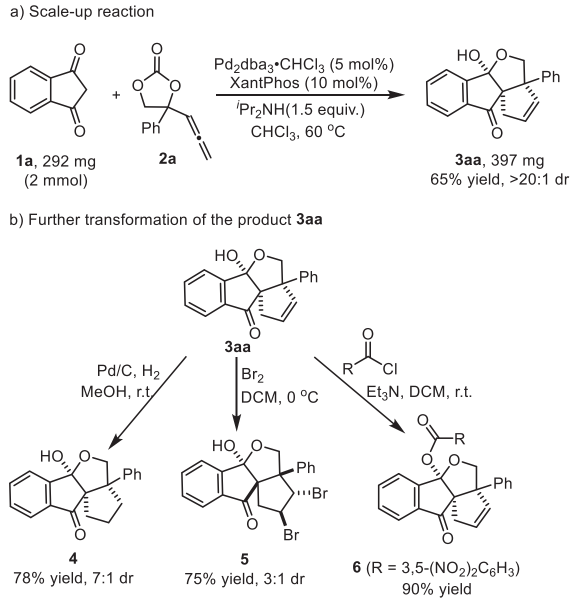
[b] Isolated yield. >20:1 *dr*, determined by ^{1}H NMR.

ter yield was obtained (entries 7–9). We then screened several other solvents, including ClCH$_2$CH$_2$Cl (DCE), CHCl$_3$, toluene, THF and CCl$_4$ (entries 10–14). Among them, CHCl$_3$ exhibited the best performance, and the product **3aa** was obtained in 44% yield (entry 11). Effect of temperature to the reaction was also investigated (entries 15–17). The reaction at 60 °C led to the product in 55% yield (entry 16). During the optimization process, we found that the AEC underwent self-polymerization to form side products, so that we increased the loading amount of AEC and the yield of **3aa** was thus increased to 64% (entry 18). In further optimization, various bases were examined as additives (detailed in Supporting information). To our great delight, when diisopropylethylamine was used as the base, the yield of product **3aa** was improved to 77% (entry 19). In order to develop asymmetric catalytic reaction, we screened various types of chiral ligands (see Supporting information for details). Unfortunately, only chiral ligand **L*** displayed catalytic activity, delivering the product in 60% yield but with 0% *ee* (entry 20).

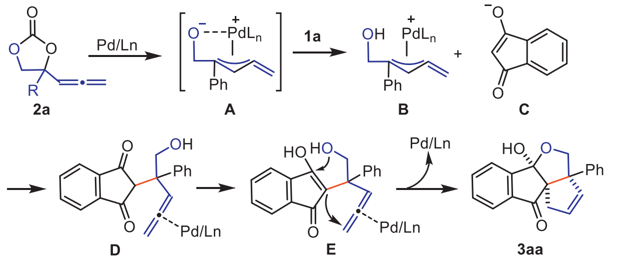
Having established the optimal conditions, we tested a variety of AECs to explore the reaction scope. The results were summarized in Table 2. The reactions of AECs **2** bearing diverse substituents with different electronic properties with 1,3-indandione **1a** were carried out under standard conditions (entries 1–18). The AECs with halogen atoms at the *meta* or *para* position of the phenyl group were tolerated, producing the desired products (**3ab**–**3ah**) in 43%–74% yield (entries 2–8). The AECs having electron-donating (Me and OMe) and electron-withdrawing (CN and CF$_3$) groups on the phenyl ring at the *meta* and *para* position were also favourable (entries 9–13), and the corresponding products were obtained in 52%–85% yields. The AECs with biphenyl moieties also performed well in the reaction, leading to the formation of the corresponding product **3an** in 70% yield (entry 14). In addition, AECs containing fused or heterocyclic aromatic groups were also suitable substrates. The AEC containing a 2-naphthyl group afforded the corresponding product **3an** in 81% yield (entry 15) while the 3-thienyl substituted one afforded the corresponding product **3ap** in 66% yield (entry 16). Unfortunately, the AECs containing methyl and ethyl groups were challenging substrates, affording the corresponding products **3aq** and **3ar** in poor 17% and 22% yield respectively (entries 17 and 18). The structure of the product **3af** was confirmed by the results of single crystal X-ray diffraction analysis (Fig. 2, CCDC 2,195,449, detailed in Supporting information).

We further evaluated various 1,3-indandione in this cascade cyclization of AECs **2a**. As indicated in Table 3, the effect of different substituents on the phenyl group of indandione **1** was tested. Delightedly, 1*H*-cyclopenta[*b*]naphthalene-1,3(2*H*)–dione (**1b**) was workable, producing the product (**3ba**) in 51% yield (entry 1). The reaction of 1,3-indandione **1c** having dioxolane moiety on the benzene ring resulted in the formation of the corresponding product **3ca** in 43% yield (entry 2). The reactivity of 5,6-dimethoxy-1*H*-indene-1,3(2*H*)–dione (**1c**) was moderate, giving 48% yield of the product **3 da** (entry 3). Unfortunately, the 4,5,6,7-tetrachcloro-1,3-indene–dione (**1e**) did not work (entry 4). The big steric hindrance may suppress the reaction.

In order to demonstrate the practical applicability of this reaction, we carried out a scale-up reaction under standard reaction conditions (Scheme 2). This cyclization reaction at 2 mmol of scale still proceeded smoothly to give the product **3aa** in 65% yield. Subsequently, the transformation of product **3aa** was conducted. As



Scheme 2. Scale-up reaction and further transformation of the product.



Scheme 3. A plausible reaction mechanism.

shown in Scheme 2, under the catalysis of palladium, the product **3aa** was reduced by hydrogen to form the product **4** in 78% yield (CCDC: 2195450, detailed in Supporting information). The double bond of **3aa** underwent addition reaction with Br$_2$ to afford the corresponding product **5** in a yield of 75% (CCDC: 2195452, detailed in Supporting information). In the presence of Et$_3$N, the hydroxyl in the product **3aa** reacted with 3,5-dinitrobenzoyl chloride to form the product **6**.

As shown in Scheme 3, a plausible reaction mechanism was proposed. In the presence of palladium catalyst, decarboxylation of AEC **2a** afforded the zwitterionic intermediate **A**, which subsequently deprotonated the 1,3-indandione **1a** to produce both the reaction partners **B** and **C**. They performed allenylic alkylation to produce the intermediate **D**. Subsequent isomerization generated the intermediate **E**, which perform hemiacetalization/intramolecular cyclization to produce the product **3aa** with regeneration of the catalyst. According to the data in Table 1, the catalytic cycle could proceed without needing a base. Therefore, the role of ^{i}Pr$_2$NH probably was to assist deprotonation.

In summary, we have developed a palladium-catalyzed cascade cyclization of allenylethylene carbonates with 1,3-indandiones. Under the standard conditions, a variety of AECs worked well with indandiones, producing biologically interesting tetracyclic dihydrocyclopentaindenofuranone derivatives having three contiguous quaternary carbon centers in moderate to high yields with excellent diastereoselectivities. Additionally, the scale-up reaction and late-stage transformations of the product **3aa** were also demonstrated. In this reaction, the allene moiety of AECs was fused into the ring system for the first time. The cascade cyclization reaction indicates that AECs may work as a versatile synthon and find more applications in construction of ring system.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

This work is supported by the Natural Science Foundation of China (Nos. 21871293 and 22071264).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.108297.

References

[1] T.K. Mohanta, Y. Tamboli, P.K. Zubaidha, Nat. Prod. Res. 28 (2014) 746–752.
[2] C. Sarkar, C. Quispe, S. Jamaddar, et al., Biomed. Pharmacother. 132 (2020) 110908.
[3] P.M. Manisha, S.M. Anuja, N.D. Prajakta, et al., GSC Biol. Pharm. Sci. 16 (2021) 229–240.
[4] J. Lu, L. Xie, K. Liu, et al., Phytother. Res. 35 (2021) 6114–6130.
[5] T. Busch, A. Kirschning, Nat. Prod. Rep. 25 (2008) 318–341.
[6] J.D. Weaver, A. Recio III, A.J. Grenning, J.A. Tunge, Chem. Rev. 111 (2011) 1846–1913.
[7] A. Khan, Y.J. Zhang, Synlett 26 (2015) 853–860.
[8] B.D.W. Allen, C.P. Lakeland, J.P.A. Harrity, Chem. Eur. J. 23 (2017) 13830–13857.
[9] W.S. Guo, J.E. Gómez, À. Cristòfol, J.N. Xie, A.W. Kleij, Angew. Chem. Int. Ed. 57 (2018) 13735–13747.
[10] N. De, E.J. Yoo, ACS Catal. 8 (2018) 48–58.
[11] L. Zuo, T. Liu, X. Chang, W. Guo, Molecules 24 (2019) 3930–3946.
[12] J.E. Gómez, A.W. Kleij, Adv. Organomet. Chem. 71 (2019) 175–226.
[13] J. James, M. Jackson, P.J. Guiry, Adv. Synth. Catal. 361 (2019) 3016–3049.
[14] Q.Z. Li, Y. Liu, M.Z. Li, et al., Org. Biomol. Chem. 18 (2020) 3638–3648.
[15] B.M. Trost, G. Mata, Acc. Chem. Res. 53 (2020) 1293–1305.
[16] J. Wang, S.A. Blaszczyk, X. Li, W. Tang, Chem. Rev. 121 (2021) 110–139.
[17] B. Niu, Y. Wei, M. Shi, Org. Chem. Front. 8 (2021) 3475–3501.
[18] B. Yan, W. Guo, Synthesis 54 (2022) 1964–1976.
[19] Y. You, Q. Li, Y.P. Zhang, et al., ChemCatChem 14 (2022) e202101887.
[20] M.M. Zhang, B.L. Qu, B. Shi, W.J. Xiao, L.Q. Lu, Chem. Soc. Rev. 51 (2022) 4146–4174.
[21] T. Pan, X. Gao, S. Yang, et al., Org. Lett. 23 (2021) 5750–5754.
[22] L. Li, P. Luo, Y. Deng, Z. Shao, Angew. Chem. Int. Ed. 58 (2019) 4710–4713.
[23] J. Sun, J. Cao, Y. Han, C.G. Yan, Chin. J. Org. Chem. 40 (2020) 4122–4146.
[24] S. Asadi, G.M. Ziarani, Mol. Divers. 20 (2016) 111–152.