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Kinetically Controllable Pd-Catalyzed Decarboxylation Enabled [5 + 2] and [3 + 2] Cycloaddition toward Carbocycles Featuring Quaternary Carbons

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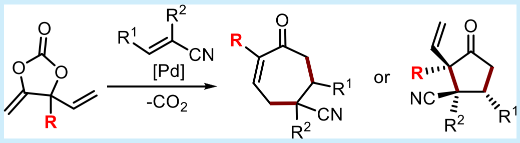
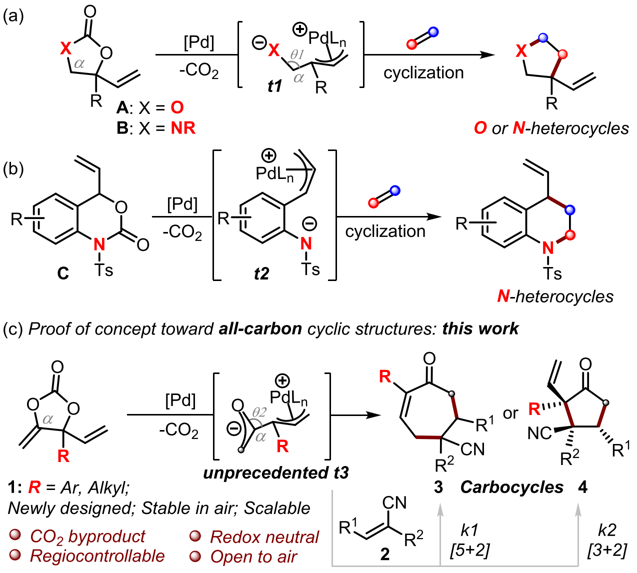
ABSTRACT: A decarboxylative protocol has been developed toward a range of carbocycles. The key success is based on the use of a batch of newly designed cyclic carbonates as substrates that can provide carbon−carbon zwitterion intermediate under palladium catalysis. The kinetics of the reactions are controllable toward either strained seven- or thermodynamically more favored five-membered carbocycles. The release of this chemistry will shed light on the synthesis of complex and valuable cyclic structures.



Cyclic structures are widespread motifs in biological active compounds, agrochemicals, and pharmaceuticals, as well as functional materials.[1] The development of efficient methodologies toward the controllable synthesis of cyclic structures generating as little waste as possible is highly desired. Catalytic generation of zwitterion/dipole intermediates and further cyclization with different acceptors proves to be one of the most powerful strategies in this event.[2,3] Specifically, transition metal catalyzed decarboxylative reactions for this purpose have attracted much research interest and advanced remarkably as a result of their advantages of easy operations, redox neutrality, and only CO_2-byproduct generation.[3] In this sense, previous work on the Pd-catalyzed decarboxylation of vinyl carbonate **A**/carbamate **B** gained great success in preparation of a huge range of useful and otherwise synthetically challenging *O*- or *N*-heterocycles (Scheme 1a).[4−6] Vinyl benzoxazinanones also showed excellent reactivity under transition metal catalysis resulting in tetrahydroquinolines (Scheme 1b).[7] The key to success of these transformations is the in situ generation of zwitterionic π-allyl-Pd intermediate **t1** or **t2** from the cyclic vinyl carbonate/carbamate precursors upon CO_2 extrusion (Scheme 1a,b).[4,5,7] Thus, to design reactive precursors toward the formation of novel zwitterionic intermediates is essential for the efficient and diverse construction of interesting and valuable cyclic structures.

Despite that decarboxylative formation of heterocycles has been well realized (Scheme 1a,b),[3−5,7] the efficient and diverse construction of carbocycles through decarboxylative strategy is yet undeveloped.[8] Encouraged by related enolate chemistry[6g,9] and our interest in exploring novel reactivities of cyclic carbonates,[2a,b] we envisaged that the vinyl carbonate **1** equipping with an extra double bond on the α-position may undergo decarboxylation under palladium catalysis yielding a π-allyl-Pd intermediate **t3** featuring an enolate anion (Scheme 1c); subsequent cyclization of intermediate **t3** with suitable Michael acceptors would offer an innovative methodology toward the synthesis of carbocycles. Herein we proved our

Scheme 1. Evolution of Pd-Catalyzed Decarboxylation of Vinyl Carbonates/Carbamates toward Cyclic Structures



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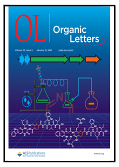

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concept with the use of malononitriles and newly designed vinyl carbonates as substrates toward the formation of synthetically challenging functionalized carbocycles under palladium catalysis; the kinetics of the catalytic system proved to be controllable under different reaction conditions giving rise to either cycloheptenones ($k_1 > k_2$) or cyclopentanones ($k_1 < k_2$), adding further to the attractiveness of this methodology (Scheme 1c).

The cycloheptenone and vinyl cyclopentanone products prevailed in a number of natural products, bioactive compounds, and pharmaceuticals, and their diverse and efficient synthesis is the continuous endeavor of chemists.[10−13]

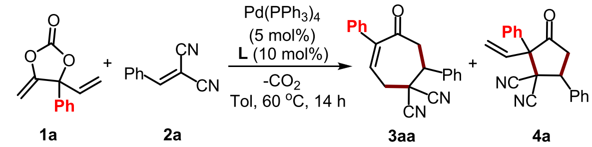
Considering the excellent reactivities of this new vinyl carbonate, we believed the present work opens up windows for the construction of novel and valuable functionalized cyclic structures.

Initial investigation suggested vinyl carbonate **1** could be easily prepared from CO_2 and is air-stable and scalable.[14] We began our research by exploring the reaction between phenyl-substituted carbonate **1a** and benzylidene malononitrile **2a** in the presence of $Pd(PPh_3)_4$ catalyst and a batch of different phosphine ligands in toluene at 60 °C (Table 1). To our delight, the precursor **1a** exhibited excellent reactivity producing either cycloheptenone **3aa** or cyclopentanone **4a** (Table 1). As expected, the formation of vinyl pentanone **4a** was more favored and could be obtained in 86% yield at rt indicating the reactive nature of the newly designed carbonate (Table 1, Entry 1). Increasing the reaction temperature to 60 °C did not improve the diastereoselectivity of **4a** significantly (Table 1, Entries 2−3). Then we investigated the ligand effect on the product distribution (**3aa** vs **4a**) via systematic variation of different phosphine ligands (Table 1, Entries 4−20). Notably, the use of ligand **L15** gave rise to strained product **3aa** in 10% yield comparing with <1% in most cases. Afterward, the effect of the palladium species, reaction temperature, and solvent were investigated utilizing **L15** as ligand in order to achieve the regioselective formation of product **3aa** (Table 2). Surprisingly, the use of other palladium catalysts did not produce any of the target product at all (Table 2, Entries 1−4), suggesting subtle intrinsic nature of the $Pd(PPh_3)_4$ precatalyst. The reaction performed in dioxane at 100 °C gave affirmative results (Entries 5−11). Interestingly, the kinetics of the reaction was remarkably affected when performed in a mixture of dioxane and toluene, illustrating the non-negligible solvent effect in current system (Entry 15).[15] Addition of molecular sieves helped further to improve the regioselectivity resulting in target product **3aa** in 95% yield with only trace amount of vinyl pentanone **4a** (Entry 18). In contrast, previously reported cycloadditions between vinyl cyclic carbonate **A**/carbamate **B** and malononitrile derivatives only gave rise to five-membered products with the seven-membered products undetected.[16,4b,c,5a] It was believed that the exceptional reactivity of carbonate **1** was related to its structural characteristics. Comparing with intermediate **t1**, the introduction of an extra double bond in **t3** changed the hybridization mode of the α-carbon from sp^3 to sp^2 and simultaneously varied the bond angle θ ($\theta_1 \neq \theta_2$) (marked in Scheme 1a,c); this structural difference of the intermediates might facilitate the formation of larger rings from **t3**.

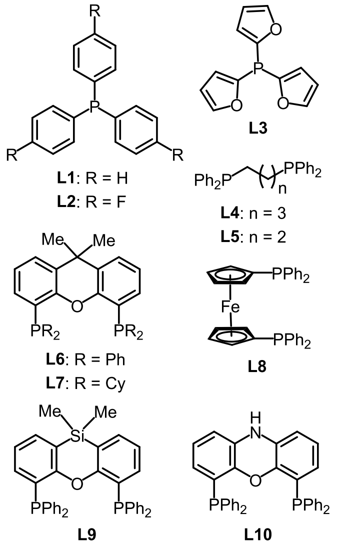
With the optimized reaction conditions in hand, we set out to evaluate the generality of the transformations toward the formation of otherwise synthetically challenging seven-membered cycloheptenones (Figure 1). The catalytic system proved to be efficient using different malononitrile derivatives and carbonates equipped with both electron-withdrawing (**3af−3ag**, **3aj**, **3ea−3ha**, **3ja−3ka**) or donating (**3ab−3ad**, **3ah−3ai**, **3ak**, **3ba−3da**) groups on the *para*-, *ortho*-, or *meta*-position of the phenyl substituent. Incorporation of a heterocycle fragment (**3am−3an**) in the target product was feasible. Alkyl-substituted malononitriles (**3ao−3ap**) showed satisfactory reactivities toward the product formation. The installation of clumsy group on the substrates (**3al**, **3ao**, **3la**, and **3ma**) was also possible, albeit the cyclohexyl-substituted ones gave rise to the desired products in a slightly reduced yield. It is noteworthy that the use of phenylsulfonyl acrylonitrile as acceptor in the reaction was well tolerated, affording the corresponding sulfone **3aq** in excellent diastereoselectivity. The use of an enantioenriched **L15** under the standard conditions gave rise to a racemic product **3aa**. The X-ray analysis of product **3aa** (inset in Figure 1), apart from the spectroscopic analysis data, further supported the seven-membered structures.[17,18]

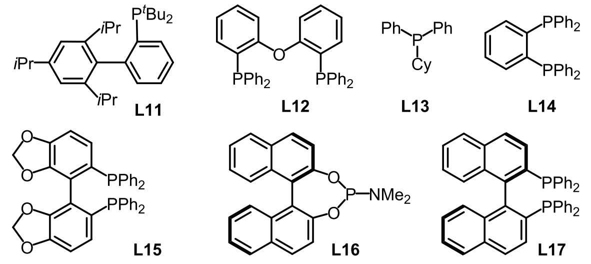
We then focused on the condition screening in order to synthesize the vinyl pentanone products in a diastereoselective

Table 1. Selected Ligand Screening Data toward the Formation of Carbocycles of 3aa and 4a[d]



Entry	L	3aa/%	4a/% (dr)[c]
1[a]	-	0	86 (1.7:1)
2[b]	-	0	88 (1.8:1)
3	-	5	83 (2.1:1)
4	**L1**	<1	77 (2:1)
5	**L2**	0	73 (1.6:1)
6	**L3**	0	70 (2.1:1)
7	**L4**	<1	70 (2:1)
8	**L5**	<1	66 (1.3:1)
9	**L6**	6	72 (1.6:1)
10	**L7**	6	76 (1.7:1)
11	**L8**	<1	80 (1.8:1)
12	**L9**	0	69 (1.9:1)
13	**L10**	0	76 (1.5:1)
14	**L11**	<1	71 (1.8:1)
15	**L12**	0	73 (1.8:1)
16	**L13**	<1	70 (1.7:1)
17	**L14**	<1	65 (1.2:1)
18	**L15**	**10**	**63** (1.5:1)
19	**L16**	0	79 (1:1)
20	**L17**	6	71 (4.9:1)





[a] Performed at rt. [b] Performed at 40 °C. [c] The *dr* value and yield determined by ^1H NMR using 2-methylnaphthalene as internal standard. [d] The reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), Pd catalyst (5 mol %), and ligand (10 mol %) in toluene (1.0 mL).

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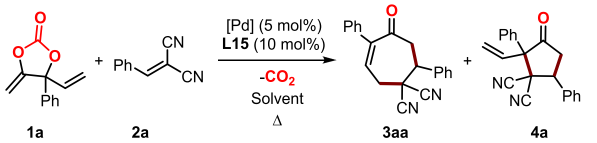
Table 2. Screening Data toward the Selective Formation of Cycloheptenone 3aa[a]



entry	[Pd]	solvent, *T* [°C]	**3aa**[b] [%]	**4a**[b] [%] (dr)
1	Pd(dba)$_2$	Tol, 60	0	0
2	Pd$_2$(dba)$_3$·CHCl$_3$	Tol, 60	0	0
3	Pd(OAc)$_2$	Tol, 60	0	0
4	white catalyst	Tol, 60	0	0
5	Pd(PPh$_3$)$_4$	Diox, 60	10	66 (1.6:1)
6	Pd(PPh$_3$)$_4$	THF, 60	<1	65 (1.3:1)
7	Pd(PPh$_3$)$_4$	TFE, 60	<1	46 (1:1)
8	Pd(PPh$_3$)$_4$	MeOH, 60	5	71 (1.6:1)
9	Pd(PPh$_3$)$_4$	Diox, 80	14	46 (2.2:1)
10	Pd(PPh$_3$)$_4$	Diox, 100	17	47 (2.6:1)
11	Pd(PPh$_3$)$_4$	Diox, 120	12	46 (3.1:1)
12[c]	Pd(PPh$_3$)$_4$	D/T (1:1), 100	61	26 (5:1)
13	Pd(PPh$_3$)$_4$	D/T (2:1), 100	64	17 (4.8:1)
14	Pd(PPh$_3$)$_4$	D/T (3:1), 100	69	16 (4.4:1)
15	Pd(PPh$_3$)$_4$	D/T (4:1), 100	80	8 (4.3:1)
16	Pd(PPh$_3$)$_4$	D/T (5:1), 100	72	15 (3.8:1)
17	Pd(PPh$_3$)$_4$	D/T (1:2), 100	49	25 (2:1)
18[d]	Pd(PPh$_3$)$_4$	D/T (4:1), 100	95	<2

[a]The reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), Pd catalyst (5 mol %), ligand **L15** (10 mol %) in solvent (1.0 mL) at elevated temperatures for 4 h. [b]The *dr* value and yield determined by ^{1}H NMR using 2-methylnaphthalene as internal standard. [c]D/T refer to the ratio of Diox/Tol. [d]6 mg 4 Å molecular sieves (MS) added.

fashion (Table S1). Performing the reaction in ethanol at rt without ligand addition increased the diastereoselectivity to 3.2:1 (Table S1, Entries 1−4). Increasing the reaction temperatures or changing the catalyst did not affect the diastereoselectivity significantly, while the reaction in diluted conditions exhibited satisfactory outcome with *dr* value of 8.2:1 (Table S1, Entries 5−9). The use of mixed solvent (EtOH:DCM = 1:1) resulted in excellent diastereoselectivity (*dr* > 15:1) at 60 °C. Afterward, the reaction scope was evaluated under the optimized conditions (Figure 2a). The protocol tolerated well with different substrates bearing *para*- (**4i**−**4l**) or *meta*-functionalized phenyl substituents (**4m**−**4n**) with decent diastereoselectivities with *dr* > 7:1. The presence of steric naphthyl or cyclohexyl group did not reduce the efficiency of the catalysis (**4h**, **4n**−**4o**). The fluoro-containing phenyl carbonate was quite reactive toward the target product formation in moderate yield (**4l**), as also observed in cycloheptenone synthesis (**3fa**−**3ga**, **3ja**, and **3ka**). In contrast, the methylene malononitrile equipping with *ortho*-substituted phenyl group only gave rise to trace amounts of product on the basis of NMR analysis, illustrating some limitations of this system. The molecular structure of the main diastereoisomer **4a** was further confirmed by X-ray analysis (inset in Figure 2a).[19] Extensive experiments were performed with an intention to achieve the enantio- and diastereoselective synthesis of cyclopentanone **4a**. We found that the target product **4a′** was obtained with the utilization of Pd$_2$dba$_3$·CHCl$_3$ precatalyst and ligand **L18** in EtOH at room temperature (Figure 2b). The present methodology can be easily scaled up as demonstrated by the gram-scale synthesis of **3aa** and **4a** (Figure 3a). These cyclic products (**3**−**4**) create great potential for usage in synthetic or medicinal chemistry as exemplified via their synthetic transformations into several highly functionalized structures (Figure 3b,c). The cycloheptenone **3aa** could be easily converted into the corresponding hydrazone **5a** in the presence of tosyl hydrazine, while the reaction of cyclopentanone **4a** under similar conditions afforded ketone **6b** with the vinyl group being reduced selectively. Treatment of the cyclic ketones with NBS[20] or copper bromide afforded the brominated products **5b** and **6c** in good yields. Interesting rearrangement was observed and led to a bridged product **5a** using **3aa** as substrate under Wittig reaction conditions. The reaction of cycloheptenone **3aa** and phenyl hydrazine under acidic conditions gave rise to a bicyclic new structure **5d**, which was further confirmed by single crystalline analysis.[21] Selective reduction of cyclopentanone **4a** yielded the corresponding secondary alcohol **6a** while keeping the pendant vinyl group intact. It is worth noting that the formation of

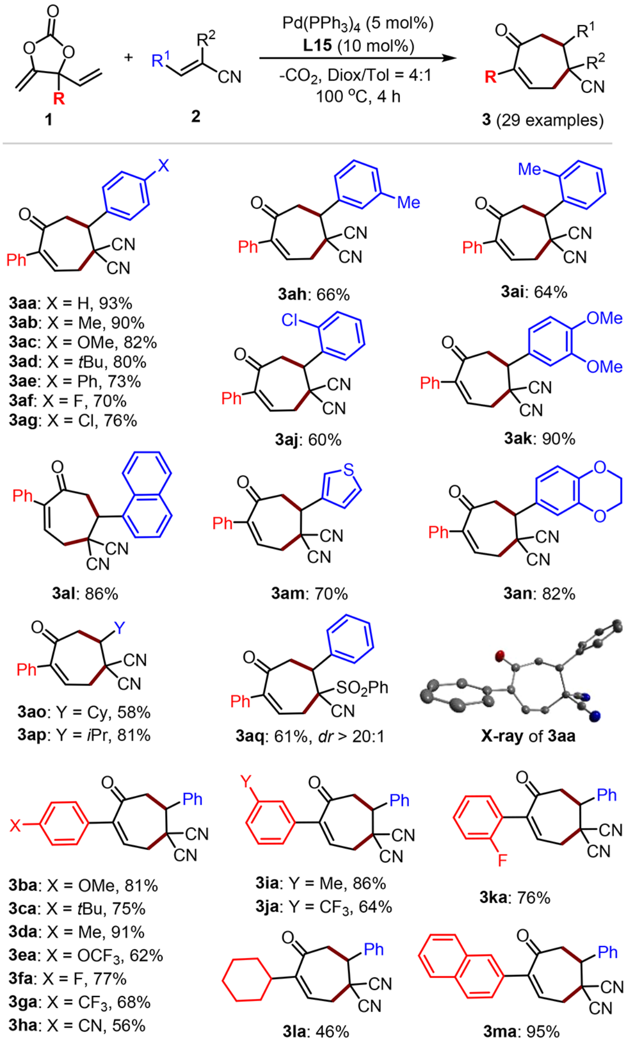


Figure 1. Reaction scope of carbonate **1** and Michael acceptor **2** toward the formation of cycloheptenone **3**. Reaction conditions: **1** (0.12 mmol), **2** (0.1 mmol), Pd(PPh$_3$)$_4$ (5 mol %), **L15** (10 mol %), 4 Å MS (6.0 mg), Diox/Tol = (4:1, 1 mL), 100 °C, 4 h. Isolated yields are reported for all the products. The inset is the solid state of product **3aa**, and hydrogen atoms are omitted for clarity at 50% probability for the drawing of thermal ellipsoids.

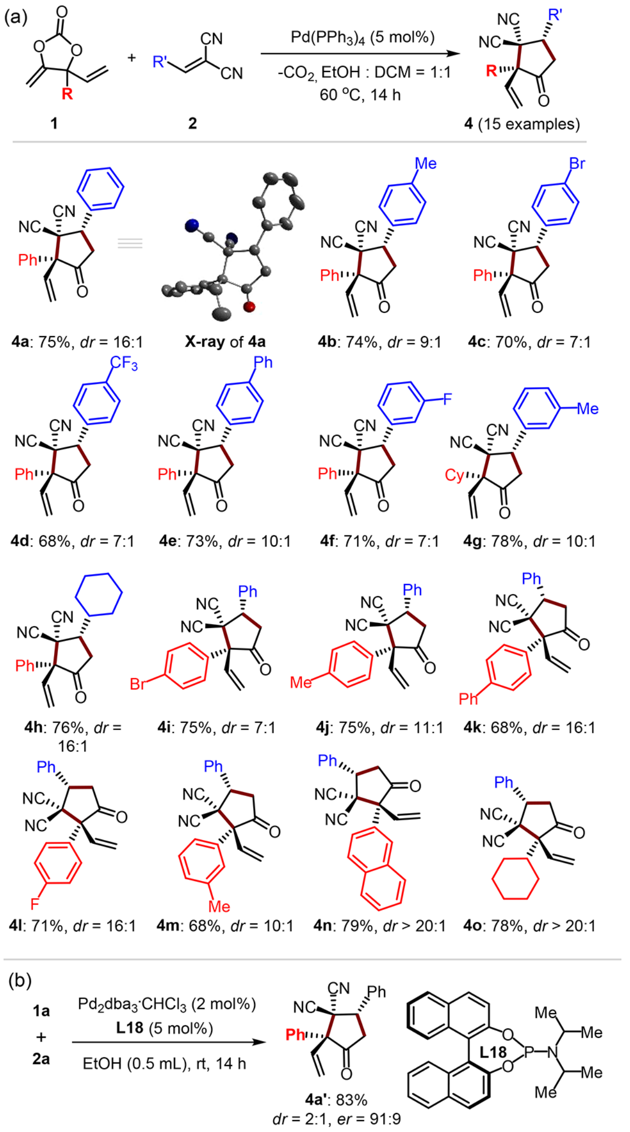


Figure 2. (a) Reaction scope of carbonates **1** and acceptors **2** toward the diastereoselective formation of cyclopentanone **4**; (b) Enantioselective synthesis of cyclopentanone **4a′** in the presence of **L18**. Reaction conditions: **1** (0.12 mmol), **2** (0.1 mmol), Pd(PPh$_3$)$_4$ (5 mol %), EtOH/DCM = (1:1, 1 mL in total), 60 °C, 4 h. Inset is the solid state of product **4a**, and hydrogen atoms are omitted for clarity at 50% probability for the drawing of thermal ellipsoids. Isolated yield of the main diastereoisomer is reported for all the products.

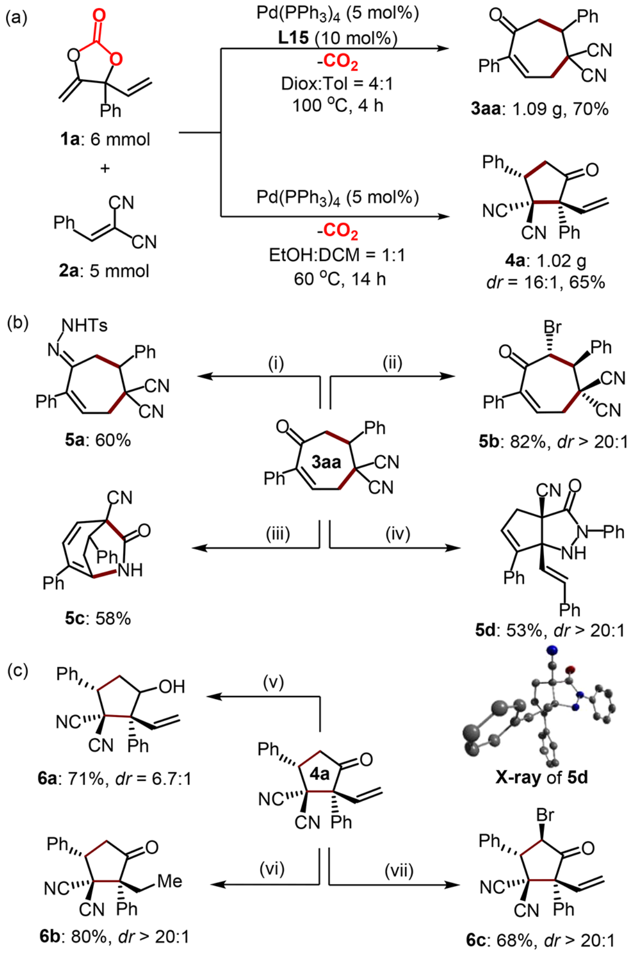


Figure 3. Representative synthetic applications of carbocycles **3** and **4** with the transformations of **3aa** and **4a** as examples. (a) Gram-scale syntheses of products **3aa** and **4a**. (b,c) Synthetic transformations of **3aa** and **4a** into highly functionalized cyclic structures under different reaction conditions: (i) TsNHNH$_2$ (1.5 equiv), 4 Å MS (100 mg), MeOH (2 mL), 50 °C, 10 h; (ii) NBS (1.1 equiv), SiMe$_3$OTf (0.8 equiv), MeCN (2 mL), rt, 5 h; (iii) PPh$_3$MeBr (3.0 equiv), *t*-BuOK (3.0 equiv), THF (2 mL), 0 °C, rt; (iv) PhNHNH$_2$ (1.2 equiv), CH$_3$COOH (0.3 mL), 130 °C, 1 h; (v) NaBH$_4$ (2 equiv), anhydrous CH$_3$OH/DCM (1/1), rt, N$_2$ protection, 2 h; (vi) TsNHNH$_2$ (5 equiv), 4 Å MS, anhydrous CH$_3$OH, 60 °C, N$_2$ protection, 10 h; (vii) CuBr$_2$ (10 equiv), CHCl$_3$/EtOAc (1/1), 80 °C, 12 h. See SI for details. Inset is the solid state of product **5d** and hydrogen atoms are omitted for clarity at 50% probability for the drawing of thermal ellipsoids.

highly functionalized cyclic structures as **5b**−**5d** and **6a**−**6c** with continuous (quaternary) carbon stereocenters is synthetically challenging, suggesting the convenience of the present catalytic system.

In summary, we herein reported a decarboxylative approach enabled the formation of a wide range of otherwise synthetically challenging carbocycles. The key success of this methodology is based on the use of a batch of newly designed and air-stable cyclic carbonates as substrates which can provide an unprecedented 1,3- or 1,5- carbon−carbon zwitterion intermediate under palladium catalysis. The kinetics of the reaction between the carbonate substrates and a number of Michael acceptors is controllable toward the formation of either strained seven- or thermodynamically more favored five-membered carbocycles. The current protocol is redox neutral, scalable, and user-friendly, and only generates CO$_2$ as the sole byproduct. The resulting carbocycles can be easily converted into a number of highly functionalized (fused) cyclic structures. We believe this piece of research would bring new light for construction of valuable and challenging complex structures.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03856.

Experimental details and characterization data (PDF)

Accession Codes

CCDC 2038887–2038889 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(16) The control experiment with the use of vinyl cyclic carbonate **A** (R = Ph) under current reaction conditions (Table 2, Entry 18) did not harvest any of the corresponding seven-membered product at all, as also observed by others in a number of cycloadditions; also see refs 4b, c, 5a.

(17) See SI and CCDC 2038887 for more details.

(18) The conversion of vinyl cyclopentanone **4a** into cycloheptenone **3aa** was not observed under reaction conditions used in Figure 1, demonstrating the formation of **3aa** is under kinetic control.

(19) See SI and CCDC 2038888 for more details.

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