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Palladium-Catalyzed Carboxylation of Activated Vinylcyclopropanes with CO_2

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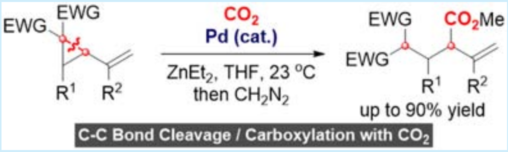
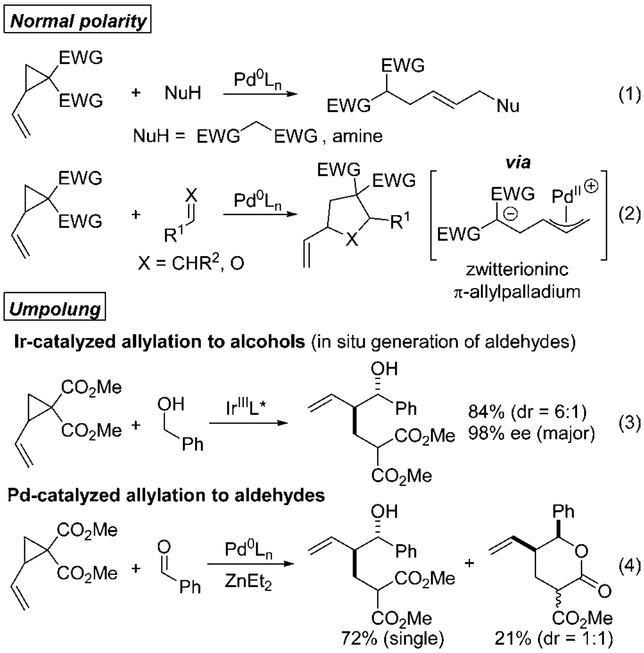
Ⓢ *Supporting Information*

ABSTRACT: By using a palladium catalyst with $ZnEt_2$, activated vinylcyclopropanes were successfully converted into the corresponding β,γ-unsaturated carboxylic acids in high yields under a CO_2 atmosphere (1 atm). The intermediate in this reaction is thought to be a nucleophilic η^1-allylethylpalladium species, which would be produced from π-allylpalladium and $ZnEt_2$ (umpolung reactivity).



Vinylcyclopropanes bearing two electron-withdrawing groups (EWGs) at the *gem*-carbon of the ring are well-known precursors for the generation of π-allylpalladium species in the presence of palladium(0) species (Scheme 1).[1] This process consists of palladium-assisted C−C bond cleavage of the strained cyclopropane ring. The resultant zwitterioninc π-allylpalladium intermediate is highly reactive toward nucleophiles and multiple bonds: This species readily couples with carbon and nitrogen nucleophiles (eq 1)[2] and works as a dipole for alkenes and aldehydes in [3 + 2] cycloadditions (eq 2).[3]

Scheme 1. Reactivities of Vinylcyclopropanes



In contrast, umpolung transformations of these vinylcyclopropanes with electrophiles such as aldehydes catalyzed by a transition-metal complex are limited, but a few examples have been reported recently. Krische reported iridium-catalyzed ring opening of vinylcyclopropanes followed by enantioselective nucleophilic addition to aldehydes generated from alcohols in situ, giving homoallylic alcohols with high efficiency (eq 3).[4] Kimura reported palladium-catalyzed allylation of aldehydes and imines using $ZnEt_2$ as a transmetalation reagent (eq 4).[5] However, nucleophilic addition to much less reactive electrophiles such as CO_2 has never been reported. Since CO_2 is an abundant, inexpensive, and relatively nontoxic C1 source, catalytic incorporation of CO_2 into simple organic compounds is one of the active research areas in current organic chemistry.[6]

Our research group recently developed umpolung carboxylations with CO_2,[7] using allylic alcohols/acetates in the presence of a catalytic amount of $PdCl_2$ and PPh_3 with $ZnEt_2$ (Figure 1).[7a,8] Nucleophilic η^1-allylethylpalladium is thought to be generated by the reaction of π-allylpalladium with $ZnEt_2$.[9] Encouraged by this finding,[7a] we next turned our attention to the development of carboxylation of vinylcyclopropanes via a similar nucleophilic η^1-allylethylpalladium. As the planned reaction, C−C bond cleavage and C−C bond formation with CO_2 would simultaneously take place to afford β,γ-unsaturated

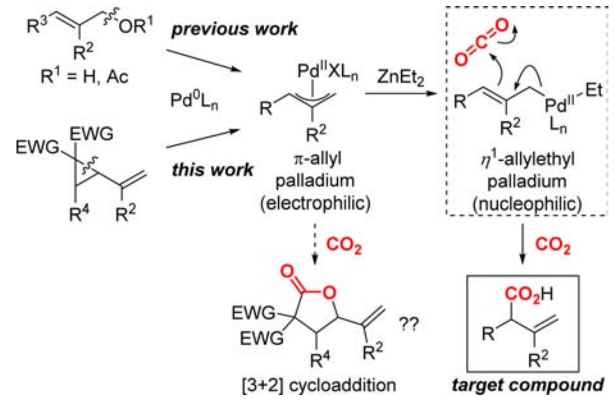


Figure 1. Strategy for carboxylation via allylpalladium species.

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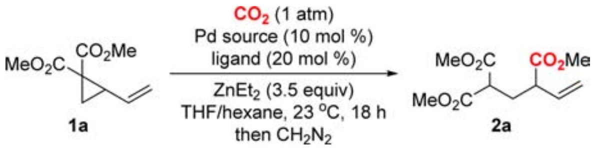
carboxylic acids. Expected [3 + 2] cycloaddition with CO_2[10] would be suppressed because transmetalation between electrophilic π-allylpalladium and $ZnEt_2$ seems to be faster under the conditions.

First, we investigated carboxylation of cyclopropane **1a** using $ZnEt_2$ in the presence of various palladium sources and ligands under 1 atm of a CO_2 atmosphere (balloon). The yields were determined after methyl esterification with CH_2N_2 (Table 1).

Table 1. Condition Screening



entry	Pd source	ligand	yield (%)[a] 2a	rec 1a
1	$PdCl_2$	PPh_3	80	–
2	–	–	–	73
3	$PdCl_2(CH_3CN)_2$	PPh_3	78	–
4	$PdCl_2(PPh_3)_2$	–	81	–
5	$Pd(PPh_3)_4$	–	81	–
6	$Pd(OAc)_2$	PPh_3	81	–
7	$Pd(acac)_2$	PPh_3	87(87)	–
8[b]	$Pd(acac)_2$	P(*o*-tol)$_3$	–	–
9	$Pd(acac)_2$	PCy_3	26	59
10	$Pd(acac)_2$	P(*n*-Bu)$_3$	45	–
11[c,d]	$Pd(acac)_2$	dppe	–	–
12[c]	$Pd(acac)_2$	(*R*)-BINAP	–	–

[a] Yields were determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yield is given in parentheses. [b] $(MeO_2C)_2CHCH_2CH_2CH{=}CH_2$ (**3aa**) and $(MeO_2C)_2CHCH_2CH{=}CHCH_3$ (**3ab**) were obtained in 38% and 39% yields, respectively. [c] 10 mol % of the ligand was used. [d] **3aa** and **3ab** were obtained in 61% and 36% yields, respectively.

According to previously established conditions,[7a] $PdCl_2$ (10 mol %) in combination with PPh_3 (20 mol %) was employed as a catalyst, and the desired carboxylate **2a** was obtained in 80% yield (entry 1). A control experiment without a palladium catalyst indicated the necessity of palladium (entry 2). The use of $PdCl_2(CH_3CN)_2/PPh_3$ and $PdCl_2(PPh_3)_2$ exhibited similar catalytic activities (entries 3 and 4). $Pd(PPh_3)_4$ and $Pd(OAc)_2/PPh_3$ were also found to be suitable catalysts (entries 5 and 6). Although the palladium catalysts listed in entries 1−6 were not dissolved completely in THF, $Pd(acac)_2$ was perfectly soluble, leading to an increase in the product yield to 87% (entry 7). Next, several phosphine ligands were screened using $Pd(acac)_2$. When P(*o*-tol)$_3$ was employed as a ligand, $(MeO_2C)_2CHCH_2CH_2CH{=}CH_2$ (**3aa**) and $(MeO_2C)_2CHCH_2CH{=}CHCH_3$ (**3ab**) were obtained instead of the carboxylated product **2a**. Lower reactivity was observed when trialkylphosphine ligands including PCy_3 and P(*n*-Bu)$_3$ were used (entries 9 and 10). A bidentate phosphine ligand such as dppe completely shut down the desired carboxylation, but **3aa** and **3ab** were preferentially obtained instead (entry 11). The use of (*R*)-BINAP led to a complex mixture (entry 12). These catalyst modification studies indicated that the carboxylation was greatly influenced by the structure of phosphine ligands.

With optimal conditions in hand (Table 1, entry 7), substrate scope and limitations were investigated (Figure 2). Various vinylcyclopropanes **1a−1f** and **1g−1i** with *anti* orientation between R^1 and R^2 were subjected to the optimal reaction conditions. Dimethyl, diethyl, dibenzyl, and di-*tert*-butyl malonate-derived vinylcyclopropanes underwent the desired carboxylations without any problem to afford the corresponding β,γ-unsaturated carboxylic acids **2a−d** in high yields. Changing one of the ester moieties to diethylphosphate decreased the yield of **2e** to 40%, because elimination of $(EtO)_2PO^-$ partly occurred under the reaction conditions. A methyl substitution at the R^2 group was tolerated to afford **2f** in 78% yield. A methyl substituent at the R^1 group was also applicable to produce **2g** and **2h** in good yields with 1.2:1 to 1.7:1 diastereomeric ratios. A bulkier substituent such as an aromatic ring increased the diastereoselectivity to 3.2:1 (**2i**).[11]

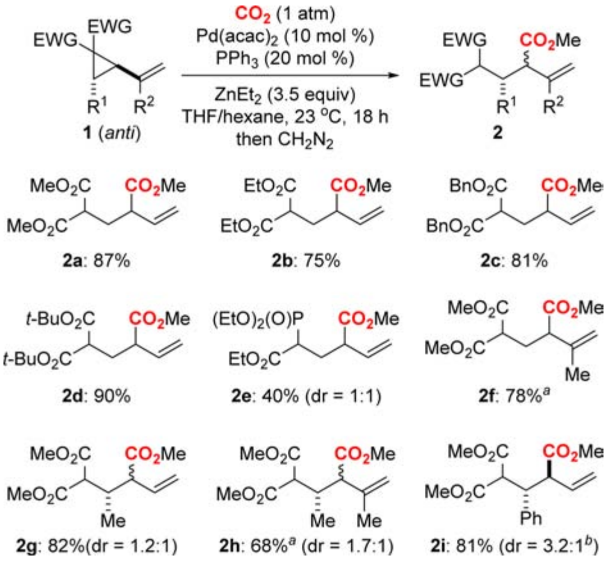
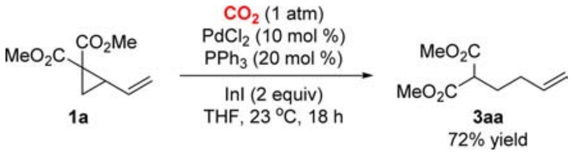


Figure 2. Substrate scope and limitations. Isolated yields are shown. [a] The reaction was conducted at 40 °C. [b] The major diastereomer was *anti*. See the Supporting Information (SI).

Allylindium species derived from allyl bromides were shown to have nucleophilicity toward CO_2.[12] To make a nucleophilic allylindium species from **1a**, 2 equiv of InI instead of $ZnEt_2$ (reductive transmetalation) were employed in combination with a catalytic amount of $PdCl_2$ and PPh_3, because analogous vinylepoxides and vinylaziridines were reported to react with aldehydes via an allylindium intermediate in the presence of a palladium-phosphine catalyst and InI.[13] The protonated compound **3aa** was, however, obtained exclusively (72%), suggesting that allylindium species probably generated in situ[13] did not possess nucleophilic ability toward CO_2 under this reaction condition but underwent protonation by quenching (Scheme 2).

A plausible catalytic cycle is depicted in Figure 3. First, vinylcyclopropane **1** undergoes oxidative addition to palladium(0), leading to π-allylpalladium **I**, which would be transmetalated with $ZnEt_2$. The resulting π-allylpalladium **II** bearing an ethyl ligand should be in equilibrium with sterically

Scheme 2. Use of InI as a Reductant



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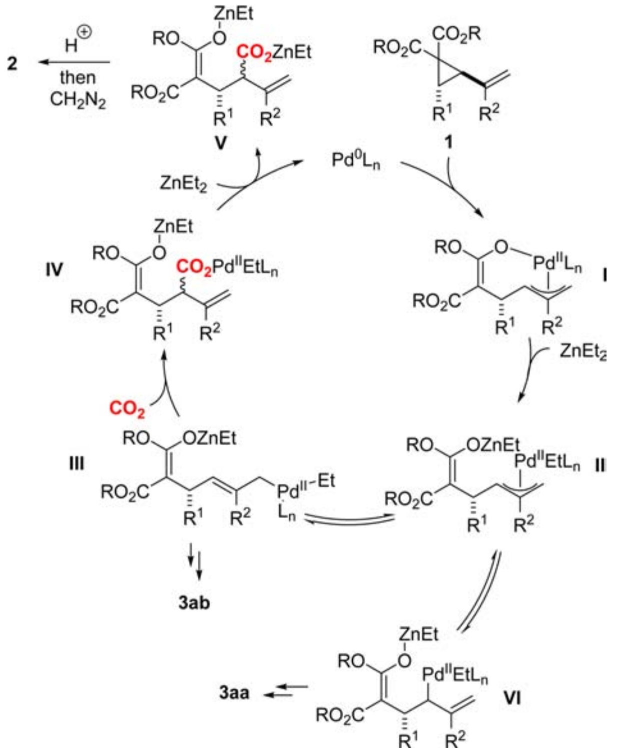

Figure 3. Plausible catalytic cycle.

favorable terminal η^1-allylethylpalladium **III**, which undergoes carboxylation with CO_2 at the γ-position[8e,g,i,l,9] of the allyl ligand to afford palladium carboxylate **IV**. Bulkier substituents of R^1 increase the selectivity for carboxylation. Carboxylate **IV** would then be reduced by $ZnEt_2$ to regenerate palladium(0), along with the release of zinc carboxylate **V**. Unless an appropriate ligand such as PPh_3 is used, **3aa** and **3ab** are produced through β-hydride elimination from η^1-allylethylpalladium species **III** and **VI** followed by reductive elimination (Table 1, entries 8 and 11). Intermediates **III** and **VI** are thought to be under an equilibrium via intermediate **II**.

In summary, we have developed the first palladium-catalyzed carboxylation of activated vinylcyclopropanes via C−C bond cleavage followed by a C−C bond forming process. Much effort toward the development of an asymmetric variant is actively ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01231.

Details of experimental procedures and physical properties of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews on transition-metal-catalyzed transformations using vinylcyclopropanes, see: (a) Khusnutdinov, R. I.; Dzhemilev, U. M. *J. Organomet. Chem.* **1994**, *471*, 1. (b) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117. (c) Jiao, L.; Yu, Z.-X. *J. Org. Chem.* **2013**, *78*, 6842.

(2) (a) Burgess, K. *Tetrahedron Lett.* **1985**, *26*, 3049. (b) Burgess, K. *J. Org. Chem.* **1987**, *52*, 2046. (c) Moreau, P.; Maffei, M. *Tetrahedron Lett.* **2004**, *45*, 743.

(3) (a) Shimizu, I.; Ohashi, Y.; Tsuji, J. *Tetrahedron Lett.* **1985**, *26*, 3825. (b) Yamamoto, K.; Ishida, T.; Tsuji, J. *Chem. Lett.* **1987**, 1157. (c) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541. (d) Trost, B. M.; Morris, P. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 6167. (e) Goldberg, A. F. G.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 4474.

(4) Moran, J.; Smith, A. G.; Carris, R. M.; Johnson, J. S.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 18618.

(5) (a) Hirata, G.; Onodera, G.; Kimura, M. *Synlett* **2014**, *25*, 2306. For a recent transition-metal-free method, see: (b) Ieki, R.; Kani, Y.; Tsunoi, S.; Shibata, I. *Chem. - Eur. J.* **2015**, *21*, 6295.

(6) For recent reviews on CO_2 incorporation reactions, see: (a) Sakakura, T.; Choi, J.-C.; Yasuda, H. *Chem. Rev.* **2007**, *107*, 2365. (b) Mori, M. *Eur. J. Org. Chem.* **2007**, *2007*, 4981. (c) Correa, A.; Martin, R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6201. (d) Riduan, S. N.; Zhang, Y. *Dalton Trans.* **2010**, *39*, 3347. (e) Boogaerts, I. I. F.; Nolan, S. P. *Chem. Commun.* **2011**, *47*, 3021. (f) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3842. (g) Zhang, Y.; Riduan, S. N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6210. (h) Cokoja, M.; Bruckmeier, C.; Rieger, B.; Herrmann, W. A.; Kühn, F. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 8510. (i) Huang, K.; Sun, C.-L.; Shi, Z.-J. *Chem. Soc. Rev.* **2011**, *40*, 2435. (j) Martin, R.; Kleij, A. W. *ChemSusChem* **2011**, *4*, 1259. (k) Tsuji, Y.; Fujihara, T. *Chem. Commun.* **2012**, *48*, 9956. (l) Zhang, L.; Hou, Z. *Chem. Sci.* **2013**, *4*, 3395. (m) Kielland, N.; Whiteoak, C. J.; Kleij, A. W. *Adv. Synth. Catal.* **2013**, *355*, 2115. (n) Cai, X.; Xie, B. *Synthesis* **2013**, *45*, 3305. (o) Maeda, C.; Miyazaki, Y.; Ema, T. *Catal. Sci. Technol.* **2014**, *4*, 1482. (p) Yu, B.; He, L.-N. *ChemSusChem* **2015**, *8*, 52.

(7) (a) Mita, T.; Higuchi, Y.; Sato, Y. *Chem. - Eur. J.* **2015**, *21*, 16391. For our recent achievements of α-amino acid synthesis from CO_2, see: (b) Mita, T.; Chen, J.; Sugawara, M.; Sato, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 1393. (c) Mita, T.; Chen, J.; Sugawara, M.; Sato, Y. *Org. Lett.* **2012**, *14*, 6202. (d) Mita, T.; Higuchi, Y.; Sato, Y. *Chem. - Eur. J.* **2013**, *19*, 1123. (e) Mita, T.; Chen, J.; Sato, Y. *Org. Lett.* **2014**, *16*, 2200. (f) Mita, T.; Sugawara, M.; Saito, K.; Sato, Y. *Org. Lett.* **2014**, *16*, 3028.

(8) For selected examples of palladium-catalyzed carboxylations with CO_2 through C−C bond formation, see: (a) Sasaki, Y.; Inoue, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1976**, 605. (b) Hung, T.; Jolly, P. W.; Wilke, G. *J. Organomet. Chem.* **1980**, *190*, C5. (c) Sugimoto, H.; Kawata, I.; Taniguchi, H.; Fujiwara, Y. *J. Organomet. Chem.* **1984**, *266*, C44. (d) Shi, M.; Nicholas, K. M. *J. Am. Chem. Soc.* **1997**, *119*, 5057. (e) Johansson, R.; Wendt, O. F. *Dalton Trans.* **2007**, 488. (f) Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2008**, *130*, 7826. (g) Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2008**, *130*, 15254. (h) Correa, A.; Martin, R. *J. Am. Chem. Soc.* **2009**, *131*, 15974. (i) Wu, J.; Green, J. C.; Hazari, N.; Hruszkewycz, D. P.; Incarvito, C. D.; Schmeier, T. J. *Organometallics* **2010**, *29*, 6369. (j) Hruszkewycz, D. P.; Wu, J.; Hazari, N.; Incarvito, C. D. *J. Am. Chem. Soc.* **2011**, *133*, 3280. (k) Wu, J.; Hazari, N. *Chem. Commun.* **2011**, *47*, 1069. (l) Takaya, J.; Sasano, K.; Iwasawa, N. *Org. Lett.* **2011**, *13*, 1698. (m) Nakano, R.; Ito, S.; Nozaki, K. *Nat. Chem.* **2014**, *6*, 325. (n) Yu, B.; Zhao, Y.; Zhang, H.; Xu, J.; Hao, L.; Gao, X.; Liu, Z. *Chem. Commun.* **2014**, *50*, 2330. (o) Stieber, S. C. E.; Huguet, N.; Kageyama, T.; Jevtovikj, I.;

Ariyananda, P.; Gordillo, A.; Schunk, S. A.; Rominger, F.; Hofmann, P.; Limbach, M. *Chem. Commun.* **2015**, *51*, 10907.

(9) For reviews of nucleophilic η^1-allylpalladium species, see: (a) Tamaru, Y. *J. Organomet. Chem.* **1999**, *576*, 215. (b) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (c) Szabó, K. J. *Chem. - Eur. J.* **2004**, *10*, 5268. (d) Szabó, K. J. *Synlett* **2006**, *2006*, 811. (e) Zanoni, G.; Pontiroli, A.; Marchetti, A.; Vidari, G. *Eur. J. Org. Chem.* **2007**, *2007*, 3599.

(10) (a) Inoue, Y.; Hibi, T.; Satake, M.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1979**, 982. (b) Greco, G. E.; Gleason, B. L.; Lowery, T. A.; Kier, M. J.; Hollander, L. B.; Gibbs, S. A.; Worthy, A. D. *Org. Lett.* **2007**, *9*, 3817.

(11) The major diastereomer of **2i** was an *anti* isomer. See the Supporting Information (SI).

(12) Miao, B.; Ma, S. *Chem. Commun.* **2014**, *50*, 3285.

(13) (a) Ohno, H.; Hamaguchi, H.; Tanaka, T. *Org. Lett.* **2000**, *2*, 2161. (b) Araki, S.; Kameda, K.; Tanaka, J.; Hirashita, T.; Yamamura, H.; Kawai, M. *J. Org. Chem.* **2001**, *66*, 7919. (c) Anzai, M.; Yanada, R.; Fujii, N.; Ohno, H.; Ibuka, T.; Takemoto, Y. *Tetrahedron* **2002**, *58*, 5231.