EurJOC
European Journal of Organic Chemistry

A Journal of ChemPubSoc Europe

Accepted Article

Title: Synthesis of 7-Membered Ring Carbocycles via a Palladium-Catalyzed Intramolecular Allylic Alkylation-Isomerization-Cope Rearrangement Cascade

Authors: Kazuki Tsuruda, Takahisa Tokumoto, Naoya Inoue, Masaya Nakajima, and Tetsuhiro Nemoto

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201800230

Link to VoR: http://dx.doi.org/10.1002/ejoc.201800230

Supported by ACES Asian Chemical Editorial Society

WILEY-VCH

10.1002/ejoc.201800230

WILEY-VCH

Synthesis of 7-Membered Ring Carbocycles via a Palladium-Catalyzed Intramolecular Allylic Alkylation–Isomerization–Cope Rearrangement Cascade

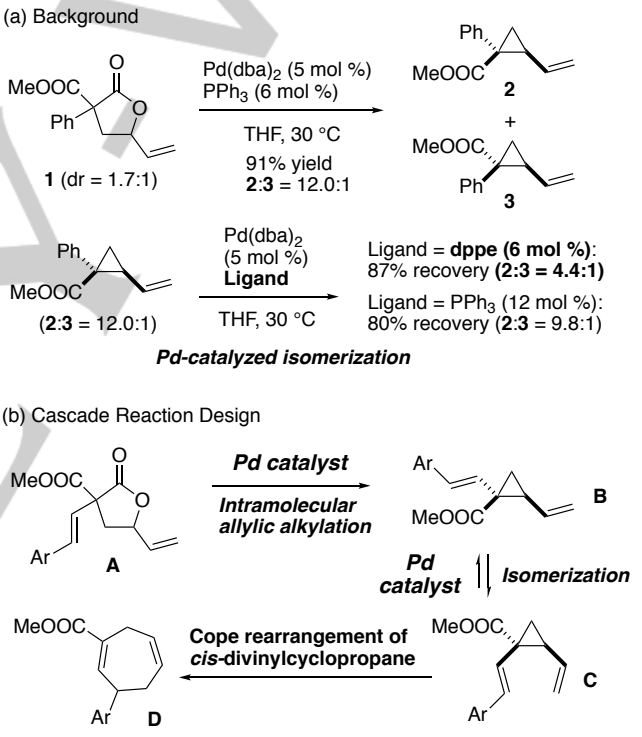
Kazuki Tsuruda,[a] Takahisa Tokumoto,[a] Naoya Inoue, [a] Masaya Nakajima, [a] and Tetsuhiro Nemoto*[a,b]

Abstract: We developed a novel method for synthesizing 7-membered ring carbocycles via a palladium-catalyzed intramolecular allylic alkylation–isomerization–Cope rearrangement cascade. Using easily available lactone derivatives as substrates, the target cascade reaction proceeded in the presence of 5 mol % of $Pd(dba)_2$ and 6 mol % of 1,3-diphenylphosphinopropane (dppp) in THF, affording a series of 7-membered ring carbocycles in 59–88% yield (11 examples). DFT calculations suggested that, in addition to the reaction cascade including the *cis*-divinylcyclopropane Cope rearrangement, there is another possible pathway based on the palladium-catalyzed intramolecular allylic substitution to construct the seven-membered ring through a retro-cyclopropanation-mediated oxidative addition.

Introduction

Seven-membered ring carbocyclic frameworks are present in various bioactive natural products and pharmaceuticals. Therefore, the development of an efficient method of constructing such molecular skeletons is an attractive research topic in the field of synthetic organic and medicinal chemistry. Considerable efforts have focused on this aim.[1]

We recently developed a diastereoselective synthetic method of trisubstituted cyclopropanes using palladium-catalyzed intramolecular allylic alkylation of α-aryl esters (Scheme 1).[2] After preparing lactone derivative **1** by $Yb(OTf)_3/BF_3{\cdot}OEt_2$-catalyzed intramolecular allylic carboxylation of a simple linear malonate derivative, compound **1** was treated with 5 mol % of $Pd(dba)_2$ and 6 mol % of PPh_3 in THF at 30 °C, providing trisubstituted cyclopropane derivative **2** with high diastereoselectivity (**2**:**3** = 12.0:1) (Scheme 1a).[3] Our mechanistic investigations revealed that **2** was isomerized into **3** upon treatment with 5 mol % of $Pd(dba)_2$ and 6 mol % of 1,3-diphenylphosphinoethane (dppe), which significantly decreased the diastereoselectivity (**2**:**3** = 4.4:1). This finding led us to design a new cascade reaction (Scheme 1b). We hypothesized that when lactone derivative **A** bearing a styryl substituent in the α-position was reacted with Pd(0) catalyst in the presence of a bidentate phosphorus ligand, a palladium-catalyzed intramolecular allylic alkylation and subsequent isomerization of cyclopropane derivative **B** would proceed to form compound **C**. *Cis*-configuration of the divinyl substituents in **C** would facilitate the sequential Cope rearrangement, producing a functionalized seven-membered ring carbocycle **D**.[4] Herein we report a novel method of synthesizing 7-membered ring carbocycles via a palladium-catalyzed intramolecular allylic alkylation–isomerization–Cope rearrangement cascade.



Scheme 1. Background and Plan of This Work.

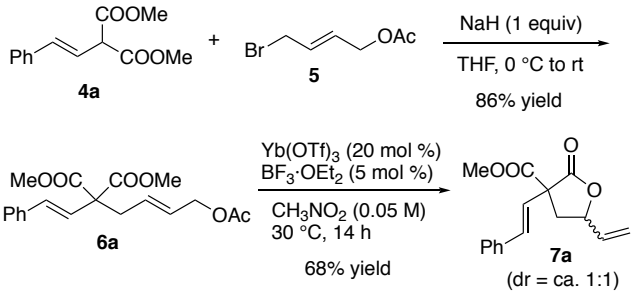
Results and Discussion

We began our investigation by preparing the model substrate (Scheme 2). α-Styryl malonate derivative **4a** was prepared using the synthetic method reported by Melnikov et al.[5] A condensation reaction between **4a** and **5** proceeded in the presence of 1 equiv of NaH to give compound **6a** in 79% yield. Intramolecular allylic carboxylation was then performed in the presence of 20 mol % of $Yb(OTf)_3$ and 5 mol % of $BF_3{\cdot}OEt_2$ in nitromethane at 30 °C, providing compound **7a** in 68% yield as an inseparable nearly 1:1 diastereomeric mixture. With the model substrate in hand, the reaction conditions were optimized for a palladium-catalyzed intramolecular allylic alkylation–isomerization–Cope rearrangement cascade using 5

[a] K. Tsuruda, T. Tokumoto, N. Inoue, Dr. M. Nakajima, Prof. Dr. T. Nemoto
Graduate School of Pharmaceutical Sciences, Chiba University
1-8-1, Inohana, Chuo-ku, Chiba 260-8675 (Japan)
E-mail: tnemoto@faculty.chiba-u.jp
URL: http://www.p.chiba-u.jp/lab/yakka/reserch,eng.html
[b] Prof. Dr. T. Nemoto
Molecular Chirality Research Center, Chiba University
1-33, Yayoi-cho, Inage-ku, Chiba 263-8522 (Japan)

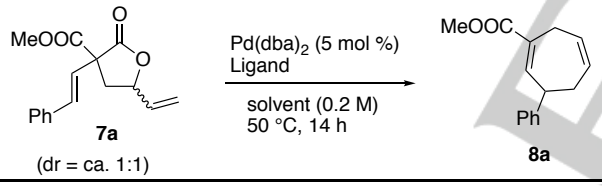
Supporting information for this article is given via a link at the end of the document.

mol % of $Pd(dba)_2$ complex (Table 1). We first screened phosphorus ligands in THF at 50 °C. Among the examined bidentate phosphorus ligands (entries 1–3), 1,3-diphenylphosphinopropane (dppp) was found to be optimal and compound **8a** was obtained in 88% yield. The target transformation was also promoted when using 12 mol % of PPh_3 (Entry 4). The solvent effect was next examined using dppp as a ligand (Entries 2, 5–9). The reaction media did not affect the chemical yield and THF was determined to be the best solvent. No reaction occurred when the reaction was performed in the absence of the palladium catalyst (Entries 10 and 11), indicating the requirement of palladium catalysis in this cascade process. Thus, we selected the reaction conditions in entry 2 as the optimum conditions.



Scheme 2. Preparation of Model Substrate **7a**

Table 1. Optimization of the Reaction Conditions.



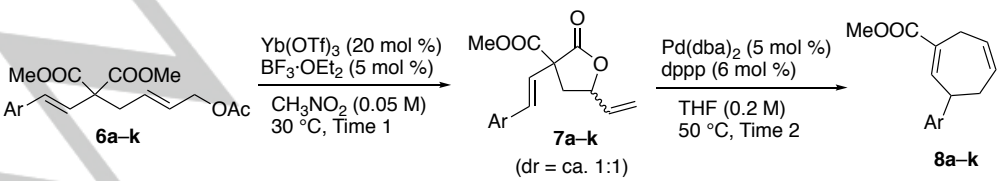
Entry	Ligand (mol %)	Solvent	Yield (%)[a]
1	dppe (6)	THF	71
2	dppp (6)	THF	88
3	dppb (6)	THF	85
4	PPh_3 (12)	THF	79
5	dppp (6)	1,2-dichloroethane	83
6	dppp (6)	toluene	82
7	dppp (6)	1,4-dioxane	81
8	dppp (6)	CH_3CN	81
9	dppp (6)	DMF	63
10[b]	dppp (6)	THF	0
11[b]	–	THF	0

[a] Isolated yield. [b] The reaction was performed in the absence of Pd catalyst.

We next examined the scope and limitations of the reaction under the optimized conditions (Table 2). Intramolecular allylic carboxylation of malonate derivatives **6a**–**k**[6] was examined using 20 mol % of $Yb(OTf)_3$ and 5 mol % of $BF_3{\cdot}OEt_2$ in nitromethane at 30 °C. When malonate derivatives with an alkyl group-substituted styryl group were utilized as substrates, the corresponding lactone derivatives were obtained in 38–56% yield (entries 2, 3, 7, and 9). In contrast, the lactone derivative was obtained in good to excellent yield when substrates with a halide-substituted styryl group were used (65–99% yield) (entries 4–6, and 8). TLC analysis of the reaction mixture revealed that when malonate derivatives with an alkyl group-substituted styryl group were used, the starting material was consumed and several by-products formed. Thus, we speculated that the lower chemical yield in this case was due to polymerization of the electron-rich styrene units. Although the yield was moderate, this lactonization was also effective for naphthyl-type substrates (entries 10 and 11). All substrates were obtained as nearly 1:1 mixtures of diastereomers.

The palladium-catalyzed intramolecular allylic alkylation–isomerization–Cope rearrangement cascade was then examined using lactone derivatives **7a**–**k** under the optimized reaction conditions. In addition to the model substrate **7a** (entry 1), substrates with a *para*-substituted styryl group **7b**–**f** were applicable to this cascade reaction, affording the corresponding 7-membered ring carbocycles **8b**–**f** in 69–83% yield (entries 2–6). *Meta*-substituted styryl-type substrates **7g** and **7h**, as well as an *ortho*-substituted styryl-type substrate **7i**, were suitable for this cascade process, providing the corresponding product in 59–78% yield (entries 7–9). Moreover, when 1-naphthyl-type lactone **7j** and 2-naphthyl-type lactone **7k** were used as substrates, products **8j** and **8k** were obtained in 67% yield and 64% yield, respectively (entries 10 and 11).

Table 2. Scope and Limitations.

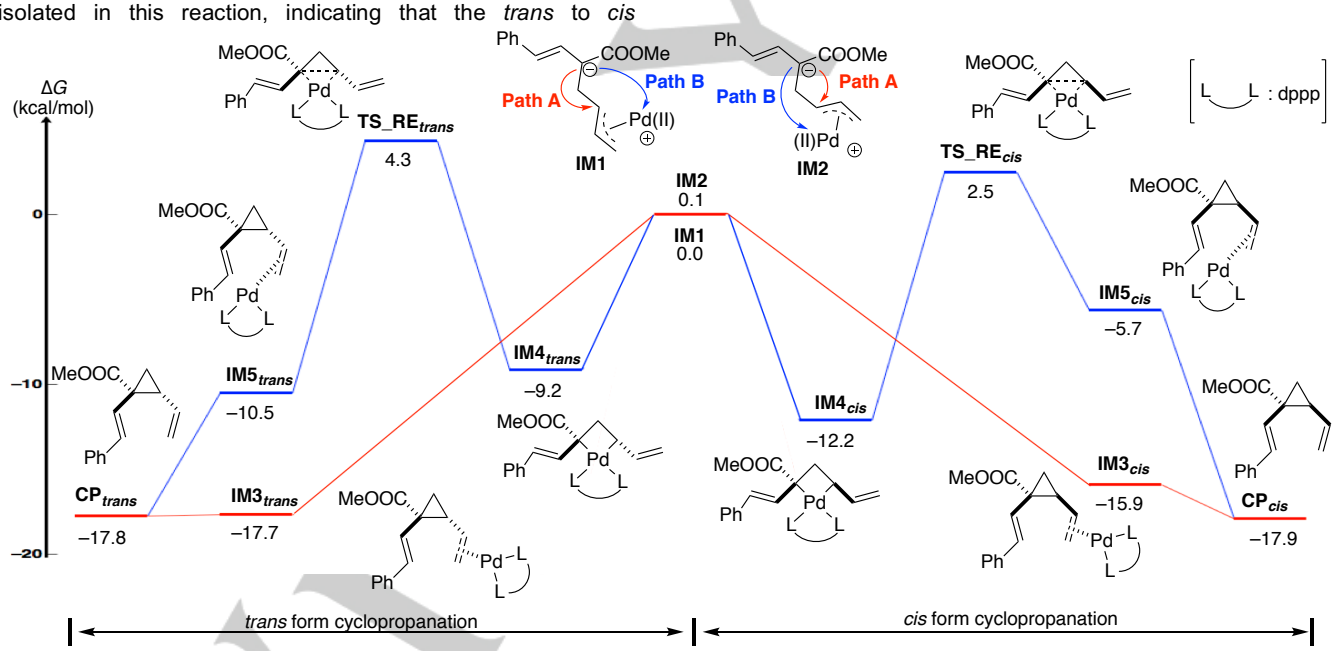


Entry	Substrate	Time 1	Yield of **7**[a]	Time 2	Yield of **8**[a]
1	**6a** (Ar = Ph)	14 h	**7a**: 68%	14 h	**8a**: 88%

2	**6b** (Ar = 4-CH_3-C_6H_4)	40 h	**7b**: 56%	22 h	**8b**: 83%
3	**6c** (Ar = 4-*t*-Bu-C_6H_4)	22 h	**7c**: 38%	18 h	**8c**: 76%
4	**6d** (Ar = 4-F-C_6H_4)	40 h	**7d**: 99%	16 h	**8d**: 69%
5	**6e** (Ar = 4-Cl-C_6H_4)	19 h	**7e**: 95%	15 h	**8e**: 69%
6	**6f** (Ar = 4-Br-C_6H_4)	50 h	**7f**: 82%	24 h	**8f**: 78%
7	**6g** (Ar = 3-CH_3-C_6H_4)	22 h	**7g**: 47%	17 h	**8g**: 59%
8	**6h** (Ar = 3-F-C_6H_4)	19 h	**7h**: 65%	19 h	**8h**: 75%
9	**6i** (Ar = 2-CH_3-C_6H_4)	22 h	**7i**: 56%	20 h	**8i**: 69%
10	**6j** (Ar = 1-naphthyl)	20 h	**7j**: 33%	21 h	**8j**: 67%
11	**6k** (Ar = 2-naphthyl)	19 h	**7k**: 54%	21 h	**8k**: 64%

[a] Isolated yield.

To elucidate the reaction pathway through a palladium-catalyzed intramolecular allylic alkylation-isomerization-Cope rearrangement cascade, we first attempted to isolate the trisubstituted cyclopropane intermediate. The postulated trisubstituted cyclopropane intermediate, however, could not be isolated in this reaction, indicating that the *trans* to *cis* isomerization and the Cope rearrangement should proceed spontaneously with low activation barrier.[7] We therefore performed a computational analysis to gain insight into the reaction mechanism.

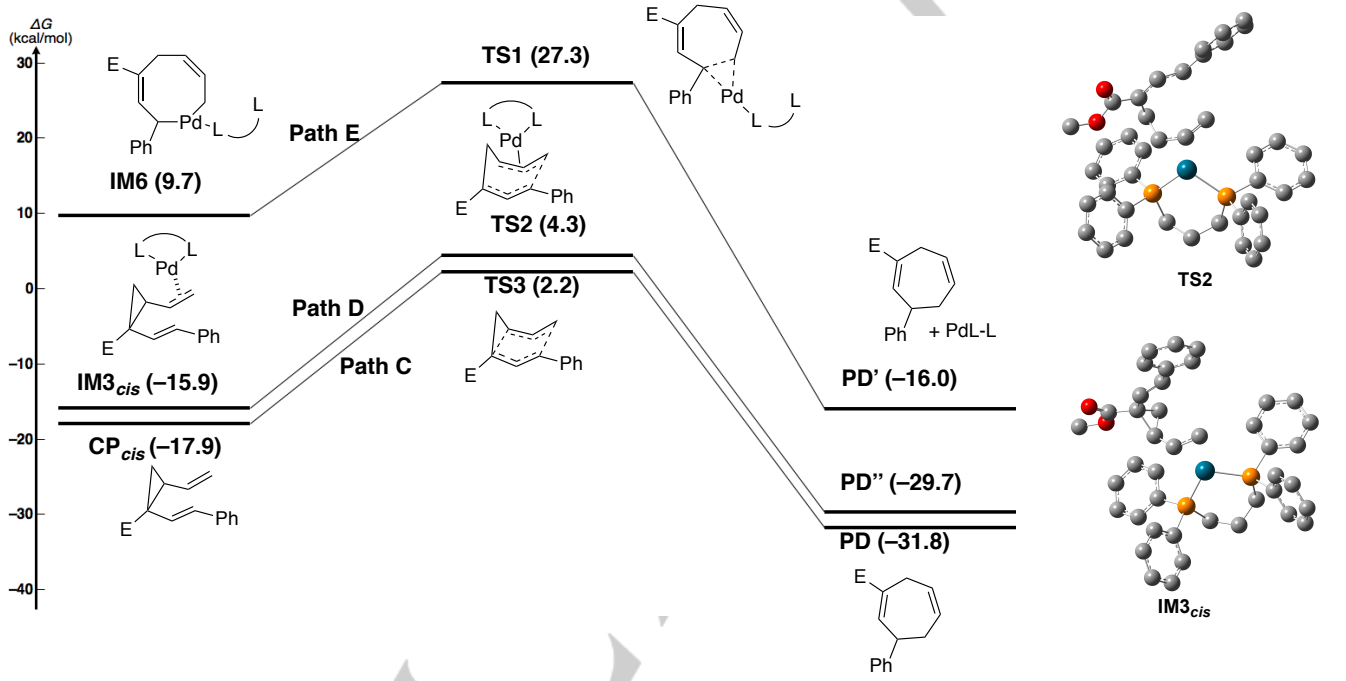


Scheme 3. DFT-Computed Pathways for the Cyclopropanations. Optimization of geometries and frequencies are computed at the M06/LANL2DZ-6-31+G* level.

We first performed DFT calculations on the reaction mechanism of cyclopropanation (Scheme 3). There are two possible pathways for this step: nucleophilic addition to the π-allylpalladium (II) complexes **IM1** or **IM2** (Path A), or reductive elimination from the four-membered palladacycle intermediates **IM4**$_{cis}$ or **IM4**$_{trans}$ (Path B). In the DFT calculation for Path A, we found no transition structure in either the transformation from **IM1** to **IM3**$_{cis}$ or that from **IM2** to **IM3**$_{trans}$, and no maximum point was confirmed in the potential energy curve related to the newly formed C–C bond length, indicating that the three-membered ring formation via Path A is a barrierless reaction with very low activation energy. On the other hand, in the DFT calculation for Path B, the activation energies of either reaction for **TS_RE** was less than 14.8 kcal/mol, leading to a cis-form

product **CP**$_{cis}$ or trans-form product **CP**$_{trans}$. These calculation data suggested that the cyclopropanation/ring-opening reactions were reversible in the presence of a palladium catalyst, leading us to conclude that isomerization from **CP**$_{trans}$ to **CP**$_{cis}$ is a reasonable process.

We next performed DFT calculations for the seven-membered ring formation (Scheme 4). There are three possible pathways for this step, including Cope rearrangement via **TS1** (Path C), nucleophilic addition of a benzylic anion to π-allylpalladium (II) complex via **TS2** (Path D), and reductive elimination of eight-membered palladacycle **IM6** via **TS3** (Path E). DFT calculations for Path C revealed that the activation energy of the Cope rearrangement from **CP**$_{cis}$ to **TS1** was 20.1 kcal/mol, forming thermodynamically significantly stabilized product **PD**. This energy profile reasonably supported the reaction cascade including a conventional Cope rearrangement step. On the other hand, contrary to our expectation, the activation energy of the intramolecular allylic substitution from **IM3**$_{cis}$ to **TS2** was calculated to be 20.2 kcal/mol, despite being mediated by the thermodynamically unfavorable anti-π-allylpalladium (II) complex. We expect that the conformational similarity between **IM3**$_{cis}$ and **TS2** affects the activation energy, facilitating the seven-membered ring formation. Although the activation energy of the reductive elimination from **IM6** to **TS3** is 17.6 kcal/mol, Path E would not be a plausible route because the potential energy of **IM6** is significantly larger than those of **CP**$_{cis}$ and **IM3**$_{cis}$. These computational studies suggest that, in addition to the reaction cascade including the *cis*-divinylcyclopropane Cope rearrangement, there is another possible pathway based on the palladium-catalyzed intramolecular allylic substitution to construct the seven-membered ring through a retro-cyclopropanation-mediated oxidative addition.



Scheme 4. DFT Calculation for Seven-Membered Ring Formations.

Conclusions

In conclusion, we developed a novel method for synthesizing 7-membered ring carbocycles via a palladium-catalyzed intramolecular allylic alkylation–isomerization–Cope rearrangement cascade. A series of 7-membered ring carbocycles were obtained from easily available lactone derivatives in 59–88% yield (11 examples). DFT calculations suggest that, in addition to the reaction cascade including the *cis*-divinylcyclopropane Cope rearrangement, there is another possible pathway based on the palladium-catalyzed intramolecular allylic substitution to construct the seven-membered ring through a retro-cyclopropanation-mediated oxidative addition.

Experimental Section

General Procedure for the 7-membered ring carbocycles *via* palladium-catalyzed intramolecular allylic alkylation–isomerization–Cope rearrangement cascade (Table 2, entry 2): A solution of **6a** (175.7 mg, 0.507 mmol), $Yb(OTf)_3$ (62.6 mg, 0.101 mmol), $BF_3 \cdot OEt_2$ (3 μL, 0.025 mmol) in CH_3NO_2 (10 mL) was stirred at 30 °C. After 14 h, the reaction mixture was cooled down to room temperature and then quenched with saturated aq. $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted twice with AcOEt. The combined organic extracts were washed with water and brine, dried over sodium sulfate. After concentration *in vacuo*, the residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 5/1) to give **7a** (94.2 mg, dr. = 1:1, 68% yield) as an

inseparable mixture of diastereomers. Ratio of the diastereomeric mixture was determined by ^{1}H-NMR analysis of the obtained mixture. A solution of **7a** (50.7 mg, 0.186 mmol), $Pd(dba)_2$ (5.3 mg, 0.00921 mmol), dppp (4.6 mg, 0.0111 mmol) in THF (0.93 mL) in an argon atmosphere was warmed to 50 °C. After being stirred for 14 h at the same temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 80/1) to give methyl 3-phenylcyclohepta-1,5-diene-1-carboxylate (**8a**) (37.1 mg, 88% yield) as pale yellow oil. **8a**: IR (ATR) ν 3026, 2365, 1711, 1435, 1242, 1195, 1074, 758, 701, 617 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.40–2.46 (1H, m), 2.54–2.58 (1H, m), 3.30 (2H, d, *J* = 5.2 Hz), 3.72 (3H, s), 3.94–3.99 (1H, m), 5.69–5.80 (2H, m), 7.13 (1H, d, *J* = 5.6 Hz), 7.23–7.26 (3H, m), 7.32–7.35 (2H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 25.7, 33.7, 43.9, 51.9, 126.7, 127.4 (2C), 127.4, 128.7 (2C), 129.6, 131.7, 144.5, 146.5, 168.0; HRMS (ESI-TOF) m/z: Calcd for $C_{15}H_{16}NaO_2$ $[M+Na]^+$: 251.1043; found: 251.1046.

Acknowledgements

This work was supported financially by JSPS KAKENHI Grant Number 15K07850, and grant from Global and Prominent Research, Chiba University.

Keywords: Cascade reaction • Catalysis • Palladium • Rearrangement • Synthetic method

[1] For reviews, see: (a) T. V. Nguyen, J. M. Hartmann, D. Enders, *Synthesis* **2013**, *45*, 845; (b) K. T. de Oliveira, B. M. Servilha, L. C. Alves, A. L. Desiderá, T. J. Brocksom, *Studies in Natural Product Chemistry* **2014**, *42*, 421; (c) S. Krüger, T. Gaich, *Beilstein J. Org. Chem.* **2014**, *10*, 163.

[2] T. Nemoto, K. Tsuruda, M. Yoshda, M. Kono, Y. Hamada, *Synthesis* **2015**, *47*, 3914.

[3] For representative examples of the synthesis of 1,1,2-trisubstituted cyclopropanes, see: (a) B. Moreau, A. B. Charette, *J. Am. Chem. Soc.* **2005**, *127,* 18014; (b) N. Okamoto, M. Sasaki, M. Kawahata, K. Yamaguchi, K. Takeda, *Org. Lett.* **2006**, *8*, 1889; (c) V. N. G. Lindsay, W. Lin, A. B. Charette, *J. Am. Chem. Soc.* **2009**, *131,* 16383; (d) C. D. Bray, F. Minicone, *Chem. Commun.* **2010**, *46*, 5867; (e) C. Deng, L. J. Wang, J. Zhu, Y. Tang, *Angew. Chem.* **2012**, *124*, 11788; *Angew. Chem. Int. Ed.* **2012**, *51*, 11620. (f) J. S. Alford, H. M. L. Davies, *Org. Lett.* **2012**, *14*, 6020; (g) N. Hoshiya, T. Kobayashi, M. Arisawa, S. Shuto, *Org. Lett.* **2013**, *15*, 6202; (h) X. Xu, S. Zhu, X. Cui, L. Wojtas, X. P. Zhang, *Angew. Chem.* **2013**, *125*, 12073; *Angew. Chem. Int. Ed.* **2013**, *52*, 11857; (i) J. Pedroni, N. Cramer, *Angew. Chem.* **2015**, *127*, 11992; *Angew. Chem. Int. Ed.* **2015**, *54*, 11826; (j) D. S. Müller, I. Marek, *J. Am. Chem. Soc.* **2015**, *137,* 15414.

[4] For representative examples of the synthesis of 7-membered carbocycles via Cope rearrangement of *cis*-divinylcyclopropane intermediates, see: (a) S. Yokoshima, H. Tokuyama, T. Fukuyama, *Angew. Chem.* **2000**, *112*, 4239; *Angew. Chem. Int. Ed.* **2000**, *39*, 4073; (b) L. Deng, A. J. Giessert, O. O. Gerlitz, X. Dai, S. T. Diver, H. M. L. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 1342; (c) Y. Ni, J. Montgomery, *J. Am. Chem. Soc.* **2006**, *128*, 2609; (d) D. Bykowski, K.-H. Wu, M. P. Doyle, *J. Am. Chem. Soc.* **2006**, *128*, 16038; (e) H. Ito, S. Takeguchi, T. Kawagishi, K. Iguchi, *Org. Lett.* **2006**, *8*, 4883; (f) S. Kesavan, J. S. Panek, J. A. Porco Jr, *Org. Lett.* **2007**, *9*, 5203; (g) B. D. Schwartz, J. R. Denton, Y. Lian, H. M. L. Davies, C. M. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 8329; (h) Y. Lian, L. C. Miller, S. Born, R. Sarpong, H. M. L. Davies, *J. Am. Chem. Soc.* **2010**, *132*, 12422; (i) S. Y. Kim, Y. Park, Y. K. Chung, *Angew. Chem.* **2010**, *122*, 425; *Angew. Chem. Int. Ed.* **2010**, *49*, 415; (j) Y. Takada, K. Nomura, S. Matsubara, *Org. Lett.* **2010**, *12*, 5204. (k) J. D. Osler, W. P. Unsworth, R. J. K. Taylor, *Org. Biomol. Chem.* **2013**, *11*, 7587; (l) Z. Cao, F. Gagosz, *Angew. Chem.* **2013**, *125*, 9184; *Angew. Chem. Int. Ed.* **2013**, *52*, 9014; (m) B. T. Parr, H. M. L. Davies, *Angew. Chem.* **2013**, *125*, 10228; *Angew. Chem. Int. Ed.* **2013**, *52*, 10044; (n) T. Yamada, F. Yoshimura, K. Tanino, *Tetrahedron Lett.* **2013**, *54*, 522; (o) W. Rao, Sally, S. N. Berry, P. W. H. Chan, *Chem. Eur. J.* **2014**, *20*, 13174; (p) T. Yokosaka, T. Nemoto, H. Nakayama, N. Shiga, Y. Hamada, *Chem. Commun.* **2014**, *50*, 12775; (q) E. T. Newcomb, P. C. Knutson, B. A. Pedersen, E. M. Ferreira, *J. Am. Chem. Soc.* **2016**, *138*, 108; (r) Y. Hato, Y. Oonishi, Y. Yamamoto, K. Nakajima, Y. Sato, *J. Org. Chem.* **2016**, *81*, 7847. (s) J. D. Osler, W. P. Unsworth, R. J. K. Taylor, *Synlett* **2016**, *27*, 70; (t) J. L. Roizen, A. C. Jones, R. C. Smith, S. C. Virgil, B. M. Stoltz, *J. Org. Chem.* **2017**, *82*, 13051.

[5] A. O. Chagarovsky, O. A. Ivanova, E. R. Rakhmankulov, E. M. Budynina, I. V.Trushkov, M. Y. Melnikov, *Adv. Synth. Catal.* **2010**, 352, 3179.

[6] For the preparation of substrates, see Supporting Information.

[7] The half-life of *cis*-divinylcyclopropane is 449 seconds at 20.4 °C, implying that isolation of the *cis*-divinylcyclopropane intermediate would be difficult. For a reference, see: J. M. Brown, B. T. Golding, J. J. Stofko, *J. Chem. Soc., Chem. Commun.* **1973**, *0*, 319b.

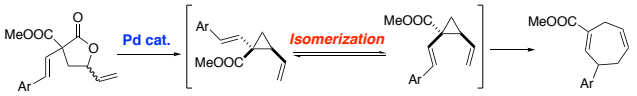
10.1002/ejoc.201800230

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION



Pd-catalyzed intramolecular allylic substitution – isomerization – Cope rearrangement cascade

59–88% yield
(11 examples)

We report a novel method for synthesizing 7-membered ring carbocycles via a palladium-catalyzed intramolecular allylic alkylation–isomerization–Cope rearrangement cascade. DFT calculation for the seven-membered ring formation step suggested that, in addition to the reaction cascade including the conventional Cope rearrangement, there is another possible pathway based on the palladium-catalyzed intramolecular allylic substitution via retro-cyclopropanation.

Cascade Reaction*

*Kazuki Tsuruda, Takahisa Tokumoto, Naoya Inoue, Masaya Nakajima, and Tetsuhiro Nemoto**

Page No. – Page No.

Synthesis of 7-Membered Ring Carbocycles via a Palladium-Catalyzed Intramolecular Allylic Alkylation–Isomerization–Cope Rearrangement Cascade