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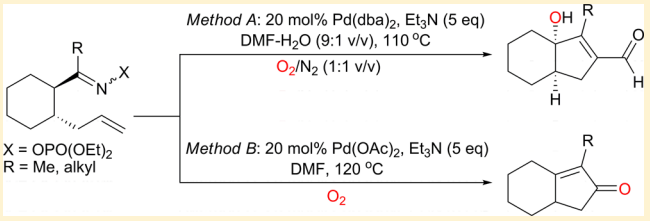
Access to Functionalized Bicyclo[4,3,0]nonenes via Palladium-Catalyzed Oxidative Cyclization of 2-Allylcyclohexyl Oximes

Jia-Liang Zhu,* Sih-Ting Wu, and Jr-Yun Shie

Department of Chemistry, National Dong Hwa University, Hualien 974, Taiwan

Supporting Information

ABSTRACT: A new palladium-catalyzed oxidative cyclization process leading to the functionalized bicyclo[4,3,0]nonenes is serendipitously discovered during attempts to form aza-heterocycle by the amino-Heck reaction of *trans*-2-vinylclohexyl phosphinyloxime. Under the influence of $Pd(dba)_2$/Et_3N/1:1 N_2−O_2 (1:1, v/v) (Method A) or $Pd(OAc)_2$/Et_3N/O_2 (Method B), the reactions afford the substituted *cis*-1-hydroxyl-8-formyl-bicyclo[4,3,0]non-8(9)-enes or bicyclo-[4,3,0]non-1(9)-en-8-ones in varying yields with the incorporation of molecular oxygen into the structures. The 5,6-bicyclic scaffold of these products is presumably derived from tandem double intramolecular cyclization followed by the ring-opening of an aza-palladium(II) tricyclic intermediate.



INTRODUCTION

Palladium(0)-catalyzed intramolecular cyclization of unsaturated oximes (amino-Heck reaction) is an important synthetic strategy for preparing various aza-heterocycles.[1,2] Pioneering works by Narasaka and Kitamura[2i] have established that these types of reactions are initiated by the oxidative addition of the N−O bond to Pd(0) species, and the resulting aza-Pd (II) complex then engages in the cyclization with internal olefins to give cyclic products. To date, the most widely employed precursors for amino-Heck reactions are *O*-pentafluorobenzoyl-oximes,[2,3] which are proved to be superior to many other kinds of oximes, such as sulfonyl-, acetyl-, and benzoyloximes, in terms of reactivity, stability, and production of fewer undesired byproducts.[4] In our continuation study on the cyclization reactions of phosphonyl compounds,[5−8] we previously demonstrated that a range of γ,δ-unsaturated diethyl-phosphinyloximes could cyclize smoothly in a 5-*exo* fashion under the catalysis of $Pd(PPh_3)_4$ in refluxing CH_3CN with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), to afford substituted pyrroles or indoles in good to high yields.[6] As compared with the acyloxime counterparts,[4] these substrates also exhibited the unique regioselectivity in adopting a 6-*endo* pathway to produce pyridines under the different catalytic conditions.[7] More recently, we further applied the cyclization reaction to 2-vinylclohexyl phosphinyloximes.[8] During the process, the selected substrates underwent the 6-*endo* cyclization exclusively upon treating with $Pd(PPh_3)_4$ (0.2 equiv)/Et_3N (5 equiv) in DMF at 80 °C, to provide tetrahedroisoquinilines after the in situ aromatization (Scheme 1). Additionally, we observed that the *trans*-oxime precursor cyclized more easily than the corresponding *cis*-isomer, as a result of the closer proximity of the Pd−N complex to the C═C double bond (equatorial−equatorial versus equatorial−axial).

After the aforementioned studies, we intended to extend the protocol to 2-allylcyclohexyl oxime system, whose cyclization reaction, as far as we know, has never been reported. For the analogous but more-rigid *ortho*-allylacetophenone acyloximes, Narasaka and co-workers[9] have shown the Pd(0)-catalyzed cyclization occurred in an 6-*exo* mode to give isoquinolines (Scheme 2). According to this report and our experience,[7,8] we had originally envisaged that the cyclization of allylcyclohexyl oximes would lead to either 3-methyl tetrahydroisoquinolines (6-*exo*) or tetrahydrobenzoazepines (7-*endo*). However, during the investigation, it was found that most attempted reactions did not give the products as we expected. Herein, we wish to report the preliminary results from this study together with a novel Pd-catalyzed oxidative cyclization process allowing the rapid construction of the highly functionalized bicyclo[4,3,0]-nonene scaffold.

RESULTS AND DISCUSSION

A *trans* methyl-substituted oxime was first prepared for the initial model studies. As shown in Scheme 3, reaction of *trans*-1-(2-allylcyclohexyl)-ethanone (**1a**)[10] with hydroxylamine hydrochloride, in the presence of sodium acetate, gave the hydroxyl oxime **2a**. Treatment of **2a** with diethyl cholorophosphate and triethyl amine in CH_2Cl_2 for 6 h furnished the oxime precursor **3a** in 77% yield solely as the (*E*)-isomer.[11] With **3a** in hand, we submitted it to the catalytic conditions in Scheme 1. It came as a surprise to us when the reaction did not yield any expected hetereocycles but rather gave the bicyclic hydroxyaldehyde **4a** (12%) along with enone **5a** (5%) upon losing a carbon unit. Besides, a large amount of ketone (52%, *trans*/*cis* = 57:43) arising from hydrolysis[4] and epimerization was isolated, which

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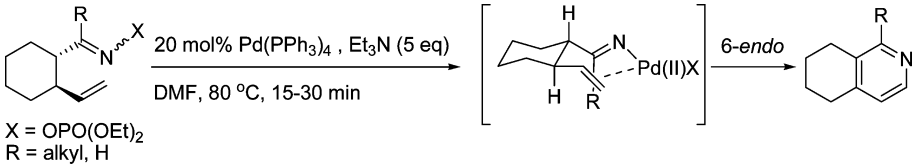
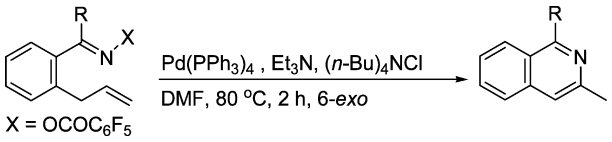
Scheme 1. Pd(PPh$_3$)$_4$-Catalyzed Cyclization of *trans*-2-Vinylclohexyl Phosphinyloximes



Scheme 2. Pd(0)-Catalyzed Cyclization of *ortho*-Allylacetophenone Oximes



could be quantitatively reconverted to **1a** by treating with a base.[10]

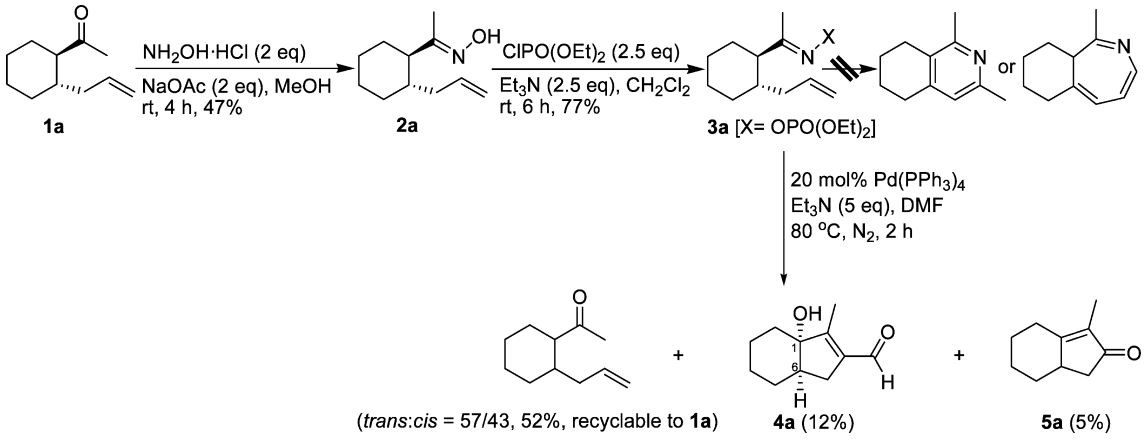
Compound **5a** is well-known,[12] and the structure of **4a** has been fully established by spectroscopic methods (^{1}H and ^{13}C NMR, DEPT, HRMS, and IR). Interestingly, **4a** was formed as a single diastereomer. To elucidate the steric relationship at the C1−C6 ring-junction positions, we further transferred it into diol **6**[13] (83:17) through hydrogenation and $NaBH_4$ reduction (Scheme 4). The X-ray crystallographic analysis of the major isomer of **6** unambiguously confirmed the *cis*-stereochemistry of **4a**. The exclusive formation of the *cis*-isomer is presumably a consequence of the prohibitively large amount of strain energy associated with the *trans* 5,6-fused skeleton.

Albeit in low yields, we were fascinated by the unexpected formation of **4a** and **5a** with the assembly of the oxygenated bicyclic skeletons in a single step. We also observed that respective submission of **1a** and **2a** to the same catalytic conditions or heating **3a** only with Et_3N in DMF for more than 10 h merely resulted in recovered starting materials. These results indicate that **4a** and **5a** were indeed the result of the catalytic annulation of **3a**. To the best of our knowledge, our finding represents a yet unprecedented access to the bicyclo[4,3,0]nonene {or bicyclo[4,3,0]nonane} ring system that occurs ubiquitously in natural[14] and synthetic molecules[15] and has always gained considerable synthetic efforts in its construction.[16] In these respects, we decided to carry out an in-depth exploration into this reaction.

For the generation of **4a**, we were particularly interested in the hydroxylation at C-1. So far, the documented Pd-catalyzed C−H hydroxylation reactions[17] have been mostly limited to the aromatic (sp^2 C−H, aryl hydroxylation)[18] or carbonyl (sp^3 C−H, α-hydroxylation)[19] precursors, and usually employ gaseous O_2[18] or other oxidants (e.g., Oxone)[20] as the oxygen sources. At the beginning, we were curious about how the C-1 hydroxylation could occur without a specific source of oxygen, regarding that the catalytic reaction in Scheme 3 was virtually conducted under N_2 protection in dry DMF. Nevertheless, closer TLC inspection of the reaction revealed that there was a transient intermediate formed after heating for 10 min, which almost vanished in about 1 h (see the Supporting Information). We then managed to isolate this intermediate after allowing the reaction to proceed for 30 min (Scheme 5). The spectroscopic analysis determined it as the hydroperoxide **7**,[21] whose structure was further validated by the chemical correlation via converting into **4a** under treatment with PPh_3.[22] The identification of **7**, the on-pathway precursor to **4a**, is important, because *it implies that an O_2-mediated process should be involved in the C-1 hydroxylation*,[19,23] and the air residue in the nondegassed reaction media was likely to serve as the aerobic source. On this basis, we further evaluated a series of catalytic conditions with Pd(PPh$_3$)$_4$. The experimental results are compiled in Table 1.

We first noted that neither **4a** nor **5a** could be formed under the strictly O_2-free conditions (Table 1, entry 1). This observation demonstrates *that oxygen is necessary not only for the generation of **4a** as reflected in the C-1 hydroxylation but also for the formation of **5a***. However, when the reaction was conducted under a balloon pressure of pure O_2, the diminished depletion of **3a** after the initial few minutes was seen even after heating for a prolonged time at the higher temperature, to afford only a trace amount of **4a** (<3%) and no detectable **5a** (entry 2). The nonproductivity in this case should be ascribed to the oxidation of Pd(0) into inactive Pd(II) by O_2.[24] Hence,

Scheme 3. Preparation and Pd(PPh$_3$)$_4$-Catalyzed Cyclization of 3a



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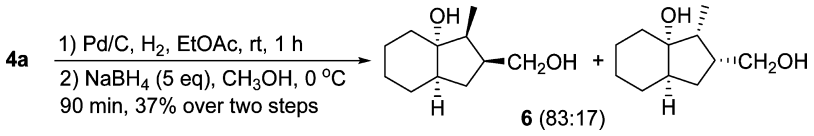
Scheme 4. Preparation of Diol Derivative 6



Scheme 5. Preparation of 7 and Its Chemical Correlation with 4a

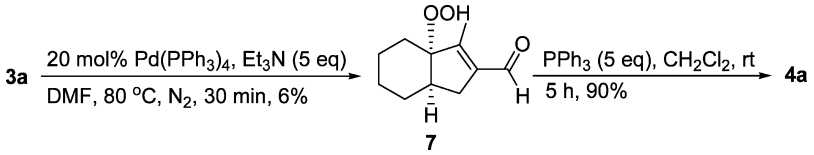


Table 1. Evaluation of Catalytic Conditions with $Pd(PPh_4)_3$

			yield (%)[b]			
entry	catalytic conditions[a]	time (h)	**4a**	**5a**	ketone[c]	**3a**[d]
1[e]	$Pd(PPh_3)_4/Et_3N/DMF/O_2$-free/80 °C	12			44	27
2	$Pd(PPh_3)_4/Et_3N/DMF/O_2$/80→95 °C	12	trace		trace	55
3	$Pd(PPh_3)_4/Et_3N/DMF$/air/80→95 °C	12	trace	5	16	41
4	$Pd(PPh_3)_4/Et_3N/DMF/N_2$:$O_2$ (30:1)/80 °C	5	trace	8	31	
5	$Pd(PPh_3)_4/Et_3N/DMF/N_2$:$O_2$ (20:1)/80 °C	5	6	10	49	
6[f]	$Pd(PPh_3)_4/Et_3N/DMF/N_2$:$O_2$ (10:1)/80 °C	5	**13**	**14**	28	
7[g]	$Pd(PPh_3)_4/Et_3N/DMF/N_2$:$O_2$ (7:1)/80 °C	5	trace	5	17	24
8[h]	$Pd(PPh_3)_4/PPh_3/Et_3N/DMF$/air/80 °C	12	trace	10	19	33
9[h]	$Pd(PPh_3)_4/P(t\text{-}Bu)_3/Et_3N/DMF$/air/80 °C	12	trace	trace	13	51
10[h]	$Pd(PPh_3)_4$/Xantphos/Et_3N/DMF/air/80 °C	12	trace	15		42
11[h]	$Pd(PPh_3)_4$/TFP/Et_3N/DMF/air/80 °C	12	trace	trace	55	34
12[i]	$Pd(PPh_3)_4/Et_3N/CH_3CN/N_2$–$O_2$/reflux	12				quant.
13[i]	$Pd(PPh_3)_4/Et_3N$/DMSO/N_2–O_2/120 °C	12				70
14[i]	$Pd(PPh_3)_4/Et_3N$/DMA/N_2–O_2/120 °C	12	trace		trace	50
15[i]	$Pd(PPh_3)_4/Et_3N$/toluene/N_2–O_2/reflux	2			quant.	
16[i]	$Pd(PPh_3)_4/Et_3N$/1,4-dioxane/N_2–O_2/reflux	12			50	40
17[i]	$Pd(PPh_3)_4$/py/DMF/N_2–O_2/80 °C	12	8	12		10
18[i]	$Pd(PPh_3)_4$/DBU/DMF/N_2–O_2/80 °C	12				quant.
19[i]	$Pd(PPh_3)_4/Na_2CO_3/DMF/N_2$–$O_2$/80 °C	12				
20[i]	$Pd(PPh_3)_4/t\text{-}BuO^-K^+/DMF/N_2$–$O_2$/80 °C	12				
21[i]	$Pd(PPh_3)_4/DMF/N_2$–O_2/80 °C	12		14	13	18

[a]0.04 M solution of **3a**, 0.2 equiv of $Pd(PPh_3)_4$, 5 equiv of base, and a balloon pressure of indicated gas were used if necessary. [b]Isolated yield. [c]Ketone was obtained as a *trans/cis* mixture. [d]Recovered. [e]The O_2-free conditions were achieved by purging the reaction mixture with highly pure N_2 (>99.9999%) prior to heating under N_2. [f]19% of 5,6,7,8-tetrahydro-1,3-dimethylisoquinoline (**8**) was isolated. [g]14% of **8** was isolated. [h]A 2:1 ratio of P/Pd was used. [i]N_2/O_2 10:1 gas system was used.

we were seemingly confronted with a dilemma between requiring oxygen for the elaboration of the products and meanwhile avoiding the O_2-induced palladium oxidation. Nonetheless, a slightly better conversion of **5a** (5%) obtained under air (entry 3) suggested that a decreased concentration of O_2 might be tolerated with Pd(0). In this regard, we evaluated several N_2/O_2 mixed gases with the increased proportions of oxygen (N_2/O_2 = 30:1, 20:1, 10:1 and 7:1, v/v) (entries 4–7). Among which, the best results were gained from the 10:1 N_2/O_2 system in giving **4a** and **5a** in 13% and 14% yields, respectively (entry 6). With increasing the N_2/O_2 ratio to 7:1, the palladium oxidation began to dominate as showcased by the dramatically decreased formation of **4a** and **5a** and the incomplete consumption of **3a** (entry 7). It is noteworthy that the reactions conducted under 10:1 and 7:1 mixed gases also produced considerable amounts of 5,6,7,8-tetrahydro-1,3-dimethylisoquinoline (**8**).[25] Hoping that the palladium oxidation could be circumvented by introducing phosphine ligands to allow the regeneration of Pd(0) from Pd(II), we further conducted several experiments under the conditions of $Pd(PPh_3)_4/Et_3N/DMF$/80 °C/air combined with a few commonly employed ligands [PPh_3,[26] $P(t\text{-}Bu)_3$,[27] Xantphos[26] or tri-2-furylphosphine (TFP)[28]]. However, these reactions all gave the unsatisfying yields of **4a** and **5a** (entries 8–11). We also screened a few solvents [CH_3CN, DMSO, *dimethylacetamide* (DMA), toluene and 1,4-dioxane] and bases (pyridine, DBU, Na_2CO_3, and $t\text{-}BuO^-K^+$) under the 10:1 N_2/O_2 mixed gas (entries 12–20). Among the tested solvents, only DMA delivered a trace amount of **4a** (entry 14), whereas other solvents failed to offer either of the products. Besides, the replacement of Et_3N with the bases merely caused the lower yields of **4a** and **5a** (entry 17) or the recovery or decomposition of **3a** (entries 18–20). Notably, when base was omitted from the conditions, the reaction still provided 14% of **5a** but without giving any trace of **4a** (entry 21), suggesting that *the participation of a base is crucial for the formation of* **4a** *but may*

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Table 2. Evaluation of Catalytic Conditions with $Pd(dba)_2$ and $Pd(PPh_3)_2Cl_2$

			yield (%)[b]			
entry	catalytic conditions[a]	time (h)	**4a**	**5a**	ketone[c]	**3a**[d]
1	$Pd(dba)_2/Et_3N$/DMF-H_2O (9:1)/N_2–O_2 (10:1)/110 °C	6	9	14	36	
2	$Pd(dba)_2/Et_3N$/DMF-H_2O (9:1)/O_2/110 °C	12	7	5	24	29
3	$Pd(dba)_2/Et_3N$/DMF-H_2O (9:1)/N_2–O_2 (1:1)/110 °C	6	**16**	**trace**	**27**	
4	$Pd(PPh_3)_2Cl_2/Et_3N$/DMF/N_2–O_2 (10:1)/80 °C	12			51	12

[a]0.04 M solution of **3a**, 0.2 equiv of catalyst, 5 equiv of Et_3N, and a balloon pressure of indicated gas were employed. [b]Isolated yield. [c]Ketone was obtained as a *trans/cis* mixture. [d]Recovered.

not be for **5a**. To suppress the ketone's formation, we also introduced a molecular sieve (3 Å)[2a] to the reaction conditions in entry 6. But this effort did not lead to the improved yields (**4a**: 5%; **5a**: 7%).

The attempts with $Pd(PPh_3)_4$ did not lead to a significant improvement on the formation of the desired products. Despite this, some experimental results provided us with a mechanistic insight into the cyclization and also established some reaction parameters (e.g., solvent and base) for the following investigations.

The tedious air-sensitivity of $Pd(PPh_3)_4$ drove us to seek more robust Pd(0) catalysts. As a specific example, Larock and co-workers[29] once described a procedure of using $Pd(dba)_2/Et_3N$ in aqueous DMF solvent (9:1 DMF-H_2O) to promote the annulation between 2-iodobenzonitrile and acetylenes for preparing indenones. Drawing on this report and our findings with $Pd(PPh_3)_4$ (Table 1, entry 6), we then attempted the conditions of $Pd(dba)_2/Et_3N$/DMF-H_2O (9:1, v/v)/N_2/O_2 (10:1, v/v) to **3a** (Table 2, entry 1). This procedure led to 9% of **4a** and 14% of **5a**. Furthermore, when the reaction was performed under a pure O_2 atmosphere, the formation of **4a** (7%) and **5a** (5%) was still detectable (entry 2), thus demonstrating the better air-stability of $Pd(dba)_2$ than that of $Pd(PPh_3)_4$. In the range of 10:1 N_2/O_2 to pure O_2, we further screened several N_2/O_2 mixed gases (7:1, 5:1, 3:1, 1:1, v/v). These reactions afforded **4a** and **5a** in up to 16% and 11% yield, respectively, and the best conversion of **4a** was received from the 1:1 N_2/O_2 system (entry 3). Besides, the preferential generation of **4a** over **5a** (<2%) was attended under these conditions. The catalytic system in entry 3 was consequently chosen as an option for the selective formation of the aldehyde (Method A). Apart from $Pd(dba)_2$, we also examined $Pd(PPh_3)_2Cl_2$[24c] as indicated in entry 4, but the reaction did not yield any desired products.

We next probed the possibility of applying palladium(II) acetate to the reaction. Initial efforts were directed to forming catalytically active Pd(0) complexes from Pd(II).[30] To this end, a series of combinations of $Pd(OAc)_2$ with phosphine ligands[26−28,31] or *n*-Bu_4NCl[32] were examined (see the Supporting Information). However, little success was achieved in such a manner. After considerable experimentation, we found that the reaction performed with $Pd(OAc)_2/Et_3N$ under a pure O_2 atmosphere could afford 25% of **5a** and a scarcely detectable amount of **4a** (Table 3, entry 1). In comparison with this, the use of 1:1, 3:1, and 5:1 N_2:O_2 (v/v) mixed gases caused a steady yielding decline (entries 2−4). Because there was no actual Pd(0) catalyst introduced to the reactions, we assumed that triethylamine employed herein might serve as a reducing agent to convert Pd(II) into Pd(0),[29,33] and the mechanism for this reduction has been well-proposed in the literature.[33,34] To clarify the role of Et_3N in our case, we further conducted a few experiments without a base[35] or using pyridine or DBU to replace Et_3N (entries 5−7). The dropped yields of **5a** in these reactions seem to support our hypothesis. In view of the dominating generation of **5a**, the catalytic system in entry 1 was designated as Method B for producing the enone.

Table 3. Evaluation of Catalytic Conditions with $Pd(OAc)_2$

			yield (%)[b]			
entry	catalytic conditions[a]	time (h)	**4a**	**5a**	ketone[c]	**3a**[d]
1	$Pd(OAc)_2/Et_3N$/DMF/O_2/120 °C	**8**		**25**	**17**	trace
2	$Pd(OAc)_2/Et_3N$/DMF/N_2–O_2 (1:1)/120 °C	8		13	24	13
3	$Pd(OAc)_2/Et_3N$/DMF/N_2–O_2 (3:1)/120 °C	8	trace	11	18	16
4	$Pd(OAc)_2/Et_3N$/DMF/N_2–O_2 (5:1)/120 °C	8	trace	7	23	31
5	$Pd(OAc)_2$/DMF/O_2/120 °C	12		5	14	32
6	$Pd(OAc)_2$/pyridine/DMF/O_2/120 °C	12		trace	18	29
7	$Pd(OAc)_2$/DBU/DMF/O_2/120 °C	12	trace	5		77

[a]0.04 M solution of **3a**, 0.2 equiv of $Pd(OAc)_2$, 5 equiv of base, and a balloon pressure of indicated gas were employed. [b]Isolated yield. [c]Ketone was obtained as a *trans/cis* mixture. [d]Recovered.

By using $Pd(dba)_2$ and $Pd(OAc)_2$, two catalytic procedures have been developed for the selective production of the aldehyde (Methods A) or enone (Method B). For the $Pd(dba)_2$-catalyzed system, deliberate control of the amount of reagent O_2 is obviously required in order to maintain the activity of Pd(0). It should be noted that using less than 20 mol % catalysts (e.g., 15 mol %) with these methods unexceptionally led to the poorer or inconsistent generation of **4a** and/or **5a**. On the other hand, increasing the loading to 25 mol % also had no effect on improving the yields.

On the basis of the experimental results, a mechanism is tentatively proposed in Scheme 6. A few cyclization products including **4a**, **5a**, and **8** were observed during the studies. We assume they all originate from the oxidative addition of the N–O bond to Pd(0) species of the catalysts or generated in situ from Pd(II),[33,34] yielding a Pd(II)-imino intermediate **A**. The 6-*exo* cyclization of **A** leads to the formation of **8**, as spotted in some cases (Table 1, entries 6 and 7). According to previous examples,[7,8,36] it is highly possible that **A** can also undergo a 7-*endo* cyclization to afford a 6,7-bicyclic intermediate **B**. The relatively high structural flexibility of **B** should permit a second intramolecular cyclization between the C–Pd(II) complex and the C=N bond[37] to occur rapidly to produce a rigid tricyclic complex **C** in either *endo* or *exo*-orientation. To release the ring strain, the azetidine ring of **C** then immediately opens accompanied by the concomitant formation of the C=C

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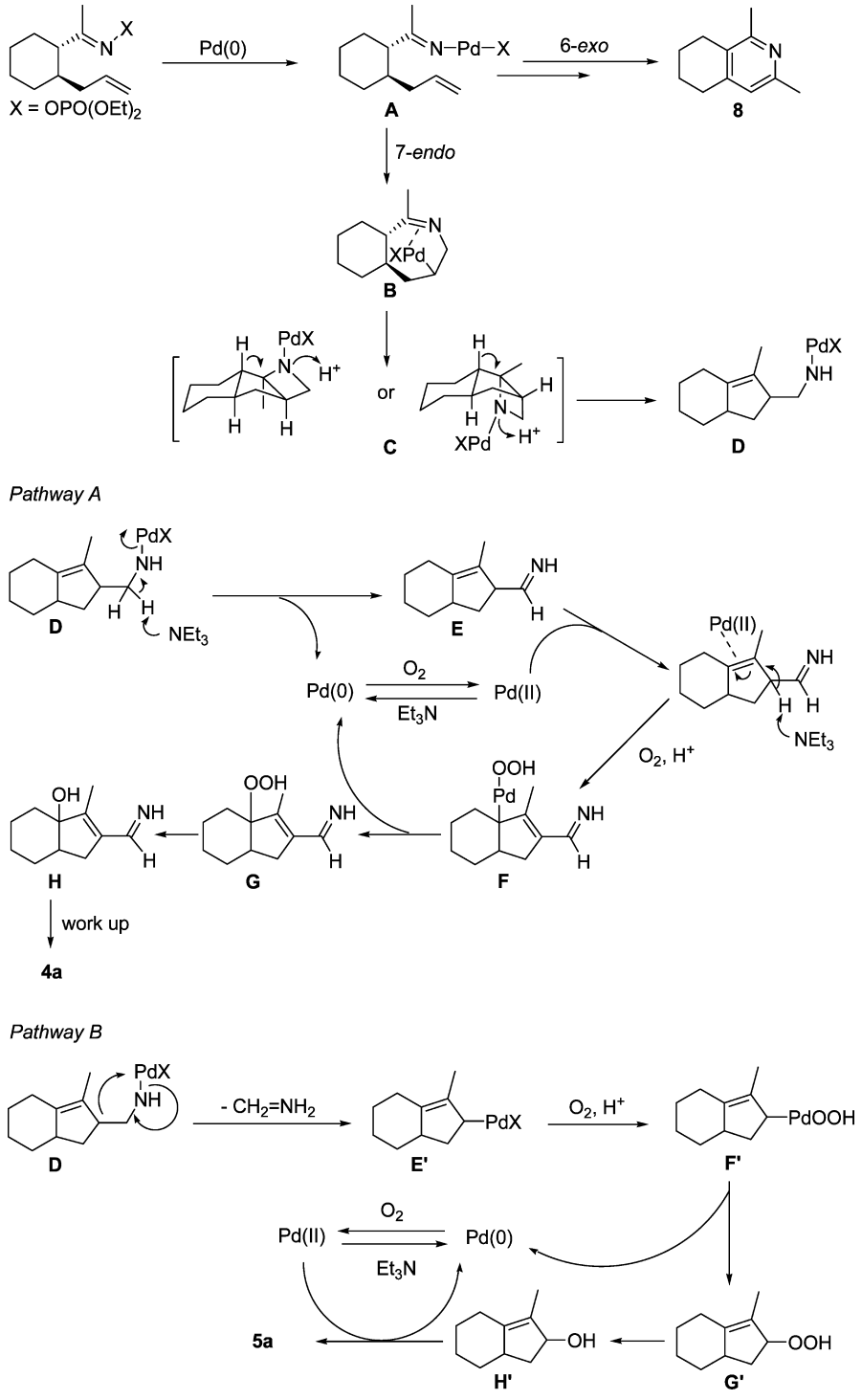
Scheme 6. Proposed Mechanism for the Formation of Cyclization Products



bond to give intermediate **D** with the creation of the bicyclo[4,3,0]nonene core.

There are two putative pathways (Pathways A and B), respectively, leading to **4a** and **5a** from **D**. In Pathway A, **D** first undergoes a base-induced β-elimination to afford an unsaturated imine **E**. Meanwhile, the coexistence of Pd(0)/Pd(II) in the reaction media is possible upon a synergistic action of diluted O_2 atmosphere[24] and Et_3N.[33,34] In accordance with this hypothesis, the complexation of the C=C bond to Pd(II) coupled with the double bond migration and O_2–Pd coordination[18,38] convert **E** into a Pd-hydroperoxide intermediate **F**. Subsequent reductive elimination gives the formation of a hydroperoxide **G**. Reduction of **G**[39] followed by an aqueous workup furnishes **4a** (**G**→**H**→**4a**). This proposed pathway is consistent with the observed base-dependent formation of **4a** (Table 1, entry 21) as well as the isolation of **7**.

Without the participation of a base, the formation of **5a** is supposed to start from the β-carbon elimination[40] of **D** with losing an imine unit, to give a complex **E**′ (Pathway B). After this, the O_2–Pd coordination[38] combined with the elimination and hydroperoxide reduction[39] lead to the generation of an

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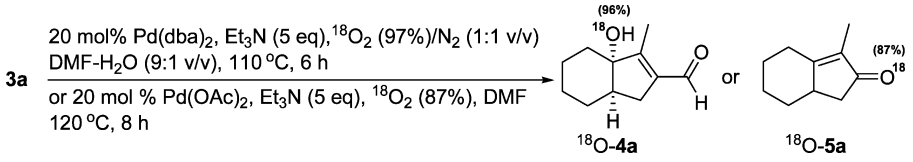
Scheme 7. ^{18}O-Labeling Isotopic Experiment of 3a

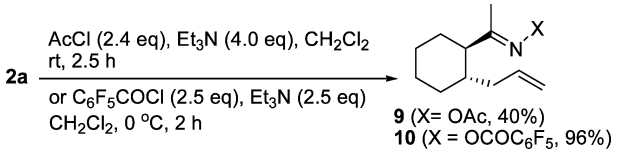


allylic alcohol **H′** (**E′**→**F′**→**G′**→**H′**). Finally, the oxidation of **H′** by Pd(II)[41] completes the formation of **5a**. Although there was no hydroperoxide intermediate detected, the NMR analysis of the crude mixture of a 1 h reaction of Method C indicated the presence of trace allylic alcohol [δ: 4.05 (m), 1.71 (s) ppm] to possibly support the Pathway B. Furthermore, the proposed oxygen source can be validated by the isotopic labeling experiment with $^{18}O_2$ (97% and 87% ^{18}O-enriched) affording the ^{18}O-isotopologues in 96% and 87% isotopic purities (Scheme 7) as determined by mass spectrometry (see the Supporting Information).

To probe the effect of N-substitution on the annulation, we synthesized the acetyl[42] and *O*-pentafluorobenzoyl[2,3] oxime analogues **9** and **10** (Scheme 8), and we applied the developed conditions to them. As illustrated in Table 4, the reactions all led to the lower conversions of **4a** and **5a** than those received from **3a**. Besides, the *6-exo* pathway was shown to prevail for the cyclization of **9** to afford **8** as the major product. These results ruled out the necessity to further explore these types of substrates.

Focusing on phosphinyloximes, we subsequently synthesized precursors **3b**–**d**[43] through the alkylation of **1a** followed by the oximination and phosphonylation (**1a** → **1b**–**d** → **2b**–**d** → **3b**–**d**) (Scheme 9). In the sequence, oximes **2b**–**d** and **3b**–**d** were all formed as the inseparable mixtures of (*E*/*Z*)-isomers.[44] When **3b**–**d** were subjected to the Pd(dba)$_2$-catalyzed conditions (Method A), we were pleased to find that the reactions could afford aldehydes **4b**–**d** in much higher yields than **4a** and no detectable enones (Scheme 10). Besides, these products were uniformly produced as the single diastereomers, and their *cis*-stereochemistry was assigned on the basis of the similar coupling patterns of proton signals to those of **4a**. On the other hand, application of Method B to **3b**–**d** led to the generation of enones **5b**–**d**[45] as the only isolated cyclization products in moderate yields (Scheme 11). Apparently, the oxime precursors bearing the bulkier alkyl substituents are more suited for the cyclization than **3a**, which is probably attributed to the increased steric hindrance between the alkyl appendages and the allyl group to thus bring the N–Pd(II) center and the

Scheme 8. Preparation of Acetyloxime 9 and *O*-Pentafluorobenzoyloxime 10



Scheme 10. Pd(dba)$_2$-Catalyzed Cyclization of 3b–d

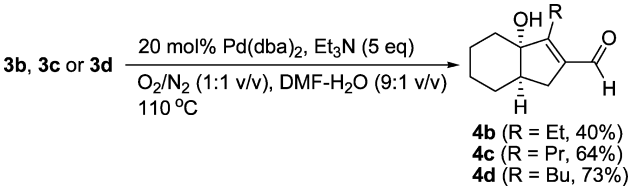
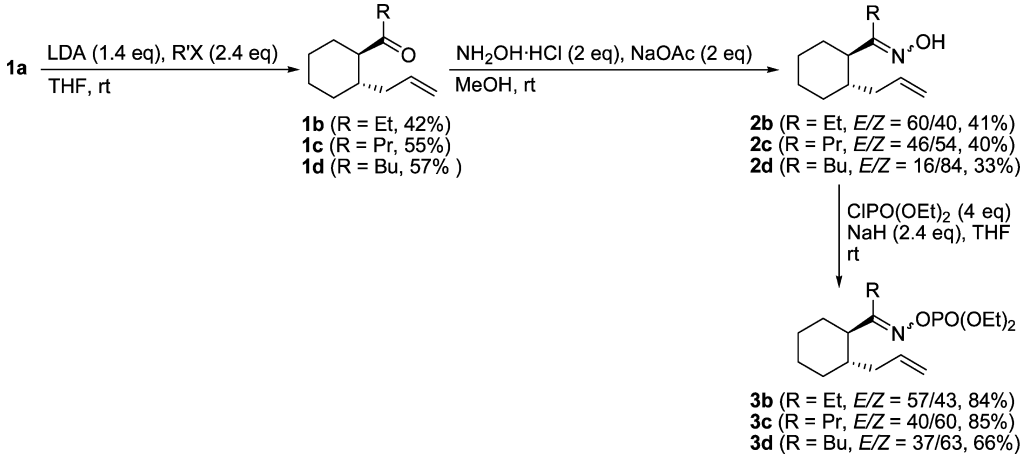


Table 4. Pd-Catalyzed Reactions of 9 and 10

				yield (%)[b]		
entry	substrate	catalytic method[a]	time (h)	**4a**	**5a**	**8**
1[c]	**9**	method A	6	6		27
2	**9**	method B	6		13	40
3[d]	**10**	method A	6	14	trace	trace
4	**10**	method B	8		11	

[a]0.04 M solution of **9** or **10** was used. [b]Isolated. [c]19% of the ketone was obtained. [d]27% of the ketone was isolated.

Scheme 9. Preparation of Phosphinyloximes 3b–d



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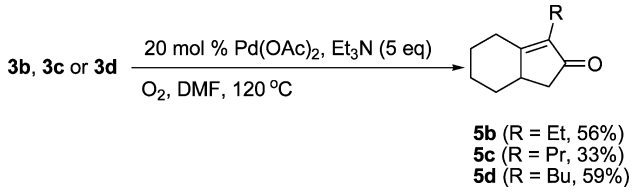
Scheme 11. $Pd(OAc)_2$-Catalyzed Cyclization of 3b−d



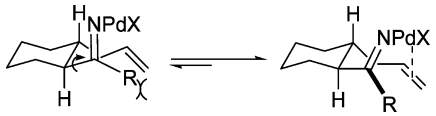


Figure 1. Possible steric influence of bulkier alkyl groups on cyclization.

C=C bond closer with the rotation of the C1-CN single bond (Figure 1).

In summary, our preliminary studies on the Pd(0)-catalyzed cyclization of 2-vinylclohexyl phosphinyloxime system has led to the discovery of a novel cyclization process into the functionalized bicycle[4,3,0]nonenes. Through optimization, two catalytic procedures have been developed for the selective generation of the bicyclic hydroxyaldehydes or enones. A tandem process involving double 7-*endo*/imine cyclization followed by the ring-opening of the resulting tricyclic complex is proposed for the assembly of the core structure. The detailed mechanistic rationalization and the more efficient catalytic system are currently under active investigation, as is the evaluation of the scope of the process because it might pertain to other bicyclic systems and/or interesting target molecules.

EXPERIMENTAL SECTION

General Remarks. All of the reagents and gases were purchased from commercial suppliers and used without further purification. All of the solvents for the reactions were properly dried and freshly distilled before each use. Flash chromatography was performed using silica gel (70−230 mesh) with the indicated solvents. All of the reactions were monitored by thin-layer chromatography on 0.25 mm silica plates (60F-254) and visualized with UV light, ethanolic solution of vanillin (5%), or aqueous $KMnO_4$ solution (10%). The NMR spectra (^1H, ^{19}F, ^{13}C, DEPT, and 2D-NOESY) were recorded on 400 or 600 MHz spectrometers using deuteriochloroform ($CDCl_3$) or deuteriobezene (C_6D_6) as the solvents. The ^1H NMR data are reported as the chemical shift in parts per million, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m. multiplet), coupling constants (J) in Hertz, and number of protons. The resonances of infrared (IR) spectra are reported in wave numbers (cm^{-1}). High-resolution and low-resolution mass spectra (HRMS and LRMS) were performed with electron impact (EI) ionization and a magnetic sector analyzer.

Preparation of *trans*-1-(2-Allyl-cyclohexyl)-ethanone (1a). According to the literature precedure,[10] **1a** was synthesized from 1-acetylcyclohexene (1.4 g, 11.27 mol) in 90% yield (1.69 g) over two steps. ^1H NMR (400 MHz, $CDCl_3$): δ 5.73 (dddd, J = 16.7, 10.0, 7.9, 6.4 Hz, 1H), 4.99 (dm, J = 10.0 Hz, 1H), 4.95 (dm, J = 16.7 Hz, 1H), 2.21 (ddd, J = 11.3, 11.2, 3.4 Hz, 1H), 2.13 (s, 3H), 2.08−2.01 (m, 1H), 1.89−1.66 (m, 6H), 1.32−1.15 (m, 3H), 1.01−0.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.9, 136.4, 116.3, 56.8, 39.2, 38.0, 30.8, 29.8, 29.3, 25.7, 25.6.

Typical Procedure for Oximination; *trans*-(*E*)-1-(2-Allyl-cyclohexyl)-ethanone Oxime (2a). To a solution of **1a** (4.39 g, 26.4 mmol) in methanol (90 mL) at 20 °C, NaOAc (4.33 g, 52.8 mmol) and $NH_2OH{\cdot}HCl$ (3.67 g, 52.8 mmol) were successively added. The resulting suspension was stirred at rt for 3 h, then diluted by CH_2Cl_2 (200 mL), washed with H_2O (50 mL × 3), and brine (50 mL) and concentrated in vacuo. The crude mixture was subjected to chromatographic purification (hexane/EtOAc 40:1, 30:1, 20:1, 15:1) to afford **2a** as a white solid (2.25 g, 47%). mp: 79−81 °C; IR (neat): 3333, 3075, 1639, 992, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (br s, 1H), 5.74 (dddd, J = 16.2, 9.6, 8.1, 6.6 Hz, 1H), 4.97 (dm, J = 9.6 Hz, 1H), 4.96 (dm, J = 16.2 Hz, 1H), 2.12−2.04 (m, 1H), 2.00 (ddd, J = 11.3, 11.3, 3.4 Hz, 1H), 1.90−1.64 (m, 5H), 1.81 (s, 3H), 1.54−1.41 (m, 1H), 1.41−1.29 (m, 1H), 1.29−1.16 (m, 2H), 1.01−0.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.6, 136.6, 116.1, 49.4, 38.8, 38.7, 31.4, 30.8, 26.1, 25.8, 10.4; HRMS-EI: m/z $[M]^+$ calcd for $C_{11}H_{19}NO$, 181.1467; found, 181.1455.

Preparation of *trans*-(*E*)-Diethyl-1-(2-allylcyclohexyl)-ethylideneaminooxyphosphonate (3a). Et_3N (2.27 mL, 16.27 mmol) was added to a solution of **2a** (1.18 g, 6.51 mmol) in dry CH_2Cl_2 (70 mL) under N_2. The solution was stirred at 0 °C for 30 min prior to addition of $(EtO)_2POCl$ (2.36 mL, 16.27 mmol). The reaction mixture continued to stir at rt for 6 h, then diluted by CH_2Cl_2 (150 mL), washed with H_2O (50 mL × 2) and brine (50 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The crude mixture was purified by flash chromatography (hexane/EtOAc 5:1, 2:1, 1:1, 1:2) to give **3a** as a pale yellow oil (1.59 g, 77%). IR (neat): 3076, 2982, 1640, 1275, 1166, 1038, 838, 813 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78−5.66 (m, 1H), 4.97 (dm, J = 10.8 Hz, 1H), 4.96 (dm, J = 16.4 Hz, 1H), 4.27−4.11 (m, 4H), 2.20 (ddd, J = 11.4, 11.4, 3.3 Hz, 1H), 2.07−1.96 (m, 1H), 1.90 (s, 3H), 1.89−1.60 (m, 6H), 1.54−1.44 (m, 1H), 1.34 (td, J = 7.1, 3.5 Hz, 6H), 1.31−1.16 (m, 2H), 1.03−0.91 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (d, J_{C-P} = 12.2 Hz), 136.1, 116.5, 64.3 (d, J_{C-P} = 5.5 Hz), 64.2 (d, J_{C-P} = 5.7 Hz), 48.7, 38.7, 38.6, 31.3, 30.6, 25.9, 25.6, 16.2 (d, J_{C-P} = 6.6 Hz), 11.9; HRMS-EI: m/z $[M]^+$ calcd for $C_{15}H_{28}NO_4P$, 317.1756; found, 317.1760; Anal. Calcd for $C_{15}H_{28}NO_4P$: C, 56.77; H, 8.89. Found: C, 56.72; H, 8.83.

Formation of 4a and 5a under $Pd(PPh_3)_4$-Catalyzed Conditions (Table 1, entry 6). Under N_2 protection, $Pd(PPh_3)_4$ (106.8 mg, 99%, 0.092 mmol) was added to a DMF (11.4 mL) solution of **3a** (145.2 mg, 0.458 mmol, 0.04 M) in a 25 mL round-bottom flask. The solution was stirred at rt for 5 min prior to addition of Et_3N (0.32 mL, 2.29 mmol). The resulting yellow suspension was degassed with N_2 for 3 min. The flask was then attached to a condenser equipped with a joint fitted with a balloon of N_2/O_2 (10:1, v/v, 1 L) and placed into an oil bath at 80 °C. The reaction mixture was stirred vigorously at 80 °C for 5 h, cooled to rt, quenched with H_2O (11 mL) and extracted with EtOAc (30 mL × 3). The organic layers were combined and washed with H_2O (10 mL × 2) and brine (10 mL). After concentration, the crude products were subjected to chromatographic purification (hexane/EtOAc 20:1, 5:1, 2:1, 3:1 1:1) to give 1-(2-allyl-cyclohexyl)-ethanone[10] (*trans*/*cis* = 57/43, 21.3 mg, 28%), **4a** (10.7 mg, 13%), **5a** (9.9 mg, 14%) and **8** (14 mg, 19%).

cis-1-Hydroxyl-8-formyl-9-methyl-bicyclo[4,3,0]non-8(9)-ene (4a). IR (neat): 3418, 2854, 2742, 1668, 1632, 1203, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 10.02 (s, 1H), 2.55 (dd, J = 15.0, 7.7 Hz, 1H), 2.19−2.11 (m, 1H), 2.10 (s, 3H), 2.09−1.98 (m, 1H), 1.82−1.69 (m, 2H), 1.68−1.44 (m, 4H), 1.44−1.32 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.5 (CH), 165.5 (C), 136.1 (C), 83.8 (C), 44.9 (CH), 32.7 (CH_2), 30.8 (CH_2), 25.5 (CH_2), 21.8 (CH_2), 20.7 (CH_2), 9.5 (CH_3); HRMS-EI: m/z $[M]^+$ calcd for $C_{11}H_{16}O_2$, 180.1150; found, 180.1156; Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.27; H, 8.97.

9-Methyl-bicycle[4,3,0]non-1(9)-en-8-one[12] (5a). ^1H NMR (400 MHz, $CDCl_3$): δ 2.84 (dd, J = 13.8, 1.8 Hz, 1H), 2.60−2.49 (m, 1H), 2.54 (br d, J = 13.8 Hz, 1H), 2.19−2.05 (m, 2H), 2.05−1.96 (m, 1H), 1.93 (d, J = 16.4 Hz, 1H), 1.83 (dm, J = 13.5 Hz, 1H), 1.68 (s, 3H), 1.50 (qt, J = 13.2, 3.4 Hz, 1H), 1.32 (qt, J = 13.1, 3.7 Hz, 1H), 1.04 (ddd, J = 14.1, 11.0, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 209.3, 176.0, 132.8, 41.3, 40.3, 35.0, 28.6, 26.6, 25.6, 7.6; HRMS-EI: m/z $[M]^+$ cacld. for $C_{10}H_{14}O$, 150.1045; found, 150.1049.

5,6,7,8-Tetrahydro-1,3-dimethylisoquinoline[25] (8). ^1H NMR (400 MHz, $CDCl_3$): δ 6.70 (s, 1H), 2.68 (br t, J = 6.32 Hz, 2H), 2.58 (br t, J = 6.16 Hz, 2H), 2.43 (s, 3H), 2.40 (s, 3H), 1.87−1.79 (m, 2H), 1.79−1.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.2, 153.4, 146.2, 127.7, 121.3, 29.4, 25.7, 23.8, 23.2, 22.2, 22.0.

dx.doi.org/10.1021/jo5005422 | J. Org. Chem. 2014, 79, 3623−3633

Synthesis of Octahydro-2-(hydroxymethyl)-3-methyl-1*H*-inden-3a-ol (6). Palladium on activated carbon (10 mg, 5%) was added to a solution of **4a** (51 mg, 0.28 mmol) in EtOAc (10 mL). The suspension was stirred under H_2 (balloon) for 1 h and filtrated through a Celite pad. The filtrate was concentrated, and the crude saturated hydroxyl aldehyde was dissolved in 3 mL of CH_3OH. After stirring at 0 °C for 10 min, $NaBH_4$ (53.5 mg, 1.41 mmol) was added to the solution. The reaction mixture was stirred at 0 °C for an additional 90 min, poured into EtOAc (40 mL), washed with H_2O (10 mL) and brine (10 mL), and concentrated in vacuo. The crude residue was subjected to chromatographic purification (hexane/EtOAc 3:1, 1:1) to give **6** as a mixture of two isomers (83:17) in 37% yield over two steps (19.3 mg). IR (neat): 3367, 2927, 1133, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) major isomer: δ 3.72 (dd, J = 10.4, 6.3, 1H), 3.47 (dd, J = 10.4, 8.0 Hz, 1H), 2.36−2.24 (m, 1H), 2.12−2.00 (m, 1H), 1.95−1.85 (m, 1H), 1.85−1.75 (m, 1H), 1.75−1.66 (m, 1H), 1.62−1.21 (m, 10H), 0.92 (d, J = 7.52 Hz, 3H); minor isomer: δ 3.65 (dd, J = 10.2, 4.76, 1H), 3.52 (dd, J = 10.2, 6.68 Hz, 1H); 2.45−2.35 (m, 1H), 2.12−2.00 (m, 1H), 1.95−1.85 (m, 1H), 1.85−1.75 (m, 1H), 1.75−1.66 (m, 1H), 1.62−1.21 (m, 10H), 0.92 (d, J = 7.52 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer: δ 78.6, 65.6, 46.4, 44.3, 33.7, 30.5, 29.2, 23.8, 21.5, 20.3, 8.5; minor isomer: δ 78.6, 65.6, 43.8, 43.7, 33.7, 28.5, 28.0, 23.8, 21.1, 20.3, 8.5; HRMS-EI: m/z $[M]^+$ calcd for $C_{11}H_{20}O_2$, 184.1463; found, 184.1466. The major isomer was crystallized from CH_2Cl_2-EtOAc (3/1, v/v) and used for the X-ray analysis.

Preparation of *cis*-1-Hydroperoxy-8-formyl-9-methylbicyclo[4,3,0]non-8(9)-ene (7); Conversion of 7 into 4a. $Pd(PPh_3)_4$ (211.5 mg, 99%, 0.18 mmol) was added to a solution of **3a** (287.5 mg, 0.906 mmol) in dry DMF (22.6 mL) under N_2. The mixture was stirred at rt for 5 min followed by the addition of Et_3N (0.64 mL, 4.53 mmol). The reaction mixture was continued to stir at 80 °C for 30 min under N_2, then quenched with H_2O (20 mL) and extracted with EtOAc (40 mL × 3). The organic layers were combined, washed with H_2O (30 mL × 2) and brine (30 mL), and concentrated in vacuo. The light-proof chromatographic purification of the crude mixture (hexane/EtOAc 20:1, 5:1, 3:1, 2:1, 1:1) afforded **7** in 6% yield as a colorless oil (10.7 mg) together with the ketone[10] (51.2 mg, 34%), **4a** (11.4 mg, 7%) and **5a** (8.2 mg, 6%). **7**: IR (neat): 3388, 2938, 2863, 2821, 1671, 1606, 1162, 1051 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 9.88 (s, 1H), 2.63 (ddd, J = 14.9, 7.4, 1.4 Hz, 1H), 2.42−2.33 (m, 1H), 2.04 (ddm, J = 14.9, 8.4 Hz, 1H), 1.69 (s, 3H), 1.58 (dm, J = 14.2 Hz, 1H), 1.52−1.41 (m, 1H), 1.30−1.16 (m, 3H), 1.13−1.03 (m, 2H), 0.96 (ddd, J = 14.2, 11.1, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6): δ 187.9, 161.3, 137.5, 94.6, 36.9, 31.2, 29.3, 25.2, 21.3, 20.6, 9.5; HRMS-EI: m/z $[M]^+$ calcd for $C_{11}H_{16}O_3$, 196.1099; found, 196.1106.

To a solution of **7** (12 mg, 0.061 mmol) in CH_2Cl_2 (3 mL), PPh_3 (80.2 mg, 0.31 mmol) was added in one portion. The reaction mixture was stirred at rt for 5 h and concentrated in vacuo. The crude products were purified by flash chromatography (hexane/EtOAc 60:1, 2:1) to afford **4a** in 90% yield (9.9 mg).

Typical Procedure for the Pd(dba)$_2$-Catalyzed Cyclization (Method A). To a 25 mL round-bottom flask containing a solution of **3a** (127.4 mg, 0.401 mmol, 0.04 M) in a 9:1 (v/v) DMF-H_2O mixed solvent (10 mL), palladium bis(dibenzylideneacetone) (46.2 mg, 0.08 mmol) and Et_3N (0.28 mL, 2.0 mmol) were successively added. The resulting dark brown suspension was degassed with N_2 for 3 min. The flask was then attached to a condenser equipped with a joint fitted with a balloon of N_2/O_2 (1:1, v/v, 1.2 L), and placed into an oil bath at 110 °C. The reaction mixture was stirred vigorously for 6 h, cooled to rt, diluted by H_2O (8 mL) and extracted with EtOAc (30 mL × 3). The organic layers were combined and washed with H_2O (10 mL × 2) and brine (10 mL). After concentration, the crude mixture was purified by flash chromatography (hexane/EtOAc 20:1, 5:1, 2:1) to afford the ketone[10] (17.9 mg, 27%), **4a** (11.6 mg, 16%) ,and a trace amount of **5a** (∼1 mg).

Typical Procedure for the Pd(OAc)$_2$-Catalyzed Cyclization (Method B). Palladium acetate (21.8 mg, 0.097 mmol) and Et_3N (0.39 mL, 2.42 mmol) were successively added to a DMF (11.9 mL) solution of **3a** (154 mg, 0.485 mmol, 0.04 M) in a 25 mL round-bottom flask. The mixture was degassed with N_2 for 3 min. The flask was then attached to a condenser equipped with a joint fitted with a balloon of oxygen (1 L), and placed into an oil bath at 120 °C. After stirring for 8 h, the reaction mixture was cooled to rt, diluted by H_2O (11 mL), and extracted with EtOAc (30 mL × 3). The organic layers were combined and washed with H_2O (30 mL × 2) and brine (30 mL). After concentration, the crude mixture was purified by flash chromatography (hexane/EtOAc 20:1, 5:1, 2:1) to afford 13.7 mg the ketone[10] (17%), 18.5 mg of **5a** (25%), and a trace amount of recovered **3a** (∼1 mg) .

Synthesis of *trans*-(*E*)-Diethyl-1-(2-allylcyclohexyl)-ethylideneaminooxyacetate (9). Et_3N (0.92 mL, 6.6 mmol) was added to a solution of **2a** (299 mg, 1.65 mmol) in dry CH_2Cl_2 (10 mL) under N_2 protection. After stirring in an ice-bath for 15 min, a solution of acetyl chloride (0.29 mL, 98%, 3.96 mmol) in dry CH_2Cl_2 (2 mL) was dropwise added via a syringe in 2 min. The resulting yellow suspension was continued to stir at rt for 2.5 h, then diluted by CH_2Cl_2 (70 mL), and successively washed with saturated $NaHCO_3$ aqueous solution (15 mL), water (15 mL × 2), and brine (15 mL). After concentration, the crude mixture was purified by flash chromatography (hexane/EtOAc 30:1, 10:1, 5:1, 3:1, 1:1) to give **3b** as a colorless oil (147 mg, 40%). IR (neat) 3075, 2928, 1766, 1639, 1202 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.78−5.67 (m, 1H), 4.97 (dm, J = 10.7 Hz, 1H), 4.96 (dm, J = 15.4 Hz, 1H), 2.28 (ddd, J = 11.3, 11.3, 3.0 Hz, 1H), 2.16 (s, 3H), 2.05−1.99 (m, 1 H), 1.90 (s, 3H), 1.88−1.68 (m, 5H), 1.54−1.43 (m, 1H), 1.41−1.31 (m, 1H), 1.29−1.18 (m, 2H), (qd, J = 12.7, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 168.8, 136.3, 116.5, 49.1, 38.9, 38.6, 31.3, 30.6, 25.9, 25.6, 19.8, 12.1; HRMS-EI: m/z $[M]^+$ calcd for $C_{13}H_{21}NO_2$, 223.1572; found, 223.1564.

Synthesis of *trans*-(*E*)-Diethyl-1-(2-allylcyclohexyl)-ethylideneaminooxypentafluorobenzonate (10). Et_3N (0.14 mL, 0.99 mmol) was added to a solution of **2a** (71.5 mg, 0.39 mmol) in dry CH_2Cl_2 (5 mL) under N_2 protection. After stirring at 0 °C for 20 min, a solution of pentafluorobenzoyl chloride (0.14 mL, 99%, 0.99 mmol) in dry CH_2Cl_2 (1 mL) was added. The reaction mixture was continued to stir at 0 °C for 2 h, then diluted by CH_2Cl_2 (50 mL) and successively washed with saturated $NaHCO_3$ aqueous solution (10 mL), water (10 mL × 2) and brine (10 mL). After concentration, the crude mixture was subjected to chromatographic purification (hexane/EtOAc 50:1, 40:1, 20:1, 8:1) to afford **3c** as a pale yellow oil (142 mg, 96%). IR (neat): 3100, 2931, 1762, 1651, 1523, 1195, 857 cm^{-1}; ^{19}F NMR (400 MHz, $CDCl_3$): δ −137.2, −148.1, −160.1; ^1H NMR (400 MHz, $CDCl_3$): δ 5.79−5.68 (m, 1H), 5.00 (dm, J = 11.4 Hz, 1H), 4.99 (dm, J = 15.7 Hz, 1H), 2,34 (ddd, J = 11.3, 11.3, 3.2 Hz, 1H), 2.09−2.03 (m, 1H), 1.97 (s, 3H), 1.92−1.74 (m, 5H), 1.57−1.49 (m, 1H), 1.45−1.33 (m, 1H), 1.32−1.21 (m, 2H), 1.01 (qd, J = 12.4, 1.2 Hz, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 171.7, 156.6, 145.4 (d, J_{C-F} = 260.5 Hz), 145.3 (d, J_{C-F} = 260.5 Hz), 142.9 (d, J_{C-F} = 260.5 Hz), 137.9, 136.0, 116.7, 49.1, 38.9, 38.6, 31.4, 30.6, 25.9, 25.5, 12.7; HRMS-EI: m/z $[M]^+$ calcd. for $C_{18}H_{18}F_5NO_2$, 375.1258; found, 375.1260.

Typical Procedure for Alkylation of 1a; *trans*-1-(2-allylcyclohexyl)propan-1-one (1b). Under a N_2 atmosphere, a solution of *n*-BuLi (1.75 mL, 1.6 M in hexane, 2.80 mmol) was slowly added to a stirred solution of diisopropylamine (0.393 mL, 2.8 mmol) in dry THF (7.9 mL) precooled to 0 °C via a syringe in 5 min. The mixture was then cooled at −78 °C and stirred for 30 min. After this, a solution of **1a** (332.8 mg, 2.0 mmol) in dry THF (4.4 mL) was added dropwise via a syringe in 10 min, and stirring was continued for an additional 30 min at −78 °C before the quick addition of iodomethane (0.3 mL, 99%, 4.72 mmol). The mixture was allowed to stir at room temperature for 21 h, then diluted with saturated aqueous NH_4Cl solution (10 mL) and extracted with diethyl ether (100 mL). The organic layer was separated and washed with water (20 mL × 2) and brine (20 mL). The combined aqueous layers were re-extracted with another portion of diethyl ether (100 mL) and the organic layer was washed with water and brine. The combined organic layers were concentrated under reduced pressure, and the crude reside was purified by flash chromatography (hexane/EtOAc 150:1, 120:1, 100:1,

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80:1) to give **1b** in 42% yield (151.6 mg) as a colorless oil. IR (neat): 3075, 1710, 1640, 996, 948 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.76−5.65 (m, 1H), 4.95 (dm, J = 9.4 Hz, 1H), 4.94 (dm, J = 17.8 Hz, 1H), 2.52 (dq, J = 17.9, 7.3 Hz, 1H), 2.36 (dq, J = 17.9, 7.3 Hz, 1H), 2.22 (td, J = 10.7, 2.4 Hz, 1 H), 2.03−1.99 (m, 1H), 1.93−1.65 (m, 7H), 1.32−1.15 (m, 3 H), 1.02 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.3, 136.6, 116.1, 55.9, 39.4, 38.1, 35.7, 30.9, 30.2, 25.9, 25.7, 7.6; HRMS-EI: m/z $[M]^+$ calcd for $C_{12}H_{20}O$, 180.1514; found, 180.1521.

***trans*-1-(2-Allylcyclohexyl)butan-1-one (1c).** The title compound was similarly prepared as **1b** from **1a** (791.9 mg, 4.76 mmol) by using iodoethane as the alkylating reagent. The reaction proceeded for 16 h at rt. After chromatographic purification (hexane/EtOAc 250:1, 200:1, 100:1), 509 mg of **1c** was obtained (55%) as a yellow oil. IR (neat): 3075, 1708, 1665, 910, 995 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.76−5.67 (m, 1H), 4.96 (dm, J = 8.6 Hz, 1H), 4.95 (dm, J = 17.3 Hz, 1H), 2.46 (dt, J = 17.2, 7.4 Hz, 1H), 2.34 (dt, J = 17.2, 7.2 Hz, 1H), 2.20 (tm, J = 10.1 Hz, 1H), 2.05−2.00 (m, 1H), 1.84−1.67 (m, 6 H), 1.60 (sextet, J = 7.4 Hz, 2H), 1.31−1.13 (m, 3H), 1.02−0.94 (m, 1 H), 0.90 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.8, 136.6, 116.2, 56.1, 44.5, 39.3, 37.9, 30.9, 30.0, 25.9, 25.7, 16.8, 13.8; HRMS-EI: m/z $[M]^+$ calcd for $C_{13}H_{22}O$, 194.1671; found, 194.1668.

***trans*-1-(2-Allylcyclohexyl)pentan-1-one (1d).** The title compound was similarly prepared as **1b** from **1a** (716.6 mg, 4.31 mmol) by using iodopropane as the alkylating reagent. The reaction proceeded for 21 h at rt. After chromatographic purification (hexane/EtOAc 100:1), 514 mg of **1d** was obtained (57%) as a yellow oil. IR (neat): 3074, 1707, 1642, 995, 968, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.80−5.65 (m, 1H), 4.96 (br d, J = 9.2 Hz, 1H), 4.95 (br d, J = 17.9 Hz, 1H), 2.48 (dt, J = 17.1, 7.5 Hz, 1H), 2.36 (dt, J = 17.1, 7.3 Hz, 1H), 2.21 (tm, J = 10.9 Hz, 1H), 2.05−2.01 (m, 1H), 1.83−1.70 (m, 5H), 1.57−1.49 (m, 2H), 1.35−1.20 (m, 6 H), 0.99−0.94 (m, 1H), 0.90 (t, J = 7.32 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 214.9, 136.6, 116.2, 56.1, 42.3, 39.3, 37.9, 30.9, 30.1, 25.9, 25.7, 25.5, 22.4, 13.9; HRMS-EI: m/z $[M]^+$ calcd for $C_{14}H_{24}O$, 208.1827; found, 208.1832.

***trans*-1-(2-Allylcyclohexyl)propan-1-one Oxime (2b).** From **1b** (240.2 mg, 1.33 mmol), the title compound was similarly prepared as **2a**. The reaction proceeded for 20 h at rt. After chromatographic purification (hexane/EtOAc 40:1, 20:1, 10:1), 106.7 mg of **2b** was obtained (41%) as an isomeric mixture (E/Z = 60:40). IR (neat): 3247, 3079, 1640, 996, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *E*-form: 9.33 (br s, 1H), 5.81−5.68 (m, 1H), 4.97−4.94 (m, 2H), 2.41 (dq, J = 16.0, 8.0 Hz, 1H) 2.29−2.12 (m, 2H) 2.09−1.92 (m, 1H); 1.91−1.83 (m, 1H), 1.82−1.61 (m, 4H), 1.61−1.18 (m, 4H), 1.11 (t, J = 7.4 Hz, 3H), 1.01−0.80 (m, 1H); *Z*-form: 9.60 (br s, 1H), 5.72−5.64 (m, 1H), 5.00−4.92 (m, 2H), 2.40−2.32 (m, 1H), 2.29−2.12 (m, 2H), 2.09−1.92 (m, 1H), 1.91−1.83 (m, 1H), 1.82−1.61 (m, 4H), 1.61−1.18 (m, 4H), 1.13 (t, J = 7.6 Hz, 3H), 1.01−0.80 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *E*-form: 163.8, 137.0, 115.8, 49.2, 39.1, 38.9, 31.6, 31.4, 26.2, 26.0, 20.0, 10.5; *Z*-form: 165.0, 136.8, 116.0, 49.2, 38.9, 38.5, 31.6, 31.4, 26.1, 26.0, 20.0, 10.5; HRMS-EI: m/z $[M]^+$ calcd for $C_{12}H_{21}NO$, 195.1623; found, 195.1616.

***trans*-1-(2-Allylcyclohexyl)butan-1-one Oxime (2c).** From **1c** (266.3 mg, 1.37 mmol), the title compound was similarly prepared as **2a**. The reaction proceeded for 24 h at rt. After chromatographic purification (hexane/EtOAc 30:1, 20:1, 10:1, 5:1), 117 mg of **2c** was obtained (40%) as an isomeric mixture (E/Z = 46/54). IR (neat): 3579, 3100, 1640, 993, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *E*-form: 8.36 (br s, 1H), 5.81−5.68 (m, 1H), 4.97 (dm, J = 10.8 Hz, 2H), 2.36−2.32 (m, 1H), 2.22−2.01 (m, 2H), 1.98−1.83 (m, 2H), 1.83−1.68 (m, 4H), 1.68−1.45 (m, 4H), 1.37−1.11 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H), 0.95−0.85 (m, 1H); *Z*-form: 8.14 (br s, 1H), 5.81−5.68 (m, 1H), 4.97 (dm, J = 10.8 Hz, 2H), 2.35 (dt, J = 18.0, 6.8 Hz, 1H), 2.22−2.01 (m, 2H), 1.98−1.83 (m, 2H), 1.83−1.68 (m, 4H), 1.68−1.45 (m, 4H), 1.37−1.11 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H), 0.95−0.85 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *E*-form: 163.0, 137.0, 115.9, 49.2, 39.1, 38.4, 31.6, 29.2, 26.1, 25.9, 19.5,14.2; *Z*-form: 164.3, 136.9, 115.9, 49.2, 39.1, 38.9, 31.5, 29.2, 26.1, 26.0, 19.5, 14.9; HRMS-EI: m/z $[M]^+$ calcd for $C_{13}H_{23}NO$, 209.178; found, 209.1778.

***trans*-1-(2-Allylcyclohexyl)pentan-1-one Oxime (2d).** From **1d** (556.4 mg, 2.67 mmol), the title compound was similarly prepared as **2a**. The reaction proceeded for 22 h at rt. After chromatographic purification (hexane/EtOAc 30:1, 20:1, 10:1, 5:1), 198 mg of **2d** was obtained (33%) as an isomeric mixture (E/Z = 16/84). IR (neat): 3266, 1642, 1448, 1101, 993, 951, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *E*-form: 9.39 (br s, 1H), 5.83−5.61 (m, 1H), 4.99 (dm, J = 10.9 Hz, 2H), 2.38 (dt, J = 17.8, 5.2 Hz, 1H), 2.36−2.31 (m, 1H), 2.24−2.02 (m, 1H), 2.00−1.82 (m, 2H), 1.80−1.61 (m, 4H), 1.60−1.44 (m, 3H), 1.43−1.31 (m, 3H), 1.30−1.15 (2H), 1.01−0.85 (m, 1H), 0.92 (t, J = 8.0 Hz, 3H); *Z*-form: 8.96 (br s,, 1H), 5.83−5.61 (m, 1H), 4.96 (dm, J = 11.8 Hz, 2H), 2.15 (dt, J = 21.9, 8.6 Hz, 1H), 2.23−2.02 (m, 2H), 1.99−1.83 (m, 2H), 1.80−1.69 (m, 4H), 1.60−1.45 (m, 3H), 1.44−1.30 (m, 3H), 1.29−1.15 (m, 2H), 1.01−0.83 (m, 1H), 0.93 (t, J = 7.04 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *E*-form:163.1, 137.0, 115.8, 49.2, 39.1, 38.4, 31.6, 31.6, 29.2, 26.9, 26.2, 25.8, 22.7, 13.9; *Z*-form: 164.2, 136.9 115.9, 49.2, 39.1, 38.9, 31.6, 31.6, 28.3, 28.1, 26.1, 26.0, 23.5, 13.8; HRMS-EI: m/z $[M]^+$ calcd for $C_{14}H_{25}NO$, 223.1936; found, 223.1936.

General Procedure for Preparing 3b−d; *trans*-Diethyl-1-(2-allylcyclohexyl)propylideneaminooxyphosphonate (3b). Under N_2 protection, sodium hydride (50.6 mg, 60%, 1.26 mmol) and diethyl chlorophosphate (0.31 mL, 2.11 mmol) were successively added to a solution of **2b** (102.9 mg, 0.527 mmol) in THF (6.4 mL) precooled at 0 °C. The mixture was stirred at rt for 20 h, then diluted by EtOAc (150 mL), and washed with saturated NH_4Cl aqueous solution (20 mL), water (20 mL × 2) and brine (20 mL). After concentration, the crude mixture was purified by chromatography (hexane/EtOAc 8:1, 5:1, 2:1, 1:1) to afford **3b** (146 mg, 84%, E/Z = 57/43) as a colorless oil. IR (neat): 3076, 1640, 1548, 1274, 1034, 974, 910 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *E*-form: 5.79−5.66 (m, 1H), 4.98 (dm, J = 10.0 Hz, 1H), 4.97 (dm, J = 17.2 Hz, 1H); 4.29−4.11 (m, 4H); 2.48 (dq, J = 13.9, 7.7 Hz, 1H) 2.34−2.25 (m, 2H), 2.25−1.97 (m, 3H), 1.94−1.82 (m, 1H), 1.82−1.48 (m, 5H), 1.35 (t, J = 7.04 Hz, 6H), 1.29−1.18 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H), 1.04−0.88 (m, 1H); *Z*-form: 5.79−5.66 (m, 1H); 4.98 (dm, J = 10.0 Hz, 1H); 4.97 (dm, J = 17.2 Hz, 1H); 4.29−4.11 (m, 4H), 2.37−2.30 (m, 1H); 2.34−2.25 (m, 2H), 2.25−1.97 (m, 3H), 1.94−1.82 (m, 1H), 1.82−1.48 (m, 5H), 1.35 (t, J = 7.04 Hz, 6H), 1.29−1.18 (m, 1H), 1.14 (t, J = 7.2 Hz, 3H), 1.04−0.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *E*-form: 172.5 (d, J_{C-P} = 12.1 Hz), 136.3, 116.3, 64.3 (d, J_{C-P} = 3.9 Hz), 64.2 (d, J_{C-P} = 6.2 Hz), 48.8, 39.1, 38.4, 31.4, 31.3, 29.4, 25.9, 25.8, 21.0, 16.2 (d, J_{C-P} = 6.3 Hz), 10.6; Z-form: 173.7 (d, J_{C-P} = 11.9 Hz), 136.2, 116.2, 64.4 (d, J_{C-P} = 4.7 Hz), 64.3 (d, J_{C-P} = 3.9 Hz), 48.8, 38.8, 38.6, 31.0, 30.9, 29.4, 25.8, 25.7, 21.0, 16.2 (d, J_{C-P} = 6.3 Hz), 10.9; HRMS-EI: m/z $[M]^+$ calcd for $C_{16}H_{30}NO_4P$, 331.1912; found, 331.1904.

***trans*-Diethyl-1-(2-allylcyclohexyl)-butylideneaminooxyphosphonate (3c).** From **2c** (37.9 mg, 0.18 mmol), the title compound was similarly synthesized as **3b**. The reaction proceeded for 18 h at rt. After chromatographic purification (hexane/EtOAc 10:1, 5:1, 1:1), **3c** (53.2 mg, 85%, E/Z = 40/60) was obtained as a pale yellow oil. IR (neat): 3075, 1662, 1640, 1274, 1035, 979, 927 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *E*-form: 5.79−5.66 (m, 1H), 4.97 (dm, J = 9.6 Hz, 1H), 4.96 (dm, J = 17.6 1H), 4.28−4.11 (m, 4H), 2.42 (dt, J = 17.9, 5.4 Hz, 1H), 2.16−2.08 (m, 2H), 2.08−2.08−1.83 (m, 3H), 1.83−1.51 (m, 7H), 1.35 (t, J = 7.04 Hz, 6H), 1.29−1.14 (m, 1H), 0.95 (t, J = 7.32 Hz, 3H), 0.91−0.83 (m, 1H); *Z*-form: 5.79−5.66 (m, 1H), 4.97 (dm, J = 9.6 Hz, 1H), 4.96 (dm, J = 17.6 1H), 4.28−4.11 (m, 4H), 2.22 (dt, J = 15.4, 7.9 Hz, 1H), 2.16−2.08 (m, 2H), 2.08−1.83 (m, 3H), 1.83−1.51 (m, 7H), 1.35 (t, J = 7.04 Hz, 6H), 1.29−1.14 (m, 1H), 0.97 (t, J = 7.24 Hz, 3H), 0.91−0.83 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *E*-form: 171.4 (d, J_{C-P} = 12.2 Hz), 136.3, 116.3, 64.2 (d, J_{C-P} = 5.9 Hz), 48.8, 38.7, 38.3, 31.3, 31.1, 29.2, 25.9, 25.7, 19.4, 16.1 (d, J_{C-P} = 6.3 Hz), 14.0; *Z*-form: 172.7 (d, J_{C-P} = 11.8 Hz), 136.3, 116.3; 64.3 (d, J_{C-P} = 5.9 Hz), 48.8, 39.1, 38.8, 31.4, 31.1, 30.1, 25.8, 25.8, 19.9, 16.1 (d, J_{C-P} = 6.3 Hz), 14.8; HRMS-EI: m/z $[M]^+$ calcd for $C_{17}H_{32}NO_4P$, 345.2069; found, 345.2061.

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***trans*-Diethyl-1-(2-allylcyclohexyl)pentylidene-aminooxyphosphonate (3d).** From **2d** (197 mg, 0.882 mmol), the title compound was similarly synthesized as **3b**. The reaction proceeded for 20 h at rt. The flash chromatography was performed on silica gel [prewashed with hexane/Et_3N (200:1)] and eluted with hexane/EtOAc (20:1, 10:1, 5:1, 1:1) to give **3d**[44] (210 mg, 66%, *E*/*Z* = 37/63) as a colorless yellow oil. IR (neat): 3076, 1644, 1549, 1217, 1043, 909 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ *E*-form: 5.79−5.64 (m, 1H), 4.98 (br d, *J* = 9.76 Hz, 1H), 4.97 (br d, *J* = 16.9 Hz, 1H), 4.35−4.00 (m, 4H), 2.43 (dt, *J* = 17.8, 6.6 Hz, 1H), 2.31−2.06 (m, 3H), 1.92−1.83 (m, 2H), 1.81−1.74 (m, 4H), 1.65−1.54 (m, 3H), 1.43−1.30 (m, 2H), 1.35 (t, *J* = 8.0 Hz, 6H), 1.29−1.15 (m, 2H), 1.01−0.85 (m, 1H), 0.91 (t, *J* = 7.52 Hz, 3H); *Z*-form: 5.79−5.64 (m, 1H), 4.98 (br d, *J* = 9.76 Hz, 1H), 4.97 (br d, *J* = 16.9 Hz, 1H), 4.35−4.00 (m, 4H), 2.31−2.00 (m, 4H), 1.92−1.83 (m, 2H), 1.81−1.74 (m, 4H), 1.65−1.54 (m, 3H), 1.43−1.30 (m, 2H), 1.35 (t, *J* = 8.0 Hz, 6H), 1.29−1.15 (m, 2H), 1.01−0.85 (m, 1H), 0.92 (t, *J* = 7.28 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ *E*-form: 171.7 (d, J_{C-P} = 12.3 Hz), 136.9, 116.1, 64.2 (d, J_{C-P} = 6.2 Hz), 52.0, 39.1, 38.4, 31.3, 31.0, 28.2, 28.0, 25.9, 25.6, 22.4, 16.2 (d, J_{C-P} = 6.4 Hz), 13.8; *Z*-form: 172.8 (d, J_{C-P} = 11.8 Hz), 136.3, 116.3, 64.3 (d, J_{C-P} = 5.3 Hz), 48.9, 38.8, 38.7, 31.4, 31.2, 28.4, 27.8, 25.8, 25.7, 22.6, 16.2 (d, J_{C-P} = 6.4 Hz), 13.7; HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{18}H_{34}NO_4P$, 359.2225; found, 359.2219.

***cis*-1-Hydroxyl-8-formyl-9-ethyl-bicyclo[4,3,0]non-8(9)-ene (4b).** In Method A, the title compound was synthesized from **3b** (139 mg, 0.419 mmol) after heating for 4 h. The chromatographic purification (hexane/EtOAc 20:1, 10:1, 3:1) gave **4b** (32.6 mg, 40%) as a yellow oil. IR (neat): 3437, 2805, 1654, 1199 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 9.96 (s, 1H), 2.48 (dd, *J* = 15.5, 7.6 Hz, 1H), 2.27−2.21 (m, 1H), 2.10−2.07 (m, 1H), 2.02 (dd, *J* = 15.5, 9.0 Hz, 1H), 1.61−1.60 (m, 1H), 1.54−1.49 (m, 2H), 1.36−1.24 (m, 3H), 1.14−1.01 (m, 4H), 0.94 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 188.2, 169.7, 135.9, 83.5, 45.4, 33.2, 30.5, 25.0, 21.5, 20.6, 17.6, 15.6; HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{12}H_{18}O_2$, 194.1307; found, 194.1297.

***cis*-1-Hydroxyl-8-formyl-9-propyl-bicyclo[4,3,0]non-8(9)-ene (4c).** In Method A, the title compound was synthesized from **3c** (115.7 mg, 0.335 mmol) after heating for 3 h. The chromatographic purification (hexane/EtOAc 20:1, 10:1, 3:1) gave **4c** (44.8 mg, 64%) as a yellow oil. IR (neat): 3488, 2857, 1659, 1196 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 9.97 (s, 1H), 2.50 (dd, *J* = 15.4, 7.6 Hz, 1H), 2.29−2.20 (m, 1H), 2.10−1.97 (m, 1H), 2.03 (dd, *J* = 15.4, 9.2 Hz, 1H), 1.66−1.57 (m, 1H), 1.53−1.42 (m, 2H), 1.39−1.20 (m, 5H), 1.19−0.92 (m, 4H), 0.79 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 188.3, 167.8, 136.7, 83.4, 45.4, 33.2, 30.5, 26.5, 25.0, 23.9, 21.5, 20.6, 14.2; HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{13}H_{20}O_2$, 208.1463; found, 208.1460.

***cis*-1-Hydroxyl-8-formyl-9-butyl-bicyclo[4,3,0]non-8(9)-ene (4d).** In Method A, the title compound was synthesized from **3d** (86 mg, 0.239 mmol) after heating for 4 h. The chromatographic purification (hexane/EtOAc 20:1, 10:1, 3:1) gave **4d** (39 mg, 73%) as a yellow oil. IR (neat): 2858, 1648, 1546 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 10.01 (s, 1H), 2.50 (dd, *J* = 15.4, 7.7 Hz, 1H), 2.32−2.25 (m, 1H), 2.15−2.08 (m, 1H), 2.04 (dd, *J* = 15.4, 8.5 Hz, 1H), 1.61−1.59 (m, 1H), 1.51−1.47 (m, 2H), 1.39−1.27 (m, 5H), 1.26−1.15 (m, 3H), 1.08−0.97 (m, 2H), 0.88−0.72 (m, 1H), 0.83 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 188.2, 168.2, 136.4, 83.4, 45.5, 33.2, 33.0, 30.5, 25.0, 24.4, 23.1, 21.5, 20.6, 13.8; HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{14}H_{22}O_2$, 222.162; found, 222.1617; Anal. Calcd for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.68; H, 9.94.

9-Ethyl-bicyclo[4,3,0]non-1(9)-en-8-one (5b). In Method B, the title compound was synthesized from **3b** (40.6 mg, 0.123 mmol) after heating for 4 h. The chromatographic purification (hexane/EtOAc 20:1, 10:1, 5:1) afforded **5b**[45a] (11.2 mg, 56%) as a yellow oil. IR (neat): 2931, 1698, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.85 (dd, *J* = 14.4, 1.7 Hz, 1H), 2.61−2.45 (m, 1H), 2.53 (d, *J* = 14.4 Hz, 1H), 2.17 (q, *J* = 7.5 1.50 (qt, *J* = 13.2, 3.4 Hz, 1H), 1.32(qt, *J* = 13.0, 3.8 Hz, 1H), 1.11−0.99 (m, 1H), 0.97 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.7, 175.8, 138.7, 41.5, 40.1, 35.2, 28.5, 26.9, 25.6, 15.8, 13.6; HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{11}H_{16}O$, 164.1201; found, 164.1198.

9-Propyl-bicyclo[4,3,0]non-1(9)-en-8-one (5c). In Method B, the title compound was synthesized from **3c** (66.3 mg, 0.192 mmol) after heating for 3 h. The chromatographic purification (hexane/EtOAc 20:1, 10:1, 5:1) afforded **5c** (11.3 mg, 33%) as a pale yellow oil. IR (neat): 2929, 1697, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.85 (br d, *J* = 14.4 Hz, 1H), 2.61−2.47 (m, 1H), 2.53 (d, *J* = 14.4 Hz, 1H), 2.20−2.05 (m, 2H), 2.13 (t, *J* = 7.4 Hz, 2H), 2.04−1.96 (m, 1H), 1.95−1.87 (m, 1H), 1.87−1.80 (m, 1H), 1.50 (qt, *J* = 13.2, 3.3 Hz, 1H), 1.40 (sextet, *J* = 7.4 Hz, 2H), 1.31 (qt, *J* = 13.2, 3.8 Hz, 1H),1.04 (dddd, *J* = 12.3, 12.3, 12.3, 3.0 Hz, 1H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.9, 176.4, 137.0, 41.5, 40.2, 35.2, 28.7, 26.9, 25.6, 24.5, 22.0, 13.9; HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{12}H_{18}O$, 178.1358, found, 178.1364; Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.86 ; H, 10.16.

9-Butyl-bicyclo[4,3,0]non-1(9)-en-8-one (5d). In Method B, the title compound was synthesized from **3d** (138 mg, 0.384 mmol) after heating for 4 h. The chromatographic purification (hexane-EtOAc 20:1, 10:1, 5:1) afforded **5d**[45b] (43.7 mg, 59%) as a yellow oil. IR (neat): 2929, 1696, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): 2.84 (br d, *J* = 13.2 Hz, 1H), 2.58−2.45 (m, 1H), 2.53 (br d, *J* = 13.2 Hz, 1H), 2.21−2.05 (m, 4H), 2.04−1.95 (m, 1H), 1.91 (dd, *J* = 20.0, 4.2 Hz, 1H), 1.83 (br d, *J* = 13.3 Hz, 1H), 1.50 (qt, *J* = 12.8, 3.0 Hz, 1H), 1.38−1.22 (m, 5H), 1.04 (qd, *J* = 12.8, 2.2 Hz, 1H), 0.88 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 208.8, 176.2, 137.3, 41.5, 40.1, 35.2, 31.0, 28.7, 26.9, 25.6, 22.6, 22.3, 13.9; HRMS-EI *m*/*z* $[M]^+$ calcd for $C_{13}H_{20}O$, 192.1514; found, 192.1519.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The NMR spectra of all compounds in this article, the ORTEP structure and CIF file of **6**, the TLC analysis of the catalytic reaction in Scheme 3, the optimization results with $Pd(OAc)_2$/ligands or *n*-Bu_4NCl, the mass spectra of ^{18}O-isotopic experiments, this material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*jlzhu@mail.ndhu.edu.tw

Notes

The authors declare no competing financial interest.

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