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# Controllable Cyclization Reactions of 2-(2′,3′-Allenyl)acetylacetates Catalyzed by Gold and Palladium Affording Substituted Cyclopentene and 4,5-Dihydrofuran Derivatives with Distinct Selectivity

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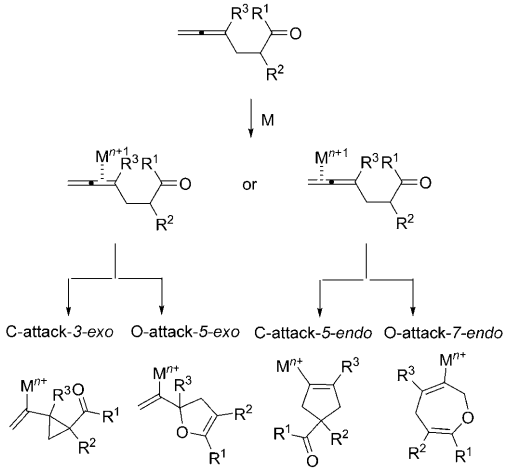
*Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday*

**Abstract:** Efficient room-temperature syntheses of cyclopentenes and 4,5-dihydrofurans with different substitution patterns were performed starting from the same materials (i.e., 2-(2′,3′-allenyl)acetylacetates). Depending on the choice of metal catalyst, the Au-catalyzed reaction afforded C-attack-5-*endo* cyclization products **2**, whereas the Pd-catalyzed one led to the formation of O-attack-5-*exo* cyclization products **3**. The selectivity may be explained by the steric and electronic effects of the substrates and catalysts.

**Keywords:** allenes · chemoselectivity · gold · palladium · regioselectivity

## Introduction

Recently, much attention has been paid to the synthesis of various cyclic compounds by using easily available functionalized allenes as the starting materials.[1,2] In addition to the oxidative addition/insertion/intramolecular allylic substitution mechanism,[1d,f] we[3] and others[4] also noted that the cyclization of functionalized allenes may be initiated by nucleometallation. Thus, we envisioned that the nucleometallation of 2-(2′,3′-allenyl)acetylacetates may, in principle, form cyclopropanyl, 4,5-dihydrofuryl, cyclopentenyl, or 2,5-dihydroxepinyl organometallic intermediates, which form oxa- or carbocycles, respectively (Scheme 1). On the other hand, the ene reaction between an enol and an alkyne is a well-established synthetic reaction with respect to its carbon-ring-forming variant, which is known as the Conia reaction.[5] In addition to the thermal Conia reactions, which were usually carried out under harsh conditions, such as at high temperatures or in the vapor phase,[5] $[In(NTf_2)_3]$ (Tf = trifluorosulfonyl),[6a] $Au^I$,[6b,f,g] $Pd^{II}$,[6c,e] $Ni(acac)_2$ with $Yb(OTf)_3$,[6d] $[CoCp(CO)_2]$ (Cp = cyclopentadienyl),[6h,m] CuI,[6i] $TiCl_4$,[6j] $[Mo(CO)_5(NEt_3)]$,[6k] and $ZnBr_2$[6l] have been reported as the catalysts. Widenhoefer et al. applied $[PdCl_2(CH_3CN)_2]$-catalyzed hydroalkylation of 5,7-dioxoalkenes to afford 2-acetylcyclohexanone derivatives.[7] Because cyclopentenes[8]




Scheme 1. Possible transition-metal-catalyzed cyclization modes of 2-(2′,3′-allenyl)acetylacetates.

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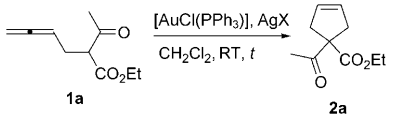
and dihydrofurans[9] are all-important units in natural products and pharmaceutically interesting compounds, we wish to report in this paper a highly selective synthesis of these two classes of compounds by using 2-(2′,3′-allenyl)acetylacetates as the starting materials and by a subtle choice of $[AuCl(PPh_3)]$, $[PdCl_2(PhCN)_2]$, or $[Pd(dba)_2]$ (dba = dibenzylideneacetone) as the catalyst.

## Results and Discussion

In this study, we first tested $[AuCl(PPh_3)]$ as the catalyst to cyclize 2-(2′,3′-allenyl)acetylacetate **1a**. However, no reaction was observed in $CH_2Cl_2$ (entry 1, Table 1). Further studies indicated that the addition of 5 mol% of $AgBF_4$ afforded a carbocycle, that is, 1-acetyl-1-(ethoxycarbonyl)-3-cyclopentene **2a**, very slowly (entry 2, Table 1). The addition of AgOTf or $AgSbF_6$ was much better, affording **2a** in 43 or 68% isolated yields, respectively (entries 3 and 4, Table 1). This is different from the Conia-ene reaction of ketoesters with alkynes observed by Toste's group, in which AgOTf is superior to $AgSbF_6$.[6b,f,g] AgOTf alone may also catalyze this transformation very slowly (entry 5, Table 1). To the best of our knowledge, this is the first allene Conia-ene-type reaction.

Table 1. Optimization of $Au^I$-catalyzed cyclization of 2-(2′,3′-allenyl)acetylacetate **1a**.

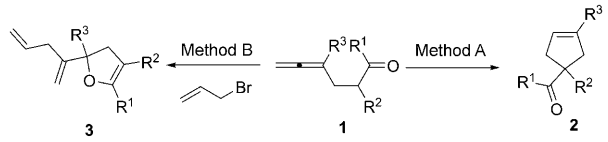



| Entry | $[AuCl(PPh_3)]$ [mol%] | AgX (X [mol%]) | $t$ [h] | Isolated Yield of **2a** [%] |
|---|---|---|---|---|
| 1 | 5 | 0 | 24 | 0[a] |
| 2 | 5 | $BF_4$ (5) | 17 | 5[b] |
| 3 | 5 | OTf (5) | 3 | 43 |
| 4 | 5 | $SbF_6$ (5) | 1 | 68 |
| 5 | 0 | OTf (5) | 12 | 8[c] |
| 6[d] | 5 | $SbF_6$ (5) | 24 | 64 |

[a] 80% of **1a** was recovered. [b] A mixture of **1a** and **2a** was isolated in a combined isolated yield of 77%. The ratio of **1a**/**2a** is 100:7, as determined by $^1H$ NMR analysis. [c] A mixture of **1a** and **2a** was isolated in a combined isolated yield of 70%. The ratio of **1a**/**2a** is 100:13, as determined by $^1H$ NMR analysis. [d] The reaction was conducted in the presence of allyl bromide (5 equiv).

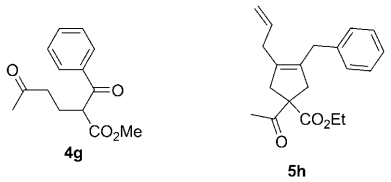
In fact, this $Au^+/Ag^+$ co-catalyzed reaction (Table 1, entry 4, method A) is quite general, and some of the typical results are presented in Table 2. $R^1$ may not only be a normal alkyl group, such as Me, Et, and *n*Pr (entries 1–4, Table 2), but also an *i*Pr (entry 5, Table 2), Bn (entry 6, Table 2), and Ph (entry 7, Table 2) group. A substituent may also be introduced onto the allene moiety to afford the same type of product **2h** in 73% yield (entry 8, Table 2). The structures of these cyclopentenes were further confirmed by the X-ray diffraction study of 4-benzoyl-4-(methoxycarbonyl)cyclopentene **2g** (Figure 1).[10] It should be noted that the formation of all-carbon quaternary centers is not easy, because the process requires the creation of a new C–C bond at a sterically hindered carbon center.[11]

Table 2. Cyclization of 2-(2′,3′-allenyl)acetylacetates **1** by using methods A or B.[a]




| Entry | **1** $R^1$ | $R^2$ | $R^3$ | | Method A Isolated yield of **2** [%] | Method B Isolated yield of **3** [%] |
|---|---|---|---|---|---|---|
| 1 | Me | $CO_2Et$ | H | **1a** | 68 (**2a**) | 73 (**3a**) |
| 2 | Me | $CO_2Me$ | H | **1b** | 51 (**2b**) | 57 (**3b**) |
| 3 | Et | $CO_2Me$ | H | **1c** | 42 (**2c**) | 60 (**3c**) |
| 4 | *n*Pr | $CO_2Et$ | H | **1d** | 93 (**2d**) | 82 (**3d**) |
| 5 | *i*Pr | $CO_2Me$ | H | **1e** | 76 (**2e**)[b] | 77 (**3e**) |
| 6 | Bn | $CO_2Me$ | H | **1f** | 71 (**2f**) | 33 (**3f**) |
| 7 | Ph | $CO_2Me$ | H | **1g** | 67 (**2g**)[c] | 60 (**3g**) |
| 8 | Me | $CO_2Et$ | Bn | **1h** | 73 (**2h**) | 40 (**3h**)[d] |

[a] Method A: A mixture of 0.15–0.50 mmol of **1**, $[AuCl(PPh_3)]$ (5 mol%), and $AgSbF_6$ (5 mol%) in $CH_2Cl_2$ (2 mL) was stirred under Ar at RT for 1 h. Method B: 0.25 mmol of **1** was stirred with $[PdCl_2(PhCN)_2]$ (5–7 mol%), $K_2CO_3$ (2 equiv), and allyl bromide (2 equiv) in MeCN (2 mL) under Ar at room temperature for 4 h. [b] The reaction was conducted in dichloroethane at reflux instead of $CH_2Cl_2$ (76% of **1e** was recovered when the reaction was conducted by using Method A. [c] 31% of hydrated product **4g** was also formed. [d] 30% of the carbocyclic product **5h** was also formed.



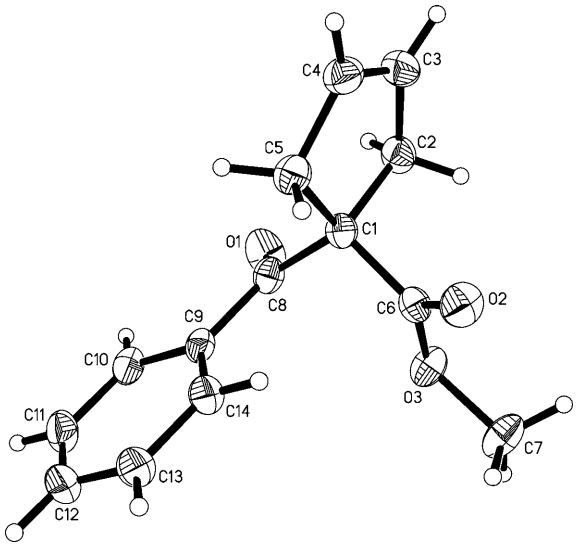




Figure 1. ORTEP representation of **2g** with thermal ellipsoids at the 30% probability level.

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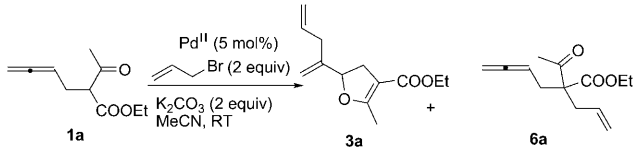
Furthermore, $[PdCl_2(MeCN)_2]$, which has also been successfully used to catalyze the intramolecular Conia-ene reaction of enols with alkenes,[6c,e,7] was applied to see if it would catalyze this transformation. However, no reaction was observed in the absence or presence of $K_2CO_3$ (entries 1 and 2, Table 3). Luckily and unexpectedly, it was observed that the same reaction in the presence of two equivalents of allyl bromide and $K_2CO_3$ afforded the oxymetallation–allylation product 4,5-dihydrofuran **3a** in 56% yield (entry 3, Table 3).[12] $PdCl_2$ (entry 4, Table 3), $Pd(OAc)_2$ (entry 5, Table 3), or $[PdCl_2(PhCN)_2]$ (entry 7, Table 3) all catalyze this transformation and $[PdCl_2(PhCN)_2]$ was the best catalyst. $[PdCl_2(PPh_3)_2]$ failed to catalyze this reaction (entry 6, Table 3). Under this new set of conditions, that is, method B (entry 7, Table 3), 4,5-dihydrofuran derivatives were formed in 33–82% isolated yields (Table 2). It should be noted that the [AuCl(PPh$_3$)]-catalyzed cyclization reaction of **1a** in the presence of allyl bromide failed to afford the allylated product (entry 6, Table 1).[13]

Table 3. Different $Pd^{II}$-complex-catalyzed coupling–cyclization reactions of 2-(2′,3′-allenyl)acetylacetate **1a** with allyl bromide.

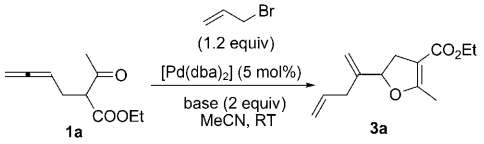



| Entry | Catalyst | $t$ [h] | Isolated yield of **3a** [%] | Isolated yield of **6a** [%] |
|---|---|---|---|---|
| 1[a] | $[PdCl_2(MeCN)_2]$ | 5 | 0 | 0 |
| 2[b] | $[PdCl_2(MeCN)_2]$ | 5 | 0 | 0 |
| 3 | $[PdCl_2(MeCN)_2]$ | 4 | 56 | 0 |
| 4 | $PdCl_2$ | 4 | 47 | 0 |
| 5 | $Pd(OAc)_2$ | 4 | 62 | 0 |
| 6 | $[PdCl_2(PPh_3)_2]$ | 3 | 0 | 95 |
| 7 | $[PdCl_2(PhCN)_2]$ | 4 | 73 | 0 |

[a] The reaction was conducted in the absence of allyl bromide and 39% of **1a** was recovered. [b] The reaction was conducted without $K_2CO_3$. 2-(2′,3′-Allenyl)acetylacetate **1a** (59%) was recovered.

However, it should be noted that in some cases, the yield or selectivity is not very good (entries 6 and 8, Table 2). Further screening led to the observation that $[Pd(dba)_2]$ may be the catalyst of choice for promoting this cyclization reaction. Then, we tested the base and solvent effects in this $[Pd(dba)_2]$-catalyzed reaction of **1a** with allyl bromide. The reaction in MeCN failed to yield the coupling–cyclization product **3a** with $Et_3N$ (entry 1, Table 4), $Na_2CO_3$ (entry 2, Table 4), $NaHCO_3$ (entry 3, Table 4), or KOAc (entry 4, Table 4) as the base; the reaction was complicated when PhthK (entry 5, Table 4, PhthK = potassium phthalimide) or *t*BuOK (entry 6, Table 4) was used; KF (entry 7, Table 4) and KOH (entry 8, Table 4) afforded the product **3a** in 44 and 56% yields, respectively; and $K_2CO_3$ (entry 9, Table 4) and $K_3PO_4 \cdot 3H_2O$ (entry 10, Table 4) both afforded the product **3a** in 66% yield.

Table 4. The effect of bases on the Pd-catalyzed coupling–cyclization of 2-(2′,3′-allenyl)acetylacetate **1a** with allyl bromide.

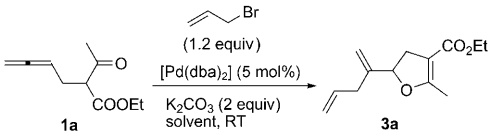



| Entry | Base | Reaction time [h] | Isolated yield of **3a** [%] |
|---|---|---|---|
| 1 | $Et_3N$ | 4 | NR (91%)[a] |
| 2 | $Na_2CO_3$ | 12 | trace |
| 3 | $NaHCO_3$ | 12 | trace |
| 4 | KOAc | 24 | 0 |
| 5 | PhthK | 24 | complicated |
| 6 | *t*BuOK | 4 | complicated |
| 7 | KF | 4 | 44 |
| 8 | KOH | 4 | 56 |
| 9 | $K_2CO_3$ | 4 | 66 |
| 10 | $K_3PO_4 \cdot 3H_2O$ | 4 | 66 |

[a] NR = no reaction. The number in parenthesis is the yield of recovered allene **1a**.

Furthermore, a comprehensive study on the solvent effect indicated that MeCN was the best (entry 1, Table 5). Thus, we developed method C for the reaction of relatively sterically hindered **1** and allylic halides: $[Pd(dba)_2]$ (5 mol%), $K_2CO_3$ (2 equiv), and allyl bromide **7** in MeCN under Ar at room temperature for 4 h.

Table 5. Solvent effects in the Pd-catalyzed coupling–cyclization of 2-(2′,3′-allenyl)acetylacetate **1a** with allyl bromide.




| Entry | Solvent | $t$ [h] | Isolated yield of **3a** [%] |
|---|---|---|---|
| 1 | MeCN | 4 | 66 |
| 2 | toluene | 24 | 40 |
| 3 | $CH_2Cl_2$ | 24 | 56 |
| 4 | $MeNO_2$ | 19 | 58 |
| 5 | THF | 27 | 52 |
| 9 | DMF | 10 | 49 |
| 7 | acetone | 5 | 63 |

Thus, we demonstrated that the $[Pd(dba)_2]$-catalyzed coupling–cyclization reaction of methyl 2-(2′,3′-butadienyl)-4-phenylacetoacetate **1f** and sterically hindered ethyl 2-(2′-benzyl-2′,3′-butadienyl)acetylacetate **1h** in the presence of allyl bromide proceeded smoothly to afford **3f** and **3h** in 70 and 61% yields, respectively (compare entries 6 and 8 of Table 2 with entries 1 and 2 of Table 6). Furthermore, the coupling–cyclization reaction of **1c**, **1e**, **1i**, and **1j** with structurally different allylic compounds **7** also afforded the related allylated cyclization products **3cb–jb** smoothly, showing the generality of method C (Table 6).

It should be noted that the cyclization reaction of **1a** or **1e** in the presence of (*E*)-cinnamyl bromide **7e** afforded the coupling–cyclization products (*E*)-**3ae** and (*E*)-**3ee** with the

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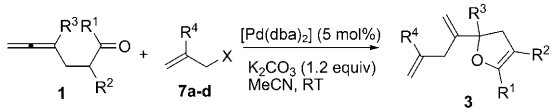
Table 6. Pd-catalyzed coupling–cyclization of 2-(2′,3′-allenyl)acetylacetates **1** with symmetric allylic halides **7a–d** by using Method C.[a]



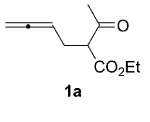
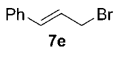
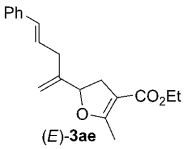
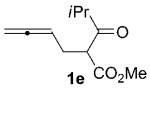
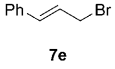
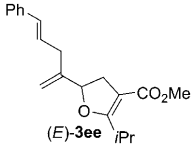
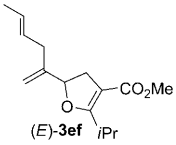
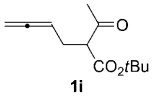
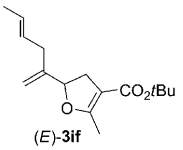

| Entry | 1 | | | | 7 | | | Isolated yield of 3 [%] |
|---|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | $R^3$ | | $R^4$ | X | | |
| 1 | Bn | $CO_2Me$ | H | **(1f)** | H | Br | **(7a)** | 70 (**3f**) |
| 2 | Me | $CO_2Et$ | Bn | **(1h)** | H | Br | **(7a)** | 61 (**3h**)[b] |
| 3 | Et | $CO_2Me$ | H | **(1c)** | Ph | Br | **(7b)** | 59 (**3cb**) |
| 4 | *i*Pr | $CO_2Me$ | H | **(1e)** | Ph | Br | **(7b)** | 51 (**3eb**) |
| 5 | *i*Pr | $CO_2Me$ | H | **(1e)** | *n*Bu | Br | **(7c)** | 66 (**3ec**) |
| 6 | *i*Pr | $CO_2Me$ | H | **(1e)** | Me | Cl | **(7d)** | 55 (**3ed**) |
| 7 | Me | $CO_2tBu$ | H | **(1i)** | Ph | Br | **(7b)** | 52 (**3ib**) |
| 8 | *n*Pr | $CO_2Me$ | H | **(1j)** | Ph | Br | **(7b)** | 53 (**3jb**) |

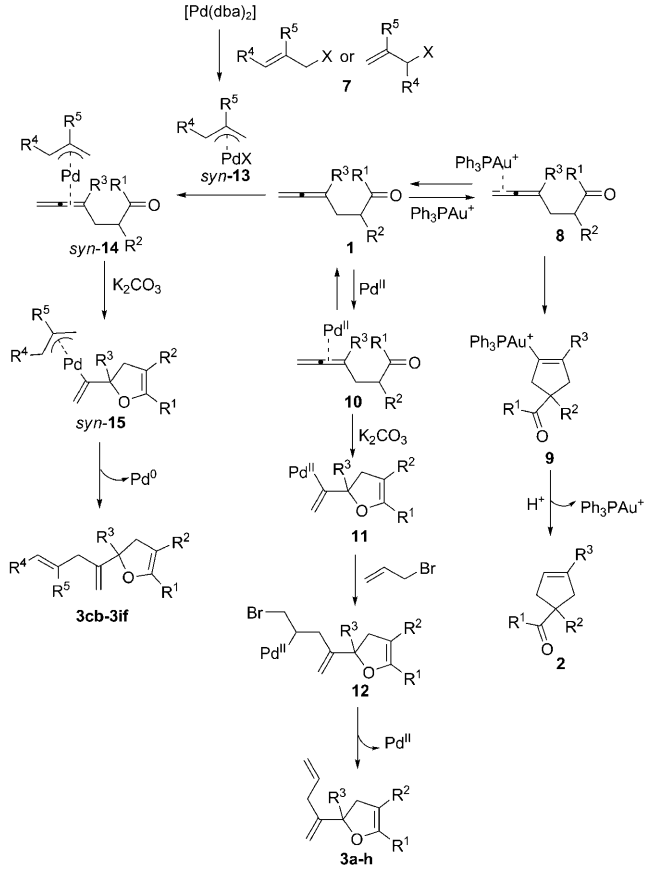
[a] Method C: The reaction was conducted with of **1** (0.25 mmol), $[Pd(dba)_2]$ (5 mol%), $K_2CO_3$ (1.2 equiv), and allyl bromide **7** (2 equiv) in MeCN (2 mL) under Ar at room temperature for 4 h. [b] 22% of product **5h** was also formed.

phenyl group at the terminal position of the (*E*)-carbon–carbon double bond. In addition, even the reaction of **1e** and **1i** with 3-chlorobutene **7f** afforded the corresponding products (*E*)-**3ef** and (*E*)-**3if** with the methyl group at the terminal position of the (*E*)-carbon–carbon double bond (Table 7).

To explain the different selectivity demonstrated by Au and Pd, we reasoned that $Au^+$ may be preferable for coordination with the terminal carbon–carbon double bond of 2-(2′,3′-allenyl)acetylacetate **1** due to the steric bulk caused by its relatively large ionic radius[14] and the bulkier phosphine ligand to afford coordination complex **8** (Scheme 2), then, the carbon atom of the enol unit in the β-ketoester acted as a nucleophile, which has been clearly demonstrated[15] in the context of $Au^+$-catalyzed enyne cyclization reactions,[16] the Conia-ene reaction of ketoesters with alkynes,[6b,f,g] and the nucleophilic substitution reaction of alkynes with arenes or heteroarenes,[17] to form the five-membered cyclic intermediate **9**. On the other hand, $Pd^{2+}$ favors coordination with the more substituted relatively electron-rich double bond of allenes to afford the coordination complex **10**,[1a,f,18] the oxygen atom in the enolate form of β-ketoesters then attacked the carbon atom connected with $R^3$ to form the 4,5-dihydrofuran intermediate **11** exclusively, probably due to the "harder" Lewis acidic nature of $Pd^{2+}$.[19] Subsequent intermolecular insertion with allyl bromide to form **12** and the subsequent β-dehalopalladation afforded

Table 7. Pd-catalyzed coupling–cyclization of 2-(2′,3′-allenyl)acetylacetates **1** with unsymmetric allylic halides **7e–f** by using Method C.

| Entry | 1 | 7 | 3 | Isolated yield of 3 [%] |
|---|---|---|---|---|
| 1 |  |  |  | 58 |
| 2 |  |  |  | 49 |
| 3 | **1e** |  |  | 56 |
| 4 |  |  |  | 53 |




Scheme 2. Proposed mechanisms for gold- and palladium-catalyzed cyclization reactions of 2-(2′,3′-allenyl)acetylacetates.

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the **3**-type allylated products **3a**–**h** and the catalytically active $Pd^{II}$. In the presence of relatively sterically hindered allylic halides **7a**–**e**, the related insertion is obviously slow. However, in the presence of $Pd^0$, the oxidative addition of differently substituted allylic halides with $Pd^0$ would afford the thermodynamically more stable divalent π-allyl palladium complex *syn*-**13**.[20] When this complex coordinated with **1**, *syn*-**14** was formed highly regioselectively due to the same reason, which would also trigger the oxymetallation to produce *syn*-**15**.[12b] Subsequent highly regioselective reductive elimination would form the carbon–carbon bond at the less-substituted terminus of the allylic moiety to yield the products **3cb**–**if** and regenerate $Pd^0$. This also explains the regio- and stereoselectivity demonstrated in Table 7.

## Conclusion

We have demonstrated two different types of cyclization reactions of 2-(2′,3′-allenyl)acetylacetates that enable highly selective syntheses of substituted cyclopentenes with a quaternary stereocenter[11] and 4,5-dihydrofuran derivatives by applying $[AuCl(PPh_3)]$ or $[PdCl_2(PhCN)_2]$ as the catalyst in C-attack-5-*endo* cyclization reactions or by using catalytic $[Pd(dba)_2]$ in O-attack-5-*exo* cyclization processes. The different cyclization modes are probably due to the steric and electronic effects of the substrates and catalysts. In the $[Pd(dba)_2]$-catalyzed cyclization reaction, the regio- and stereoselectivity for the unsymmetric allylic halides is very high, affording products with the allylic substituent at the terminal position of the (*E*)-carbon–carbon double bond in the products. In view of the easy availability of the starting materials and the catalysts, these types of transformations may be useful in organic synthesis. Further studies, such as the asymmetric variants of these cyclization reactions are being conducted in our laboratory.

## Experimental Section

**General**: $^1H$ (300 MHz) and $^{13}C$ (75.4 MHz) spectra were recorded in $CDCl_3$ with a Varian Mercury 300 MHz spectrometer. Chemical shifts are reported in ppm with reference to the signals of the residual $CHCl_3$ in $CDCl_3$ ($^1H$ NMR ($\delta = 7.26$ ppm) and $^{13}C$ NMR ($\delta = 77.0$ ppm)). Mass spectra of the products were obtained by using a HP 5989A instrument. IR spectra were obtained with a Perkin–Elmer 983 instrument. Elemental analyses were carried out by using a Vario EL III system and high-resolution (HR) MS analyses were performed by using a Finnigan MAT 8430 instrument. Thin-layer chromatography (TLC) was carried out by using plates coated with 0.15–0.20 mm thick silica gel (Huanghai, Yantai, China), and column chromatography was performed by using silica gel H (Huanghai, Yantai, China). DCM and MeCN were distilled over $CaH_2$ before use. All of the reactions were carried out under a dry argon atmosphere. The starting materials 2-(2′,3′-allenyl)acetylacetates were synthesized by $S_N2$ substitution reactions of acetylacetates with 2,3-allenyl bromide.[21]

**Method A: Synthesis of 4-acetyl-4-(ethoxycarbonyl)cyclopentene (2a)**:[22] A mixture of **1a** (47 mg, 0.26 mmol), $[AuCl(PPh_3)]$ (6 mg, 0.0121 mmol), and $AgSbF_6$ (3 mg, 0.0117 mmol) in $CH_2Cl_2$ (2 mL) was stirred under Ar in a flame-dried Schlenk tube at room temperature for 1 h. After the reaction was complete (monitored by TLC, petroleum ether/ethyl acetate 10:1), rotary evaporation and flash chromatography on silica gel (petroleum ether/ethyl ether 20:1) afforded **2a** (32 mg, 68%) as a liquid. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 5.57$ (s, 2H), 4.20 (q, $J = 6.9$ Hz, 2H), 2.92 (s, 4H), 2.17 (s, 3H), 1.25 ppm (t, $J = 6.9$ Hz, 3H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 202.6$, 172.8, 127.6, 65.3, 61.5, 39.1, 25.8, 13.9 ppm; IR (neat): $\tilde{\nu} = 3062$, 2983, 2928, 2856, 1716, 1626, 1446, 1358, 1237, 1157 $cm^{-1}$; MS (ESI): *m/z*: 183 $[M+H^+]$; HRMS (EI): *m/z* calcd for $C_{10}H_{14}O_3$: 182.0943 $[M^+]$; found: 182.0935.

**Method B: Synthesis of 2-methyl-3-(ethoxycarbonyl)-5-(penta-1,4-dien-2-yl)-4,5-dihydrofuran (3a)**: A mixture of **1a** (28 mg, 0.15 mmol), $[PdCl_2(PhCN)_2]$ (4 mg, 0.010 mmol), $K_2CO_3$ (42 mg, 0.30 mmol), and allyl bromide (27 mg, 0.22 mmol) in MeCN (2 mL) was stirred at room temperature under Ar in a flame-dried Schlenk tube for 4 h. After the reaction was complete (monitored by TLC, petroleum ether/ethyl acetate 10:1), rotary evaporation and flash chromatography on silica gel (petroleum ether/ethyl ether 20:1) afforded **3a** (25 mg, 73%) as a liquid. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 5.90$–$5.75$ (m, 1H), 5.20–4.95 (m, 4H), 4.91 (s, 1H), 4.15 (q, $J = 7.8$ Hz, 2H), 3.10–2.95 (m, 1H), 2.90–2.75 (m, 2H), 2.75–2.65 (m, 1H), 2.21 (s, 3H), 1.27 ppm (t, $J = 6.9$ Hz, 3H); $^{13}C$ NMR (75.4 MHz, $CDCl_3$): $\delta = 167.7$, 166.0, 146.2, 135.2, 116.9, 111.5, 101.7, 83.8, 59.4, 35.6, 34.9, 14.4, 14.0 ppm; IR (neat): $\tilde{\nu} = 3080$, 2980, 2928, 2873, 1700, 1650, 1433, 1384, 1342, 1321, 1259, 1225, 1143, 1127, 1084 $cm^{-1}$; MS (EI): *m/z* (%): 223 (0.40) $[M+H^+]$, 222 (0.08) $[M^+]$, 194 (2.91) $[M-Et+H^+]$, 43 (100); HRMS (ESI): *m/z* calcd for $C_{13}H_{18}O_3$: 222.1256 $[M+H^+]$; found: 222.1265.

**Method C: Synthesis of 2-ethyl-3-(methoxycarbonyl)-5-(4-phenylpenta-1,4-dien-2-yl)-4,5-dihydrofuran (3cb)**: A mixture of **1c** (45 mg, 0.25 mmol), $[Pd(dba)_2]$ (7 mg, 0.0122 mmol), $K_2CO_3$ (42 mg, 0.30 mmol), and **7b** (99 mg, 0.50 mmol) in MeCN (2 mL) was stirred in a flame dried Schlenk tube at room temperature for 13 h. After the reaction was complete (monitored by TLC, petroleum ether/ethyl acetate 10:1), rotary evaporation and flash chromatography on silica gel (petroleum ether/diethyl ether 50:1) afforded **3cb** (43 mg, 59%) as a liquid. $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 7.48$–$7.40$ (m, 2H), 7.36–7.24 (m, 3H), 5.52 (s, 1H), 5.17 (s, 1H), 5.11 (s, 1H), 5.06 (dd, $J = 10.5$, 8.7 Hz, 1H), 4.93 (s, 1H), 3.70 (s, 3H), 3.32 (d, $J = 16.5$ Hz, 1H), 3.23 (d, $J = 16.5$ Hz, 1H), 3.05 (dd, $J = 14.4$, 11.7 Hz, 1H), 2.85–2.60 (m, 3H), 1.15 ppm (t, $J = 7.2$ Hz, 3H); $^{13}C$ NMR ($CDCl_3$, 75.4 MHz): $\delta = 172.7$, 166.3, 145.4, 144.3, 140.3, 128.3, 127.5, 126.0, 115.4, 112.7, 100.3, 83.6, 50.8, 37.2, 34.8, 21.2, 11.2 ppm; IR (neat): $\tilde{\nu} = 3083$, 2975, 2947, 1704, 1642, 1435, 1247, 1136, 1096 $cm^{-1}$; MS (EI): *m/z* (%): 298 (7.00) $[M^+]$, 43 (100); HRMS (EI): *m/z* calcd for $C_{19}H_{22}O_3$: 298.1569 $[M^+]$; found: 298.1577.

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[1] For reviews on the chemistry of allenes, see: a) R. Zimmer, C. U. Dinesh, E. Nandanan, F. A. Khan, *Chem. Rev.* **2000**, *100*, 3067; b) J. Marshall, *Chem. Rev.* **2000**, *100*, 3163; c) X. Lu, C. Zhang, Z. Xu, *Acc. Chem. Res.* **2001**, *34*, 535; d) S. Ma in *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed.: E. Negishi), Wiley, New York, **2002**, 1491–1523; e) R. Bates, V. Satcharoen, *Chem. Soc. Rev.* **2002**, *31*, 12; f) S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701; g) L. K. Sydnes, *Chem. Rev.* **2003**, *103*, 1133; h) M. Tius, *Acc. Chem. Res.* **2003**, *36*, 284; i) L.-L. Wei, H. Xiong, R. P. Hsung, *Acc. Chem. Res.* **2003**, *36*, 773; j) S. Ma, *Chem. Rev.* **2005**, *105*, 2829; k) S. Ma in *Topics in Organometallic Chemistry* (Ed.: J. Tsuji), Springer, Heidelberg, **2005**, 183–210; l) S. Ma, *Aldrichimica Acta* **2007**, *40*, 91.

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[2] For books, see: *Modern Allene Chemistry* (Eds.: N. Krause, A. S. K. Hashmi), Wiley-VCH, Weinheim, **2004**.

[3] For some of the most recent reports from this group, see: a) Z. Gu, X. Wang, W. Shu, S. Ma, *J. Am. Chem. Soc.* **2007**, *129*, 10948; b) Q. Yang, X. Jiang, S. Ma, *Chem. Eur. J.* **2007**, *13*, 9310; c) S. Ma, Z. Zheng, X. Jiang, *Org. Lett.* **2007**, *9*, 529; d) F. Yu, X. Lian, S. Ma, *Org. Lett.* **2007**, *9*, 1703; e) S. Ma, F. Yu, J. Li, W. Gao, *Chem. Eur. J.* **2007**, *13*, 247; f) Y. Deng, Y. Yu, S. Ma, *J. Org. Chem.* **2008**, *73*, 585.

[4] For some of the recent reports on cyclization of allenes from other groups, see: a) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496; b) R. L. Lalonde, B. D. Sherry, E. J. Kang, F. D. Toste, *J. Am. Chem. Soc.* **2007**, *129*, 2452; c) S. T. Staben, J. J. Kennedy-Smith, D. Huang, B. K. Corkey, R. L. Lalonde, F. D. Toste, *Angew. Chem.* **2006**, *118*, 6137; *Angew. Chem. Int. Ed.* **2006**, *45*, 5991; d) B. M. Trost, J. Xie, *J. Am. Chem. Soc.* **2006**, *128*, 6044; e) H. Hamaguchi, S. Kosaka, H. Ohno, N. Fujii, T. Tanaka, *Chem. Eur. J.* **2007**, *13*, 1692; f) Z. Zhang, R. Widenhoefer, *Angew. Chem.* **2007**, *119*, 287; *Angew. Chem. Int. Ed.* **2007**, *46*, 283; g) L. Xu, X. Huang, F. Zhong, *Org. Lett.* **2006**, *8*, 5061; h) K. Parthasarathy, M. Jeganmohan, C.-H. Cheng, *Org. Lett.* **2006**, *8*, 621; i) R. Grigg, C. Kilner, E. Mariani, V. Sridharan, *Synlett* **2006**, 3021; j) G. Liu, X. Lu, *Tetrahedron Lett.* **2003**, *44*, 127; k) G. Liu, X. Lu, *Org. Lett.* **2001**, *3*, 3879; l) H.-U. Reissig, S. Hormuth, W. Schade, M. Okala Amombo, T. Watanabe, R. Pulz, A. Hausherr, R. Zimmer, *J. Heterocycl. Chem.* **2000**, *37*, 597; m) H.-U. Reissig, W. Schade, M. G. Okala Amombo, R. Pulz, A. Hausherr, *Pure Appl. Chem.* **2002**, *74*, 175; n) J. Dash, T. Lechel, H.-U. Reissig, *Org. Lett.* **2007**, *9*, 5541; for metal-catalyzed regiodivergent cyclization of functional allenes, see: o) B. Alcaide, P. Almendros, T. M. Campo, *Angew. Chem.* **2007**, *119*, 6804; *Angew. Chem. Int. Ed.* **2007**, *46*, 6684; p) S.-H. Kim, S.-J. Oh, P.-S. Ho, S.-C. Kang, K.-J. O, C.-M. Yu, *Org. Lett.* **2008**, *10*, 265.

[5] J. M. Conia, P. Le Perchec, *Synthesis* **1975**, 1.

[6] a) H. Tsuji, K. Yamagata, Y. Itoh, K. Endo, M. Nakamura, E. Nakamura, *Angew. Chem.* **2007**, *119*, 8206; *Angew. Chem. Int. Ed.* **2007**, *46*, 8060; b) A. Ochida, H. Ito, M. Sawamura, *J. Am. Chem. Soc.* **2006**, *128*, 16486; c) B. K. Corkey, F. D. Toste, *J. Am. Chem. Soc.* **2005**, *127*, 17168; d) Q. Gao, B.-F. Zheng, J.-H. Li, D. Yang, *Org. Lett.* **2005**, *7*, 2185; e) T. Lomberget, D. Bouyssi, G. Balme, *Synthesis* **2005**, 311; f) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526; g) S. T. Staben, J. J. Kennedy-Smith, F. D. Toste, *Angew. Chem.* **2004**, *116*, 5464; *Angew. Chem. Int. Ed.* **2004**, *43*, 5350; h) J.-L. Renaud, C. Aubert, M. Malacria, *Tetrahedron* **1999**, *55*, 5113; i) D. Bouyssi, N. Monteiro, G. Balme, *Tetrahedron Lett.* **1999**, *40*, 1297; j) O. Kitagawa, T. Suzuki, T. Inoue, Y. Watanabe, T. Taguchi, *J. Org. Chem.* **1998**, *63*, 9470; k) E. Nakamura, G. Sakata, K. Kubota, *Tetrahedron Lett.* **1998**, *39*, 2157; l) F. E. McDonald, T. C. Olson, *Tetrahedron Lett.* **1997**, *38*, 7691; m) P. Cruciani, R. Stammler, C. Aubert, M. Malacria, *J. Org. Chem.* **1996**, *61*, 2699.

[7] It should be noted that $[PdCl_2(MeCN)_2]$ has been used to catalyze the Conia-ene reaction of an enol with an intramolecular alkene to afford 2-cyclohexenones: a) R. A. Widenhoefer, *Pure Appl. Chem.* **2004**, *76*, 671; b) T. Pei, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2001**, *123*, 11290; c) H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2056; d) T. Pei, R. A. Widenhoefer, *Chem. Commun.* **2002**, 650; e) X. Wang, T. Pei, X. Han, R. A. Widenhoefer, *Org. Lett.* **2003**, *5*, 2699; f) T. Pei, X. Wang, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 648.

[8] a) R. Noyori, M. Suzuki, *Science* **1993**, *259*, 44; b) M. H. Beale, J. L. Ward, *Nat. Prod. Rep.* **1998**, *15*, 533; c) S. C. Sutton, M. T. S. Rinaldi, J. M. McCarthy, K. E. Vukovinsky, *J. Pharm. Sci.* **2002**, *91*, 1046; d) B. Li, S. E. Laszlo, T. M. Kamenecka, I. E. Kopka, P. L. Durette, T. Lanza, M. MacCoss, S. Tong, R. A. Mumford, E. D. McCauley, G. V. Riper, J. A. Schmidt, W. K. Hagmann, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2141; e) A. Kim, J. H. Hong, *Arch. Pharm.* (Weinheim Ger.) **2005**, *338*, 522; f) A. Kim, J. Hong, *Nucleosides Nucleotides Nucleic Acids* **2006**, *25*, 1.

[9] a) F. M. Dean, M. V. Sargent in *Comprehensive Heterocyclic Chemistry, Vol. 4* (Eds.: A. R. Katritzky, C. W. Rees), Pergamon, Oxford, **1984**, 531–712; b) R. Benassi in *Comprehensive Heterocyclic Chemistry II, Vol. 2* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, 259–436.

[10] Crystal data for compound **2g**: $C_{14}H_{14}O_3$, MW = 230.25, monoclinic, space group $P2(1)/c$, final $R$ indices $[I > 2\sigma(I)]$, $R_1 = 0.0528$, $wR_2 = 0.1345$, $R$ indices (all data), $R_1 = 0.0670$, $wR_2 = 0.1428$, $a = 9.7929$ (12) Å, $b = 14.7272$ (19) Å, $c = 8.1348$ (10) Å, $\alpha = 90°$, $\beta = 95.334(2)°$, $\gamma = 90°$, $V = 1168.1(3)$ Å$^3$, $T = 293$ (2) K, $Z = 4$, reflections collected/unique: 6751/2542 ($R$(int) = 0.1460). CCDC-671103 (**2g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.).

[11] For selected recent reviews, see: a) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (Eds.: J. Christoffers, A. Baro), Wiley-VCH, Weinheim, **2005**; b) B. M. Trost, C. H. Jiang, *Synthesis* **2006**, 369.

[12] a) S. Ma, W. Gao, *Tetrahedron Lett.* **2000**, *41*, 8933; b) S. Ma, L. Li, *Org. Lett.* **2000**, *2*, 941; c) S. Ma, W. Gao, *J. Org. Chem.* **2002**, *67*, 6104; d) S. Ma, Z. Yu, *Angew. Chem.* **2003**, *115*, 1999; *Angew. Chem. Int. Ed.* **2003**, *42*, 1955; e) S. Ma, F. Yu, W. Gao, *J. Org. Chem.* **2003**, *68*, 5943; f) S. Ma, Z. Yu, *J. Org. Chem.* **2003**, *68*, 6149; g) W. F. J. Karstens, D. Klomp, F. P. J. T. Rutjes, H. Hiemstra, *Tetrahedron* **2001**, *57*, 5123; h) H. Ohno, Y. Takeoka, K. Miyamura, Y. Kadoh, T. Tanaka, *Org. Lett.* **2003**, *5*, 4763; for the cycloisomerization of 2-(2′,3′-allenyl)acetylacetates, see: i) T. Delair, A. Doutheau, *Tetrahedron Lett.* **1986**, *27*, 2859.

[13] S. Porcel, V. López-Carrillo, C. García-Yebra, A. M. Echavarren, *Angew. Chem.* **2008**, *120*, 1909; *Angew. Chem. Int. Ed.* **2008**, *47*, 1883.

[14] P. Pyykkö, *Angew. Chem.* **2004**, *116*, 4512; *Angew. Chem. Int. Ed.* **2004**, *43*, 4412.

[15] a) E. Jiménez-Núòez, A. M. Echavarren, *Chem. Commun.* **2007**, 333; b) H. C. Shen, *Tetrahedron* **2008**, *64*, 3885.

[16] a) C. Nieto-Oberhuber, M. P. Muòoz, E. Buòuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem.* **2004**, *116*, 2456; *Angew. Chem. Int. Ed.* **2004**, *43*, 2402; b) C. Nieto-Oberhuber, S. López, M. P. Muòoz, D. J. Cárdenas, E. Buòuel, C. Nevado, A. M. Echavarren, *Angew. Chem.* **2005**, *117*, 6302; *Angew. Chem. Int. Ed.* **2005**, *44*, 6146; c) L. Zhang, S. A. Kozmin, *J. Am. Chem. Soc.* **2005**, *127*, 6962; d) M. P. Muòoz, J. Adrio, J. C. Carretero, A. M. Echavarren, *Organometallics* **2005**, *24*, 1293; e) C. Nieto-Oberhuber, S. López, M. P. Muòoz, E. Jiménez-Núòez, E. Buòuel, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1694; f) M.-Y. Lin, A. Das, R.-S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 9340.

[17] a) C. Nevado, A. M. Echavarren, *Synthesis* **2005**, 167; b) M. T. Reetz, K. Sommer, *Eur. J. Org. Chem.* **2003**, 3485; c) Z. Shi, C. He, *J. Org. Chem.* **2004**, *69*, 3669; d) Z. Li, Z. Shi, C. He, *J. Organomet. Chem.* **2005**, *690*, 5049; e) A. Fürstner, V. Mamane, *J. Org. Chem.* **2002**, *67*, 6264; f) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556; g) C. Ferrer, A. M. Echavarren, *Angew. Chem.* **2006**, *118*, 1123; *Angew. Chem. Int. Ed.* **2006**, *45*, 1105; h) L. Zhang, *J. Am. Chem. Soc.* **2005**, *127*, 16804; i) N. Marion, S. Díez-González, P. de Frémont, A. R. Noble, S. P. Nolan, *Angew. Chem.* **2006**, *118*, 3729; *Angew. Chem. Int. Ed.* **2006**, *45*, 3647; j) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *J. Am. Chem. Soc.* **2000**, *122*, 11553; k) A. S. K. Hashmi, T. M. Frost, J. W. Bats, *Org. Lett.* **2001**, *3*, 3769; l) A. S. K. Hashmi, L. Ding, J. W. Bats, P. Fischer, W. Frey, *Chem. Eur. J.* **2003**, *9*, 4339; m) A. S. K. Hashmi, M. Rudolph, J. P. Weyrauch, M. Wölfle, W. Frey, J. W. Bats, *Angew. Chem.* **2005**, *117*, 2858; *Angew. Chem. Int. Ed.* **2005**, *44*, 2798; n) A. S. K. Hashmi, J. P. Weyrauch, E. Kurpejovic, T. M. Frost, B. Miehlich, W. Frey, J. W. Bats, *Chem. Eur. J.* **2006**, *12*, 5806.

[18] a) C. Jonasson, J.-E. Bäckvall, *Tetrahedron Lett.* **1998**, *39*, 3601; b) R. D. Walkup, L. Guan, M. D. Mosher, S. W. Kim, Y. S. Kim, *Synlett* **1993**, 88.

[19] a) R. G. Pearson, *J. Am. Chem. Soc.* **1963**, *85*, 3533; b) R. G. Pearson, J. Songstad, *J. Am. Chem. Soc.* **1967**, *89*, 1827; c) R. G. Pearson, *Survey of Progress in Chemistry*, **1969**, *5*, 1; d) H. D. Zook, J. A. Miller, *J. Org. Chem.* **1971**, *36*, 1112; e) H. D. Zook, T. J. Russo, E. F. Ferrand, D. S. Stotz, *J. Org. Chem.* **1968**, *33*, 2222; f) H. D.

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Zook, T. J. Russo, *J. Am. Chem. Soc.* **1960**, *82*, 1258; for cyclic hydrocarbonation of allenes with activated methylene groups leading to carbocycles, see: g) M. Meguro, S. Kamijo, Y. Yamamoto, *Tetrahedron Lett.* **1996**, *37*, 7453.
[20] C. G. Frost, J. Howarth, J. M. J. Williams, *Tetrahedron: Asymmetry* **1992**, *3*, 1089.
[21] S. Ma, N. Jiao, L. Ye, *Chem. Eur. J.* **2003**, *9*, 6049.
[22] S. Brandänge, L. Flodman, Å. Norberg, *J. Org. Chem.* **1984**, *49*, 927.

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