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Palladium-Catalyzed Reaction of Acylzirconocene Chloride and Stereoselective Formation of Bicyclo[3.3.0] Compounds

Yuji Hanzawa,* Masaya Yabe, Yusuke Oka, and Takeo Taguchi*

School of Pharmacy, Tokyo University of Pharmacy and Life Science,
1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

hanzaway@ps.toyaku.ac.jp

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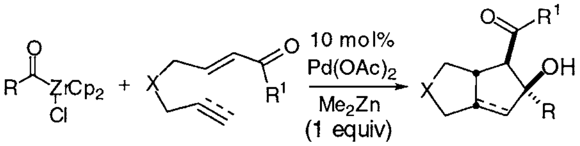
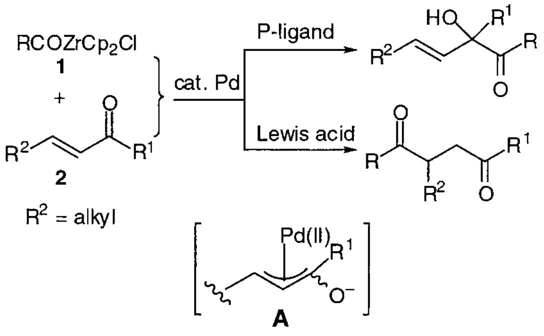
ABSTRACT



The acylzirconocene chloride complex as an acyl group donor reacts with ω-unsaturated α,β-enones and -ynones under Pd-$Me_2Zn(Me_2AlCl)$-catalyzed conditions to give stereoselectively bicyclo[3.3.0] compounds through (i) formation of a Pd(II) intermediate by an oxidative addition of the Pd(0) catalyst to an enone function, (ii) cyclization of the Pd intermediate to an ω-unsaturated group, (iii) an acyl group transfer from zirconium to Pd metal, (iv) reductive elimination of the Pd metal, and (v) intramolecular cis-selective aldol reaction.

The search for new reactivity of stable acylzirconocene chloride complexes **1**, which can be easily prepared through the hydrozirconation of unsaturated compounds and subsequent carbon monoxide insertion,[1] is the focus of our current investigation.[2] Recently, we reported regioselective access to α-ketol and 1,4-diketone compounds through Pd(0)-catalyzed reactions of **1** with α,β-unsaturated enone derivatives **2** (Scheme 1).[2d,e] In these reactions, we postulated a series of reactions: the formation of Pd(II) intermediate species **A** generated by an electron transfer from a Pd(0) catalyst to α,β-enones, the transfer of an acyl group from **1** to Pd(II) intermediate **A** (transmetalation), and the reductive elimination of Pd(0) giving acylation product. The regioselectivity of the reaction was efficiently controlled by the choice of additives; that is, an addition of Lewis acid or phosphine ligand to the reaction mixture afforded 1,4-addition or 1,2-addition product, respectively.

Scheme 1. Pd-Catalyzed Regioselective Addition of Acylzirconocene Chloride to α,β-Enones



As a working hypothesis, when ω-unsaturated α,β-enone compound **3** was treated with **1** under identical conditions to that of α,β-enone **2**, one would expect cyclization−

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[1] Bertelo, C. A.; Schwartz, J. *J. Am. Chem. Soc*., **1975**, *97*, 228.

[2] (a) Hanzawa, Y.; Kakuuchi. A.; Yabe, M.; Narita, K.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett*. **2001**, *42*, 1737. (b) Hanzawa, Y.; Narita, K.; Taguchi, T. *Tetrahedron Lett*. **2000**, *41*, 109. (c) Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett*. **2001**, *42*, 1547. (d) Hanzawa, Y.; Tabuchi, N.; Saito, K.; Noguchi, S.; Taguchi, T. *Angew. Chem., Int. Ed*. **1999**, *38*, 2395. (e) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett*. **1998**, *39*, 8141. (f) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett*. **1998**, *39*, 6249. (g) Harada, S.; Taguchi, T.; Tabuchi, N.; Narita, K.; Hanzawa, Y. *Angew. Chem., Int. Ed*. **1998**, *37*, 1696.

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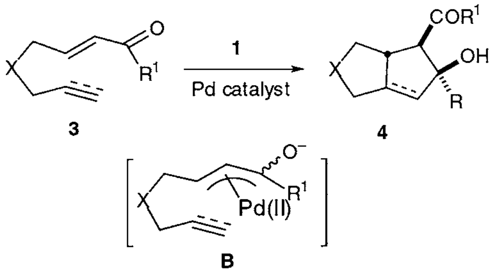
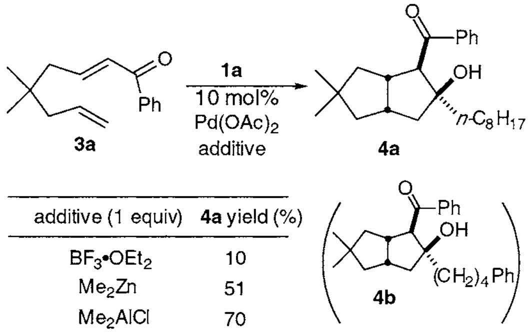
acylation to occur through an intramolecular reaction of Pd(II) intermediate species **B** to the ω-unsaturated bond (Scheme 2). In this paper, we describe the stereoselective formation of bicyclo[3.3.0] compound **4** by the Pd-catalyzed cyclization−acylation reaction of acylzirconocene chlorides **1** with ω-unsaturated α,β-enone **3** (Scheme 2).

Scheme 2



A series of reactions were involved in the conversion from **3** to **4**: (i) cyclization of Pd intermediate **B**, (ii) regioselective acylation, and (iii) subsequent intramolecular aldol reaction of the intermediately formed diketone. Recently, Montgomery et al. reported on the stereoselective formation of bicyclo[3.3.0] compounds from ω-alkynyl-α,β-enone compounds through cyclization of the π-allylic nickel complex and subsequent reaction with electrophiles.[3] They also reported on the usability of vinylzirconocene chloride as a nucleophilic reagent in a similar type of reaction.[4] In our preliminary experiment, the validity of our hypothesis was confirmed by the use of a $Pd(OAc)_2-BF_3{\cdot}OEt_2$ catalyst, which gave the 1,4-addition products in the reaction of acylzirconocene chloride **1** with α,β-enones **2**.[2e] Thus, the reaction of *n*-nonanoylzirconocene chloride (**1a**, 1.3−2.0 equiv) with compound **3a** (1 equiv) in the presence of 10 mol % $Pd(OAc)_2$ and $BF_3{\cdot}OEt_2$ (1 equiv) in THF−ether (1:2) at ambient temperature gave mostly a 1,4-addition product together with a small amount (10% yield) of bicyclo[3.3.0]octane derivative **4a** as the sole stereoisomer (Scheme 3).

Scheme 3



additive (1 equiv)	**4a** yield (%)
$BF_3{\cdot}OEt_2$	10
Me_2Zn	51
Me_2AlCl	70

Catalysts such as $Ni(COD)_2$, $Ni(acac)_2$/DIBAL-H, $PdCl_2(PPh_3)_2$, and $Pd(acac)_2$ or the use of a Lewis acid other than $BF_3{\cdot}OEt_2$ as an additive (e.g., $TiCl_4$, $ZnCl_2$, AlC_3) did not improve the yield of **4a**. Use of an equivalent amount of dimethylzinc (Me_2Zn) or dimethylaluminum chloride (Me_2AlCl) as an additive, however, significantly increased the yields of **4a** to 51% or 70%, respectively, and the presence of the stereoisomer of **4a** was not observed. The structure of **4a** was determined by NMR experiments (DEPT, H−H COSY, HMQC, and NOESY) as shown in Scheme 3, and the structure of **4a** was secured by comparing the NMR data of **4b**, which were obtained in a crystalline form, and the stereochemistry was confirmed by X-ray analysis.[5] The results of the reactions of **1** (2.0 equiv) with ω-unsaturated α,β-enones **3** (1 equiv) under the catalytic conditions [$Pd(OAc)_2$ (10 mol %)−Me_2Zn (1 equiv) or −Me_2AlCl (1 equiv)] are listed in Table 1. The Thorpe−Ingold effect[6] plays a vital role in the formation of **4** (entries 1−5). A heteroatom-containing substrate can be an efficient reactant, as well. Thus, a heterocyclic bicyclo[3.3.0] compound was obtained in fair yields (entries 6−9). For the present transformation, acylzirconocene chloride complex **1** is not restricted to saturated acylzirconocene chloride, and α,β-unsaturated acylzirconocene chloride can be used as an acyl group donor, as well (entries 7 and 8). ω-Alkynyl substrate **3** also reacted with **1a** to give the acid-labile bicyclo[3.3.0] compound (entry 10).[7] The structure of product **4** in Table 1 was determined by analogy of the NMR data with that of **4b**. It should be stressed that Montgomery's procedure,[4] which is reported for formation of bicyclo[3.3.0] compounds, is restricted to *ω-alkynyl-α,β-enone* compounds as a starting material, and the cyclization product could not be obtained in the reaction of *ω-alkenyl-α,β-enone* compounds.

It is worth noting that the catalyst generated *in situ* by the reduction of $Pd(OAc)_2$ with DIBAL-H (1 equiv) in THF−ether (1:2) indicates a comparable efficiency with $Pd(OAc)_2/Me_2Zn$ for the formation of **4**.[8] Attempted cyclization reactions of an ene−yne compound, which has no conjugated enone system, did not give the cyclized product. Thus, the α,β-enone functionality in **3** is necessary for bringing about

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(3) (a) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467. (b) Montgomery, J.; Chowdhury, S. K.; Amarasinghe, K. K. D.; Heeg, M. J. *J. Am. Chem. Soc.* **2000**, *122*, 6775. (c) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911.

(4) Ni, Y.; Amarasinghe, K. K. D.; Montgomery, *J. Org. Lett.* **2002**, *4*, 1743.

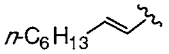
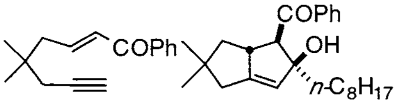
(5) Crystal data for **4b**: $C_{27}H_{34}O_2$, $M = 390.567$, triclinic, $P\bar{1}$, $a = 5.8860(13)$ Å, $b = 12.4020(14)$ Å, $c = 30.931(9)$ Å, $\alpha = 84.576(11)°$, $\beta = 85.879(9)°$, $\gamma = 85.835(9)°$, $V = 2237.1(8)$ Å^3, $Z = 4$, $D_x = 1.160$ Mg m^{-3}, Mo Kα radiation, $\lambda = 0.71073$, $\mu = 0.07$ mm^{-1}, $T = 150$ K.; 7835 independent reflections, R(gt) = 0.079, wR(gt) = 0.142 for 3534 observed reflections [$|F_o| > 1\sigma(|F_o|)$, $2\theta = 54.26°$] and 524 parameters. CCDC-186221.

(6) Beesley, R. M.; Ingold, C. K.;, Thorpe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 1080.

(7) Transposition of the hydroxyl and the double bond was observed during the isolation by silica gel column chromatography, and a similar observation has been made by Montgomery et al.[3]

(8) A reduction of $Ni(acac)_2$ by 1 equiv of DIBAL-H has been reported to give a low-valent nickel catalyst. (a) Dayrit, F. M.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4466. (b) Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333. (c) Dayrit, F. M.; Gladkowski, D. E.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 4466.

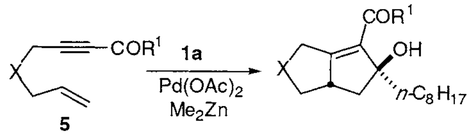
Table 1. Formation of 4 through $Pd(OAc)_2$-Catalyzed Reaction[a]

entry	**1** R	**3** X	 R^1	**4** (yield %)[b]
1	n-C_8H_{17}	CH_2	Ph	26
2	**1a** n-C_8H_{17}	Me_2C **3a**	Ph	**4a** 70[c] 51[d]
3	$Ph(CH_2)_4$	Me_2C	Ph	**4b** 52[d]
4	n-C_8H_{17}	$(BnOCH_2)_2C$		53[c] 63[d]
5	n-C_8H_{17}	$(BnOCH_2)_2C$	Me	48[c]
6	n-C_8H_{17}	O	Ph	54[c] 83[d]
7		O	Ph	60[d]
8		O	Ph	72[d]
9	n-C_8H_{17}	BocN	Ph	38[c] 41[d]
10	n-C_8H_{17}			48[c]

[a] All reactions were carried out by the use of $Pd(OAc)_2$ (10 mol %)−Me_2AlCl (1 equiv) or Me_2Zn (1 equiv) in THF/Et_2O (1:2) at ambient temperature. [b] Isolated yield was calculated from **3**. [c] Me_2AlCl as an additive. [d] Me_2Zn as an additive.

the present transformation.[9] ω-Alkenyl-α,β-ynone compound **5** also reacts with **1a** to give unsaturated bicyclo[3.3.0] compounds in fair yields (Table 2).

Table 2. Reaction of ω-Alkenyl-α,β-ynones **5** with **1a**

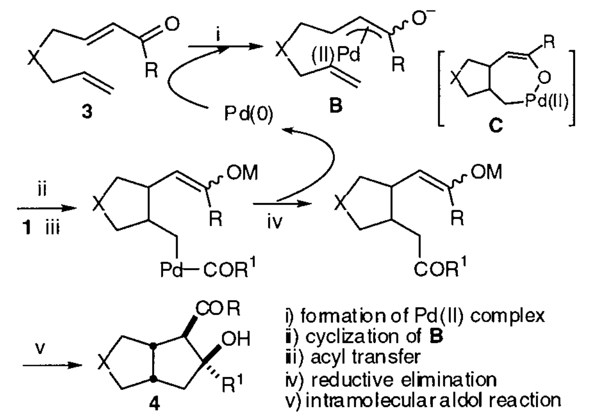


entry	**5** X	 R^1	yield (%)[a]
1	Me_2C	Ph	56
2	O		45
3	$BnO(CH_2)_2C$		55
4	$BnO(CH_2)_2C$	Me	48

[a] Isolated yield based on **5**.

Thus, the formation of bicyclo[3.3.0] compound **4** is a sequential result of (i) formation of Pd(II) complex **B** through an oxidative addition to the enone function from the *in situ* generated Pd(0) catalyst, (ii) cyclization of Pd(II) complex intermediate **B** to the ω-unsaturated group, (iii) acyl group transfer from Zr to Pd (transmetalation), (iv) reductive elimination of the Pd(0), and (v) intramolecular aldol reaction (Scheme 4).[10] It should be mentioned that we cannot rigorously rule out the possibility of the intervention of an oxapalladacycle complex **C** (Scheme 4) in the present transformation.[11] The *cis*-stereochemistry between the hydroxyl and ketone functional groups in products **4** indicates that the intramolecular aldol reactions in the present transformation have to be *cis*-selective. To confirm the cis-selectivity of the intramolecular aldol reaction, the reaction of keto−enone compound **6** with **1a** was examined under the same catalytic conditions [$Pd(OAc)_2$ (10 mol %)/Me_2Zn (1 equiv), 3 h at ambient temperature in THF/ether (1:2)] (Scheme 5). Two isomers **7a** and **b** (1:1.8 ratio) derived from the 1,4-addition of **1a** and the subsequent intramolecular aldol reaction of the enolate intermediate were obtained in 65% yield. It turned out that both isomers **7a**,**b** possess *cis* stereochemistry between the hydroxyl group and the phenyl ketone (Scheme 5).

Scheme 4



Although the stereochemistry and the metal species of the enolate generated *in situ* is unclear, we could confirm that the intramolecular aldol reaction *did* proceed to provide *cis* stereochemistry.[12] Regarding the role of additives (Me_2Zn or Me_2AlCl) in the present transformation we must await further study.[13] In summary, we are able to show that an acylzirconocene chloride complex as an acyl group donor reacts with ω-unsaturated α,β-enone and -ynone under Pd-

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(9) Ester instead of a ketone carbonyl in **3** failed to yield the corresponding product. The length of the tethering chain in **3** or **5** affected the reactivity; that is, a shorter or longer tethering chain did not give the cyclization product.

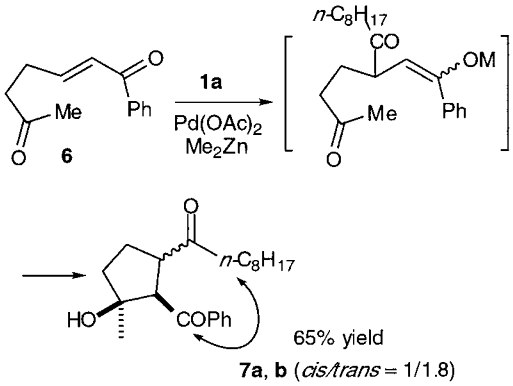
(10) The same type of transformations with Ti complex were reported. (a) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc.* **1997**, *119*, 10014. (b) Suzuki, K.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 8729.

(11) Recently, Montgomery et al. reported the formation of metallacycle through the reaction of alkynyl enals with Ni(0). Amarasinghe, K. K.; Chowdhury, S. K.; Heeg, M. J.; Montgomery, J. *Organometallics* **2001**, *20*, 370.

(12) An attempted trapping of the enolate intermediate with TMSCl gave a complex mixture of products, and we could not isolate the TMS-enol ether.

(13) We have examined other organozinc or organoaluminum reagents. However, only Me_2Zn or Me_2AlCl showed reasonable efficiency. The effect of organozinc has been discussed in the Ni-catalyzed reactions. See ref 3.

Scheme 5. Conjugate Addition of **1** and Intramolecular Aldol Reaction



Me_2Zn (Me_2AlCl)-catalyzed conditions to give bicyclo[3.3.0] compounds. The stereoselective preparation of bicyclo[3.3.0] compounds is an important subject and excellent procedures have been devised.[14] We hope to demonstrate soon various means for utilizing our strategy to construct significant molecules.

Acknowledgment. We thank the Ministry of Education, Science, Sports and Culture of Japan (Grant No. 13672233) for financial support and Mr. H. Fukaya for X-ray analysis.

Supporting Information Available: General experimental procedure and characterization data for products reported in Tables 1 and 2 and Scheme 5 (^{1}H NMR, ^{13}CNMR, IR, and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) Schore N. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds; Pergamon: Oxford, UK, 1991; Vol. 5, p 1037. (b) Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds; Pergamon: Oxford, UK, 1991; Vol 5, p 1163 and the references therein.