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Cyclization/acylation reactions by nickel-catalyzed reactions of 1,6-ynal and 1,6-enyne derivatives with acylzirconocene chloride

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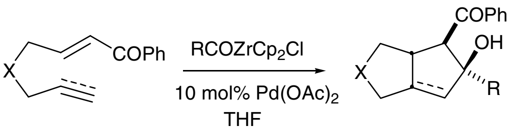
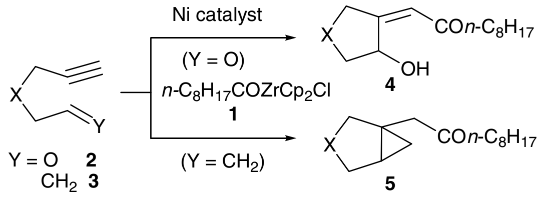
Abstract—$NiCl_2(PPh_3)_2$-catalyzed reactions of 1,6-ynal or 1,6-enyne compounds with *n*-nonanoylzirconocene chloride afforded stereoselectively cyclopentane derivatives or bicyclo[3.1.0] compounds by catalytic cyclization/acylation reactions, which would involve (i) the primary formation of a metallacycle followed by (ii) the transfer of an acyl group from the acylzirconocene complex (transmetalation).

Acylzirconocene chloride is a stable and readily accessible complex,[1] and we reported for the first time about the efficient carbon–carbon bond formation by the use of acylzirconocene chloride complexes as a donor of an acyl anion in reactions with electrophiles such as aldehydes or imines.[2] Because of the poor nucleophilicity of acylzirconocene chloride complexes to electrophiles, a catalyst or mediator is required to bring about the efficient formation of carbon–carbon bonds.[3] During the study of transition metal-catalyzed reactions of acylzirconocene chlorides, we found the formation of bicyclo[3.3.0]octane derivatives by $Pd(OAc)_2$-catalyzed reactions of acylzirconocene chlorides with ω-unsaturated α,β-enone compounds (Scheme 1).[4]



Scheme 1. $Pd(OAc)_2$-Catalyzed reaction of acylzirconocene chloride.

In the $Pd(OAc)_2$-catalyzed formation of the bicyclo[3.3.0]octane compounds, the presence of an α,β-enone functional group is essential to bring about the reaction, and thus the reaction of ω-unsaturated aldehydes or 1,ω-bisunsaturated compounds with acylzirconocene chlorides did not yield acylation/cyclization products. In this report, we describe the unprecedented formation of cyclopentanol derivatives and bicyclo[3.1.0] compounds by the Ni-catalyzed reaction of *n*-nonanoylzirconocene chloride (**1**), with 1,6-ynals **2** and 1,6-enynes **3** (Scheme 2).[5]



Scheme 2. Ni-Catalyzed reactions of acylzirconocene chloride.

n-Nonanoylzirconocene chloride (**1**), which is generated by the hydrozirconation of 1-octene followed by the insertion of carbon monoxide (1 atm, CO-balloon), is used as a typical acylzirconocene chloride complex throughout this letter. The evaluation of nickel catalysts was conducted by the reaction of **1** with 1,6-ynal **2a**, and the results are shown in Table 1. $Ni(COD)_2$ catalyst yielded cyclization product **4a** in 81% yield as a mixture of *E*,*Z*-isomers (1/2.4) (Table 1, entry 1). Ni-catalyst, which is generated in situ from nickel acetylacetonate

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Keywords: Nickel catalyst; Acylzirconocene chloride complex; Cyclization; Acylation.

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[Ni(acac)$_2$] and an equivalent amount of diisobutylaluminum hydride (DIBAL-H) in THF,[6] showed the formation of **4a**, albeit lower yield (68%, $E/Z = 1/5.7$) (entry 2).[7] The catalytic activity of Ni(acac)$_2$ its own (entry 3) was less efficient compared to the Ni(acac)$_2$-DIBAL-H catalyst. It is interesting to note that the addition of triphenylphosphine to the Ni(COD)$_2$ catalyst (Ni/P = 1/4) (entry 4) or the use of triphenylphosphine ligand-containing Ni catalysts afforded *Z*-**4a** as a solely isolated product (entries 4–7).[8] Bidentate phosphine ligand-containing Ni catalysts indicated the comparable formation of **4a** with that of the triphenylphosphine ligand except for the formation of

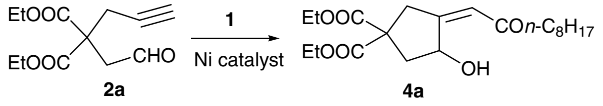


Table 1. Ni catalysts for the reaction of **2a**[a]

Entry	Ni catalyst	Yield (%)[b]	Ratio (*E*/*Z*)[c]
1	Ni(COD)$_2$	81	1/2.4
2	Ni(acac)$_2$/DIBAL-H	68	1/5.7
3	Ni(acac)$_2$	55	1/3.3
4	Ni(COD)$_2$-PPh$_3$[d]	55	*Z* only[e]
5	Ni(PPh$_3$)$_4$	45	*Z* only
6	NiCl$_2$(PPh$_3$)$_2$	74	*Z* only
7	Ni(CO)$_2$(PPh$_3$)$_2$	32	*Z* only
8	NiCl$_2$(dppe)	62	1/5.2
9	NiCl$_2$(dppf)	44	1/3.4
10	NiCl$_2$(dppp)	46	1/8

[a] The reaction was carried out at ambient temperature for 8 h by stirring a solution of **2a** (1 equiv) and **1** (2 equiv) in THF in the presence of a Ni catalyst (5 mol %).

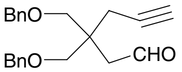
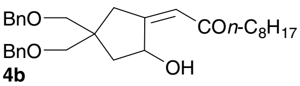
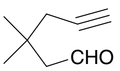
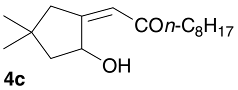
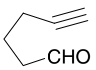
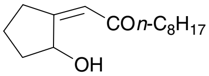
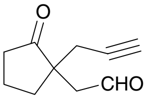
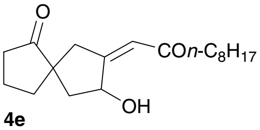
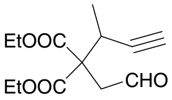
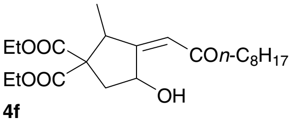
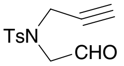
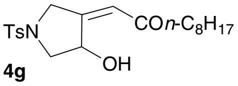
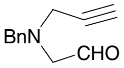
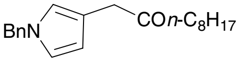
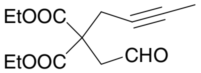
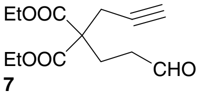
[b] Isolated yields.

[c] Determined by the ^{1}H NMR of the crude reaction mixture.

[d] Ni:P = 1:4.

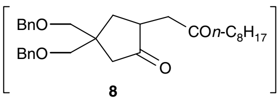
[e] See, Ref. 8.

Table 2. Formation of **4**

Entry	2	4	Yield (%)[a]
1	**2a**	**4a**	74
2	 **2b**	 **4b**	67[b]
3	 **2c**	 **4c**	87
4	 **2d**	 **4d**	<5
5[c]	 **2e**	 **4e**	58 (1.6:1)
6[c]	 **2f**	 **4f**	64 (2.6:1)
7[d]	 **2g**	 **4g**	43
8	 **2h**	 **6**	46
9	 **2i**	—	
10	 **7**	—	

[a] Isolated yields.

[b] By-product compound **8** was isolated in a trace amount (<5% yield).


8

[c] 3 equiv of **1** was used.

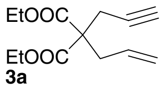
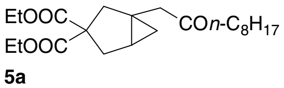
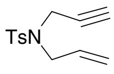
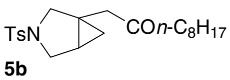
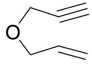
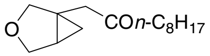
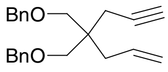
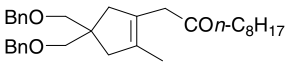
[d] Reaction was carried out at 0 °C.

the E/Z-isomers (entries 8–10). For the sake of the experimental simplicity and the formation of a single stereoisomer in a good yield, the rest of reactions of **2** was carried out by the use of a $NiCl_2(PPh_3)_2$ (5 mol %) catalyst (entry 6).

The results of $NiCl_2(PPh_3)_2$-catalyzed reactions of ω-unsaturated aldehydes with **1** are shown in Table 2.[7] The Thorpe–Ingold effect[9] would play an important role, since 5-hexynal (**2d**) showed very poor reactivity (entry 4). No selectivity in the formation of diastereoisomers was observed (entries 5 and 6). It should also be mentioned that the unexpected formation of pyrrole product **6** (46%) by the reaction of *N*-benzyl compound **2h** (entry 8), while *N*-tosyl derivative **2g** afforded the expected cyclization product **4g** (entry 7). The olefinic geometry of the α,β-enone functional group in products **4** was confirmed to be *Z*-stereochemistry.[8] The Ni-catalyzed reactions of ω-unsaturated aldehyde derivatives with acylzirconocene chloride complexes were restricted to the formation of five-membered ring compounds from 1,6-ynal compounds **2**, and the formation of a six-membered ring compound from 1,7-ynal **7** was unattainable (entry 10). The introduction of a methyl group to the terminal alkynyl carbon of **2a** made the substrate **2i** unreactive (entry 9).

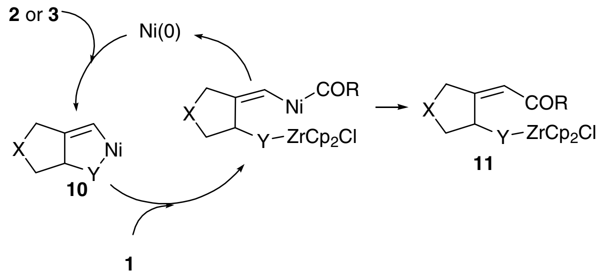
The reactions of **2** prompted us to examine the reaction of 1,6-enyne compounds **3**. It soon turns out that the reaction of 1,6-enyne compounds **3** with **1** under $NiCl_2(PPh_3)_2$-catalyzed conditions also gave cyclization/acylation products. The reaction of compounds **3** with **1**, however, gave unexpectedly bicyclo[3.1.0] compounds **5** (Table 3).[7] Thus, bicyclo[3.1.0] compound **5a** was obtained in 53% yield by the $NiCl_2(PPh_3)_2$ (5 mol %)-catalyzed reaction of **3a** with **1** in THF at ambient temperature for 18 h (entry 1). Other examined 1,6-enyne derivatives gave bicyclo[3.1.0] compounds **5** in fair yields as well (entries 1–3).[10] The reaction of *gem*-benzyloxymethyl compound **3d**, however, gave β,γ-unsaturated ketone **9** instead of the bicyclo[3.1.0] compound (entry 4). The tendency of the reaction of 1,6-enyne **3** was similar to that of 1,6-ynal **2**. Thus, the 1,6-bisunsaturation and terminal alkyne are necessary to yield products, bicyclo[3.1.0] compounds **5**.

Table 3. Formation of **5**[a]

Entry	3	5	Yield (%)[b]
1	 **3a**	 **5a**	53
2	 **3b**	 **5b**	55
3	 **3c**	 **5c**	57
4	 **3d**	 **9**	42

[a] Reaction was carried out at ambient temperature for 18 h by stirring a solution of **3** (1 equiv) and **1** (3 equiv) in THF in the presence of $NiCl_2(PPh_3)_2$ (5 mol %).

[b] Isolated yields.



Scheme 3. A plausible catalytic cycle.

Although there are questions yet to be solved, a catalytic cycle, which involves Ni(0) as an active catalyst is considered at the present stage as shown in Scheme 3.[11] Thus, the catalytic cycle would consist of (i) the intervention of a nickelacycle **10**,[12,13] (ii) the regioselective transfer of an acyl group from **1** to **10** (transmetalation),[14] and (iii) the reductive elimination of Ni(0). Thus, the formation of **5** would be the result of the intramolecular Michael-type addition of organometallic intermediate **11** ($Y = CH_2$). As to the formation of **8** or **9** by the reaction of *gem*-benzyloxymethyl compound **2b** or **3d** with **1**, the isomerization of the α,β-enone function to β,γ-position in **11** would be responsible.[15]

In summary, the stereoselective formation of five-membered ring compounds by the reaction of the acylzirconocene chloride complex with 1,6-enyne or 1,6-ynal compounds under $NiCl_2(PPh_3)_2$-catalyzed conditions was elucidated. Particularly, the formation of bicyclo[3.1.0] compounds from 1,6-enyne compounds is noteworthy. We believe that these findings opened new possibilities of acylzirconocene chloride complexes as an acyl group donor in organic synthesis. Although, we have to wait for a moment to clarify the exact reaction mechanism, the Ni(0)-participating catalytic cycle would be suspected for the present reactions. Based on the hypothesis, the enantioselective version and the synthetic application of the present reactions are the current focus in our group.

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Yabe, M.; Taguchi, T. *Tetrahedron* **2002**, *58*, 7559; (c) Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Eur. J. Org. Chem.* **2003**, 116.

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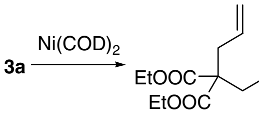
5. Montgomery et al. have reported similar Ni-catalyzed cyclizations and couplings of 1,6-ynal derivatives by the use of vinylzirconocene reagents: Ni, Y.; Amarasinghe, K. K. D.; Mongomery, J. *Org. Lett.* **2002**, *4*, 1743.
6. (a) Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045; (b) Loots, M. J.; Schwartz, J. *Tetrahedron Lett.* **1978**, 4381; (c) Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333.
7. All new compounds exhibited satisfactory spectroscopic and exact mass data.
8. The stereochemistry was confirmed by ^{1}H NMR and NOE correlations between olefinic and allylic methylene protons. The major *Z*-isomers can be converted to furan compounds in good yields by acid treatment.
9. (a) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962, pp 197–202; (b) Jung, M. E.; Garvay, J. *J. Am. Chem. Soc.* **1991**, *113*, 224; (c) Kirby, A. J. *Adv. Phys. Org. Chem.* **1980**, *17*, 183; (d) Forbes, M. D. E.; Patton, J. T.; Myers, T. L.; Maynard, H. D.; Smith, D. W., Jr.; Schulz, G. R.; Wagener, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 10978.
10. An attempted reaction of *N*-benzyl compound instead of *N*-Ts compound **3b** afforded a complex reaction mixture even under ice- or dry ice-acetone cooling conditions.
11. About the Ni catalyst, Ni(0) or Ni(II) is considered to be possible. However, Ni(0) species would be considered a catalyst in the present experiments, since (i) the formation of a small amount of 1,2-diketone, which is derived from the coupling of **1** by the use of Ni(II) catalyst followed by the reductive elimination of Ni(0), and (ii) the efficient catalytic activity of Ni(0) catalyst have been observed. Ni-catalyzed reactions of *n*-octyne with **1** under the identical conditions did not show the acylation reaction. Therefore the following sequential mechanism is considered less possible; (i) the primary formation of acyl Ni species by the reaction of **1** and Ni catalyst, (ii) the addition of the acyl Ni to the terminal alkynyl group of **2** or **3** giving a vinyl metal species, and (iii) an intramolecular attack of the vinyl metal to the carbonyl or alkene. Efficient Ni-catalyzed additions of acyltin compounds to alkynes have been reported. See: Shirakawa, E.; Nakao, Y.; Yoshida, H.; Hiyama, T. *J. Am. Chem. Soc.* **2000**, *122*, 9030.
12. Treatment of **3a** with a stoichiometric amount of $Ni(COD)_2$ in the absence of **1** afforded a cyclodimerization compound **12** in 45% yield. The formation of **12** is considered to be suggesting a primary formation of nickelacycle **10** ($Y = CH_2$) since the cyclodimerization of **3a** via the similar metalacycle intermediate to **10** giving **12** has also been proposed for $ClCo(PPh_3)_3$-catalyzed reaction of **3a**. See: Rhyoo, H.-Y.; Lee, B. Y.; Yu, H. K. B.; Chung, Y. K. *J. Mol. Catal.* **1994**, *92*, 41.



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13. The formation of oxanickelacycle **10** ($Y = O$) has been reported for the Ni(0)-catalyzed reaction of 1,6-ynals. See: Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.
14. Similar regioselective transmetalation of oxanickelacycle **10** ($Y = O$) by $ZnEt_2$ has been reported. See Ref. 13.
15. It is not clear for us at this moment to explain why *gem*-benzyloxymethyl compounds **2b** and **3d** showed the isomerization.