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Copper-catalyzed acylations of *o*-vinylbenzylzirconocene intermediate and synthetic application toward steroid skeleton

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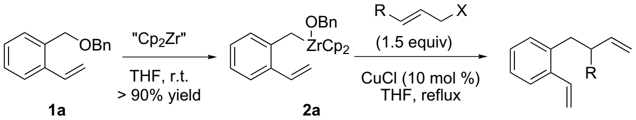
Abstract—Benzylzirconocene intermediate, which was readily prepared by a reaction of *o*-alkoxymethylstyrene with ‘Cp_2Zr’ under mild conditions, reacted with acyl chlorides in the presence of a catalytic amount of $CuBr–SMe_2$ to give ketone derivatives in moderate to good yields.

Alkyl or alkenylzirconocene chlorides are easily prepared by hydrozirconation of alkenes or alkynes with Schwartz reagent ($Cp_2Zr(H)Cl$, Cp = cyclopentadienyl). The nucleophilic reactivity of organozirconocene chloride complexes, however, is very poor, and the addition to nucleophiles scarcely takes place. To increase the reactivity of the organozirconocene complexes, a few activation procedures have been devised, and thus the utility of organozirconocene chloride complexes as an organometallic reagent is highly recognized in organic synthesis.[1]

Recently, we reported on the generation and reaction of *o*-vinylbenzylzirconocene intermediate **2a** by treatment of *o*-benzyloxymethylstyrene **1a** with ‘Cp_2Zr’ (zirconocene–butene complex, *zirconocene equivalent*) followed by copper-catalyzed allylation with allyl halides or phosphates (Scheme 1).[2]

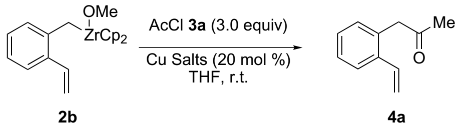


Scheme 1.

In general, benzylic metal species that contain an *o*-vinyl substituent would be a useful intermediate as it is a reactive benzyl metal attached to a reactive styrene–olefin unit. To the best of our knowledge, only a few examples[3] of *o*-vinylbenzyl metal species are known because of the difficulty in their preparation due to the high reactivity of the styrene–olefin unit.

Therefore, for the purpose of presenting further synthetic use of **2a**, we examined the acylation of **2a**. The reaction of acid chlorides with organometallic reagents is one of the most direct and convenient procedures for the synthesis of ketones.[4]

Although it is well-known that alkylzirconocene species can be directly acylated with acid chloride,[5] the transmetalation of organozirconocene species to copper species is more often employed.[6] At the outset, various copper salts acting as a catalyst for the reaction of **2b**[7] with acetyl chloride **3a** at room temperature in THF were examined (Scheme 2), and the results are summarized in Table 1.



Scheme 2.

Keywords: Benzylzirconocene; Styrene; Acylation; Steroid skeleton.

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Table 1. Copper-catalyzed reactions of **2b** with **3a**[a]

Entry	Cu salt (20 mol%)	**4a** Yield (%)[b]
1	None	No reaction
2	CuCl	27
3	CuBr	Trace
4	CuBr–SMe_2	29
5	CuI	Trace
6	CuCN	Trace
7	CuCN–2LiCl	Trace
8	Cu_2O	No reaction
9	$Cu(OTf)_2$	17
10	$CuCl_2$	10
11	$CuBr_2$	17

[a] The reaction of **2b** (0.1 mmol) with **3a** (0.3 mmol) was carried out in the presence of Cu salt (0.02 mmol) in THF (1 mL) at room temperature for 5 h.

[b] HPLC yields.

Since the benzylic zirconocene complex **2a** is considered to be more reactive than the alkylzirconocene complex, it is curious for us that **2a** did not react with acetyl chloride **3a** in the absence of the copper catalyst (entry 1). Although CuCl and CuBr–SMe_2 showed low catalytic activity (entries 2 and 4), other Cu^I salts, such as: CuBr, CuI, CuCN, and Cu_2O, did not act as catalysts for the reaction (entries 3, 5–8), and Cu^{II} salts, such as $Cu(OTf)_2$, $CuCl_2$, and $CuBr_2$, were inferior (entries 9–11).

Based on the results shown in Table 1, we optimized the reaction conditions for the acylation of **2a** or **2b** with **3a** (Table 2). It turned out that the reflux of the reaction mixture dramatically increased yields of **4a** (Scheme 3).

As a copper catalyst, CuBr–SMe_2 was superior to CuCl under the present conditions (entries 1 and 2). With a reduction in the amount of CuBr–SMe_2 (20, 10–5 mol%), the yields of **4a** were slightly lowered (entries 2–4). Using benzylzirconocene intermediate **2a** instead of **2b**, ketone derivative **4a** was obtained in an excellent yield (93%) (entry 5).[8] Therefore, the reaction conditions described in entry 5 in Table 2 are optimal. The scope and limitations of the present acylation of **2a** are shown in Table 3.

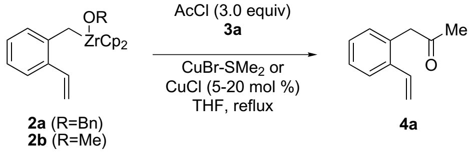
All reactions were carried out by using **2a** (1.0 equiv), acid chlorides **3a–f** (3.0 equiv), and CuBr–SMe_2 (20 mol%) in THF at reflux temperature.[9] A variety of acid chlorides could be used in the present acylation. Bulky pivaloyl chloride **3b** reacted with **2a** to give ketone derivative **4b** in a moderate yield (entry 2). Benzoyl chloride **3c** and alkenoyl chloride represented by cinnamoyl chloride **3d** gave the corresponding ketones **4c** and **4d** in good yields (entries 3 and 4). Alkynoyl chloride, such as **3e**, however, gave a complex mixture (entry 5). Other alkynoyl chlorides, such as 3-trimethylsilylpropynoyl chloride or 2-hexynoyl chloride also gave a complex mixture. Thus, α,β-alkynoyl chlorides were inadequate substrates for the present acylation. Acid chloride **3f**, which contained an ester group, gave a γ-keto ester derivative **4f** in good yield (entry 6).

Table 2. Optimization of reaction conditions of **2a** or **2b** with **3a** in the presence of CuCl or CuBr–SMe_2[a]

Entry	Cu salt (mol%)	**2** (R =)	**4a** Yield (%)[b]
1	CuCl (20)	**2b** (Me)	68
2	CuBr–SMe_2 (20)	**2b** (Me)	78
3	CuBr–SMe_2 (10)	**2b** (Me)	75
4	CuBr–SMe_2 (5)	**2b** (Me)	72
5	CuBr–SMe_2 (20)	**2a** (Bn)	93

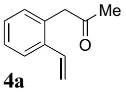
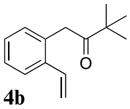
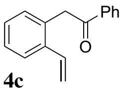
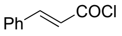
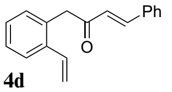
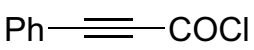
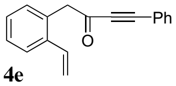
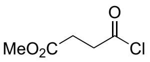
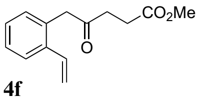
[a] Unless otherwise noted, the reaction of **2a** or **2b** (1 mmol) with **3a** (3 mmol) was carried out in the presence of CuCl or CuBr–SMe_2 (0.05–0.2 mmol) in THF (10 mL) at reflux for 5 h.

[b] Isolated yields.



Scheme 3.

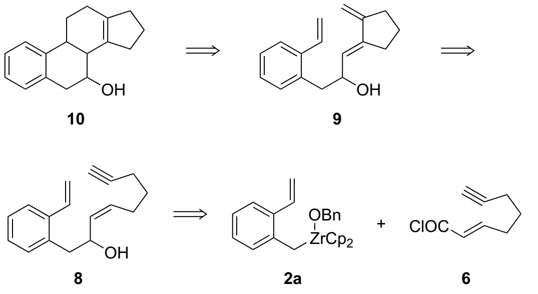
Table 3. Copper catalyzed acylations of benzylzirconocene intermediate **2b** with acid chlorides[a]

Entry	Acyl halide	Product	Yield (%)[b]
1	AcCl **3a**	 **4a**	93
2	*t*-BuCOCl **3b**	 **4b**	69
3	PhCOCl **3c**	 **4c**	87
4	 **3d**	 **4d**	88
5	 **3e**	 **4e**	Complex mixture
6	 **3f**	 **4f**	77

[a] Unless otherwise noted, the reaction of **2a** (1 mmol) with acyl chloride **3a–f** (3.0 mmol) was carried out in the presence of CuBr–SMe_2 (0.2 mmol) in THF (10 mL) at reflux temperature for 5 h.

[b] Isolated yields.

As for the synthetic application of the present acylated product, a preliminary study for the synthesis of a steroid framework was examined. A retrosynthetic pathway is shown in Scheme 4.



Scheme 4. Retrosynthetic analysis for the synthesis of steroid skeleton.

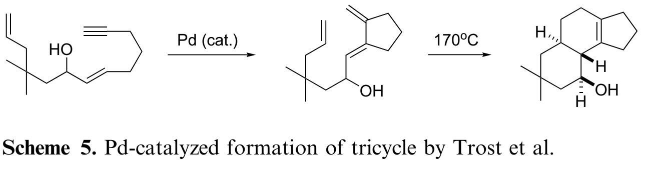
The construction of steroid skeleton **10** would be achieved by the intramolecular Diels–Alder reaction of the styrene–olefin unit with the cyclic *exo*-1,3-diene unit of **9**, which would be prepared from ene–yne precursor **8**.

The ene–yne compound **8** would be prepared by the acylation of **2a** with acid chloride **6**.

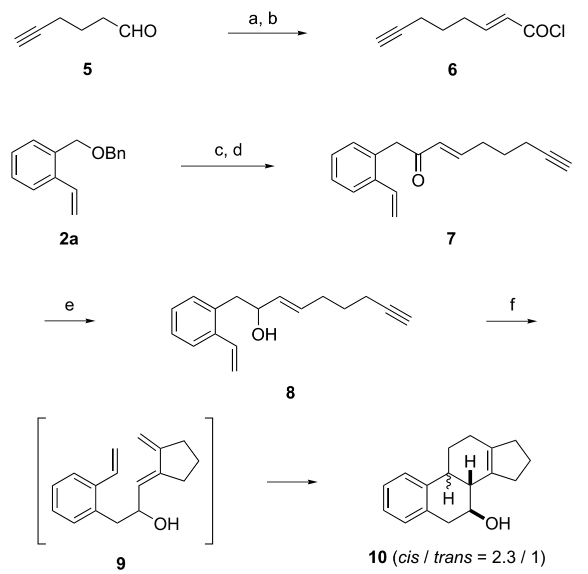
The synthesis of 1,3-diene derivatives from nonconjugated ene–yne compounds using a Pd-catalyst and its intramolecular Diels–Alder reaction were studied in detail by Trost.[10] It has also been suggested that the hydroxy group adjacent to the internal alkenyl group controls not only the regioselectivity in the Pd-catalyzed cyclization, but also the diastereofacial-selectivity of the subsequent intramolecular Diels–Alder reaction (Scheme 5).

The ene–yne acid chloride **6** prepared from 5-hexynal **5**[11] in two steps reacted with **2a** to give a corresponding ketone derivative **7** in 81% yield (Scheme 6). The ω-alkyne of **6** is tolerable in the present acylation. The reduction of the carbonyl group by $LiAlH_4$ gave an allyl alcohol derivative **8** in 73% yield. Under the Pd-catalyzed 1,3-diene synthesis conditions (($(dba)_3Pd_2$–$CHCl_3$ (2.5 mol%), PPh_3 (5 mol%), AcOH (5 mol%), toluene, 60 °C), tetracyclic compounds **10** were obtained directly in 74% yield as a mixture of two diastereomers in the ratio of 2.3/1 (*cis*/*trans*). The structures were determined by NMR spectra (Fig. 1).[12] In contrast to the results of Trost et al., *cis*-product **10** was obtained as a major product.[13]

Although the more precise control for the stereoselectivity in the intramolecular Diels–Alder reaction and further introduction of functional groups are necessary toward the synthesis of steroid derivatives, we were able to achieve the construction of a steroid framework in short steps and in good yields through a combination of the 'Cp$_2$Zr'-mediated chemistry and the Pd-catalyzed chemistry.



Scheme 5. Pd-catalyzed formation of tricycle by Trost et al.



Scheme 6. Reagents and conditions: (a) (i) $(EtO)_2P(O)CH_2CO_2TMS$, *n*-BuLi, THF; (ii) H_3O^+, quant; (b) $(COCl)_2$, CH_2Cl_2, 77%; (c) Cp_2ZrCl_2, *n*-BuLi, THF; (d) **6**, CuBr–SMe_2, THF, reflux, 81% (two steps); (e) $LiAlH_4$, THF, 73%; (f) $(dba)_3Pd_2$–$CHCl_3$, Ph_3P, AcOH, toluene, 60 °C, 74%.

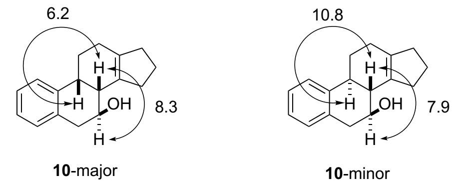


Figure 1. Coupling constants (Hz) of tetracyclic compounds **10**.

In conclusion, a copper-catalyzed effective acylation of *o*-vinylbenzylzirconocene intermediate **2a** with various acid chlorides was found. A wide variety of *o*-styrylmethyl alkyl, alkenyl, and aryl ketone derivatives can be synthesized by this protocol. Studies of the reactions of **2a** with more functionalized acid chlorides and a stereoselective synthesis of optically pure steroid derivatives are now in progress.

References and notes

1. For recent reviews, *Titanium and Zirconium in Organic Synthesis*; (a) Marek, I., Ed.; Wiley–VCH: Germany, 2002; (b)'Recent advances in the chemistry of zirconocenes' in Symposium-in print *Tetrahedron*, **2004**, *60*, 1267; Suzuki, K.; Wipf, P., Eds.; (c) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853, and references cited therein.
2. (a) Hanzawa, Y.; Ikeuchi, Y.; Nakamura, T.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 6503; (b) Ikeuchi, Y.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2004**, *45*, 3717.
3. To the best of our knowledge, Li species is not known. Although corresponding Mg species are known in several examples, most synthetic applications of 2-vinylbenzyl magnesium species are limited to polymer chemistry (a)

Hatada, K.; Shiozaki, T.; Ute, K.; Kitayama, T. *Polym. Bull.* **1988**, *19*, 231; (b) Kuendig, E. P.; Perret, C. *Helv. Chim. Acta* **1981**, *64*, 2606; (c) Duboudin, J. G.; Jousseaume, B.; Pinet, M. *J. Chem. Soc., Chem. Commun.* **1977**, *23*, 454.

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5. Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115.
6. Wipf, P.; Xu, W. *Synlett* **1992**, 718.
7. For an easy analysis on HPLC, intermediate **2b** was used instead of **2a**, although the yield of **2b** was lower than **2a**.
8. Although the reason is unclear, the similar phenomenon has been observed in the copper-catalyzed allylation of **2** (unpublished data). See also Ref. 7.
9. Typical experimental procedure: A mixture of **1a** (1 mmol) and $Cp_2Zr(n\text{-}Bu)_2$, which was generated by the addition of *n*-BuLi (2 equiv) to Cp_2ZrCl_2 in THF (5 mL) at −78 °C, was gradually warmed to room temperature and the mixture was stirred for 3 h. To this solution, **3a** (3.0 equiv) in THF (2 mL) and $CuBr–SMe_2$ (20 mol %) were added at 0 °C, and then refluxed for 5 h. After cooling to room temperature, saturated $NaHCO_3$ aq was added, filtration on Celite, and extracted with ether. The organic layer was washed with brine, dried over anhydrous $MgSO_4$, and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (*n*-hexane/AcOEt = 20/1), and further purification was carried out by MPLC (*n*-hexane/AcOEt = 9/1) to give **4a** in 93% yield.
10. Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34, and references cited therein.
11. Adams, T. C.; Combs, D. W.; Daves, C. D., Jr.; Hauser, F. M. *J. Org. Chem.* **1981**, *46*, 4582.
12. ^{1}H, ^{13}C, DEPT, COSY, HMQC, and decoupling measurement.
13. The present *cis*-selective formation of **10** would be the result of the enhanced *endo*-transition state due to the π-orbital interaction between the phenyl and diene components.