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Preparation of Ester-group Substituted Allylic Zinc by Palladium-catalyzed Umpolung of γ-Acyloxy-α,β-unsaturated Ester by Bis(iodozincio)methane

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Treatment of γ-acyloxy-α,β-unsaturated ester with bis(iodozincio)methane in the presence of palladium catalyst gave an allylic zinc carrying an ester group; the allylic zinc, which is prepared by this umpolung process, reacts with ketones regioselectively.

The Reformatsky reaction is one of the most efficient C–C bond forming reactions. Treatment of α-haloester with zinc in the presence of aldehyde or ketone gives β-hydroxy esters in good yields.[1] Its vinylog, however, starting from γ-bromo-α,β-unsaturated ester, has been shown to form a mixture of regioisomers, that is, α-vinyl-β-hydroxy ester and δ-hydroxy-α,β-unsaturated ester in a low yield.[1b,2] Improved Reformatsky reactions have given the better yields, but have not realized high regioselectivity of the adducts.[3] As shown in Figure 1, the reaction intermediate is mainly an allylic zinc species, but the reaction may accompany single electron transfer processes such as the Barbier reaction. In order to realize selective reaction, it is necessary to prepare the intermediary allylic zinc without a single electron transfer. For this purpose, we tried to prepare the corresponding allylic zinc species by a palladium-catalyzed umpolung of γ-acyloxy-α,β-unsaturated ester with various organozinc reagents.[4]

Tamaru reported formation of an allylic zinc by diethylzinc-mediated umpolung of a π-allyl palladium, which was formed from an allylic benzoate and Pd(0) (eq 1).[4b] The crucial step is considered to be transmetallation from the π-allyl palladium to the allylic zinc, which is driven by diethylzinc (eq 1, in parentheses). Following Tamaru's procedure, a mixture of (*E*)-benzyl 4-(benzoyloxy)but-2-enoate (**1a**)[5] and acetophenone (**2a**) was treated with diethylzinc (**3a**) in the presence of a catalytic amount of $Pd(PPh_3)_4$. Although the corresponding adduct **4a**[6] was formed selectively, it could not be obtained in a reasonable yield (Entry 1). The main product was a dimer of π-allyl palladium intermediate [(*E*)-dibenzyl 5-vinylhex-2-enedioate (**6**)]. Increased amount of diethylzinc did not change the yield so much (Entry 2). Dimethylzinc (**3b**, Entry 3), methylzinc iodide (**3c**, Entry 4), and zincate (**3d**, Entry 5) were examined instead of diethylzinc (**3a**), but the adduct could not be obtained in a reasonable yield in all cases. On the contrary, use of bis(iodozincio)methane (**3e**)[7] improved the yield of the adduct **4a** without formation of **6** (Entry 6). Optimization of the reaction conditions using **3e**, the yield of the adduct **4a** was raised to 61% (Entries 6–9). Instead of benzoate **1a**, the acetate **1b** gave the better yield (73%, Entry 10). In these reactions of Table 1, the corresponding regioisomeric adduct, benzyl 2-(1-hydroxy-1-phenylethyl)but-3-enoate (**5a**), was not detected.

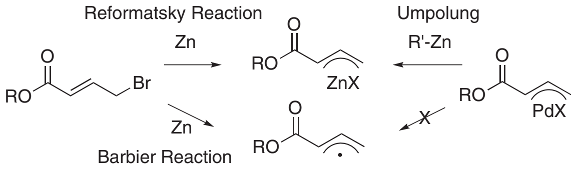
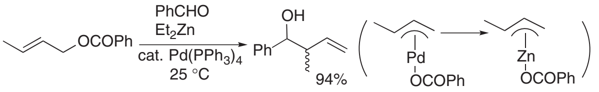


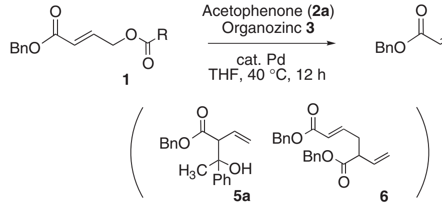
Figure 1. Plausible pathway of the Reformatsky reaction and umpolung method.



(1)

The different results using diethylzinc (**3a**) and bis(iodozincio)methane (**3e**) in Table 1 can be rationalized by the following reaction pathway. It is presumed based on Tamaru's umpolung of allylic benzoate. As shown in Figure 2, starting from **1**, π-allyl palladium **7** is formed via an oxidative insertion. When a transmetallation between **7** and an organozinc **3** is not efficient, a self-transmetallation of **7** would form bisallyl palladium **8**. In the case of Tamaru's reaction using allylic

Table 1. Reactions of (*E*)-benzyl 4-acyloxybut-2-enoate **1** with acetophenone (**2a**) mediated by organozinc **3** and Pd(0) catalyst[a]



Entry	R	Organozinc **3**	Pd catalyst	**4a**/%[b]
1	Ph (**1a**, 1.1)	Et_2Zn (**3a**, 1.2)	$Pd(PPh_3)_4$ (0.1)	21 (30)[c]
2	Ph (**1a**, 2.2)	Et_2Zn (**3a**, 2.4)	$Pd(PPh_3)_4$ (0.2)	31 (30)
3	Ph (**1a**, 1.1)	Me_2Zn (**3b**, 1.2)	$Pd(PPh_3)_4$ (0.1)	16 (54)[d]
4	Ph (**1a**, 1.1)	MeZnI (**3c**, 1,2)	$Pd(PPh_3)_4$ (0.1)	24 (64)[d]
5	Ph (**1a**, 1.1)	$^{t}Bu_3ZnLi$ (**3d**,1.2)	$Pd(PPh_3)_4$ (0.1)	<1 (30)[e]
6	Ph (**1a**, 1.1)	$CH_2(ZnI)_2$ (**3e**, 1.2)	$Pd(PPh_3)_4$ (0.1)	48 (23)
7	Ph (**1a**, 1.1)	$CH_2(ZnI)_2$ (**3e**, 1.2)	Pd(P(2-Furyl)$_3$)$_2$ (0.1)[f]	18 (17)
8	Ph (**1a**, 1.1)	$CH_2(ZnI)_2$ (**3e**, 1.2)	Pd(P(*p*-Anisyl)$_3$)$_2$ (0.1)[f]	15 (25)
9	Ph (**1a**, 2,2)	$CH_2(ZnI)_2$ (**3e**, 2.4)	$Pd(PPh_3)_4$ (0.2)	61 (3)
10	Me (**1b**, 2.2)	$CH_2(ZnI)_2$ (**3e**, 2.4)	$Pd(PPh_3)_4$ (0.2)	73 (<1)
11	CF_3 (**1c**, 2.2)	$CH_2(ZnI)_2$ (**3e**, 2.4)	$Pd(PPh_3)_4$ (0.2)	29 (16)

[a] To a mixture of **1**, **2a** (1.0), and Pd catalyst in THF, organozinc **3** was added dropwise at 25 °C. The ratio of the reactants is shown in parentheses. The whole was stirred at 40 °C for 12 h. [b] The yields were determined by ^{1}H NMR using dibromomethane as an internal standard. The numbers in parentheses are yields of recovered acetophenone (**2a**). [c] The dimer **6** was obtained in 48% yield. [d] Trace amount of **6** (<3%) was observed. [e] Benzyl 5,5-dimethyl-2-hexenoate, which is a *t*-Bu-adduct, was obtained in 37% yield. [f] Palladium catalyst was prepared in situ from Pd_2dba_3 and triarylphosphine in THF.

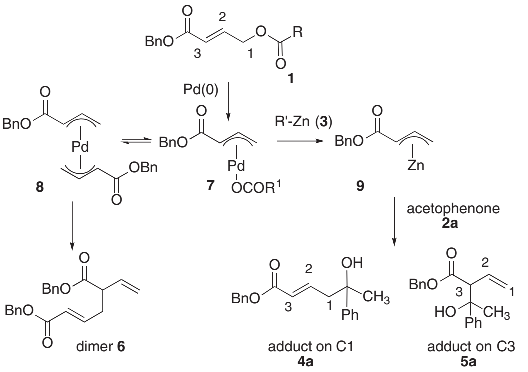
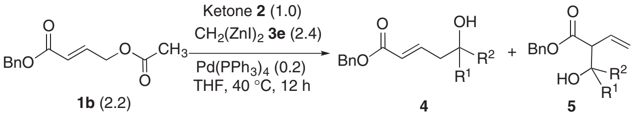


Figure 2. Plausible reaction pathway.

Table 2. Reactions of ketones **2** with allylic zinc prepared by umpolung of (*E*)-benzyl 4-acetoxybut-2-enoate (**1b**) with **3e** and Pd(0)[a]



Entry	Ketone 2		4/%[b]		5/%[b]	
1	Acetophenone	**2a**	73	**4a**	<1	**5a**
2	Propiophenone	**2b**	47	**4b**	<1	**5b**
3	Cyclohexanone	**2c**	78	**4c**	<1	**5c**
4	4-*t*-Butylcyclohexanone	**2d**	77	**4d**	<1	**5d**
5	Cycloheptanone	**2e**	80	**4e**	<1	**5e**
6	2-Butanone	**2f**	63	**4f**	<1	**5f**
7	Acetone	**2g**	8	**4g**	74	**5g**
8	Acetone[c]	**2g**	45	**4g**	<1	**5g**

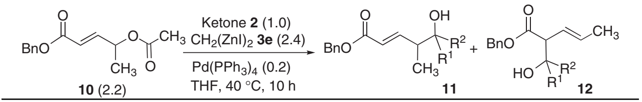
[a] To a mixture of **1b** (2.2 mmol), **2** (1.0 mmol), and Pd catalyst (0.2 mmol) in THF, dizinc **3e** (2.4 mmol) was added dropwise at 25 °C. The whole was stirred at 40 °C. [b] The yields were determined by ^{1}H NMR using dibromomethane as an internal standard. [c] The reaction period was 90 h.

benzoate (eq 1), the bisallyl palladium would not allow reductive elimination, as it is stable. In the present case however, electron withdrawing groups in **8** accelerate the reductive elimination to give the dimer **6**.[8] In order to prevent the formation of the dimer **6**, the transmetallation to allylic zinc species (from **7** to **9**) should be accelerated by using a stronger nucleophilic reagent. For this purpose, the dianion equivalent **3e** is considered to be more suitable.

The reaction was applied to other ketones as shown in Table 2. In most cases, adduct **4** was obtained selectively,[9] and regioisomer **5** was not detected. When the reaction was applied to acetone, **5g** was obtained as a major product (Entry 7). The extended reaction period, however, gave **4g** as a sole product (Entry 8). In Entries 7 and 8, the adduct **5g** is formed initially, and then isomerizes into adduct **4g**, which is thermodynamically more favored, under the reaction conditions.[10] In the reaction of using acetophenone (**2a**), the reaction was quenched after the whole was stirred for 3.5 h. In the resulting mixture, the adduct corresponding **5a** was not detected. Use of an aldehyde instead of a ketone for this transformation resulted in methylenation of the aldehyde.[11]

To examine the effect of introduction of a methyl group at the *γ*-position of **1**, (*E*)-benzyl 4-acetoxypent-2-enoate (**10**) was used as a substrate. As shown in Table 3, treatment of **10** and a ketone **2** with bis(iodozincio)methane (**3e**) in the presence of palladium catalyst gave the adduct in good yields. Unlike the reactions using primary acetate **1**, the products were **12**, which corresponds with **5** in Table 2. As the isomerization from **5g** to **4g** was observed under longer reaction times in Entries 7 and 8 of Table 2, the reaction period was also prolonged to 24 h in the reaction of **10** and acetone (Entry 3). In this case, however, the adduct **12b** was obtained in 72% yield without formation of **11b**.

Table 3. Reaction of ketones **2** with allylic zinc prepared by umpolung of (*E*)-benzyl 4-acetoxypent-2-enoate (**10**) with **3e** and Pd(0)[a]



Entry	Ketone 2		11/%[b]		12/%[b]	
1	Cyclohexanone	**2c**	<5	**11a**	91	**12a**
2	Acetone	**2g**	<5	**11b**	89	**12b**
3	Acetone[c]	**2g**	<5	**11b**	72	**12b**

[a] To a mixture of **1b** (2.2 mmol), **2** (1.0 mmol), and Pd catalyst (0.2 mmol) in THF, dizinc **3e** (2.4 mmol) was added dropwise at 25 °C. The whole was stirred at 40 °C. [b] The yields were determined by ^{1}H NMR using dibromomethane as an internal standard. [c] The reaction period was 24 h.

Thus, we have shown umpolung of *γ*-acyloxy-*α*,*β*-unsaturated esters to the corresponding allylic zinc reagents by use of a *gem*-dizinc reagent. The reagent reacts with ketones to give the adducts with high regioselectivity. It has been shown that *gem*-dizinc possesses unique reactivity as a dianion equivalent,[12] and now we have shown it to function as an efficient reducing reagent of *π*-allyl palladium.

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