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Palladium-catalyzed reaction of 4-cyclopentene-1,3-diol monoacetate with Grignard reagents producing hitherto unreachable *cis*-1,2-isomers†

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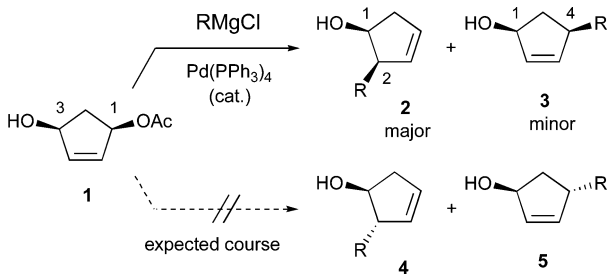
Reaction of 4-cyclopentene-1,3-diol monoacetate with RMgCl (R = alkyl, aryl) in the presence of a palladium catalyst proceeded with retention of configuration to give *cis*-1,2-regioisomers as the major products.

Controlling the regio- and stereo-chemistries in the transition metal-catalyzed reaction of secondary allylic substrates with nucleophiles is an important issue, especially for construction of a chiral carbon–carbon bond in organic synthesis.[1] Regioselectivity is usually controlled by steric as well as electronic factors in the allylic partners, while the stereochemical outcome being retention or inversion with respect to stereochemistry of a leaving group is substantially dictated by the nature of the nucleophiles. Nucleophiles classified as being 'hard' proceed with inversion,[2] and *vice versa*.[3] This generalization is well understood by the reaction courses for hard and soft nucleophiles. Hard nucleophiles react with the metal in the π-allylmetal intermediates generated transiently from the allylic substrates, while soft nucleophiles approach a π-allyl carbon from the side opposite to the metal.

Allylation of cis 4-cyclopentene-1,3-diol monoacetate (**1**), a readily available[4] and functional group-rich compound for organic synthesis, is not an exception. Reaction with soft anions such as those derived from malonate[5] and nitromethane[6] with palladium catalysts produces the *cis*-1,4-isomers (retention products) stereoselectively. In this case, regioselectivity is controlled as well by the hydroxy group, which prevents reaction at the proximal carbon of the allylic moiety due to steric as well as electronic reasons. On the other hand, an example of a reaction with hard nucleophiles was reported by us using aryl- and alkenyl-borates and a nickel catalyst to afford, as expected, *trans* products as a mixture of the regioisomers in an almost 1:1 ratio, which was then improved to a 5–20:1 ratio with the additives (NaI and MeCN).[7–9] Nickel-catalyzed alkylation with RMgX (R = alkyl) also affords a mixture of regioisomers with *trans* stereochemistry.[10] However, we found that palladium-catalyzed reaction of **1** and RMgCl affords *cis*-1,2-isomers **2** as major products, for the first time, as depicted in Scheme 1. Herein, we present the results of this reaction.



Scheme 1 Palladium-catalyzed reaction of monoacetate **1** and RMgCl giving *cis*-1,2-isomers **2**. R for **2** and **3**: **a**, *n*-Bu; **b**, $(CH_2)_3Ph$; **c**, $(CH_2)_6OMOM$ (MOM = $MeOCH_2$); **d**, c-C_6H_{11}; **e**, *t*-Bu; **f**, Ph; **g**, *o*-MeO-C_6H_4; **h**, *p*-MeO-C_6H_4; **i**, *p*-F-C_6H_4.

An unexpected result to produce *cis*-1,2-isomer **2a** (R = *n*-Bu) was observed when reaction of monoacetate **1** with *n*-BuMgCl (3 equiv.) was carried out in the presence of $Pd(PPh_3)_4$ (10 mol%) in THF at 0 °C for 1 h (Table 1, entry 1). Reaction proceeded in a stereospecific manner with good regioselectivity as judged by ^1H NMR spectroscopy. The expected *trans*-1,2- and *trans*-1,4-isomers were not produced. The chloride anion was indispensable for the selectivities since *n*-BuMgBr gave a complex mixture of products, among which *cis* isomer **2a** could be detected spectroscopically, as well as by TLC analysis (entry 2).[11] Regioselectivity and yield were influenced by additional ligands (entries 3 and 4), while the use of $Pd(PPh_3)_2$, generated *in situ* from $Pd_2(dba)_3{\cdot}CHCl_3$ and PPh_3, did not show an appreciable difference (entry 5). Reactions in diethyl ether (entry 6) and in dioxane/THF (entry 7) did not improve the selectivity and yield of entry 1.

Next, we examined other alkyl Grignard reagents (RMgCl) listed in Table 2 (entries 1–4). Reactions with primary alkyl reagents proceeded with regioselectivities and yields similar to those for the

Table 1 Palladium-catalyzed reaction of monoacetate **1** with *n*-BuMgX[a]

Entry	X of BuMgX	Catalyst	Additional ligand	Solvent	Yield (%)[b]	Ratio **2a**	Ratio **3a**
1	Cl	$Pd(PPh_3)_4$	–	THF	67 (67)	91	9
2	Br	$Pd(PPh_3)_4$	–	THF	—[c]	—	—
3	Cl	$Pd(PPh_3)_4$	dppp[d]	THF	56 (44)	88	12
4	Cl	$Pd(PPh_3)_4$	dppb[d]	THF	48	83	17
5	Cl	$Pd(PPh_3)_2$[e]	—	THF	62 (68)	89	11
6	Cl	$Pd(PPh_3)_4$	—	Et_2O	51	75	25
7	Cl	$Pd(PPh_3)_4$	dioxane[f]	THF	61	80	20

[a] Reactions of **1** (50–100 mg) and *n*-BuMgX (3 equiv.) were carried out with a palladium catalyst (10 mol%) at 0 °C in THF until all of **1** was consumed (usually 1 h). [b] Calculated by ^1H NMR spectroscopy using pyridine as an internal standard which was added after the reaction. Isolated yields are indicated in parentheses. [c] A complex mixture of products was obtained. [d] 10 mol%. [e] Prepared from $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mol%) and PPh_3 (20 mol%). [f] 20 equiv.

Table 2 Palladium-catalyzed reaction of monoacetate **1** with RMgCl[a]

Entry	R for **2**,**3**, and RMgCl	Products No.	Yield (%)[b]	Ratio **2**:**3**
1	$Ph(CH_2)_3$	**2b**,**3b**	62 (60)	90:10
2	$MOMO(CH_2)_6$	**2c**,**3c**	62 (52)	90:10
3	c-C_6H_{11}[c]	**2d**,**3d**	(87)	81:19
4	*t*-Bu	**2e**,**3e**	37	79:21
5	Ph	**2f**,**3f**	59	88:12
6	$C_6H_4(OMe)$-*o*	**2g**,**3g**	39	85:15
7	$C_6H_4(OMe)$-*p*	**2h**,**3h**	57 (64)	85:15
8	$C_6H_4(F)$-*p*	**2i**,**3i**	(41)	86:14

[a] Reactions were carried out with RMgCl (3 equiv.) and $Pd(PPh_3)_4$ (10 mol%) at 0 °C in THF. [b] Calculated by ^1H NMR spectroscopy using pyridine as an internal standard which was added after the reaction. Isolated yields are indicated in parentheses. [c] The prefix 'c-' denotes a cyclo group.

† Electronic supplementary information (ESI) available: typical procedure for the palladium-catalyzed reaction, determination of the structures and spectral data of products. See http://www.rsc.org/suppdata/cc/b3/b316596e/

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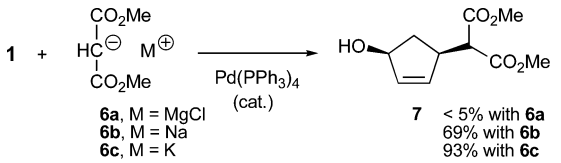
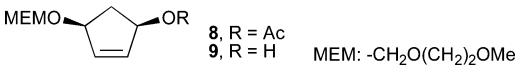
butylation, thus producing *cis*-1,2-isomers **2b** and **2c** as the major products (entries 1 and 2). The cyclohexyl group, selected as a representative example of the secondary alkyl group, was also installed efficiently (entry 3). However, *t*-BuMgCl afforded *cis*-1,2-product **2e** in low yield, though stereospecificity and good regioselectivity were maintained as well (entry 4). Similar selectivity was also observed in arylation to give *cis*-1,2-isomers **2f**–**i** as major products (entries 5–8 of Table 2). However, yields varied much depending on the substitution on the aromatic ring. Thus, good yields were recorded with Ph- and *p*-(MeO)C_6H_4-MgCl, while lower yields were obtained with *o*-(MeO)C_6H_4- and *p*-(F)C_6H_4-MgCl, probably due to steric and electronic reasons, respectively.

In order to obtain information on the stereo- and regioselectivities disclosed above, the following reactions were examined under the conditions used for the production of *cis*-1,2-isomers. As shown in eqn. (1),

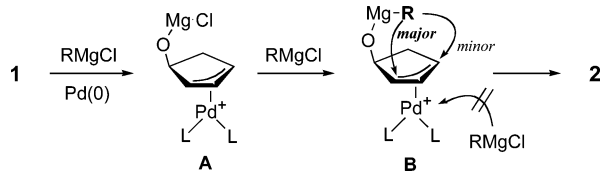


(1)

reaction of **1** with the magnesium anion **6a** derived from *t*-BuMgCl and dimethyl malonate produced a mixture of products, while sodium and potassium anions **6b** and **6c** furnished **7** in 69 and 93% yields, respectively. On the other hand, reaction of the MEM ether **8** with *n*-BuMgCl afforded alcohol **9**.

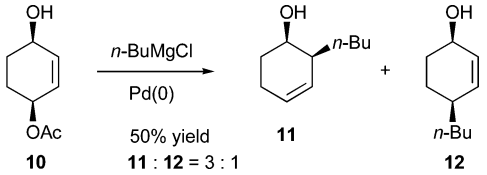


On the basis of these results, we consider a pathway illustrated in Scheme 2, in which complex **B** derived from **A** is a key complex leading to the *cis*-1,2-product **2**. Thus, RMgCl and the Pd(0) catalyst react with the substrate **1** to provide complex **A**. Further reaction with RMgCl takes place preferentially on the magnesium rather than on the palladium to furnish an advanced complex **B**, which undergoes intramolecular delivery of the R group from the Mg atom to the π-allyl moiety, thus producing the *cis*-1,2-product **2**. In the literature, the 1,4-addition of γ-hydroxy-α,β-unsaturated ketones and nitriles with RMgX is controlled by the hydroxy group at the γ-position by forming (alkoxy)MgR followed by intramolecular delivery of the R group to the β-position.[12,13] These reports indirectly support the mechanism proposed in Scheme 2. In addition, potency of the hydroxy group to arrest the R group by forming alkoxy oxygen–Mg–R was revealed to be stronger than that of the MEM group working through chelation[14] to RMgCl.



Scheme 2 A probable pathway leading to *cis*-1,2-isomers **2**.

Finally, we examined a similar reaction with cyclohexenyl monoacetate **10**, which afforded the *cis*-1,2-product **11** as a major product [eqn. (2)].



(2)

The structures of most of the products **2a**–**c**,**f**,**g** were determined unambiguously by the method described in the ESI.†

In summary, the palladium-catalyzed reaction of monoacetate **1** with RMgCl was found to produce *cis*-1,2-isomers **2**, which were previously inaccessible by other methods. This reaction is applicable to alkyl as well as aryl Grignard reagents. We believe that *cis*-1,2-isomers **2** would open up a new strategy for the synthesis of biologically active cyclopentanoids.

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