Retention of regiochemistry of monosubstituted allyl acetates in the ruthenium catalysed allylic alkylation with malonate anion†

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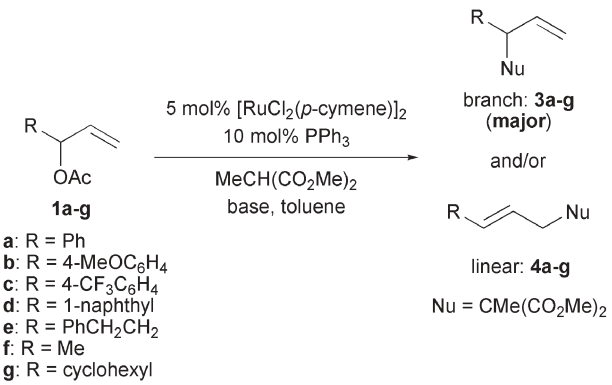
In the $RuCl_2$(*p*-cymene)/PPh_3 catalysed regioselective allylic alkylation of monosubstituted allyl acetates with malonate anion, the selective substitution at the position originally substituted with acetate was observed.

The transition metal catalysed allylic alkylation of allyl substrates is one of the most well studied reactions.[1] Usually, the reaction of monosubstituted allyl substrates potentially forms two regioisomers, and it is known that its control to form linear and branched isomers is very difficult, and the regioselectivity depends on the type of transition metal catalyst employed in the reaction. For example, ruthenium catalysts generally form a branch-type product in preference to a linear-type product, which requires some special ruthenium catalysts.[2] To the best of our knowledge, there are only a few examples of highly branch selective allylic alkylation by a ruthenium catalyst; these were reported by the groups of Mitsudo,[3] Trost[4] and Bruneau.[5] Pregosin and co-workers also reported mechanistic studies of ruthenium catalysed branch selective allylic alkylations.[6] On the other hand, we recently reported the first example of the highly linear selective allylic alkylation of allylic acetate by a ruthenium catalyst.[7] During the course of our study, we found a strong memory effect in the ruthenium catalysed allylic alkylation of monosubstituted allylic esters by some ruthenium catalysts. It had been generally accepted that, in the transition metal catalysed allylic substitution which proceeds through an unsymmetrically monosubstituted π-allylmetal intermediate, the regiochemistry of the starting allylic substrate is lost during the formation of the π-allylmetal intermediate, and the regiochemistry of the substituted product is determined by the attack of the nucleophile on the π-allylmetal. However, there are some exceptions to the palladium catalyst system, and such an unusual regioselectivity has been reported by several groups.[8–12] Furthermore, similar phenomena was also observed in the rhodium,[13] molybdenum,[14] tungsten[15] and iron[16] catalysed allylic alkylations of unsymmetrical mono-substituted allyl substrates. However, there has been no report yet about such an unusual regiochemical phenomenon in the ruthenium catalyst system. Herein, we report the regiospecific nucleophilic substitution in the ruthenium catalysed allylic alkylation of monosubstituted allylic acetates.

During our previous study, we examined several ruthenium complexes for the allylic alkylation of monosubstituted allylic acetates, and became aware that the $[RuCl_2$(*p*-cymene)$]_2$ also catalyses the reaction with or without phosphine ligands. Typically, the reaction was carried out as follows: for the 5 mol% $[RuCl_2$(*p*-cymene)$]_2$, the α-substituted allyl acetate **1a** was allowed to react with the dimethyl methylmalonate anion in toluene at 60 °C for 12 h (Scheme 1).‡ The reaction proceeded smoothly and provided **3a** with a high regioselectivity (**3a/4a** = 92/8) (Table 1, entry 1). The branch selectivity increased to 96% with the addition of 10 mol% of PPh_3 (ruthenium/phosphine = 1/1) (entry 2). We confirmed that the base, which was employed to generate the malonate anion, slightly affected the regioselectivity. The reaction using LiHMDS exhibited a higher branch selectivity than when NaHMDS was used (entries 2 and 3).[17] This branch selective allylic alkylation was observed for the reaction of other monosubstituted allyl acetates, such as **1b** and **1c**, which contained



Scheme 1

Table 1 $RuCl_2$(*p*-cymene)/PPh_3 catalyzed allylic alkylation of **1a–g**[a]

Entry	1	Base	3 : 4[b]	Yield[c] (%)
1[d]	**1a**	LiHMDS	92 : 8	89
2	**1a**	LiHMDS	96 : 4	88
3	**1a**	NaHMDS	88 : 12	94
4	**1b**	LiHMDS	93 : 7	99
5	**1c**	LiHMDS	85 : 15	99
6	**1d**	LiHMDS	96 : 4	99
7	**1e**	LiHMDS	99 : 1	91
8	**1f**	LiHMDS	99 : 1	91
9	**1g**	LiHMDS	45 : 55	41

[a] All reactions were carried out in toluene at 0 to 60 °C for 12 h under nitrogen unless otherwise noted: toluene (1.0 mL), allylic acetate **1** (1.0 mmol), $MeCH(CO_2Me)_2$ (1.5 mmol), base (1.4 mmol), $[RuCl_2$(*p*-cymene)$]_2$ (0.05 mmol), and PPh_3 (0.10 mmol). [b] The ratio was determined by 500 MHz ^{1}H NMR analysis of crude materials. [c] Isolated yield by silica gel column chromatography. [d] The reaction was conducted without PPh_3.

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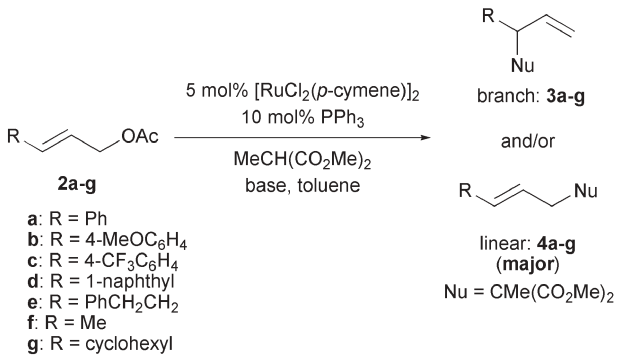

Scheme 2

Table 2 Ruthenium catalyzed allylic alkylation of **2a–g**[a]

Entry	2	Base	Temp/°C	3 : 4[b]	Yield[c] (%)
1[d]	**2a**	LiHMDS	60	20 : 80	92
2	**2a**	NaHMDS	60	11 : 89	79
3	**2a**	NaHMDS	100	1 : 99	91
4	**2b**	NaHMDS	100	1 : 99	83
5	**2c**	NaHMDS	100	9 : 91	99
6	**2d**	NaHMDS	100	1 : 99	94
7	**2e**	NaHMDS	100	1 : 99	40
8	**2e**	NaHMDS	60	1 : 99	87
9	**2f**	NaHMDS	100	9 : 91	88
10	**2g**	NaHMDS	100	1 : 99	83

[a] All reactions were carried out in toluene for 12 h under nitrogen unless otherwise noted: toluene (1.0 mL), allylic acetate **2** (1.0 mmol), $MeCH(CO_2Me)_2$ (1.5 mmol), base (1.4 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.05 mmol), and PPh_3 (0.10 mmol). [b] The ratio was determined by 500 MHz ^1H NMR analysis of crude materials. [c] Isolated yield by silica gel column chromatography. [d] THF was used as the solvent.

a methoxy group and trifluoromethyl group on the aromatic ring, respectively (entries 4 and 5). The 1-naphthyl group substituted allyl substrate **1d** also exhibited a 96% branch selectivity (entry 6). We further found that the alkyl group substituted allyl acetates **1e** (R = $PhCH_2CH_2$) and **1f** (R = CH_3) provided the branched-type products **3e** and **3f** as a single regioisomer (entries 7 and 8). Unfortunately, cyclohexyl substituted substrate **1g** gave both **3g** and **4g** with low regioselectivity (**3g**/**4g** = 45/55) in 41% yield (entry 9).

Based on the conventional regioselective trend, we postulated that the reaction of allyl acetates **2**, which are the regioisomers of **1**, would proceed with the same regioselectivity as the $[RuCl_2(p\text{-cymene})]_2/2PPh_3$ catalyst, and provide the branch-type alkylation product as the major regioisomer. However, the reaction of allyl acetates **2** exhibited the opposite regioselectivity and produced linear-type products **4** as a major isomer (Scheme 2). For example, under the same reaction conditions in which **1a** indicated a 96% branch selectivity, the allyl acetate **2a** provided the linear-type product **4a** as the major regioisomer with an 80% linear selectivity (E/Z = 99/1)[18] (Table 2, entry 1). This result clearly indicated that the selective substitution at the position originally substituted with an acetate occurred during the $[RuCl_2(p\text{-cymene})]_2/2PPh_3$ catalysed allylic alkylation of the monosubstituted allyl acetate. The linear selectivity of the reaction of **2a** was improved to 89% using NaHMDS in toluene,[19] and a perfect linear selectivity was attained at 100 °C (entries 2 and 3). This regiospecific nucleophilic substitution was observed for the reaction of several monosubstituted allyl acetates. The aromatic substituted allyl acetates **2b** (R = 4-methoxyphenyl) and **2d** (R = 1-naphthyl) gave **4b** and **4d** as single regioisomers, respectively (entries 4 and 6). The allyl acetate **2c** (R = 4-trifluoromethylphenyl) gave alkylation products **3c** and **4c** in a quantitative isolated yield, but the linear selectivity slightly decreased to 91% (entry 5). The reaction of the alkyl group substituted allyl acetate **2e** (R = $PhCH_2CH_2$) also proceeded with perfect linear selectivity, but the yield was low because a large amount of undesired $PhCH{=}CHCH{=}CHCH_3$ was formed (entry 7). However, the reaction at a lower temperature (60 °C) inhibited the formation of this elimination product, and gave the desired substituted product **4e** with a 99% linear selectivity in an 87% isolated yield (entry 8). Furthermore, the cyclohexyl group substituted allyl acetate **2g** provided **4g** as a single regioisomer (entry 10), even though **1g** did not exhibit any regioselectivities.

We confirmed that the combination of $[RuCl_2(p\text{-cymene})]_2$ and two equivalents of PPh_3 formed the known $RuCl_2(p\text{-cymene})(PPh_3)$ complex,[20] and it exhibited same regioselectivities as well as catalytic reactions. This regiospecific nucleophilic substitution in the ruthenium catalyst system suggests that both reactions of the regioisomeric allyl acetates **1** and **2** proceed through different reaction intermediates and/or reaction pathways. We also examined blank experiments, which were done without ruthenium catalyst, then we confirmed both reaction with **1** and **2** did not gave any alkylated products **3** and **4**. These results clearly showed this regiospecific nucleophilic substitutions of **1** and **2** with malonate anion were catalysed by ruthenium complex. However, it is not clear so far whether the reaction intermediates are π-allyl or σ-allyl ruthenium species. These mechanistic details about the reaction intermediates and/or reaction pathways will be studied in the future.

In conclusion, we found a regiospecific nucleophilic substitution in the ruthenium catalysed allylic alkylation of monosubstituted allyl acetates with malonate anion. The nucleophile was introduced at the position originally substituted with acetate that occurred during the $RuCl_2(p\text{-cymene})/PPh_3$ catalysed allylic alkylation of the monosubstituted allyl acetate.

Notes and references

‡ *General procedure of catalytic allylic alkylation*: The reaction conditions and results are shown in Tables 1 and 2. A typical procedure is given for the reaction of 1-phenyl-2-propenyl acetate (**1a**) (Table 1, entry 2). To a solution of $[RuCl_2(p\text{-cymene})]_2$ (30.6 mg, 0.05 mmol), PPh_3 (26.2 mg, 0.10 mmol) in toluene (1 mL) was added 1-phenyl-2-propenyl acetate (**1a**) (176 mg, 1.0 mmol) and dimethyl methylmalonate (219 mg, 1.5 mmol). LiHMDS (1.4 mmol. 1.4 mL of 1.0 M in THF) was slowly added at 0 °C, and stirred at 60 °C for 12 h. The reaction mixture was quenched with 1 M HCl (0.5 mL), then extracted with diethyl ether (3 × 2 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane–EtOAc = 10 : 1) to give 231 mg (88%) of a mixture of branch isomer **3a** and linear isomer **4a**. The ratio of **3a** and **4a** was determined to be 96 : 4 by ^1H NMR of the crude materials. **Branch-type product 3a**:[10b] ^1H NMR (500 MHz, $CDCl_3$) δ 1.43 (s, 3H), 3.62 (s, 3H), 3.71 (s, 3H), 4.15 (d, J = 8.70 Hz, 1H), 5.09–5.15 (m, 2H), 6.32 (ddd, J = 16.96, 10.10, 8.7 Hz, 1H), 7.22–7.28 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.37, 52.35, 54.49, 58.83, 117.75, 127.11, 128.14, 129.46, 136.84, 139.03, 171.25, 171.45. **Linear-type product 4a**:[10b] ^1H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 3H), 2.77 (dd, J = 1.40, 7.33 Hz, 2H), 3.74 (s, 6H), 6.05–6.11 (m, 1H), 6.45 (d, J = 15.55 Hz, 1H), 7.20–7.34 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.05, 39.47, 52.53, 53.97, 124.12, 126.12, 127.39, 128.47, 134.12, 137.08, 172.32.

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17 We also examined the reaction by KHMDS and NaH, but they resulted in a <90% branch selectivity.

18 The reaction without PPh_3 also proceeded with an 80% linear selectivity, but the linear type product was a mixture of the *E* and *Z* stereoisomers (*E*/*Z* = 90/10).

19 The linear selectivities with LiHMDS in toluene and NaHMDS in THF were 77% (89% yield) and 82% (85% yield), respectively.

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