Ruthenium-catalysed linear-selective allylic alkylation of allyl acetates†

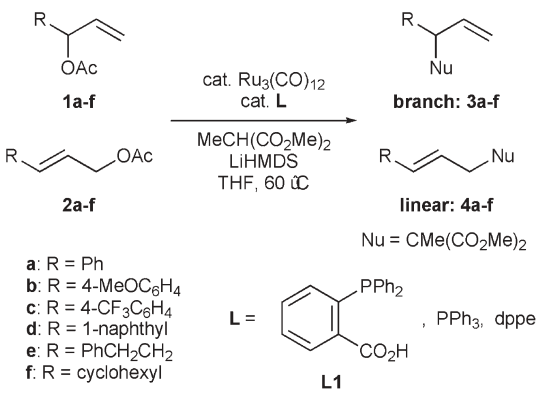
Motoi Kawatsura,*[a] Fumio Ata,[a] Shohei Wada,[a] Shuichi Hayase,[a] Hidemitsu Uno[b] and Toshiyuki Itoh*[a]

Received (in Cambridge, UK) 26th September 2006, Accepted 17th October 2006
First published as an Advance Article on the web 27th October 2006
DOI: 10.1039/b614015g

The regioselectivity in the ruthenium-catalysed allylic alkylation of mono substituted allyl acetates with the malonate anion was highly controlled by $Ru_3(CO)_{12}$ with 2-(diphenylphosphino)-benzoic acid, and the linear-type alkylated product was obtained.

Transition metal-catalysed allylic substitution is a useful process in organic synthesis, and many excellent results have been reported for the reaction of symmetrically disubstituted substrates.[1] On the other hand, the regioselective allylic substitution of unsymmetrical allyl substrates is a difficult problem and very challenging topic in this field of chemistry. In particular, it is known that the control of mono-substituted allyl substrates that forms both linear and branched isomers is very difficult and the regioselectivity depends on the type of transition metal–catalyst which was employed in the reaction. Palladium-catalysed reactions tend to cause nucleophilic substitution at the sterically less hindered allylic terminus and produces linear-type products,[2,3] while other metals such as tungsten,[4] molybdenum,[5] rhodium,[6] iridium[7] and ruthenium[8,9] preferentially yield branched-type products, by attack at the more hindered allylic terminus. On the other hand, common ruthenium catalysts exhibited a slightly low reactivity for the allylic alkylation of unsymmetrical monosubstituted allyl substrates when compared to palladium. The first regioselective ruthenium-catalysed reaction with a carbon nucleophile was reported by Mitsudo; the [Ru(cod)(cot)] catalysed highly regioselective reactions with several carbon nucleophiles. However, no regioselectivity was obtained for the reaction of the malonate anion.[8e] Recently, Trost reported that a branched type of alkylation with the malonate anion proceeded with a high selectivity using $[Cp^*Ru(NCCH_3)_3]PF_6$.[8b] Bruneau also reported some ruthenium catalysed reactions that exhibited a branched-type selectivity,[9a–e] and Pregosin also reported examples of a number of π-allylruthenium intermediates that generated branched products.[9f–i] However, there are still no examples of a ruthenium-catalysed linear-type allylic alkylation of monosubstituted allyl substrates by the malonate anion. We here report the first example of a ruthenium-catalysed perfect linear-type of allylic alkylation with malonate anion.

We discovered that $Ru_3(CO)_{12}$ with an appropriate ligand system accomplished the highly regioselective allylic alkylation of unsymmetrical allyl substrates with the malonate anion. Typically, the reaction was carried out as follows: for the ruthenium catalyst, which was prepared *in situ* by mixing 3.3 mol% $Ru_3(CO)_{12}$ with a ligand, γ-substituted allyl acetates **1** and α-substituted allyl acetates **2** were allowed to react with the dimethyl methylmalonate anion in THF at 0 to 60 °C for 12 h (Scheme 1). When PPh_3 or dppe was used as a ligand for the reaction of the γ-substituted allyl acetate **1a** with the malonate anion, the reaction proceeded smoothly, but the regioselectivity was low, and the branched isomer **3a** was obtained as the major product. Fortunately, we discovered that the reaction using 2-(diphenylphosphino)benzoic acid (**L1**)[10] as a ligand exhibited an unusual regioselectivity. The alkylation of **1a** with the malonate anion in the presence of the ruthenium catalyst coordinated with **L1** took place with a 99% linear selectivity in a 97% isolated yield (Table 1, entry 3). The reaction with 1 mol% of $Ru_3(CO)_{12}$ also proceeded with a perfect linear type of regio-selectivity, though it required a longer reaction time to complete (entry 4). The γ-substituted acetates **1b–f** exhibited a similar reactivity with an excellent high linear selectivity (entries 5–9). The linear selectivity which we observed here was higher than that of a palladium-catalysed reaction.[2e,11] We next investigated the reaction with α-substituted allyl acetates **2a–f**, which are regioisomers of **1a–f**. Most of the α-substituted allyl acetates **2** also exhibited the same linear selectivity as obtained for the reaction of the γ-substituted acetates **1**, while a slight reduction in reactivity was recorded (entries 10–16). The fact that the same regioselectivities are observed for the reactions of **1** and **2** suggests that the reaction proceeds through a shared π-allylruthenium intermediate as is usual in transition metal-catalysed allylic substitutions.



Scheme 1 Ruthenium-catalysed allylic alkylation of **1a–f** and **2a–f**.

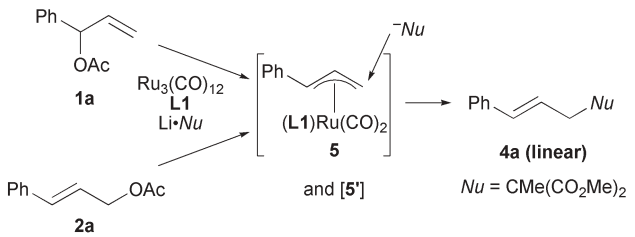
[a]*Department of Materials Science, Faculty of Engineering, Tottori University, Koyama, Tottori, 680-8552, Japan. E-mail: kawatsur@chem.tottori-u.ac.jp; titoh@chem.tottori-uac.jp; Fax: +81 857 31 5179; Tel: +81 857 31 5179*
[b]*Integrated Center for Science, Ehime University, Matsuyama Ehime, 790-8577, Japan*

† Electronic supplementary information (ESI) available: Experimental details, NMR spectra of all new compounds and X-ray data for **5**. See DOI: 10.1039/b614015g

Table 1 $Ru_3(CO)_{12}$ catalysed allylic alkylation of **1a–f** and **2a–f**[a]

Entry	Acetate	L	Yield[b] (%) of **3** and **4**	Ratio[c] **3** : **4**
1	**1a**	PPh_3	70	77 : 23
2	**1a**	dppe	90	79 : 21
3	**1a**	**L1**	97	1 : 99
4[d,e]	**1a**	**L1**	90	1 : 99
5	**1b**	**L1**	98	3 : 97
6	**1c**	**L1**	98	1 : 99
7	**1d**	**L1**	96	1 : 99
8	**1e**	**L1**	98	1 : 99
9	**1f**	**L1**	87	1 : 99
10	**2a**	**L1**	96	1 : 99
11[d,e]	**2a**	**L1**	86	1 : 99
12	**2b**	**L1**	86	3 : 97
13	**2c**	**L1**	98	1 : 99
14	**2d**	**L1**	96	1 : 99
15	**2e**	**L1**	81	1 : 99
16	**2f**	**L1**	79	1 : 99

[a] All reactions were carried out in THF at 0 to 60 °C for 12 h under nitrogen unless otherwise noted: THF (1.0 mL), allylic acetate (1.0 mmol), $MeCH(CO_2Me)_2$ (1.5 mmol), base (1.4 mmol), $Ru_3(CO)_{12}$ (0.03 mmol), and ligand (0.1 mmol). [b] Isolated yield by silica gel column chromatography. [c] The ratio was determined by 500 MHz ^1H NMR analysis of crude materials. [d] 1 mol% of $Ru_3(CO)_{12}$ and 3 mol% of **L1** were used. [e] 24 h.



Scheme 2 Reaction pathway in the ruthenium-catalysed allylic alkylation of **1a–f** and **2a–f**.

Following these reaction results, we attempted to prepare the π-allylruthenium complex, which might be a key intermediate of our highly linear selective allylic alkylation reaction (Scheme 2). Mixing $Ru_3(CO)_{12}$, the ligand **L1** and allyl acetate **1a** at 60 °C gave no new specific signals in the ^{31}P NMR spectrum. However, when the lithium salt of dimethyl methylmalonate (1 equivalent to Ru metal) was added to the reaction mixture, two new signals (major isomer **5**: δ 28.2 ppm. minor isomer **5′**: δ 34.6 ppm) appeared in the ^{31}P NMR spectrum. The ^1H NMR spectra of this complex clearly indicated the formation of π-allylruthenium complexes. The subsequent workup and recrystallization afforded orange crystals of the major π-allylruthenium complex [Ru(1-phenyl-allyl)(**L1**)$(CO)_2$] (**5**) in a 71% isolated yield, based on the Ru metal. The neutral ruthenium(II) complex **5** was stable under atmospheric conditions for the solid state and we succeeded in solving the structure by an X-ray crystallographic analysis (Fig. 1). The bond length of Ru–C3 (2.298(5) Å) is slightly longer than that of Ru–C1 (2.224(5) Å), and this relative difference in the bond lengths between Ru and the two π-allyl termini, C1 and C3, is similar to the reported results[9c,d,f–i] for the key intermediates of the ruthenium-catalysed branch selective allylic alkylations by Bruneau and Pregosin. Although branched-type alkylations were reported for Bruneau's and Pregosin's cationic ruthenium (IV) complexes, the stoichiometric reactions of the neutral

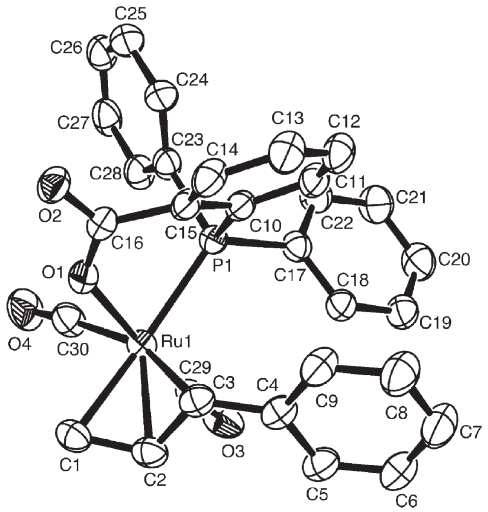


Fig. 1 Crystal structure of **5** with thermal ellipsoids at the 30% probability level. All hydrogen atoms and ethyl acetate were omitted for clarity. Selected bond lengths (Å): Ru(1)–C(1), 2.224(5); Ru(1)–C(2), 2.239(5); Ru(1)–C(3), 2.298(5); Ru(1)–C(29), 1.853(6), Ru(1)–C(30), 1.914(6); Ru(1)–P(1), 2.3345(14); Ru(1)–O(1), 2.121(4).

π-allylruthenium(II) complex **5** with the lithium enolate of dimethyl methylmalonate in THF gave a linear-type product **4a** in 100% conversion with a 99% regioselectivity, which is in good agreement with our catalytic reactions. Furthermore, we confirmed that the same π-allyl complex **5** was also formed from the allyl acetate **2a**. The ^1H NMR spectra showed that the major ruthenium complex **5** slowly converts to another new π-allyl complex **5′**. We isolated the minor π-allylruthenium species **5′** as a yellow powder, which was then subjected to a stoichiometric reaction with the malonate anion; the reactivity of **5′** was, however, very low and the reaction gave a mixture of branched- and linear-type isomers in a 79 : 21 ratio with an 80% conversion. From these results, we concluded that the π-allyl complex **5** might be the key intermediate in the linear selective allylic alkylation reaction, and nucleophilic attack selectively occurred at the sterically less hindered π-allyl terminus. The regioselectivity might be due to the difference in oxidation state [Ru(0)/Ru(II) or Ru(II)/Ru(IV)] and the absence of the Cp* ligand.[8e] These mechanistic studies will be performed in the future.‡

Notes and references

‡ **Preparation of π-allylruthenium complex 5 [Ru(1-phenyl-allyl)(L1)$(CO)_2$] and 5′.** $Ru_3(CO)_{12}$ (1.0 g, 1.56 mmol), 2-(diphenylphosphino)benzoic acid (**L1**) (1.4 g, 4.69 mmol), 1-phenyl-2-propenyl acetate (**1a**) (3.3 g, 18.7 mmol) and dimethyl methylmalonate (2.1 g, 14.0 mmol) were suspended in 15 mL of THF in a screw-capped vial. The mixture was stirred at 0 °C for 5 min, then LiHMDS (14.0 mmol. 14 mL of 1.0 M in THF) was slowly added at same temperature. The reaction mixture was then stirred at 60 °C for 2 h. The mixture was absorbed onto silica gel and chromatographed with ethyl acetate/hexane (50 : 50 to 100 : 0), then evaporated. The gummy residue was dissolved in a minimum amount of ethyl acetate and recrystallized by slow diffusion of pentane into the concentrated ethyl acetate solution at room temperature, yielding orange prismatic crystals of **5**; yield 660 mg (71% as ethyl acetate co-crystals). A suitable crystal was selected for the X-ray study. On the other hand, the mother liquor was concentrated and gave ruthenium complex **5′** as a yellow powder; *ca.* 100 mg. The ^1H NMR and ^{31}P NMR revealed that the ruthenium complex **5** (28.2 ppm in ^{31}P NMR) slowly converts to ruthenium complex **5′** (34.6 ppm in ^{31}P NMR).

Ruthenium complex 5: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.58 (dd, J = 4.55, 12.90 Hz, 1H), 3.12 (d, J = 12.90 Hz, 1H), 4.42 (dd, J = 4.55, 7.80 Hz, 1H), 5.94 (dt, J = 7.80, 12.90 Hz, 1H), 6.32–6.37 (m, 3H), 6.50–6.54 (m, 2H), 7.07–7.13 (m, 5H), 7.32–7.40 (m, 4H), 7.44–7.48 (m, 3H), 7.65–7.68 (m, 1H), 8.38 (ddd, J = 1.35, 4.6, 7.8 Hz, 1H). selected ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.16, 21.00, 61.64 (d, J = 17.30), 80.53 (d, J = 4.80), 102.96, 139.51, 140.37 (d, J = 11.54), 169.28 (d, J = 7.69), 171.09, 195.36 (d, J = 4.81), 197.76 (d, J = 11.54). ^{31}P NMR (202 MHz, $CDCl_3$) δ 28.2. mp 144–147 °C (decomp).

Ruthenium complex 5′: selected ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.74 (d, J = 12.58 Hz, 1H), 3.60 (d, J = 7.80 Hz, 1H), 4.48 (dd, J = 12.58 Hz, J_{HP} = 5.50 Hz, 1H), 5.88 (dt, J = 7.80, 12.58 Hz, 1H). selected ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.20, 21.06, 57.07, 60.41, 89.12, 89.32, 104.76, 139.65, 139.68, 140.36. ^{31}P NMR (202 MHz, $CDCl_3$) δ 34.6. mp 174–176 °C (decomp).

Crystal data for **5**·EtOAc: $C_{34}H_{31}O_6RuP$, M_W = 667.66, T = 173 K, Monoclinic, space group $P2_1/c$, a = 12.846(2), b = 16.061(3), c = 14.566(4) A, U = 3005.1(11) A^3, Z = 4, μ(Mo-Kα) = 0.711 mm^{-1}, 25 776 reflections measured, 6696 unique [R_{int} = 0.125], Final R_1 [$I > 2\sigma I$] = 0.075, wR_2 = 0.173 (all data). CCDC 622374. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b614015g

1 (*a*) J. Tsuji, *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*, John Wiley & Sons, Chichester, 2004; (*b*) B. M. Trost and M. L. Crawley, *Chem. Rev.*, 2003, **103**, 2921–2943; (*c*) J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*,Wiley & Sons, Chichester, 2000.

2 (*a*) B. M. Trost, *Tetrahedron*, 1977, **33**, 2615–2649; (*b*) G. Consiglio and M. Waymouth, *Chem. Rev.*, 1989, **89**, 257–276; (*c*) G. C. Frost, J. Holwarth and J. M. J. Williams, *Tetrahedron: Asymmetry*, 1992, **3**, 1089–1122; (*d*) M. P. T. Sjögren, S. Hansson, B. Akermark and A. Vitagliano, *Organometallics*, 1994, **13**, 1963–1971; (*e*) M. Kawatsura, Y. Uozumi and T. Hayashi, *Chem. Commun.*, 1998, 217–218.

3 (*a*) J. W. Faller and N. Sarantopoulos, *Organometallics*, 2004, **23**, 2179–2185; (*b*) R. Prétôt and A. Pfaltz, *Angew. Chem., Int. Ed.*, 1998, **37**, 323–325; (*c*) T. Hayashi, M. Kawatsura and Y. Uozumi, *Chem. Commun.*, 1997, 561–562.

4 (*a*) B. M. Trost and M.-H. Hung, *J. Am. Chem. Soc.*, 1983, **105**, 7757–7759; (*b*) J. Lehmann and G. C. Lloyd-Jones, *Tetrahedron*, 1995, **51**, 8863–8874; (*c*) F. Håkan and B. Åkermark, *Organometallics*, 1995, **14**, 561–563; (*d*) G. C. Lloyd-Jones and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 462–464.

5 (*a*) B. M. Trost, K. Dogra, I. Hachiya, T. Emura, D. L. Hughes, S. W. Krska, R. A. Reamer, M. Palucki, N. Yasuda and P. J. Reider, *Angew. Chem., Int. Ed.*, 2002, **41**, 1929–1932; (*b*) B. M. Trost, S. Hildbrand and K. Dogra, *J. Am. Chem. Soc.*, 1999, **121**, 10416–10417; (*c*) F. Glorious, M. Neuburger and A. Pfatltz, *Org. Lett.*, 1999, **1**, 141–144.

6 (*a*) B. L. Ashfeld, K. A. Miller and S. F. Martin, *Org. Lett.*, 2004, **6**, 1321–1324; (*b*) T. Hayashi, A. Okada, T. Suzuka and M. Kawatsura, *Org. Lett.*, 2003, **5**, 1713–1715; (*c*) P. A. Evans and D. K. Leahy, *J. Am. Chem. Soc.*, 2002, **124**, 7882–2883; (*d*) J. Tsuji, I. Minami and I. Shimizu, *Tetrahedron Lett.*, 1984, **25**, 5157–5160; (*e*) R. Takeuchi and N. Kitamura, *New J. Chem.*, 1998, **22**, 659–660.

7 (*a*) T. Ohmura and J. F. Hartwig, *J. Am. Chem. Soc.*, 2002, **124**, 15164–15165; (*b*) R. Takeuchi, N. Ue, K. Tanabe, K. Yamashita and N. Shiga, *J. Am. Chem. Soc.*, 2001, **123**, 9525–9534; (*c*) B. Bartels and G. Helmchen, *Chem. Commun.*, 1999, 741–742.

8 (*a*) E. C. Burger and J. A. Tunge, *Chem. Commun.*, 2005, 2835–2837; (*b*) B. M. Trost, P. L. Fraisse and Z. T. Ball, *Angew. Chem., Int. Ed.*, 2002, **41**, 1059–1061; (*c*) T. Kondo, H. Ono, N. Satake, T. Mitsudo and Y. Watanabe, *Organometallics*, 1995, **14**, 1945–1953; (*d*) S.-W. Zhang, T. Mitsudo, T. Kondo and Y. Watanabe, *J. Organomet. Chem.*, 1995, **485**, 55–62; (*e*) S.-W. Zhang, T. Mitsudo, T. Kondo and Y. Watanabe, *J. Organomet. Chem.*, 1993, **450**, 197–207; (*f*) I. Minami, I. Shimizu and J. Tsuji, *J. Organomet. Chem.*, 1985, **296**, 269–280; (*g*) C. Bruneau, J.-L. Renaud and B. Demerseman, *Chem.–Eur. J.*, 2006, **12**, 5178–5187.

9 (*a*) N. Gürbüz, I. Özdemir, B. Cetinkaya, J.-L. Renaud, B. Demerseman and C. Bruneau, *Tetrahedron Lett.*, 2006, **47**, 535–538; (*b*) M. D. Mbaye, B. Demerseman, J.-L. Renaud and C. Bruneau, *J. Organomet. Chem.*, 2005, **690**, 2149–2158; (*c*) M. D. Mbaye, B. Demerseman, J.-L. Renaud, L. Toupet and C. Bruneau, *Adv. Synth. Catal.*, 2004, **346**, 835–841; (*d*) M. D. Mbaye, B. Demerseman, J.-L. Renaud, L. Toupet and C. Bruneau, *Angew. Chem., Int. Ed.*, 2003, **42**, 5066–5068; (*e*) J.-L. Renaud, C. Bruneau and B. Demerseman, *Synlett*, 2003, 408–410; (*f*) R. Hermatschweiler, I. Fernández, P. S. Pregosin and F. Breher, *Organometallics*, 2006, **25**, 1440–1441; (*g*) I. Fernández, R. Hermatschweiler, P. S. Pregosin, A. Albinati and S. Rizzato, *Organometallics*, 2006, **25**, 323–330; (*h*) R. Hermatschweiler, I. Fernández, F. Breher, P. S. Pregosin, L. F. Veiros and M. Calhorda, *Angew. Chem., Int. Ed.*, 2005, **44**, 4397–4400; (*i*) R. Hermatschweiler, I. Fernández, P. S. Pregosin, E. J. Watson, A. Albinati, S. Rizzato, L. F. Veiros and M. J. Calhorda, *Organometallics*, 2005, **24**, 1809–1812.

10 (*a*) D. Ikeda, M. Kawatsura and J. Uenishi, *Tetrahedron Lett.*, 2005, **46**, 6663–6666; (*b*) J. Uenishi, M. Kawatsura, D. Ikeda and N. Muraoka, *Eur. J. Org. Chem.*, 2003, 3909–3912.

11 We confirmed the regioselectivities in the reaction of **1a** by $[PdCl(\pi\text{-allyl})]_2$ with PPh_3, dppe and **L1** instead of $Ru_3(CO)_{12}$/**L1** were 80%, 92% and 86%, respectively.

