Ir-catalysed allylic substitution: mechanistic aspects and asymmetric synthesis with phosphorus amidites as ligands

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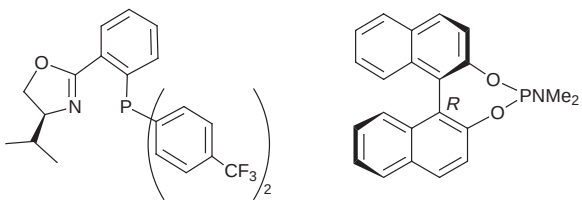
Ir-catalysed allylic alkylations of enantiomerically enriched monosubstituted allylic acetates proceed with up to 79% retention of configuration using $P(OPh)_3$ as ligand; further evidence supports the assumption of σ-allyl complexes as intermediates, and high regio- and enantioselectivity in asymmetric allylic alkylations of achiral or racemic substrates is achieved with phosphorus amidites as ligands.

The transition metal catalysed asymmetric allylic alkylation is a useful reaction in organic synthesis.[1] Over the last few years, research has been focused on finding catalysts which favour the formation of branched, chiral products **3** in the substitution of monosubstituted allylic substrates **1** or **2** (Scheme 1). With palladium complexes this is so far only possible for special cases.[2] With Mo- or W-based catalysts, so far only substrates with R = aryl gave high levels of both regio- and enantioselectivity.[3] Reactions with all these catalysts proceed *via* π-allyl complexes as intermediates which display fast π–σ–π-rearrangement. However, the substitutions catalysed by Fe- or Rh-complexes probably proceed *via* σ-allyl complexes which isomerise slowly so that almost complete chirality transfer occurs. As a consequence, even with achiral ligands, enantiomerically enriched products **3** are obtained in a double inversion process from enantiomerically enriched substrates **1**.[4]

Ir-catalysed allylic substitutions have so far been rarely studied. It was recently found that catalysts prepared by combining $[Ir(COD)Cl]_2$ with a strong π-acceptor ligand, *e.g.* triphenyl phosphite, *in situ* give rise to excellent regioselectivities in favour of the branched product **3** for both aryl and alkyl substituted allylic substrates.[5] We were able to achieve regioselectivity of 95 : 5 and enantioselectivity of 96:4 for aryl substituted substrate **2b** with phosphinooxazoline **5** as chiral ligand.[6]



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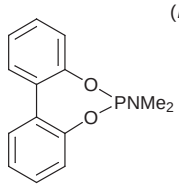
(*R*)-**6**



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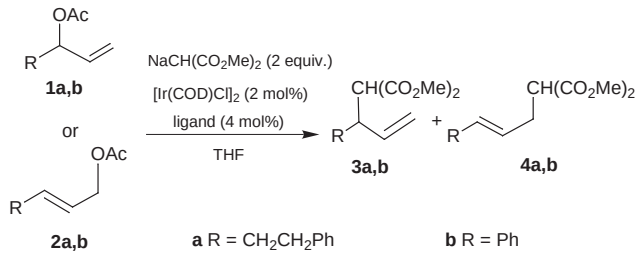
Extending this work, we have investigated the application of our catalyst to alkyl substituted allylic acetates. The reaction with substrate *rac*-**1a** using an *in situ* catalyst $[Ir(COD)Cl]_2$–**5** (24 h at 65°C) was found to be significantly slower than the reaction catalysed by $[Ir(COD)Cl]_2$–$P(OPh)_3$ or $[Ir(COD)Cl]_2$ without an additional ligand (*ca.* 3 h at room temperature) (*cf.* Table 1, entries 1,2,4). This observation led us to search for a suitable monodentate chiral ligand. Furthermore, the re-

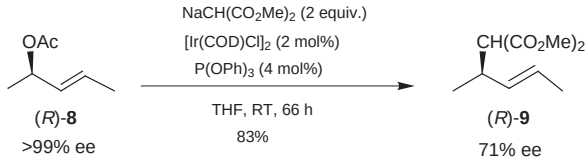


Scheme 1

Table 1 Allylic alkylation of acetates **1** and **2** catalysed by Ir^I complexes (reaction at 65 °C for 24 h with **5**, at room temperature for 3 h with all other ligands)[a]

Entry	Substrate	Ligand	Additive[b]	Yield[c] (%) **3** and **4**	Ratio **3** : **4**[d]	Ee (%)[d] of **3** (Configuration)
1	*rac*-**1a**	$P(OPh)_3$	—	99	95 : 5	—
2	*rac*-**1a**	—	—	66	89 : 11	—
3	*rac*-**1a**	PPh_3	—	—	—	—
4	*rac*-**1a**	**5**	—	99	95 : 5	8 (*S*)
5	**2a**	**5**	—	93	62 : 38	78 (*R*)
6	*rac*-**1b**	**5**		99	95 : 5	15 (*S*)
7	**2b**	**5**		99	95 : 5	91 (*R*)
8	(*R*)-**1b**[e]	$P(OPh)_3$	—	98	95 : 5	56 (*S*)
9	(*R*)-**1a**[f]	$P(OPh)_3$	—	97	95 : 5	51 (*R*)
10	(*R*)-**1a**[f]	$P(OPh)_3$	LiCl	71	93 : 7	49 (*R*)
11	*rac*-**1a**	(*R*)-**6**	—	92	98 : 2	69 (*R*)
12	**2a**	(*R*)-**6**	—	54	95 : 5	43 (*R*)
13	*rac*-**1b**	(*R*)-**6**	—	98	92 : 8	8 (*S*)
14	**2b**	(*R*)-**6**	—	99	98 : 2	37 (*R*)
15	*rac*-**1a**	(*R*)-**6**	LiF	99	> 99 : 1	58 (*R*)
16	*rac*-**1a**	(*R*)-**6**	LiCl	83	> 99 : 1	86 (*R*)
17	*rac*-**1a**	(*R*)-**6**	LiBr	69	98 : 2	83 (*R*)
18[g]	(*R*)-**1a**[h]	(*R*)-**6**	—	99	99 : 1	75 (*R*)
19	(*S*)-**1a**[i]	(*R*)-**6**	—	92	99 : 1	31 (*R*)
20	(*R*)-**1a**[h]	(*R*)-**6**	LiCl	99	99 : 1	93 (*R*)
21	(*S*)-**1a**[i]	(*R*)-**6**	LiCl	54	99 : 1	68 (*R*)
22	(*R*)-**1a**[f]	**7**	—	98	99 : 1	39 (*R*)
23	(*R*)-**1a**[f]	**7**	LiCl	61	71 : 29	32 (*R*)

[a] General procedure: A solution of $[Ir(COD)Cl]_2$ (6.7 mg, 0.01 mmol), substrate (0.5 mmol) and ligand (0.02 mmol) in dry THF (2 ml) under argon was treated with a solution of dimethyl 2-sodiomalonate in dry THF (0.5 M, 2 ml, 1.0 mmol). Water was added after stirring under the conditions stated. Extraction with Et_2O followed by flash chromatography (silica, light petroleum–EtOAc 97 : 3) gave mixtures of **3** and **4**. [b] Modification of the general procedure: Addition of 0.5 mmol of lithium halide before addition of the dimethyl 2-sodiomalonate solution. [c] Yield of isolated product. [d] Determined by HPLC on DAICEL CHIRACEL OJ column, length: 25 cm + 5 cm precolumn, flow: 0.5 ml min^{-1}, eluent: *n*-hexane–Pr^iOH (97 : 3), **3a**: $t_R(R)$ = 33 min, $t_R(S)$ = 42 min; **4a**: t_R = 50 min; **3b**: $t_R(S)$ = 53 min, $t_R(R)$ = 60 min; **4b**: t_R = 83 min. [e] 93.8% ee. [f] 90.8% ee. [g] Reaction time: 1 h. [h] 99.5% ee. [i] 96.4% ee.



Scheme 2

gioselectivity (ratio of **3**:**4**) starting from achiral **2a** was low (**3**:**4** = 62:38) and the enantioselectivity high [(*R*)-**3a** of 78% ee], whereas with the regioisomeric racemic substrate **1a** it was just the opposite: the regioselectivity was high (**3**:**4** = 95:5) and the enantioselectivity low [(*S*)-**3a** of 8% ee] (entries 4–7). These results demonstrate that properties of allyl–Ir intermediates differ from those of allyl–Pd intermediates. As a rule, in Pd-catalysed allylic substitutions regioisomeric starting materials give rise to the same products; memory effects are known, but are small for bidentate ligands.[7]

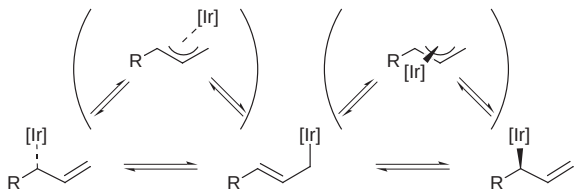
For further clarification, the configurational stability of intermediary allyl–Ir complexes and the configurative course of the substitution were investigated. First, enantiomerically enriched **1a** and **1b** were alkylated using $P(OPh)_3$ as ligand.† Starting from (*R*)-**1a** of 91% ee the product (*R*)-**3a** was obtained with 51% ee with retention of configuration, *i.e.* 79% of the substrate had reacted with retention of configuration (entry 9). Similar results were achieved with the phenyl substituted substrate **1b** (entry 8).‡ Second, enantiomerically pure pent-3-en-2-yl acetate† [(*R*)-**8**] was reacted with dimethyl 2-sodiomalonate (Scheme 2); alkylation product (*R*)-**9** with 71% ee was formed.

As of now we cannot offer a conclusive explanation of our results. As a working hypothesis we assume that the Ir-catalysed reactions proceed, similar to the mechanism proposed for Rh-catalysed reactions,[4] by substitution of acetate to give σ-allyl–Ir complexes which further react with malonate again with inversion; the σ-complexes undergo slow racemisation (or epimerisation) *via* σ–π–σ-rearrangement or sigmatropic 1,3-rearrangement (Scheme 3).

The easily accessible phosphorus amidite **6**[8] was used as a monodentate chiral ligand (ratio Ir:**6** = 1:1). For all substrates this ligand is equivalent to $P(OPh)_3$ with respect to catalytic efficiency and regioselectivity (entries 11–14). Surprisingly, and in contrast to the results obtained with the bidentate ligand **5**, enantioselectivity induced by **6** was higher for the branched substrate *rac*-**1a** than for the linear substrate **2a**.

Reactions with added halide salts were investigated (entries 15-17) because a marked influence of halide ions on allylic substitution has been reported.[9] LiCl or LiBr indeed caused a marked increase of regio- and enantioselectivity, although also a small decrease of reactivity (entry 10). The effect of chloride was further studied for alkylations of (*R*)- and (*S*)-**1a** (entries 18–23). The reaction with the substrate–ligand combination (*R*)-**1a**–(*R*)-**6** was faster and more enantioselective (matched case) than with the combination (*S*)-**1a**–(*R*)-**6** (mismatched), yielding (*R*)-**3a** in both cases, *i.e.* control by the ligand is stronger than that by the substrate. The influence of the ligand is enhanced by addition of LiCl.

As the acetates **1** and **2** do not isomerise under the usual reaction conditions,§ it was of interest to explore a kinetic resolution. The result for the reaction of *rac*-**1a** with NaHC$(CO_2CH_3)_2$, catalysed by $[Ir(COD)Cl]_2$–(*R*)-**6,** is shown in Fig. 1. According to this plot, (*R*)-**1a** is consumed *ca.* 12 times faster than (*S*)-**1a**.[10] Consequently, the slower reacting acetate is



Scheme 3

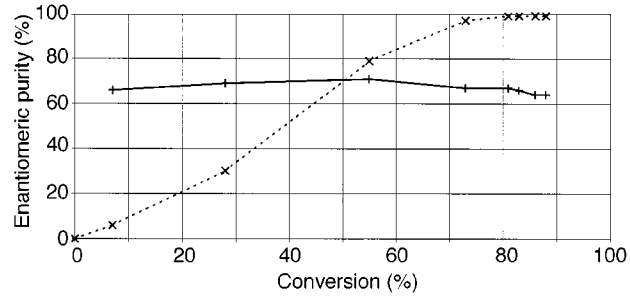


Fig. 1 Enantiomeric purity of (×) **1a** and (+) **3a** vs. conversion¶ for the reaction of (±)-**1a** with dimethyl 2-sodiomalonate catalysed by $[Ir(COD)Cl]_2$–(*R*)-**6**.

obtained in enantiomerically pure form beyond conversion of *ca*. 80%.

In conclusion, our results demonstrate that it is possible to achieve high levels of enantioselectivity in Ir-catalysed alkylations of monoalkylallyl acetates. Presently it is necessary to use racemic, branched substrates. Further progress will be achieved on the basis of detailed mechanistic investigations. It appears of particular importance to investigate the structure and dynamic properties of allyl–Ir complexes.

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Notes and references

† Enantiomerically enriched **1a** and **8** were prepared by enzyme (Novozym 435) catalysed esterification in vinyl acetate. (*R*)-**1b** was prepared from (*R*)-1-phenylprop-2-en-1-ol which was purchased from Fluka.

‡ Change of the descriptors in the starting material and product is a consequence of CIP priorities of substituents.

§ Isomerisation between **1a** and **2a** was not observed starting either from **1a** or from **2a** (reaction conditions: 2 mol% $[Ir(COD)Cl]_2$, 4 mol% $P(OPh)_3$, 2 equiv. NaOAc, 18 h, room temperature). For enantiomerically enriched **1a** (83% ee) a low degree of racemisation was obtained when the same reaction conditions were employed (70% ee).

¶ The degree of conversion was determined by HPLC.

1 B. M. Trost and D. L. Van Vranken, *Chem. Rev.*, 1996, **96**, 395; T. Hayashi, in *Catalytic Asymmetric Synthesis*, ed. I. Ojima, VCH, New York, 1993, p. 325.
2 R. Prétôt and A. Pfaltz, *Angew. Chem., Int. Ed.*, 1998, **37**, 323; T. Hayashi, K. Kishi, A. Yamamoto and Y. Ito, *Tetrahedron Lett.*, 1990, **31**, 1743; T. Hayashi, A. Ohno, S.-j. Lu, Y. Matsumoto, E. Fukuyo and K. Yanagi, *J. Am. Chem. Soc.*, 1994, **116**, 4221; T. Hayashi, M. Kawatsura and Y. Uozumi, *Chem. Commun.*, 1997, 561; B. M. Trost and F. D. Toste, *J. Am. Chem. Soc.*, 1998, **120**, 9074.
3 Mo: B. M. Trost and I. Hachiya, *J. Am. Chem. Soc.*, 1998, **120**, 1104; W: G. C. Lloyd-Jones and A. Pfaltz, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 462.
4 Fe: Y. Xu and B. Zhou, *J. Org. Chem.*, 1987, **52**, 974; Rh: P. A. Evans and J. D. Nelson, *J. Am. Chem. Soc.*, 1998, **120**, 5581.
5 R. Takeuchi and M. Kashio, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 263; R. Takeuchi and M. Kashio, *J. Am. Chem. Soc.*, 1998, **120**, 8647.
6 J. P. Janssen and G. Helmchen, *Tetrahedron Lett.*, 1997, **38**, 8025.
7 T. Hayashi, M. Kawatsura and Y. Uozumi, *J. Am. Chem. Soc.*, 1998, **120**, 1681; G. C. Lloyd-Jones and S. C. Stephen, *Chem. Eur. J.*, 1998, **4**, 2539; B. M. Trost and R. C. Bunt, *J. Am. Chem. Soc.*, 1996, **118**, 235; B. M. Trost, M. G. Morgan and G. A. O'Doherty, *J. Am. Chem. Soc.*, 1995, **117**, 9662.
8 B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos and A. H. M. de Vries, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2620.
9 U. Burckhardt, M. Baumann and A. Togni, *Tetrahedron: Asymmetry*, 1997, **8**, 155; M. Kawatsura, Y. Uozumi and T. Hayashi, *Chem. Commun.*, 1998, 217.
10 The relative rate was estimated by comparison with a published plot of conversion *vs.* ee of residual substrate for a kinetic resolution: V. S. Martin, S. S. Woodard, T. Katsuki, Y. Yamada, M. Ikeda and K. B. Sharpless, *J. Am. Chem. Soc.*, 1981, **103**, 6237.

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