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Regio- and enantioselective iridium-catalysed allylic aminations and alkylations of dienyl esters

Gunter Lipowsky and Günter Helmchen*

Organisch-Chemisches Institut der Ruprechts-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, D-69120 Heidelberg, Germany. E-mail: g.helmchen@urz.uni-heidelberg.de; Fax: +49 6221 544205; Tel: +49 6221 548401

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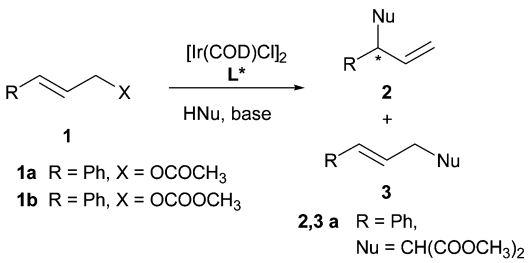
Regio- and enantioselective iridium-catalysed allylic aminations and alkylations of dienyl substrates are presented; using phosphorus amidite L1 as ligand, aminations provided ee values of up to 97% and alkylations of up to 90%.

Pd-catalysed allylic substitutions are of great importance for organic synthesis. The asymmetric variant is highly developed for symmetrically substituted substrates.[1] Except for a small number of examples,[2] the particularly easily accessible monosubstituted allylic derivatives **1** (Scheme 1) preferentially yield the achiral linear products **3** in Pd-catalysed substitutions. This is different for reactions catalysed by complexes of Ir, Mo, and Ru, which mainly give the branched product **2**.[3–5]



Scheme 1

In 1997 our group developed the first enantioselective Ir-catalysed allylic substitutions, making use of phosphinooxazoline **L4** as ligand, to give branched products with very high regio- and enantioselectivity in the case **1**, R = aryl.[6] Later we discovered that phosphorus amidites (*cf.* Fig. 1) derived from BINOL are particularly effective ligands in enantioselective alkylations and aminations of both arylated and alkylated allylic derivatives.[7,8] Particularly high degrees of enantio- and regioselectivity were very recently achieved by Hartwig *et al.* for aminations[9] and etherifications[10] of substrates **1**, R = aryl. Alkylations using chiral phosphites, *e.g.* **L3**, as ligands were reported by Fuji[11] and Takemoto.[12] In general, high degrees of regioselectivity have so far only been obtained with arylated allylic substrates.

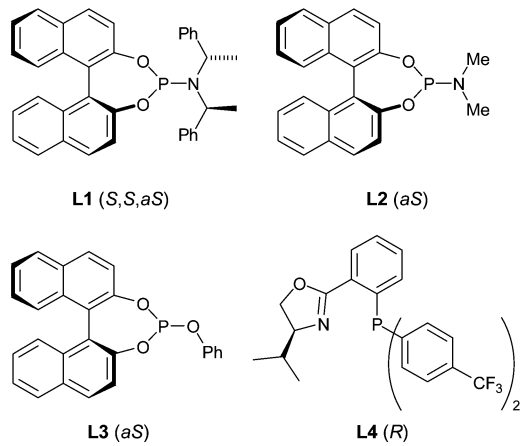


Fig. 1 Chiral ligands used in allylic substitutions.†

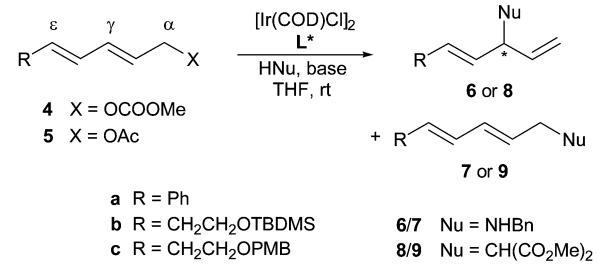
We have now explored the asymmetric Ir-catalysed substitutions of dienyl esters (Scheme 2).‡[13] Only alkylations have been reported for these substrates, yielding mainly branched products **8** using either achiral Ir complexes[3] or chiral Mo complexes as catalysts, which allowed alkylations to be accomplished with excellent regio- and enantioselectivity.[14] It was a challenge to devise the first asymmetric, regioselective amination of dienyl substrates. The value of the highly functionalised products **6** for the synthesis of biologically active compounds is obvious.

Our work began with the readjustment of reaction conditions. In previous work[8b] we used sodiomalonates as nucleophiles in conjunction with acetates and with LiCl as an additive at relatively low concentrations (0.12 M) in THF. We have now found that with lithiomalonates in combination with carbonates at high concentration (0.29 M)§ a higher level of regioselectivity can be reached. Thus, the reaction of **1b** with dimethyl lithiomalonate, using ligand **L1**, gave **2a** with a regioselectivity of **2a** : **3a** = 95 : 5 and ee of 86% for (*R*)-**2a**, while previously, with **1a**, the result was **2a** : **3a** = 90 : 10 and 86% ee.[8b]

The results obtained for both arylated and alkylated dienyl esters as substrates are presented in Table 1.[15] In general, ligand **L1** furnished better results than **L2**–**L4**. While **L2** had previously given good results in the alkylations of acetates, surprisingly, it was completely ineffective in the substitutions of carbonates **4** (entry 4). Similarly, acetates **5** did not undergo aminations with any of the ligands **L1**–**L4**. However, the aminations of carbonates **4a**–**4c** gave excellent results: 97% ee and regioselectivities in the range of > 94 : 6 (entries 1–3). Aminations were carried out at a concentration of *ca.* 2.0 M in THF. Rates were higher in toluene, CH_2Cl_2 or benzylamine (reaction time 10 min), however, enantioselectivities were lower in these solvents than in THF.

Alkylations were less sensitive to the choice of leaving group and ligand. Thus, under the control of ligand **L2** acetate **5a** reacted with a regioselectivity of 99 : 1 but only moderate enantioselectivity (entries 5,6). For reactions in the presence of ligand **L1**, additives and the counter cation of malonate were found to be important (see above). Addition of LiCl to the catalyst and use of sodium dimethyl malonate as nucleophile proved particularly effective (*cf.* entries 10,12). The phosphite **L3** gave somewhat disappointing results (entries 13,14).

The absolute configuration was determined for amine **6a** as (+)-(*S*) by transformation to sulfonamide **10** (Scheme 3), which yielded crystals suitable for X-ray crystal structure analysis.[16] The steric course of the Ir-catalysed substitution reaction at **4a** using ligand **L1** is the same as previously found for a variety of substitutions carried out with substrates **1**.[8,9] In conjunction with



Scheme 2

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Table 1 Ir-catalysed allylic amination and alkylation of carbonates **4** and acetates **5** according to Scheme 2 (E = COOMe)§

Entry	Substrate	Ligand	Nucleophile	t^a/h	Yield (%)^b of **6** + **7** or **8** + **9**	Ratio^{c,d} **6** : **7** or **8** : **9**	ee (%)^e (Confign.)
1	**4a**	**L1**	$BnNH_2$	24	61	99 : 1	**6a**: 97 (+)(*S*)
2	**4b**	**L1**	$BnNH_2$	48	72	94 : 6	**6b**: 97 (−)
3	**4c**	**L1**	$BnNH_2$	14	71	96 : 4	**6c**: 97 (−)
4	**4a**	**L2**	$LiCHE_2$	23	76	95 : 5	**8a**: 0
5	**5a**	**L2**^{f}	$LiCHE_2$	40	40	99 : 1	**8a**: 80 (+)
6	**5a**	**L2**^{f}	$NaCHE_2$	12	88	99 : 1	**8a**: 50 (+)
7	**4a**	**L1**	$LiCHE_2$	24^g	62	99 : 1	**8a**: 76 (−)
8	**4a**	**L1**	$LiCHE_2$–LiCl^h	43^g	63	79 : 21	**8a**: 66 (−)
9	**4a**	**L1**	$LiCHE_2$–$ZnCl_2$^{h}	43^g	77	95 : 5	**8a**: 78 (−)
10	**4a**	**L1**	$NaCHE_2$–LiCl^h	22^g	87	94 : 6	**8a**: 90 (−)
11	**5a**	**L1**	$LiCHE_2$	43^g	49	91 : 9	**8a**: 84 (−)
12	**5a**	**L1**	$NaCHE_2$–LiCl^h	23^g	76	92 : 8	**8a**: 89 (−)
13	**4a**	**L3**	$LiCHE_2$	17	64	94 : 6	**8a**: 58 (+)
14	**4a**	**L3**	$NaCHE_2$	72	84	95 : 5	**8a**: 10 (−)
15	**4b**	**L1**	$LiCHE_2$	24^g	84	94 : 6	**8b**: 87 (−)

^{a} Reaction time. ^{b} Yield of isolated product. ^{c} The product of ε-attack was not observed. ^{d} Determined by ^{1}H NMR of the crude products. ^{e} Determined by HPLC (Daicel columns, 250 × 4.6 mm, 5 μm, + guard cartridge 10 × 4 mm, 5 μm, flow: 0.5 ml min^{-1}); **6a**: (Daicel Chiralcel OD-H, eluent: *n*-hexane–*i*-PrOH 99 : 1 + 0.1% $HNEt_2$): t_R[(*R*)-**6a**] = 21 min, t_R[(*S*)-**6a**)] = 27 min; **6b**: determination after transformation to **6c**; **6c**: (Daicel Chiralpak AD-H, 20 °C, eluent: *n*-hexane–*i*-PrOH 99.5 : 0.5 + 0.1% $HNEt_2$): t_R[(−)-**6c**] = 79 min, t_R(+) = 111 min; **8a**: (Daicel Chiralcel OJ-H, eluent: *n*-hexane–*i*-PrOH 90 : 10): t_R[(−)-**8a**] = 26 min, t_R[(+)-**8a**] = 29 min; **8b**: determination after transformation to **8c**; **8c**: (Daicel Chiralcel AD-H, eluent: *n*-hexane–*i*-PrOH 98 : 2): t_R[(+)-**8b**] = 45 min, t_R[(−)-**8b**] = 53 min. ^{f} Ratio Ir : ligand = 1 : 2. ^{g} Reaction temperature: 50 °C. ^{h} Addition of 1 eq. of LiCl or $ZnCl_2$ to the catalyst solution.

6a **10**

Scheme 3 *Reagents and conditions*: (i) *p*-Br(C_6H_4)SO_2Cl, NEt_3, CH_2Cl_2, 0 °C, 78%.

the lack of substitution at the ε-position, this indicated that reactions of the dienyl substrates involve (allyl)Ir complexes centred at Cα–Cγ.

In conclusion, we have shown that dienyl carbonates are suitable substrates in enantioselective Ir-catalysed allylic aminations and alkylations with phosphorus amidites as ligands. For both aryl- and alkyl-substituted substrates very high regioselectivities in favour of the desired internal substitution products were obtained. Aminations afforded up to 97% ee and alkylations up to 90% ee. The absolute configuration of the reaction product **6a** was determined.

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Notes and references

† Ligands were prepared as described: **L1**,[17] **L2**,[18] **L3**,[19] **L4**.[6]

‡ Substrates **4** and **5** were prepared according to published procedures.[14]

§ *General procedure for amination.* Under argon, a solution of $[Ir(COD)Cl]_2$ (13.4 mg, 0.02 mmol), ligand (0.04 mmol) (ratio Ir : ligand = 1 : 1), substrate (1 mmol) and amine (1.3 mmol) in dry THF (0.5 ml) was stirred at rt. The solvent was removed under reduced pressure and the residue subjected to flash chromatography (silica, petroleum ether–ethyl acetate 5 : 1) to give mixtures of **6** and **7**.

General procedure for alkylation. Under argon, a solution of $[Ir(COD)Cl]_2$ (13.4 mg, 0.02 mmol), ligand (0.04 mmol) (ratio Ir : **L*** = 1 : 1) and substrate (1.0 mmol) in dry THF (0.5 ml) was treated with a solution of lithium dimethylmalonate (2.0 mmol) in dry THF (3 ml) at room temperature and stirred for the time stated in Table 1. Then Et_2O (5 ml) and aqueous NH_4Cl solution (5 ml) were added. After standard extractive work-up, including washing of the organic phase with brine, drying and concentration *in vacuo*, the crude product was subjected to flash chromatography (silica, petroleum ether–ethyl acetate 12 : 1).

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15 Enantiomeric excess of **6b**/**8b** was determined by HPLC-analysis of **6c**/**8c**. Deprotection of **6b**/**8b** followed by reaction with *p*-methoxybenzyl chloride gave **6c**/**8c** in 47/79% yield over two steps.
16 Crystal data for **10**: $C_{24}H_{22}BrNO_2S$, M = 468.40, monoclinic, space group $P2_1$, a = 11.6234(17) Å, α = 90°, b = 5.8505(9) Å, β = 109.524(3)°, c = 16.290(2) Å, γ = 90°, U = 1043.4(3) Å^3, Z = 2, μ = 2.09 mm^{-1}. 10870 reflections measured, 5045 unique (R(int) = 0.0423), 4401 observed [$I > 2\sigma(I)$]. *R1* = 0.052, *wR2* = 0.106 [$I > 2\sigma(I)$], flack 0.013(10). CCDC 220048. See http://www.rsc.org/suppdata/cc/b3/b311502j/ for crystallographic data in .cif format.
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