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First intramolecular enantioselective iridium-catalysed allylic aminations

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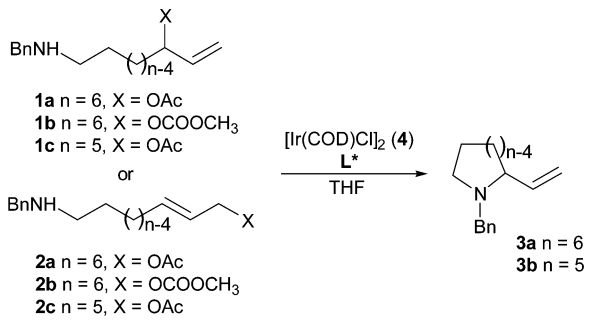
Enantioselective iridium-catalysed intramolecular allylic aminations, using phosphinooxazolines or phosphorus amidites as ligands, provided ee values of > 90%, at a catalyst loading of < 0.5 mol-%, and displayed a marked preference for intra- over corresponding intermolecular reactions.

Despite numerous reports on enantioselective allylic substitutions,[1] the number of reports on intramolecular asymmetric reactions is relatively small.[2] All of them refer to Pd-catalysed reactions. Generally, with Pd-catalysts intramolecular substitutions leading to 5-, 6- or 7-membered rings seem to be inferior to corresponding intermolecular variants, requiring, for example, a low concentration of substrate.[3] One reason for this is likely to be the pronounced preference of the Pd-catalysed reaction for the linear rather than the branched substitution product.[4] Another reason is the competition between cyclisation and equilibration of intermediary diastereomeric (π-allyl)Pd complexes.[5]

Acting on this observation, it appeared of interest to investigate corresponding Ir-catalysed cyclisations, because in allylic substitutions Ir-, Mo- and Ru-catalysts mainly give rise to the branched products.[6–8] A very important advantage of Ir-catalysis is the fact that it is broadly applicable in allylic alkylations[9] as well as aminations,[10] and high selectivity can be obtained, not only with aryl- but also with alkyl-substituted achiral allylic substrates.

Extending our previous work, we have now studied intramolecular aminations according to Scheme 1 and are able to report the first intramolecular[11] asymmetric Ir-catalysed allylic substitutions.



Scheme 1

In initial experiments, we used phosphinooxazolines **L1** and **L2**[12] (Fig. 1) in combination with $[Ir(COD)Cl]_2$ (**4**) (ratio **L1**:**4** = 2:1). With racemic branched acetates **1a** and **1c**, yields of cyclisation products were high and enantioselectivities moderate to high (Table 1†). The absolute configuration of product **3a** was determined as (-)(*S*)-**3a** by transformation into (*R*)-*N*-benzylconiine.[13] The absolute configuration of **3b** was known.[14]

Results obtained with phosphinooxazolines as ligands are presented in Table 1. The following observations are particularly interesting. (a) Alkyl-substituted allylic derivatives display very low reactivity in intermolecular substitutions. The generally high yields obtained for cyclisations indicate superiority of intra- over intermolecular substitution with Ir-catalysts. (b) Enantioselectivity is a function of temperature (*cf.* entries 1–4). It was previously observed for intermolecular substitutions[9b] that an increase of temperature gives rise to an increase of enantioselectivity, due to enhanced isomerisation of intermediary (allyl)Ir complexes.[9c,d] The reason for the decrease of enantioselectivity at 100 °C cannot presently be explained (Table 1, entry 4). (c) The influence of the solvent can be very substantial (entries 3, 5, 6). (d) The use of LiCl as an additive had previously been found to lead to enhanced levels of selectivity.[9b] For the cyclisation reactions an unusually pronounced effect of halide additives was found (entries 13–16). An explanation is not possible at present.[15] (e) The catalyst induced low selectivity with carbonate **1b** (entry 9) and was ineffective with linear substrate **2a** (entry 12).

Phosphorus amidites[16] are a second class of ligands suitable for Ir-catalysed allylic substitutions.[9b] Ligand **L3** induces high degrees of enantioselectivity in both alkylations[9d] and aminations.[10] After recently having obtained excellent degrees of regio- and enantio-

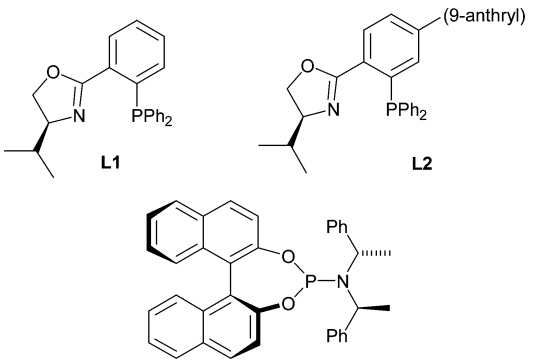


Fig. 1 Chiral ligands used in allylic substitutions.

Table 1 Ir-catalysed allylic cyclisation of substrates **1** according to Scheme 1 using phosphinooxazolines (*S*)-**L1** and (*S*)-**L2** as ligands

Entry	Substrate	Ligand/additive	Solvent	*T*/°C	*t*[a]/d	Yield (%)[b]	ee (%)[c] (confign.)
1	**1a**	**L1**	Toluene	20	4	83	**3a**: 36 (*R*)
2	**1a**	**L1**	Toluene	60	4	91	**3a**: 62 (*R*)
3	**1a**	**L1**	Toluene	80	4	92	**3a**: 80 (*R*)
4	**1a**	**L1**	Toluene	100	4	81	**3a**: 65 (*R*)
5	**1a**	**L1**	DMF	80	4	80	**3a**: 29 (*R*)
6	**1a**	**L1**	CH_3CN	80	4	80	**3a**: 48 (*R*)
7	**1a**	**L1**	THF	65	4	92	**3a**: 80 (*R*)
8	**1a**	**L2**	THF	65	4	99	**3a**: 85 (*R*)
9	**1b**	**L1**	THF	65	4	98	**3a**: 56 (*R*)
10	**1c**	**L1**	THF	65	6	83	**3b**: 83 (*R*)
11	**1c**	**L2**	THF	65	6	99	**3b**: 79 (*R*)
12	**2a**	**L1**	THF	65	4	36	**3a**: 26 (*R*)
13	**1a**	**L1**/LiF	THF	65	4	99	**3a**: 88 (*R*)
14	**1a**	**L1**/LiCl	THF	65	4	99	**3a**: 59 (*R*)
15	**1a**	**L1**/LiBr	THF	65	4	86	**3a**: 51 (*R*)
16	**1a**	**L1**/LiI	THF	65	4	97	**3a**: 6 (*R*)

[a] Reaction time. [b] Yield of isolated product. [c] Determined by HPLC (column: Daicel Chiralcel OD–H, eluent: *n*-hexane/*i*-PrOH 99.9:0.1, 250 × 4.6 mm, 5 μm, + guard cartridge 10 × 4 mm, 5 μm, flow: 0.5 ml min^{-1}), t_R[(*S*)-**3a**] = 11 min, t_R[(*R*)-**3a**] = 14 min; t_R[(*S*)-**3b**] = 11 min, t_R[(*R*)-**3b**] = 25 min.

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Table 2 Ir-catalysed allylic cyclisations of substrates **2** to give **3a** according to Scheme 1 using phosphorus amidite **L3** as ligand

Entry	Substrate	Catalyst[a]	t^b/h	Yield (%)[c]	ee (%)[d] (Confign.)
1	**2b**	0.02 eq. $[Ir(COD)Cl]_2$/**2L3**	300	74	84 (*R*)
2	**2b**	0.02 eq. $[Ir(COD)Cl]_2$/**2L3**	80[e]	77	81 (*R*)
3	**2a**	0.02 eq. $[Ir(COD)Cl]_2$/**2L3**	96	22	37 (*R*)
4	**2b**	0.02 eq. $[Ir(COD)Cl]_2$/**2L3**, 0.08 eq. P_2-tBu, 3 h	0.25	95	86 (*R*)
5	**2b**	0.02 eq. $[Ir(COD)Cl]_2$/**2L3**, 0.08 eq. TBD,[f] 5 h	1	93	91 (*R*)
6	**2b**	0.002 eq. $[Ir(COD)Cl]_2$/**2L3**, 0.008 eq. TBD, 9 h	19	85	92 (*R*)
7	**2b**	0.02 eq. $[Ir(COD)Cl]_2$/**2L3**, 1 eq. pyrrolidine, 6 h	1	96	91 (*R*)

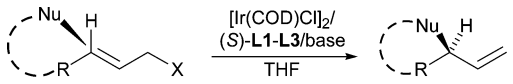
[a] Catalyst preparation is described in the general procedure. [b] Reaction time. [c] Yield of isolated product. [d] Determined by HPLC as described in Table 1. [e] Reaction temperature: 50 °C. [f] Trade name of Fluka/Sigma-Aldrich.

selectivity with dienyl carbonates,[10c] we are pleased to report remarkably efficient cyclisations here.

In early experiments using a standard procedure, a mixture of $[Ir(COD)Cl]_2$ (**4**) and **L3** was employed as catalyst. It is known[9c,10b] that these components rapidly form a complex [Ir(COD)Cl(**L3**)] (**5**). In spite of very long reaction times, results with carbonate **2b** as substrate were encouraging, because high yield and fair enantioselectivity could be obtained at a concentration as high as 1 M in THF[17] (Table 2,‡ entries 1 and 2). The reaction of acetate **2a** was sluggish (entry 3). It was previously found that active Ir-catalysts are generated by C–H activation promoted by the nucleophile or base.[9b,10b] Accordingly, complex **5** was treated with a variety of bases, of which the Schwesinger phosphazene base P_2-tBu increased catalyst activity by a factor of *ca.* 1000 (entry 4). Even better results with respect to enantioselectivity were obtained upon activation with 1,5,7-triazabicyclo-[4.4.0]undec-5-ene (TBD) as base (entry 5). Of this new *in situ* catalyst, 0.4 mol-% sufficed to produce *N*-benzyl-2-vinyl-piperidine (**3a**) with 92% ee in 85% isolated yield.

A demonstration of the high relative rate of the intramolecular reaction was accidentally found when pyrrolidine was used as base, which was previously employed by Hartwig and co-workers.[10a,b] Although pyrrolidine is a highly reactive nucleophile in intermolecular aminations and in spite of the high concentration of 1 M, the intramolecular reaction proceeded in 96% yield (entry 7).

The steric course of the intramolecular Ir-catalysed substitution reactions using ligands **L1**, **L2** or **L3**, all with (*S*)-configuration, is the same as previously found for intermolecular substitutions.[9,10] The following relationship appears to be generally valid:



In conclusion, enantioselective intramolecular allylic aminations catalysed by iridium-phosphorus amidite complexes were found to proceed with very high catalytic efficiency and ee values of > 90%. High concentrations of substrate can be employed due to a marked preference of intra- over the corresponding intermolecular reactions.

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Notes and references

† **General procedure for cyclisations using ligands L1,L2**: Under argon, a solution of $[Ir(COD)Cl]_2$ (**4**) (16.8 mg, 0.025 mmol), the ligand (0.05 mmol) (ratio Ir:ligand = 1:1) in dry toluene or THF (5 ml) was stirred at room temperature for 10 min. The substrate was added (1.0 mmol) and the mixture heated at reflux with stirring until TLC showed complete conversion. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography or Kugelrohr distillation.

‡ **General procedure for cyclisations using ligand L3**: Under argon, a solution of $[Ir(COD)Cl]_2$ (**4**) (0.01 mmol) and ligand **L3** (0.02 mmol) in dry THF (0.5 ml) was stirred at room temperature for 15 min. If base was used, it was added together with THF and the mixture was stirred for 5 h at room temperature. Then the substrate (0.5 mmol) was added and the mixture was stirred at the indicated temperature until NMR monitoring showed complete conversion. The solvent was removed under reduced pressure and the crude product was purified by Kugelrohr distillation.

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