

# Highly enantioselective iridium-catalysed allylic aminations with anionic N-nucleophiles†

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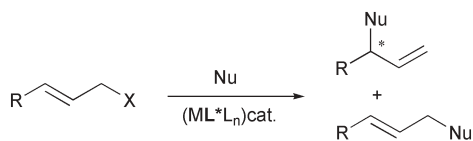
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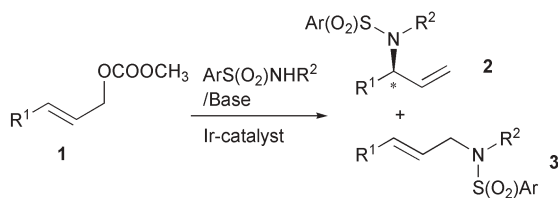
Iridium-catalysed allylic substitutions with anionic N-nucleophiles were achieved with regioselectivity of up to 49:1 and enantiomeric excess of up to 98%.

The development of asymmetric allylic substitutions has led to very successful procedures, which have enriched the methodology of organic synthesis.<sup>1</sup> Recently, reactions of monosubstituted allylic derivatives according to Scheme 1 have come into focus. While Pd-catalysts are useful in special cases,<sup>2</sup> Ir-complexes of electron-poor ligands seem to be the catalysts of choice for asymmetric allylic alkylations,<sup>3</sup> aminations<sup>4</sup> and etherifications<sup>5</sup> of aryl- as well as alkylallyl derivatives. With ligands **L1**–**L3** (Fig. 1)<sup>6</sup> regioselectivities of >95:5 in favour of the branched products and enantioselectivities of up to 98% ee have been obtained.



Scheme 1 Ir-catalysed allylic substitutions.

Substitutions with N-nucleophiles have so far been generally successful only with amines as nucleophiles.<sup>4</sup> An early attempt by this group<sup>3b</sup> of using  $\text{LiN}(\text{CH}_2\text{Ph})p\text{-Ts}$ ,<sup>7</sup> *i.e.* a nucleophile with anionic nitrogen (*cf.* Scheme 2), gave low selectivity because a less suited phosphorus amidite (MonoPhos)<sup>8</sup> was chosen. Moreover, solubility of the nucleophile was a problem. Very recently, Takemoto *et al.*<sup>9</sup> have reported on reactions of arylallyl



Scheme 2 Ir-catalysed allylic substitutions with sulfonamides as nucleophiles.

† Electronic supplementary information (ESI) available: X-ray crystal structure data for **7t** and data on separation of enantiomers by HPLC. See <http://www.rsc.org/suppdata/cc/b5/b505197e/>

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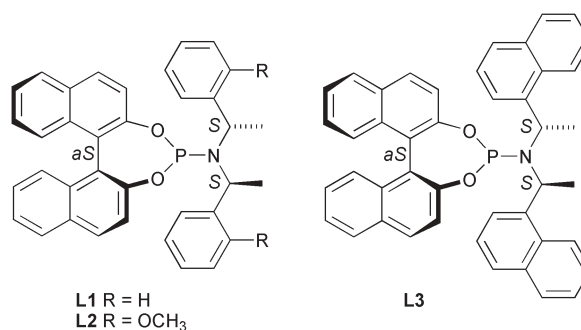


Fig. 1 Chiral phosphorus amidite ligands.

phosphates with a nucleophile  $\text{PhCONHOCH}_2\text{Ph}/\text{CsOH}$ , which furnished >90% ee in special cases (Scheme 1,  $\text{R} = \text{Ph}$  and 1-naphthyl,  $\text{X} = \text{O}(\text{PO})\text{OEt}_2$ ,  $\text{L}^* = \text{Pybox}$ ).

We have resumed activities in this field and, based on the recently accumulated knowledge cited above, found interesting and fairly general solutions. The incentive for this pursuit was: (a) The direct formation of non-basic allylamine derivatives, *i.e.* protected amines, simplifies further transformations, for example ring closing metathesis as was demonstrated by P. A. Evans *et al.*<sup>10</sup> (b) Modularity and variability of the reactants are high, which is advantageous in asymmetric catalysis. (c) Many amides and sulfonamides are crystalline; thus enantiomeric enrichment by recrystallisation is often possible.

Reactions were run using conditions previously described for intramolecular aminations<sup>4a</sup> (*cf.* General Procedure†), *i.e.*, the catalyst was prepared by *in situ* activation of a mixture of  $[\text{Ir}(\text{COD})\text{Cl}]_2$  and chiral ligand  $\text{L}^*$  with the base TBD (1,5,7-triazabicyclo-[4.4.0]dec-5-ene). The solvent was dry THF. Initial experiments were carried out with the previously employed  $\text{LiN}(\text{CH}_2\text{Ph})p\text{-Ts}$  as nucleophile (Table 1, entries 1,2). Excellent enantio- as well as acceptable regioselectivity were obtained with an allylic carbonate with a  $\text{sp}^2$ - and one with a  $\text{sp}^3$ -substituent.

Next a synthetically convenient<sup>11</sup> *N*-(*o*-nitrophenylsulfonyl)-amine, *N*-(*o*-Ns)- $\text{NHCH}_2\text{Ph}$ , was probed. In view of the relatively high acidity of *N*-nosyl-amines<sup>12</sup> we opted for an ammonium amide as nucleophile, prepared *in situ* by mixing *N*-(*o*-Ns)- $\text{NHCH}_2\text{Ph}$  with  $\text{NEt}_3$ . Again, enantioselectivity was high, however, regioselectivity was not satisfactory (entries 3–6). Furthermore, there was a surprising dependence on steric effects apparent, in that the sterically demanding ligands **L2** and **L3** gave rise to linear product **3**. According to control experiments, the formation of **3** was not caused by the non-catalysed reaction, which is very slow.

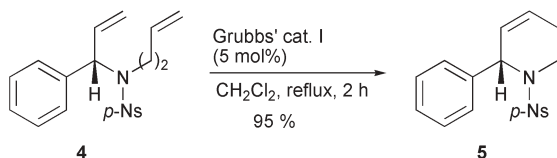
**Table 1** Ir-catalysed allylic substitutions according to Scheme 2<sup>a</sup>

Entry	R <sup>1</sup>	Nucleophile		Base	Ligand	Time <sup>b</sup> (h)	Yield (%) <sup>c</sup>	2:3	Ee (%) (Abs. Conf.) <sup>d</sup>
		ArSO <sub>2</sub>	R <sup>2</sup>						
1	Ph	<i>p</i> -Ts	CH <sub>2</sub> Ph	LiHMDS	<b>L2</b>	2.5	92	49:1	98 ( <i>S</i> )
2	CH <sub>2</sub> CH <sub>2</sub> Ph	<i>p</i> -Ts	CH <sub>2</sub> Ph	LiHMDS	<b>L2</b>	2	60	4:1	95 ( <i>R</i> )
3	Ph	<i>o</i> -Ns	CH <sub>2</sub> Ph	NEt <sub>3</sub>	<b>L1</b>	12	44	3:1	91
4	Ph	<i>o</i> -Ns	CH <sub>2</sub> Ph	NEt <sub>3</sub>	<b>L2</b>	1	82	0:1	—
5	Ph	<i>o</i> -Ns	CH <sub>2</sub> Ph	NEt <sub>3</sub>	<b>L3</b>	0.5	87	0:1	—
6	CH <sub>2</sub> CH <sub>2</sub> Ph	<i>o</i> -Ns	CH <sub>2</sub> Ph	NEt <sub>3</sub>	<b>L2</b>	0.5	79	3:1	97 ( <i>R</i> )
7	Ph	<i>p</i> -Ns	H	NEt <sub>3</sub>	<b>L2</b>	14	91	16:1	93 <sup>e</sup>
8	Ph	<i>p</i> -Ns	H	—	<b>L2</b>	18	66	32:1	90
9	Ph	<i>p</i> -Ns	CH <sub>2</sub> Ph	—	<b>L2</b>	18	91	13:1	96
10	CH=CHPh	<i>p</i> -Ns	CH <sub>2</sub> Ph	NEt <sub>3</sub>	<b>L2</b>	18	71	2.5:1	93
11	CH=CHPh	<i>p</i> -Ns	CH <sub>2</sub> Ph	—	<b>L2</b>	18	50	6:1	90
12	CH <sub>2</sub> CH <sub>2</sub> Ph	<i>p</i> -Ns	CH <sub>2</sub> Ph	NEt <sub>3</sub>	<b>L2</b>	3	85	7:1	88
13	CH <sub>2</sub> CH <sub>2</sub> Ph	<i>p</i> -Ns	CH <sub>2</sub> Ph	—	<b>L2</b>	3	93	4:1	84
14	Ph	<i>p</i> -Ns	CH <sub>2</sub> CH=CH <sub>2</sub>	NEt <sub>3</sub>	<b>L2</b>	6	89	10:1	88
15	Ph	<i>p</i> -Ns	CH <sub>2</sub> CH=CH <sub>2</sub>	—	<b>L2</b>	6	68	19:1	90
16	3-Pyridyl	<i>p</i> -Ns	CH <sub>2</sub> CH=CH <sub>2</sub>	NEt <sub>3</sub>	<b>L2</b>	18	89	4:1	91
17	3-Pyridyl	<i>p</i> -Ns	CH <sub>2</sub> CH=CH <sub>2</sub>	—	<b>L2</b>	12	86	13:1	92.5
18	Ph	<i>p</i> -Ns	(CH <sub>2</sub> ) <sub>2</sub> CH=CH <sub>2</sub>	NEt <sub>3</sub>	<b>L2</b>	18	80	19:1	96.5 <sup>e</sup>
19	Ph	<i>p</i> -Ns	(CH <sub>2</sub> ) <sub>2</sub> CH=CH <sub>2</sub>	—	<b>L2</b>	18	78	32:1	90
20	3-Pyridyl	<i>p</i> -Ns	(CH <sub>2</sub> ) <sub>2</sub> CH=CH <sub>2</sub>	NEt <sub>3</sub>	<b>L2</b>	72	60	5:1	97
21	3-Pyridyl	<i>p</i> -Ns	(CH <sub>2</sub> ) <sub>2</sub> CH=CH <sub>2</sub>	—	<b>L2</b>	18	57	32:1	95

<sup>a</sup> If not stated otherwise, reactions were carried out on a 1 mmol scale of **1** using 2 mol% of [Ir(COD)Cl]<sub>2</sub>, 4 mol% of ligand and 8 mol% of TBD (activation for 2 h). <sup>b</sup> Reaction time. <sup>c</sup> Yield of the isolated product. <sup>d</sup> Note that the descriptor of **2** can change upon variation of R<sup>1</sup> as a consequence of CIP priorities. The assignments given in the Table refer to ref. 16. <sup>e</sup> The enantiomerically pure compound was obtained by recrystallisation from *n*-pentane/ether.

In order to reduce steric effects, *p*-nosylamides were investigated. Indeed, with the parent compound *p*-Ns-NH<sub>2</sub> excellent enantio- and regioselectivity were obtained (entry 7). Considering that methyl carbonate liberated in the reaction likely dissociates into CO<sub>2</sub> and strongly basic methoxide, the reaction was run without an additional base; the result was a marked improvement of regioselectivity (entry 8). For the further examples given in Table 1 regioselectivities were found to be significantly higher in reactions run without NEt<sub>3</sub>. Enantioselectivity was little affected by NEt<sub>3</sub>, there are examples for increase (entries 10, 18 and 20) as well as for decrease (entries 14 and 16) of enantiomeric excess.

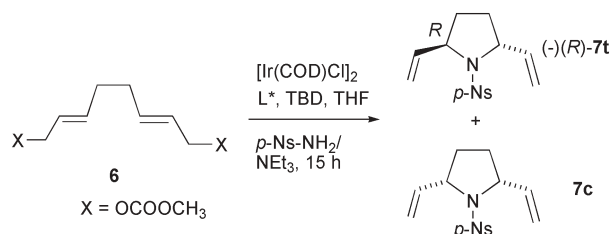
Reactions with the nucleophiles (*p*-Ns)[H<sub>2</sub>C=CH(CH<sub>2</sub>)<sub>*n*</sub>]<sup>−</sup> described in entries 14–21 of Table 1 were investigated with a view to their potential for subsequent ring closing metathesis, leading to analogues of tobacco alkaloids in the cases R = 3-pyridyl.<sup>13</sup> As an example, the diene **4**, obtained from the reaction described in entry 18, was subjected to standard RCM to furnish the tetrahydropyridine derivative **5** in excellent yield (Scheme 3).

**Scheme 3** RCM using Grubbs' catalyst I.

We have shown that Ir-catalysed intramolecular aminations are particularly facile and highly selective.<sup>14</sup> Furthermore, sequential inter- and intramolecular reactions with benzylamine

as nucleophile have opened a route to interesting N-heterocycles.<sup>14</sup> Accordingly, we have probed a corresponding reaction using *p*-Ns-NH<sup>−</sup> as nucleophile (Scheme 4). The reaction with the dicarbonate **6** proceeded smoothly to give the expected *trans*-pyrrolidine derivative in good yield and excellent selectivity. For once, the best results were obtained with ligand **L3**. The very high ee of >99% is due to double stereoselection.

The pure *trans*-isomer **7t** was obtained by recrystallisation (HCCl<sub>3</sub>/*n*-hexane) in 64% isolated yield. It was possible to determine both the absolute and the relative configuration, as given in Scheme 4, by X-ray structure analysis.<sup>15</sup> The corresponding steric course of the substitution reaction is in accordance with the general rule stated previously.<sup>4a</sup> In addition, we found that the steric course for the reactions according to entries 1 and 6 of Table 1 is the same as that of the corresponding reactions with



L\* = **L1**: **7t**:**7c** = 85:15 (65%), **7t**: 99% ee  
 L\* = **L2**: **7t**:**7c** = 84:16 (76%), **7t**: 99% ee  
 L\* = **L3**: **7t**:**7c** = 89:11 (73%), **7t**: >99% ee

**Scheme 4** Sequential inter- and intramolecular allylic aminations.

benzylamine as nucleophile.<sup>4</sup> This was established in obvious manner by *N*-tosylation of the products of the latter reactions. Further corroboration for the correctness of our assignments is based on work by Evans and Robinson.<sup>16</sup>

In summary, new reaction conditions have allowed iridium-catalysed allylic substitutions with anionic N-nucleophiles to be carried out inter- as well as intramolecularly with high degrees of enantio- and regioselectivity to give protected amines, which are useful in organic synthesis and medicinal chemistry. We are currently pursuing further investigations, concerning in particular extension of the range of nucleophiles and the choice of base, counter ion and other variables.

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## Notes and references

‡ *General procedure*: Success with the following procedure requires dry THF (<35 µg of H<sub>2</sub>O per ml, Karl Fischer titration). Under argon, a solution of [Ir(COD)Cl]<sub>2</sub> (0.02 mmol) and L\* (0.04 mmol) in dry THF (0.5 ml) was treated with TBD (0.08 mmol). After stirring for 2 h at rt the allylic carbonate (1.0 mmol) was added, and the mixture was stirred for 5 min at rt. Then the sulfonamide (1.5 mmol) and eventually NEt<sub>3</sub> (1 mmol) or a solution of LiN(CH<sub>2</sub>Ph)*p*-Ts (1.5 mmol) in dry THF (4 ml) was added and the mixture was stirred until TLC indicated complete conversion. The solvent was removed under reduced pressure and the residue analysed with respect to the content of branched and linear product by <sup>1</sup>H NMR. The pure reaction products were obtained by flash chromatography or MPLC.

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