# Iridium-catalysed asymmetric allylic substitutions†

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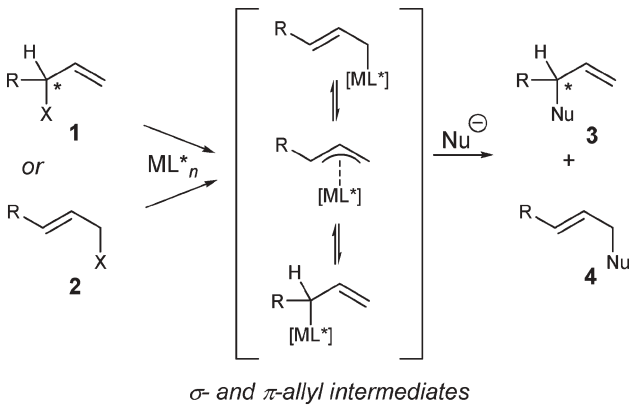
*Received (in Cambridge, UK) 29th September 2006, Accepted 8th November 2006*
*First published as an Advance Article on the web 6th December 2006*
**DOI: 10.1039/b614169b**

Ir-Catalysed allylic substitution is supplementing the traditional Pd-catalysed variant. With simple, easily available monosubstituted allylic acetates and carbonates as substrates, Ir catalysts generally favour chiral, branched products, while Pd catalysts typically give rise to linear, achiral products. With phosphorus amidites as ligands, regioselectivities >10 : 1 and enantiomeric excess in the range 95–99 %ee are currently routinely achieved. A broad range of nucleophiles can be employed: for example stabilised carbanions, amines including their sulfonyl- and diacyl-derivatives, phenolates and alkoxides. A few applications, based on combinations of the allylic substitution and ring closing metathesis, indicate considerable potential of the method for the synthesis of biologically active compounds.

## 1 Introduction

Transition metal catalysed asymmetric allylic substitutions are widely employed in organic synthesis.[1] The results of these reactions are a function of many factors, the metal ion, ligands, the nucleophile and substituents at the allyl system.

Most often, symmetrically substituted allylic derivatives are used as substrates. Synthetically more easily accessible mono-substituted allylic substrates **1** or **2** (Scheme 1) are less often employed because, in addition to enantioselectivity, regio-selectivity in favour of branched chiral products **3** must be achieved. With Pd-complexes as catalysts, linear products are generally produced. Only very recently, ligands have been developed that give rise to the branched products **3** in special cases.[2]




**Scheme 1** General scheme for the transition metal catalysed allylic substitution of monosubstituted allylic substrates.

In contrast, Mo- or W-based catalysts preferentially give rise to branched products. High levels of reactivity and enantio-selectivity were obtained in alkylations of allylic derivatives with aryl and alkenyl substituents.[3]

With Pd catalysts reactions proceed *via* π-allyl complexes, which can isomerise *via* π–σ–π rearrangement or related

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† Dedicated to Professor Peter Hofmann on the occasion of his 60th birthday.

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processes so that branched and linear substrates yield the same products. Memory effects are usually small.[4] In contrast, substitutions catalysed by Rh, Fe or Ru-complexes proceed with a high degree of conservation of enantiomeric excess.[5] Intermediates of these reactions are σ-allyl or π-allyl complexes which isomerise slowly compared to (allyl)Pd-complexes. As a consequence, linear substrates **2** give rise to linear products **4** and enantiomerically enriched substrates **1**, even with achiral ligands, yield enantiomerically enriched products **3** *via* double inversion processes. Therefore, these metal ions appeared not generally suited for asymmetric synthesis. However, asymmetric syntheses were recently accomplished with symmetrically substituted 1,3-diarylallyl derivatives[6] and branched acetates.[5f]

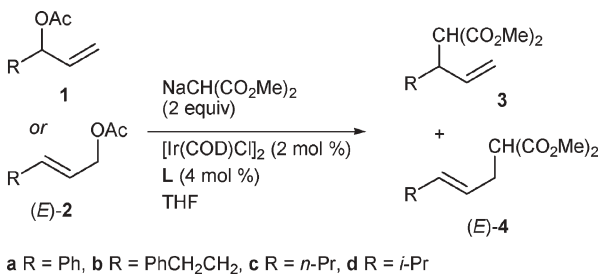
Ir-Catalysts were first probed in the allylic substitution by Takeuchi in 1997.[7] The first asymmetric variant was published by our group in the same year.[8] Since then the field has been developed with ever increasing velocity and today a wide variety of highly efficient procedures are available that render Ir-catalysed asymmetric allylic substitutions an attractive field of research and applications.

## 2 Fundamental characteristics of Ir-catalysed allylic substitutions

### 2.1 Reactivity and regioselectivity

The fundamental characteristics of the Ir-catalysed allylic substitution were worked out in the period 1998–2003.[9,10]

An important aspect is the precatalyst/ligand combination. For a series of Ir-precomplex/$P(OPh)_3$ combinations as catalysts, the following relative rates of the reaction of **2c** (Scheme 2) with $NaCH(COOEt)_2$ were found: $[Ir(COD)Cl]_2$ > $[Ir(COD)_2]BF_4$ > Ir(COD)acac > $IrH(CO)(PPh_3)_3$ > $Ir_4(CO)_{12}$ (no reaction).[9] No precatalyst better suited than $[Ir(COD)Cl]_2$ has emerged, despite considerable work of several groups.




**a** R = Ph, **b** R = $PhCH_2CH_2$, **c** R = *n*-Pr, **d** R = *i*-Pr

**Scheme 2** Ir-Catalysed allylic substitution.

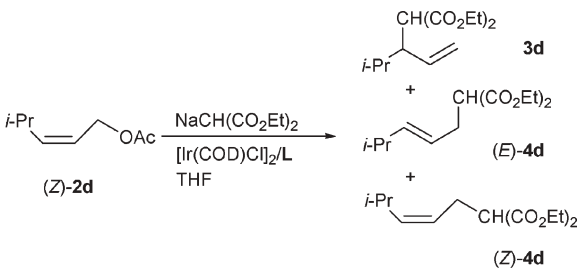
Using the complex $[Ir(COD)Cl]_2$, fine tuning with ligands and comparison of isomeric substrates uncovered the following trends: (a) reaction rate and regioselectivity are increased by electron-poor ligands and decreased by electron-rich ligands (Table 1). (b) A ratio **L**/Ir = 1 gives optimal results. Additional ligand leads to decrease in rate but not in regioselectivity. (c) The reaction rate is significantly higher for the branched than the linear substrate. These features indicate formation of (allyl)Ir intermediates *via* a $S_N2'$ type reaction, as has been postulated for Rh-catalysed reactions.[5e]

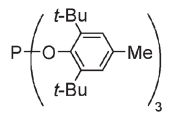
**Table 1** Influence of the ligand on the allylic alkylation of acetates **1** and (*E*)-**2** according to Scheme 2

| L | L/Ir | *T*/°C | Time/h | Yield[a] (%) | **b** : **l** |
|---|---|---|---|---|---|
| **1a**, R = Ph | | | | | |
| $P(OPh)_3$ | 1 : 1 | rt | 3 | 99 | 98 : 2 |
| — | — | rt | 3 | 98 | 98 : 2 |
| $PPh_3$ | 1 : 1 | rt | 3 | 15 | 98 : 2 |
| (*E*)-**2a**, R = Ph | | | | | |
| $P(OPh)_3$ | 1 : 1 | rt | 3 | 98 | 98 : 2 |
| — | — | 65 | 24 | 89 | 32 : 68 |
| $PPh_3$ | 1 : 1 | 65 | 24 | 58 | 64 : 36 |
| dppe[b] | 1 : 1 | 65 | 16 | 18 | 39 : 61 |
| **1b**, R = $PhCH_2CH_2$ | | | | | |
| $P(OPh)_3$ | 1 : 1 | rt | 3 | 99 | 95 : 5 |
| $P(OPh)_3$ | 2 : 1 | rt | 18 | 90 | 95 : 5 |
| — | — | rt | 3 | 66 | 89 : 11 |
| $PPh_3$ | 1 : 1 | rt | 3 | 0 | — |
| $PPh_3$ | 1 : 1 | 55 | 22 | 60 | 83 : 17 |
| (*E*)-**2b**, R = $PhCH_2CH_2$ | | | | | |
| $P(OPh)_3$ | 1 : 1 | rt | 3 | 99 | 95 : 5 |
| — | — | rt | 3 | 0 | — |
| $PPh_3$ | 1 : 1 | rt | 3 | 0 | — |

[a] Combined yield of branched and linear product. [b] $NaCH(CO_2Et)_2$ was used as nucleophile.

(d) There are distinct memory effects concerning the allylic substrate in that branched substrates **1** give branched products **3** with high selectivity and linear substrates **2** tend to give mixtures. (e) Substrates with (*Z*)-configuration of the double bond preferentially yield linear products with conservation of the (*Z*)-configuration (Scheme 3).[9]



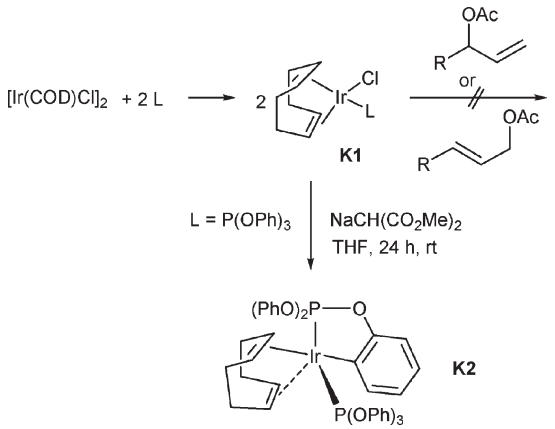

| L | Conditions | **3d**/(*E*)-**4d**/(*Z*)-**4d** | |
|---|---|---|---|
| $P(OPh)_3$ | rt, 2 h | 25 : 5 : 70 | (81 %) |
|  | 65 °C, 5 h | 2 : 7 : 90 | (85 %) |



**Scheme 3** Allylic alkylations of a (*Z*)-allyl acetate.

An interesting observation was made in the attempt to prepare a putative (allyl)Ir-intermediate.[10b] The standard catalyst system $[Ir(COD)Cl]_2/P(OPh)_3$ surprisingly did not react with typical substrates such as allylic acetates (Scheme 4). A reaction only occurred upon addition of the nucleophile. The catalytically active complex was generated by reaction of the precomplex **K1** with $NaCH(CO_2Me)_2$. The resultant complex **K2** is formed *via* orthometallation ($Ir^{III}$), elimination of HCl ($Ir^{I}$) and addition of $P(OPh)_3$.[11]



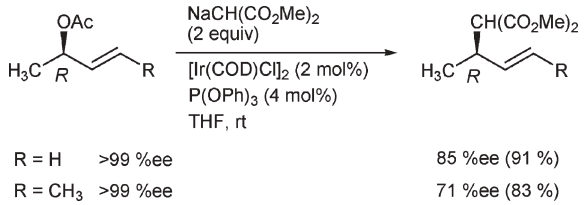

**Scheme 4** Catalyst formation *via* base-induced C–H activation.

The catalyst system $[Ir(COD)Cl]_2/P(OPh)_3$ was similarly effective in allylic aminations as in alkylations. A broad range of amines was used as nucleophiles, for example piperidine, benzylamine and aniline.[12] As allylic substrates, carbonates were found to be superior to acetates. A marked solvent dependence was observed; the best results were achieved with alcohols, particularly with ethanol (typical conditions: 50 °C, reaction time of 3 h). Stereospecificities in the reactions of (*Z*)-allylic carbonates to give linear (*Z*)-propenylamines were essentially perfect, regioselectivities for reactions of (*E*)-allylic carbonates to give branched products were high, similar to those of alkylations. Concerning applications, it is import that with primary amines as nucleophiles, for example benzylamine, mainly monoallylation products were obtained.

## 2.2 Steric course of the Ir-catalysed allylic substitution

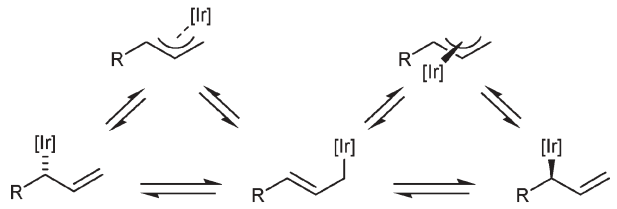
The Pd-catalysed allylic alkylation proceeds with net retention of configuration *via* a double inversion process. Using standard procedures, the same steric course was established for the Ir-catalysed alkylation.[10b]

Information on the configurational stability of intermediary (allyl)Ir complexes was gained by studying reactions of non-racemic allylic substrates (Scheme 5).




**Scheme 5** Conservation of enantiomeric excess in Ir-catalysed allylic alkylations.

These results and the results with (*Z*)-substrates suggest that the Ir-catalysed reactions, similar as proposed for Rh-catalysed reactions, proceed by substitution with inversion to give (σ-allyl)Ir complexes, which further react with a nucleophile again with inversion; the σ-complexes undergo *slow* racemisation (or epimerisation) *via* σ–π–σ-rearrangement or sigmatropic 1,3-rearrangement (Scheme 6). This behaviour

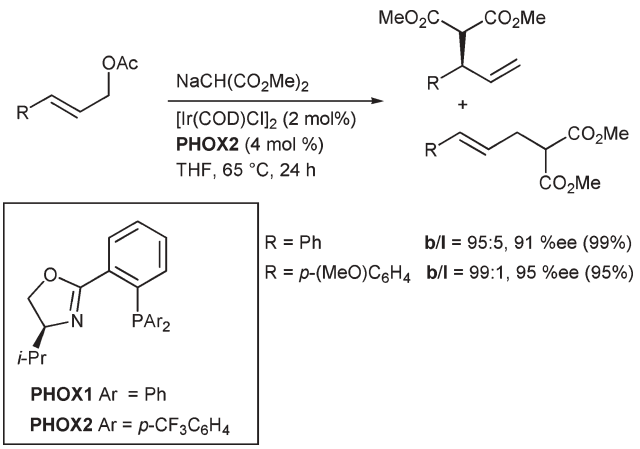



**Scheme 6** Possible intermediates of Ir-catalysed allylic substitutions.

is different from that of the corresponding Pd-complexes, which display fast isomerisation at room temperature.

## 2.3 Asymmetric catalysis: test reactions, ligands and catalyst development

**2.3.1 Phosphinooxazolines as chiral ligands.** In the first asymmetric variant of the Ir-catalysed allylic substitution, allylic acetates in conjunction with phosphinooxazolines (PHOX) as chiral ligands were used (Scheme 7).[8] The reaction was slow in comparison to the reaction catalysed by the $[Ir(COD)Cl]_2/P(OPh)_3$ system or even the parent complex $[Ir(COD)Cl]_2$; however regio- and enantioselectivity were excellent.




**Scheme 7** First asymmetric allylic substitutions.

It was relatively easy to prepare cationic (π-allyl)(PHOX)$Ir^{III}$ complexes. The crystal structure of the complex **K3** (Fig. 1) was as anticipated on the basis of *trans* influences of the ligands. Remarkably, the reaction of this complex with dimethyl sodiomalonate proceeded as addition of the nucleophile at the central rather than the terminal allylic carbon to give an iridacyclobutane.[13a] This in fact is a very typical reaction of

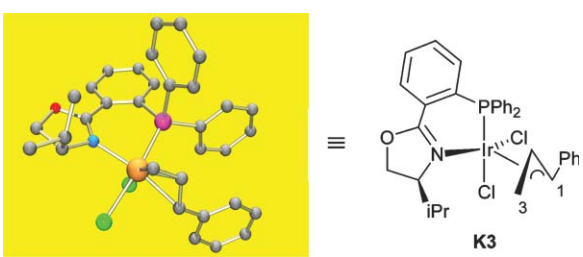
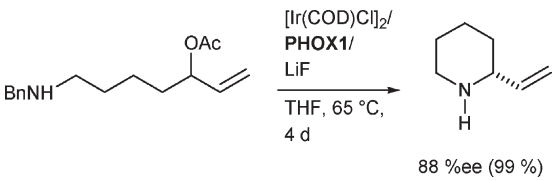



**Fig. 1** X-Ray crystal structure of the complex [$\eta^3$-(1-phenylallyl)(**PHOX1**)$Cl_2$Ir] (**K3**).

(π-allyl)$Ir^{III}$complexes with nucleophiles, which was studied years ago by the Bergman and Stryker groups.[13b,c]

Further investigation of the PHOX-Ir catalysts soon gave disappointing results in that regioselectivities were very low with alkyl-substituted substrates such as **2b**. Aminations were generally slow, nevertheless, quite interesting results were achieved in intramolecular aminations (Scheme 8).[14,22]




**Scheme 8** Intramolecular allylic amination.

**2.3.2 Phosphorus amidites as ligands and reaction conditions.** Catalysts prepared from $[Ir(COD)Cl]_2$ and phosphorus amidites derived from 2,2′-dihydroxybinaphthalene (BINOL) and 2-arylethylamines are arguably the best suited catalysts until today (Fig. 2).[10a] The ligand **Monophos-NMe$_2$** gave moderate to good results in allylic alkylations but is almost completely inactive in aminations.[10b] The set **L1–L3** has generally served very well so far. Of these, **L1** is readily available and usually the first ligand one should try. **L2** has shown the best results, but requires access to enantiomerically enriched 1-(2-methoxyphenyl)ethylamine, which is not readily commercially available from suppliers as yet.[15] **Monphos-NMe$_2$**, **L1** and **L3** were introduced by the Feringa group[16] and **L2** by the Alexakis group.[17]

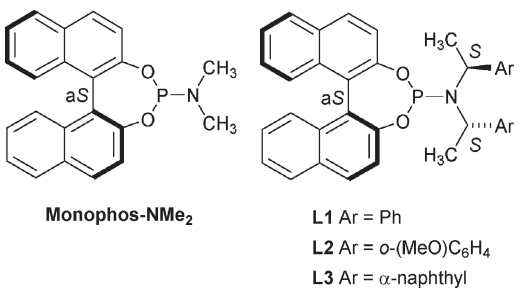



**Fig. 2** Chiral phosphorus amidites most often used in Ir-catalysed allylic substitutions.

**Preparation of phosphorus amidites.** The preparation of phosphorus amidite ligands is illustrated in Scheme 9 by compounds derived from BINOL. Phosphorus amidites can usually be handled for short periods without special precaution. Their modular make-up allows access to numerous variants. The following routes have been most often applied:

(a) Reaction of neat $PCl_3$ with a binaphthol or biphenol leads to a chlorophosphite,[18] which can usually be stored at low temperature. Treatment of the chlorophosphite with a lithiated secondary amine furnishes a phosphorus amidite.[19] The scope of this method is very broad.

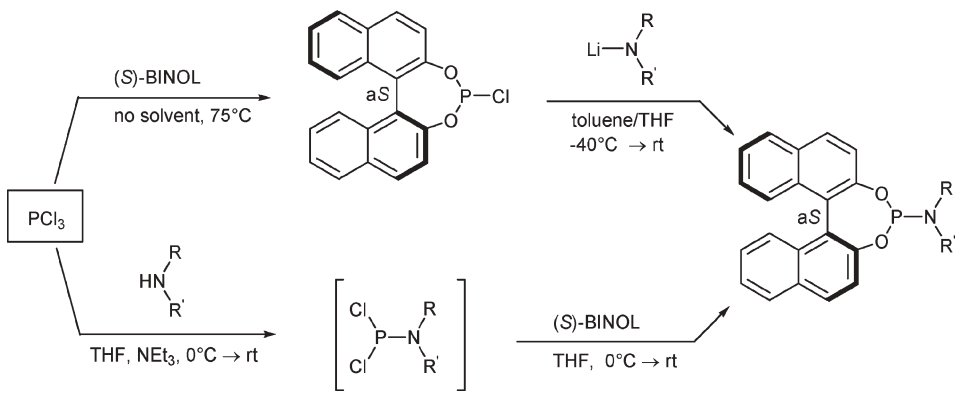
(b) An alternative route involves reaction of $PCl_3$ with the secondary amine followed by treatment of the product with the binaphthol or biphenol to give the phosphorus amidite.[20] From a practical point of view, it is important that this procedure can also be carried out with the hydrochloride of a secondary amine.[21] The choice of solvent is important, methylene chloride or THF are usually applied. In our hands, this route has been found to be particularly well suited in the case of electron-rich amines.

**Catalyst activation, reaction conditions and mechanistic aspects.** Successful application of phosphorus amidite ligands requires close attention to catalyst preparation and reaction conditions, because ligands can be altered by C–H activation (see above) at aryl or $CH_3$ groups. The following procedures were developed (THF, rt):

(A) Mixing $[Ir(COD)Cl]_2$ and ligand **L*** in 1 : 2 ratio. A complex [Ir(COD)**L***Cl] (**K1**) is formed, simply by breaking up chloro bridges. This procedure works well for aminations,[22,40] in particular with ligand **L2**,[17] which generally induces higher selectivity than **L1**.

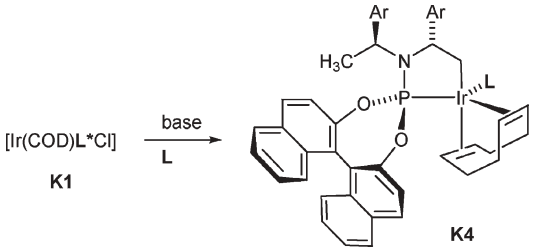
(B) Procedure A and LiCl as additive. This procedure was worked out for alkylations using ligand **L1**,[10c,23] but gave superior results in conjunction with **L2** as shown by Alexakis and Polet.[21,24] These authors recently showed that a catalytically active complex can partially be recovered.[21a] According to our own investigation, the recoverable complex is [Ir(COD)**L2**Cl], *i.e.* a simple complex of type **K1**.[25]

(C) Treatment of the mixture according to A with base (TBD,[22,26] DABCO[26,27] or propylamine[27]) in order to form an activated complex of type **K4** by *in situ* C–H activation at the $CH_3$ group (Scheme 10).[28] This complex is an analogue of the




**Scheme 9** Preparation of phosphorus amidites.




**Scheme 10** Base-induced C–H activation.

complex **K2** presented above. Note that **K4** is a coordinatively saturated (18 VE) $Ir^I$ complex. Dissociation of **L** is required in order to get a reactive species.

(D) Treatment of a mixture of $[Ir(COD)Cl]_2$, **L***, THT (tetrahydrothiophene) and THF with the base TBD for 2 h at rt, then addition of the allylic substrate and subsequently of CuI. This procedure yields an excellent catalyst for alkylations, particularly in conjunction with ligand **L1**.[29]

It should be noted that dry THF has to be used in all cases because the catalyst formation step is very sensitive to water (<35 μg $H_2O$/mL THF, Karl Fischer titration).

**Variation of the phosphorus amidite framework.** A particularly valuable feature of phosphorus amidites is their highly modular make-up, which allows numerous variations. In Fig. 3 formulae of the parent ligand **L1** and a generalised structure are presented in such a way that the connection with the cyclometalated complex **K4** is apparent. The following main results have been obtained.

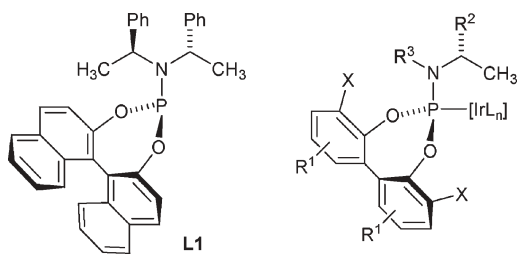
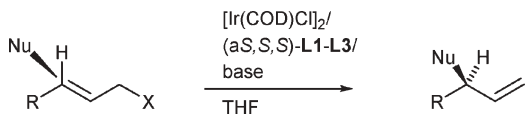



**Fig. 3** Variation of the phosphorus amidite framework.

(a) Ligands of type **L1–L3** derived from $C_2$-symmetric amines can belong to the *like* or *unlike* series of diastereoisomers, for example possess the (a*S,S,S*)- or the (a*S,R,R*)-configuration. The steric course of the allylic substitution, *i.e.* the absolute configuration of the allylation products, is controlled by the axial configuration. Remarkably, the ligands of the *like* series induce higher degrees of selectivity as well as rates. In the case of **L1**, the ligand with *unlike* configuration is completely inactive; this was demonstrated by using a mixture prepared from racemic BINOL, which induced the same enantioselectivity as the pure ligand with *like*-configuration.[30c]

(b) So far the following steric course has been found without exception:




(c) Replacement of the 1,1′-binaphthalenyl by a biphenyl unit led to reduced but often still acceptable selectivity.[10c,30b] However, ligands with X = $CH_3$ or $OCH_3$ gave rise to comparatively low selectivity.[31]

(d) Variation of the group $R^2$ is of paramount importance. Replacement of $R^2$ = aryl by $R^2$ = alkyl or cycloalkyl led to markedly reduced selectivities. So far, the best results have been obtained with ligands containing an *ortho*-substituted aryl group, for example ligands **L2** and **L3**. Though ligand **L2** with a *o*-$(MeO)C_6H_4$ moiety is probably the generally best suited ligand, similar results have been obtained with the corresponding ligand with $R^2$ = *o*-$(H_3C)C_6H_4$.[21] Likely, the effect of the increase of the steric bulk of $R^2$ is due to enhanced dissociation of ligand **L** of complex **K4**.

(e) One of the arylethyl units can be replaced by a bulky group $R^3$. The best results were obtained with $R^3$ = cyclododecyl.[30a,c] The combination of two different *N*-arylethyl substituents, for example $R^2$ = *o*-$(MeO)C_6H_4$ and $R^3$ = (*S*)-1-phenylethyl, has also led to an effective ligand,[21] which is readily available from (*S*)-1-phenylethylamine and a good substitute for **L2**.

**2.3.3 Further ligands.** Phosphites (**L4a**,[32] **L4b**[33]) and **Ph-pybox**[34] (Fig. 4) have been applied successfully as chiral ligands in reactions of arylallyl derivatives. As substitutes for cyclooctadiene, chiral [2.2.2]bicyclooctadienes, for example **L5**, prepared from (−)-carvone, have been used for kinetic resolutions with phenolates as nucleophiles.[35]

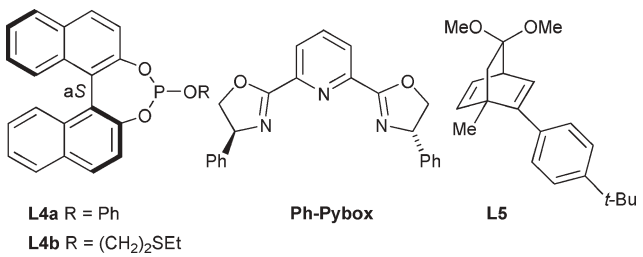
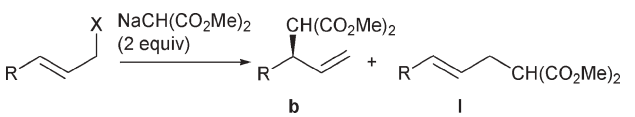



**Fig. 4** Further chiral ligands that have been used in Ir-catalysed allylic substitutions.

## 3 C-Nucleophiles

### 3.1 Intermolecular alkylations

**3.1.1 Malonates and related compounds as pronucleophiles.** Ir-catalysed allylic alkylations with malonates and related compounds according to Scheme 11 were first carried out in broad scope using allylic acetates in conjunction with ligand **L1** and procedure B (*cf.* section 2.3.2).[10c] While enantioselectivity was excellent, regioselectivity was low. Considerable




**Scheme 11** Asymmetric allylic alkylations with dimethyl malonate as nucleophile (reaction conditions see Table 2).

experimentation led to the development of procedure D, which furnished preparatively usable results for a wide range of substrates for the first time.[29]

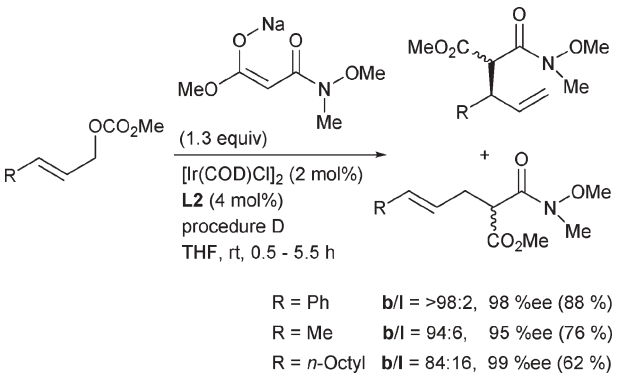
The results displayed in Table 2 show that a wide range of substrates can be alkylated with high degrees of regio- and enantioselectivity. THF was found to be the most suitable solvent,[10b] and carbonates gave better results than acetates.[23] In most cases ligand **L2** induced the highest activity as well as regio- and enantioselectivity.[24] Catalyst loadings down to 0.1 mol% have been successfully applied.[31]

**Table 2** Ir-Catalysed allylic alkylations with dimethyl malonate (Scheme 11)

| Entry | R | L* | Yield (%) | b : l | Ee (%) | Ref. |
|---|---|---|---|---|---|---|
| *Procedure B*: [Ir(COD)Cl]$_2$ (2 mol%), **L*** (4 mol%), THF, rt, LiCl (1 equiv.) | | | | | | |
| *X = OAc* | | | | | | |
| 1 | Ph | **L1** | 98 | 91 : 9 | 86 | 10*c* |
| 2 | Me | **L1** | 96 | 75 : 25 | 82 | 10*c* |
| 3 | *i*-Pr | **L1** | 56 | 55 : 45 | 94 | 10*c* |
| 4 | Ph | **L2** | 79 | 99 : 1 | 97 | 21*a* |
| 5 | *n*-Pr | **L2** | 87 | 87 : 13 | 97 | 21*a* |
| *X = OCO$_2$Me* | | | | | | |
| 6 | Ph | **L2** | 82 | 99 : 1 | 98 | 24 |
| 7 | *o*-(MeO)C$_6$H$_4$ | **L2** | 98 | >99 : 1 | 79 | 21*a* |
| 8 | Cyclohexyl | **L2** | 65 | 93 : 7 | 98 | 24 |
| 9 | *n*-Pr | **L2** | 92 | 80 : 20 | 96 | 21*a* |
| *Procedure D*: [Ir(COD)Cl]$_2$ (2 mol%), **L*** (4 mol%), THF, rt, TBD (12 mol%), CuI (20 mol%), tetrahydrothiophene (20 mol%) | | | | | | |
| *X = OCO$_2$Me* | | | | | | |
| 10 | Ph | **L1** | 88 | 99 : 1 | 96 | 29 |
| 11 | Ph | **L2** | 92 | >99 : 1 | 98 | 31 |
| 12 | PhCH=CH | **L2** | 80 | 99 : 1 | 98 | 31 |
| 13 | PhCH$_2$CH$_2$ | **L2** | 93 | 91 : 9 | 98 | 31 |

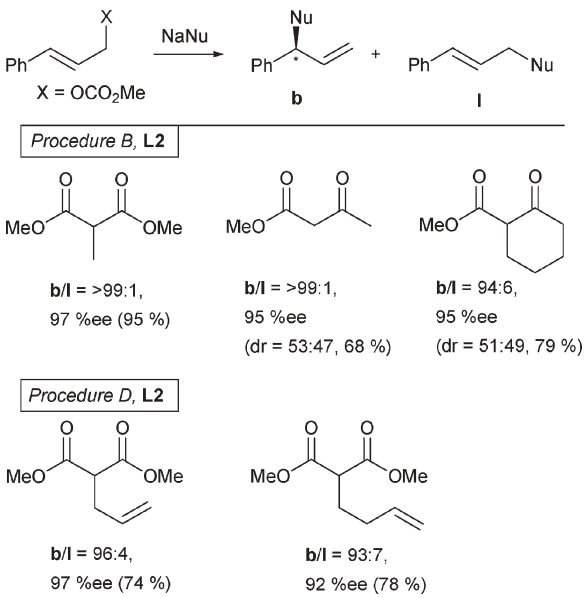
Concerning the dependence of regio- and enantioselectivity on the allylic substrate, the following conclusions can be drawn.[10,24,29,31,36] Using **L1** in conjunction with procedure D or **L2** in conjunction with procedures B or D, aryl- and alkenyl-substituted allylcarbonates are privileged substrates and substitutions generally proceed with regioselectivity **b** : **l** = >98 : 2. For alkyl-substituted allyl carbonates regioselectivity is lower, >90 : 10 in the case of small and rigid substituents (R = Me, cyclohexyl), but only 70 : 30 to 90 : 10 in the case of flexible or sterically very demanding substituents (R = *n*-Pr, *n*-octyl, $CH_2CH_2Ph$, $CH_2OSi(t\text{-}Bu)Ph_2$ (*cf.* Table 2 and Scheme 12). Generally, enantioselectivity is very high, excepting the case R = *o*-(MeO)C$_6$H$_4$.

The Weinreb-type amide shown in Scheme 12 is a useful alkylation agent, which showed reactivity comparable to dimethyl sodiomalonate.[36] As products, 1 : 1 mixtures of epimers were formed, likely because of base-catalysed isomerisation. The methoxycarbonyl group can be removed selectively by saponification/decarboxylation and the resultant Weinreb amide can be transformed into a ketone, *i.e.* the nucleophile serves as equivalent of the enolate of a methyl ketone (*cf.* section 6).




**Scheme 12** Asymmetric allylic alkylations with a Weinreb-type amide as pronucleophile.

Further pronucleophiles that have been successfully used are 2-substituted malonates and β-keto-esters (Scheme 13).[21a,31] With β-ketoesters *ca.* 1 : 1 mixtures of epimers are formed. Products derived from 2-alkenylmalonates have been transformed into cyclopentene derivatives *via* Ru-catalysed ring closing metathesis.[21a,31]

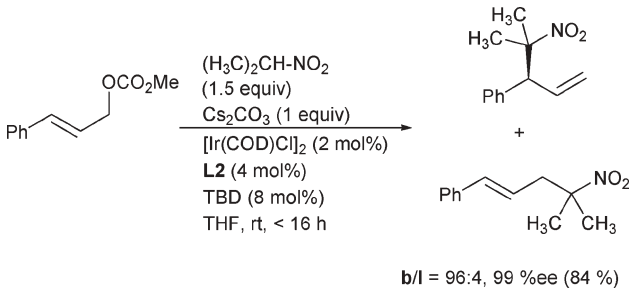



**Scheme 13** Substitutions with 2-substituted malonates (HNu) and β-ketoesters as pronucleophiles (upper row ref. 21*a*, lower row ref. 31).

**3.1.2 Aliphatic nitro compounds as pronucleophiles.** Aliphatic nitro compounds are valuable intermediates in organic synthesis, due to the diversity of their chemistry (*cf.* section 6, Scheme 37). In initial attempts to use them in allylic substitutions, nitromethane was probed, unfortunately to no avail, because complex mixtures of mono- and dialkylation products were obtained. However, primary and secondary nitro compounds were found to be suitable pronucleophiles. Cesium carbonate was used as mild base for their deprotonation. A typical reaction is described in Scheme 14.[37] A further example is presented in Scheme 37.

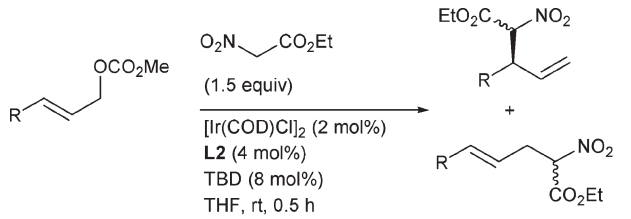
Ethyl nitroacetate is a synthetic equivalent of both nitromethane and glycine. The ethoxycarbonyl group serves as




**Scheme 14** Asymmetric allylic alkylation with an aliphatic nitro compound as pronucleophile.

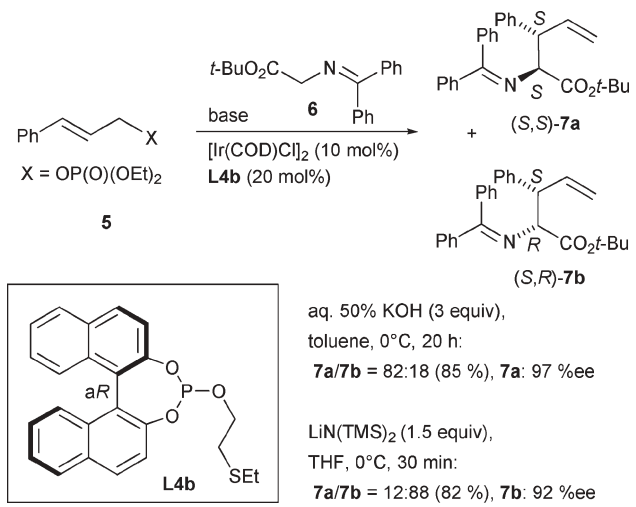
protecting group, preventing multiple alkylation. The allylic alkylation with commercially available ethyl nitroacetate proceeded fast without an additional base ("salt free" conditions) (Scheme 15).[37] Because of the high acidity of the chirality centre α to N, 1 : 1 mixtures of epimers were formed.




| | |
|---|---|
| R = Ph | **b/l** = 99:1, 98 %ee (90 %) |
| R = $PhCH_2CH_2$ | **b/l** = 78:22, 98 %ee (86 %) |
| R = *n*-Pr | **b/l** = 90:10, 99 %ee (92 %) |

**Scheme 15** Asymmetric allylic alkylations with ethyl nitroacetate.

**3.1.3 Allylic substitutions using a glycine equivalent as pronucleophile.** Takemoto and co-workers reported a regio-, diastereo- and enantioselective synthesis of amino acids, applying the diphenylimino glycinate **6** as pronucleophile. The bidentate chiral phosphite **L4b** and 3-arylallyl diethyl phosphates were used as ligand and allylic substrates, respectively (Scheme 16).[33,38]




**Scheme 16** Diastereoselective allylic alkylations with a glycine equivalent.

Remarkably, both diastereoisomeric substitution products could be formed selectively, depending on the cation provided by the base. With KOH as base the (*S*,*S*)-diastereoisomer **7a** was the major product, while with lithium bases the (*R*,*S*)-diastereoisomer **7b** was preferentially obtained. Takemoto and co-workers proposed as explanation for this stereodichotomic effect that with $LiNR_2$ a N,O-chelated *syn*-enolate and with KOH an *anti*-enolate was formed (Fig. 5). The method was successfully applied in the synthesis of α,α-disubstituted amino acids.

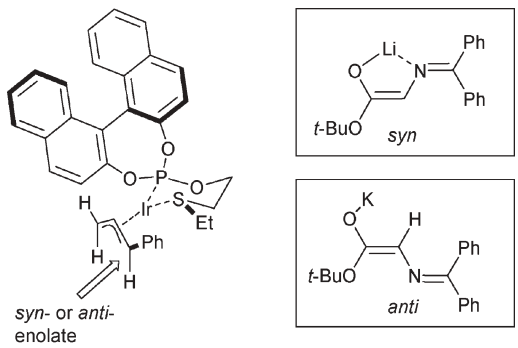
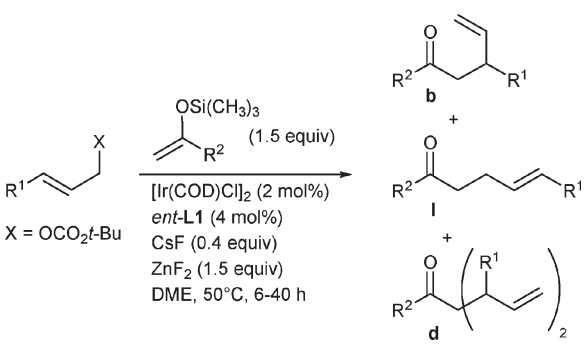



**Fig. 5** Mechanistic proposal for rationalisation of the results displayed in Scheme 16.

**3.1.4 Ketone enolates as nucleophiles.** Graening and Hartwig recently accomplished highly regio- and enantioselective reactions of allylic carbonates with enolates generated *in situ* with fluoride from trimethylsilyl enol ethers of methyl ketones (Scheme 17).[39] When cesium fluoride was used as fluoride source, the reaction proceeded with modest selectivity and diallylation was pronounced. Optimisation led to a remarkable reagent, a combination of cesium fluoride and zinc fluoride. With this, the extent of diallylation was negligible.

The procedure was applied to a variety of substrates and high degrees of regio- and enantioselectivity were achieved. So far only methyl ketones, giving rise to one stereogenic centre, have been investigated.

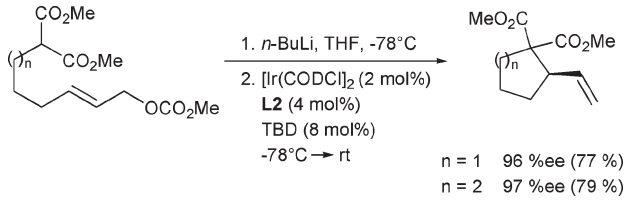



| $R^1$ | $R^2$ | Yield (%) | **b/l** | Ee (%) |
|---|---|---|---|---|
| *p*-$(MeO)C_6H_4$ | Ph | 94 | 99:1 | 96 |
| Ph | $PhCH_2CH_2$ | 54 | 99:1 | 94 |
| Ph | *i*-Pr | 46 | 95:5 | 91 |
| *n*-Pr | Ph | 92 | 87:13 | 92 |

**Scheme 17** Allylic alkylations with ketone enolates as nucleophiles.

### 3.2 Intramolecular alkylations

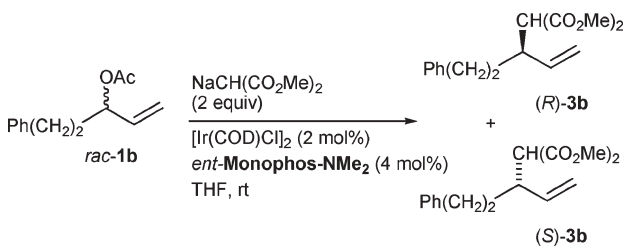
In contrast to the Pd-catalysed versions, Ir-catalysed intramolecular reactions do not require high dilution conditions. Chiral vinylcyclopentane and -hexane derivatives have been prepared with high enantioselectivity (Scheme 18).[31] To succeed in this reaction, the anion had to be prepared at −78 °C in order to suppress the competing non-catalysed reaction, which leads to the racemic product. Once more, the best results were obtained with **L2** as ligand.




**Scheme 18** Intramolecular allylic alkylation.

### 3.3 Kinetic resolution

Ir-Catalysed kinetic resolutions were realised using phosphorus amidites **Monophos-NMe$_2$**, **L1** and **L2** as chiral ligands and racemic allylic acetates as substrates (Scheme 19 and Fig. 6). With *ent*-**Monophos-NMe$_2$** as ligand, (*R*)-**1b** was consumed *ca.* 12 times faster than (*S*)-**1b**.[10a] The product (*R*)-**3b** was formed with *ca.* 63 %ee. As the enantiomerically pure acetate did not racemise under the applied reaction conditions, an isomerisation process of an intermediate, likely an allyl complex, must have occurred. Isomerisation was further enhanced by addition of LiCl (procedure B), which allowed to obtain (*R*)-**3b** with 86 %ee from *rac*-**1b**. Similar experiments were performed with acetate **1a** and **L2** as ligand.[21a]




**Scheme 19** Kinetic resolution of the racemic acetate **1b** using *ent*-**Monophos-NMe$_2$** as chiral ligand.

## 4 N-Nucleophiles

### 4.1 Aliphatic amines as nucleophiles

**4.1.1 Intermolecular aminations.** For aminations (Scheme 20) the standard combination [Ir(COD)Cl]$_2$/2**L1** was initially used as catalyst, *i. e.* procedure A (*cf.* section 2.3.2) was employed.[40] Obviously, aliphatic amines, for example benzylamine and pyrrolidine, which were mainly used as nucleophiles in exploratory experiments, are sufficiently basic to effect

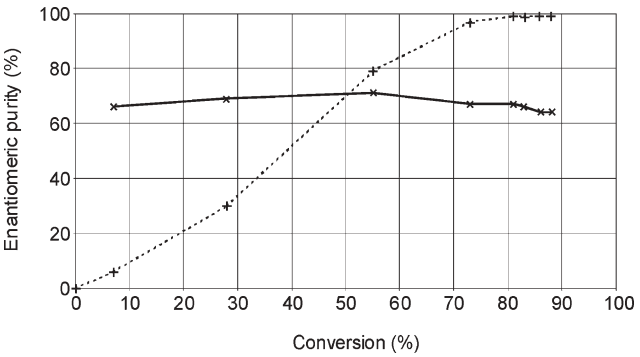
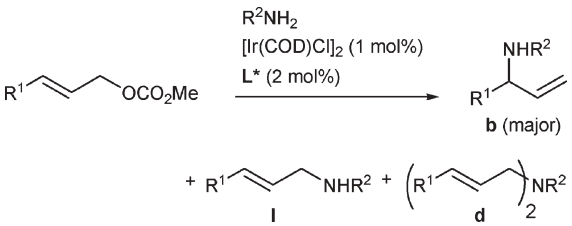



**Fig. 6** Enantiomeric purity of acetate **1b** (+) and alkylated product **3b** (×) *vs.* conversion for the reaction according to Scheme 19.

cyclometallation to give complexes of type **K4** *in situ*. However, when more bulky aliphatic amines and arylamines (see below) were used or intramolecular aminations probed, the necessity for catalyst activation became apparent.[22,28]




**Scheme 20** Allylic amination.

The influence of the solvent was assessed with non-activated [Ir(COD)Cl]$_2$/2**L1** using the reaction of cinnamyl carbonate with $BnNH_2$ (Table 3).[40] Judged by reaction time and enantioselectivity, THF was found to be the most suitable solvent. With EtOH as solvent, reversibility was observed. Thus, the reaction of cinnamyl methyl carbonate with morpholine in EtOH at room temperature gave complete conversion and excellent regioselectivity after 1 h (**b** : **l** = 99 : 1), but after 60 h the more stable linear isomer was the major product (**b** : **l** = 10 : 90).

**Table 3** Influence of the solvent on the allylic amination (Scheme 20, $R^1$ = Ph, $R^2$ = $PhCH_2$, **L*** = **L1**, rt)

| Entry | Solvent | Time/h | Ee (%) |
|---|---|---|---|
| 1 | DMF–EtOH | 1–2 | 77–80 |
| 2 | MeOH | 8–10 | 52 |
| 3 | $CH_3CN$ | 8–10 | 77–80 |
| 4 | THF | 8–10 | 95 |
| 5 | DME | 20–24 | 94 |
| 6 | $CH_2Cl_2$ | 48 | 90–92 |
| 7 | $Et_2O$ | >72 | 95 |
| 8 | Toluene–1,4-dioxane | >72 | 90–92 |

Further results with the non-activated [Ir(COD)Cl]$_2$/2**L*** (procedure A) are presented in Table 4, entries 1–10. Generally, the monoallylated branched amine was the major product.[23,40] The results were slightly better with ligand **L2** than with ligand **L1**. In the cases $R^1$ = Ph or alkenyl (entries 1–6) enantiomeric excess was high. Reactions of carbonates with an electron withdrawing (entry 7) or potentially coordinating (entry 8)

*ortho*-substituent in the aryl group proceeded with considerably reduced degrees of selectivity. As observed for alkylations, substrates with $R^1$ = alkyl yielded products with high enantio- but reduced regioselectivity (entries 9,10).

**Table 4** Ir-Catalysed allylic aminations according to Scheme 20

| Entry | $R^1$ | $R^2$ | L* | Time/ h | Yield[a] (%) | **b** : **l** : **d** | Ee (%) | Ref. |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Bn | **L1** | 10 | 84 | 98 : 1 : 1 | 95 | 40 |
| 2 | Ph | Bn | **L2** | n.d. | 88 | 98 : 2 | 97 | 17 |
| 3 | Ph | PMB | **L1** | 18 | 80 | 99 : 0 : 1 | 94 | 40 |
| 4 | Ph | *n*-$C_6H_{11}$ | **L1** | 9 | 88 | 98 : 2 | 96 | 40 |
| 5 | Ph | *n*-$C_6H_{11}$ | **L2** | n.d. | 89 | 98 : 2 | 98 | 17 |
| 6 | PhCH=CH | Bn | **L1** | 24 | 61 | 99 : 1 | 97 | 23 |
| 7 | *p*-$(NO_2)C_6H_4$ | Bn | **L1** | 12 | 67 | 83 : 13 : 4 | 86 | 40 |
| 8 | *o*-$(MeO)C_6H_4$ | Bn | **L1** | 16 | 77 | 95 : 4 : 1 | 76 | 40 |
| 9 | *n*-Pr | Bn | **L1** | 10 | 66 | 88 : 8 : 4 | 95 | 40 |
| 10 | $PhCH_2CH_2$ | Bn | **L2** | 3 | 63 | 84 : 16 | 96 | 41 |
| 11[b] | $PhCH_2CH_2$ | Bn | **L2** | 0.7 | 59 | 84 : 16 | 96 | 41 |
| 12 | Ph | $Ph_2CH$ | **L1** | 10 | 11[c] | — | — | 28 |
| 13[d] | Ph | $Ph_2CH$ | **L1** | 10 | 85 | 97 : 3 | 98 | 28 |
| 14[b,e] | $PhCH_2CH_2$ | Bn | **L1** | 72 | 0[c] | — | — | 30*a* |
| 15[b,e,f] | $PhCH_2CH_2$ | Bn | **L1** | 72 | 67 | 81 : 19 | 95 | 30*a* |

[a] Isolated yield of branched product. [b] The catalyst was activated with TBD. [c] Conversion. [d] 1 mol% **K4** + $[Ir(COD)Cl]_2$ was used as catalyst. [e] 0.4 mol% of catalyst. [f] Addition of 0.4 mol% of $Pb(NO_3)_2$ and tetrahydrothiophene.

With the bulky $Ph_2CHNH_2$, an ammonia equivalent, the standard amination using procedure A gave only 11% conversion (entry 12), the reaction with the activated catalyst gave the substitution product with excellent selectivity in 85% yield. Catalyst activation appears to be less important in the case of ligand **L2** (*cf.* entries 10 and 11).

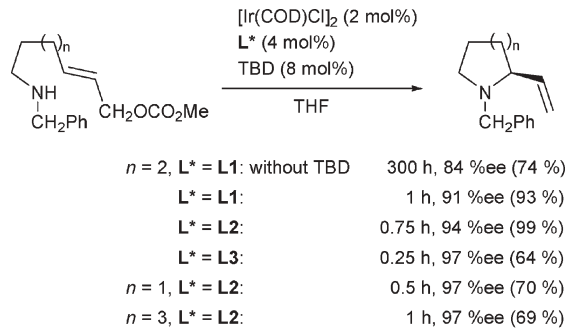
Procedure D, *i.e.* using copper iodide as additive (*cf.* section 2.3.2), which was very successful for alkylations, was not effective in aminations, because of coordination of $Cu^I$ to the amine. As a result of screening further salts of soft cations it was found that addition of $Pb^{II}$ salts in conjunction with base treatment of the precatalyst led to significantly faster reaction rates. Hence the reaction could be carried out with catalyst loading as low as 0.4 mol% (entry 15).[30a]

**4.1.2 Intramolecular aminations.** Intramolecular allylic aminations (Scheme 21) were found to proceed with very high catalytic efficiency and ee values >90% if a base activated catalyst (procedure C, section 2.3.2) was used.[22,30a] The effect of catalyst preparation is illustrated for the formation of *N*-benzyl-2-vinylpiperidine in Scheme 21. Base activation with TBD[26] increased catalyst activity by a factor of *ca.* 1000. Furthermore, substrate concentration as high as 1 M could be employed due to a marked preference of intra- over the corresponding intermolecular substitutions.

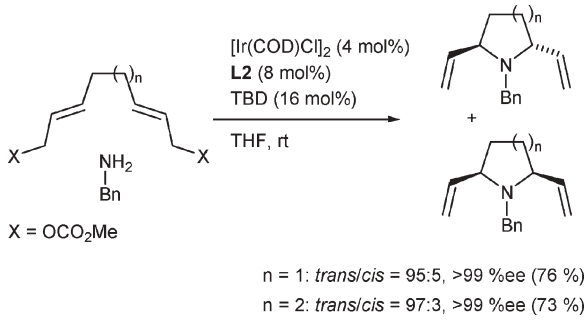
Due to double stereoselection, >99 %ee was achieved for aminations of bis-allylic carbonates to give pyrrolidines and piperidines (Scheme 22).[30a]

### 4.2 Arylamines as nucleophiles

Procedure A (*cf.* section 2.3.2), *i. e.* use of a catalyst not activated with base, was not applicable to substitutions with

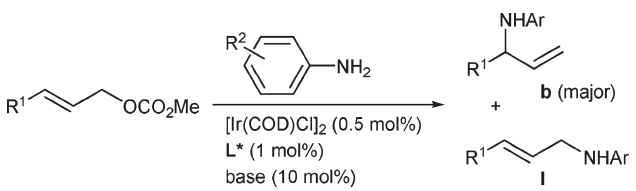



**Scheme 21** Intramolecular allylic aminations (ref. 30*a*).




**Scheme 22** Sequential inter- and intramolecular allylic aminations.

aromatic amines, obviously because these are not sufficiently basic to induce cyclometallation (Scheme 23). Accordingly, catalyst activation *via* cyclometallation by treatment with base was employed (procedure C). Hartwig and co-workers[27] successfully used *n*-$PrNH_2$ or, better in this case, DABCO[26] as activators. A very remarkable feature of these aminations is the uniformly high level of regioselectivity, even with $R^1$ being a $sp^3$-substituent such as *n*-Pr (Table 5). Enantiomeric excess was excellent when using the sterically demanding ligand **L3**.




**Scheme 23** Allylic aminations with arylamines.

**Table 5** Ir-Catalysed allylic amination with arylamines according to Scheme 23

| Entry | $R^1$ | $R^2$ | Activator | L* | Time/h | Yield (%) | **b** : **l** | Ee (%) |
|---|---|---|---|---|---|---|---|---|
| 1[a] | Ph | H | DABCO[b] | **L1** | 24 | 72 | >99 : 1 | 92 |
| 2 | Ph | H | DABCO | **L3** | 6 | 80 | >99 : 1 | 96 |
| 3 | Ph | *p*-Me | DABCO | **L3** | 6 | 76 | 99 : 1 | 94 |
| 4 | Ph | *p*-OMe | DABCO | **L3** | 4 | 91 | 98 : 2 | 95 |
| 5 | Ph | *p*-OMe | *n*-$PrNH_2$ | **L1** | 2 | 95 | 95 : 5 | 95 |
| 6[a] | Ph | *p*-$CF_3$ | DABCO | **L3** | 16 | 72 | 94 : 6 | 96 |
| 7 | *n*-Pr | H | DABCO | **L3** | 3 | 87 | 98 : 2 | 95 |
| 8 | *i*-Pr | H | DABCO[c] | **L3** | 16 | 83 | 97 : 3 | 97 |

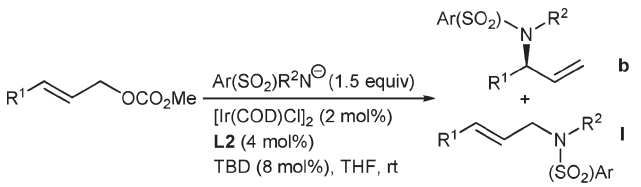
[a] 1 mol% of $[Ir(COD)Cl]_2$, 2 mol % of **L***. [b] 50 mol%. [c] 5 mol% of DABCO.

Again, the reaction with *o*-methoxycinnamyl methyl carbonate was an exception (74 %ee).

### 4.3 *N*-Sulfonyl- and *N*,*N*-diacylamines as nucleophiles

There is considerable interest in the synthesis of unprotected allylamines (*cf.* section 6). Deprotection of the *N*-benzylamines and related compounds described above with methods other than catalytic hydrogenation is difficult. In order to overcome this problem anionic N-nucleophiles, *N*-sulfonylamines and *N*,*N*-diacylamines, were investigated and excellent results were finally obtained.[42,43]

An early attempt with $LiN(CH_2Ph)p$-Ts gave low selectivity because an unsuited phosphorus amidite (**Monophos-NMe$_2$**) was used as ligand.[10b] High enantioselectivity was achieved with **L2** as ligand and activation of the catalyst with TBD (Scheme 24).[42] With cinnamyl carbonate as substrate yield (92%), regioselectivity (**b** : **l** = 98 : 2) and enantiomeric excess (98 %ee) were excellent. However, with a substrate containing a $sp^3$-substituent, yield (60%) and regioselectivity (**b** : **l** = 80 : 20) were not completely satisfactory.




| | | | |
|---|---|---|---|
| $R^1$ = Ph, | $R^2$ = Bn, | Ar = *p*-$(CH_3)C_6H_4$ | **b**/**l** = 98:2, 98 %ee (92 %) |
| $R^2$ = $PhCH_2CH_2$, | $R^2$ = Bn, | Ar = *p*-$(CH_3)C_6H_4$ | **b**/**l** = 80:20, 95 %ee (60 %) |
| $R^1$ = Ph, | $R^2$ = Bn | Ar = *p*-$(NO_2)C_6H_4$ | **b**/**l** = 93:7, 96 %ee (91 %) |
| $R^1$ = Ph, | $R^2$ = H | Ar = *o*-$(NO_2)C_6H_4$ | **b**/**l** = 95:5, 95 %ee (64 %) |

**Scheme 24** Allylic aminations with sulfonamides as pronucleophiles.

*N*-Nitrophenylsulfonylamines (*o*- and *p*-$NsNH_2$) are attractive pronucleophiles, because the N-protecting group of the substitution products can be removed under mild conditions. With N-(*p*-Ns)$NHCH_2Ph$ and *o*-$NsNH_2$ as nucleophiles, the branched product was obtained. However, the reaction of N-(*o*-Ns)$NHCH_2Ph$ and cinnamyl methyl carbonate gave the linear product. Careful monitoring revealed that initially the branched product was formed and rearranged to the more stable linear regioisomer.[43]

A variety of further *p*-nosylamides (Fig. 7) were prepared according to Scheme 24. *N*-Nosylamines are sufficiently acidic to react without additional base. Gas evolution during the reaction indicated that liberated methyl carbonate dissociated into $CO_2$ and the strongly basic methoxide. Yet, yield and regioselectivity were slightly affected by addition of $NEt_3$.

With carboxamides no reaction could be obtained so far, however, substitutions with *N*,*N*-diacylamines, for example phthalimide, $HN(Boc)_2$ and HN(Boc)(CHO), furnished excellent yields and selectivities (Scheme 25, Table 6).[43]

The reaction with $HN(Boc)_2$ was very slow upon use of **L2** as ligand and activation of the catalyst; however, complete conversion was obtained with the sodium salt $NaN(Boc)_2$. The pronucleophile HN(Boc)(CHO) is likely more acidic than

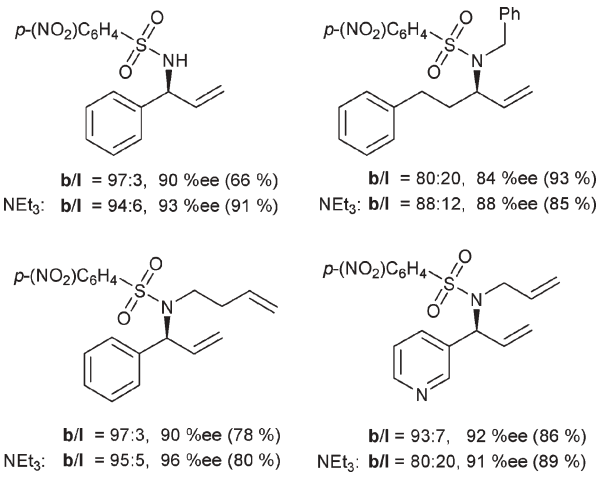
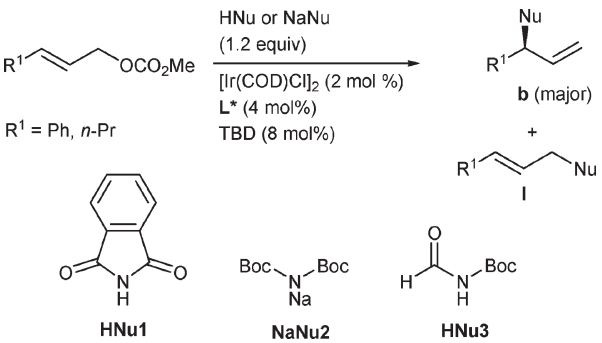



**Fig. 7** Products of Ir-catalysed substitutions with *p*-nosylamides according to Scheme 24.




**Scheme 25** Allylic substitutions with *N*,*N*-diacylamines.

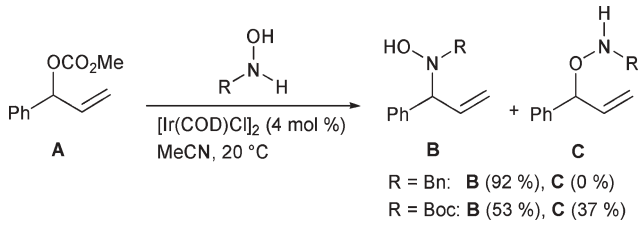
**Table 6** Ir-Catalysed allylic amination with *N*,*N*-diacylamines according to Scheme 25

| Entry | $R^1$ | Prenucleophile | L* | Time/h | Yield (%) | **b** : **l** | Ee (%) |
|---|---|---|---|---|---|---|---|
| 1 | Ph | **HNu1** | **L1** | 18 | 66 | 93 : 7 | 96 |
| 2 | *n*-Pr | **HNu1** | **L1** | 18 | 86 | 90 : 10 | 95 |
| 3 | Ph | **NaNu2** | **L1** | 18 | 80 | 97 : 3 | 97.5 |
| 4 | Ph | **NaNu2** | **L2** | 0.7 | 80 | 97 : 3 | 99 |
| 5 | Ph | **HNu3** | **L1** | 18 | 86 | 97 : 3 | 97.5 |
| 6 | Ph | **HNu3** | **L2** | 0.7 | 96 | 98 : 2 | 98.5 |
| 7 | *n*-Pr | **HNu3** | **L1** | 24 | 98 | 92 : 8 | 97 |

$HN(Boc)_2$, no additional base was required. The reaction products were readily transformed into the unprotected allylic amines.

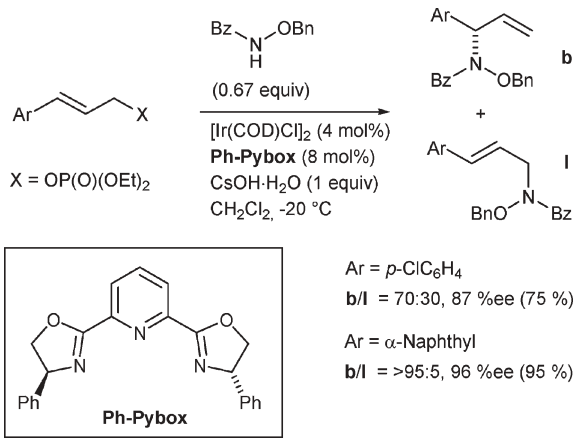
### 4.4 Hydroxylamine derivatives as N-nucleophiles

Hydroxylamine derivatives are ambident nucleophiles, *i. e.* they can react at nitrogen or oxygen (Scheme 26). *N*-Benzylhydroxylamine behaves as N-nucleophile in the Ir-catalysed allylic substitution, while *N*-Boc-hydroxylamine gives mixtures of the N- and O-substituted product, both in the Ir- and the Pd-catalysed allylic substitution. Because of this non-selectivity, it is necessary to use either O- or N,O-protected hydroxylamine as nucleophile.[44]




**Scheme 26** Ambident character of hydroxylamine derivatives.

The base-activated Ir/phosphoramidite complexes described above, which are the catalysts of choice for allylation of amines and stabilised amides, were found not to be suited for allylation of hydroxylamine and hydrazine derivatives.[45] Better results were obtained by Takemoto and co-workers with **Pybox** ligands, employed under appropriate conditions (Scheme 27).[34] Phosphates rather than carbonates, which did not react, had to be used as substrates and $CH_2Cl_2$ rather than THF was the solvent. The addition of a base, which strongly affected regio- and enantioselectivity, was necessary; with $Cs(OH)\cdot H_2O$ or $Ba(OH)_2\cdot H_2O$ good results were obtained.




**Scheme 27** A hydroxylamine derivative as nucleophile.

Further nucleophiles were tested with cinnamyl diethyl phosphate as substrate (Scheme 27, Ar = Ph) and $Cs(OH)\cdot H_2O$ as base (Fig. 8).[34] The base was required in the case of *N*,*O*-dibenzoylhydroxylamine, while the reaction with *N*,*O*-dibenzylhydroxylamine proceeded without. *N*-Benzoylbenzylamine did not react under these conditions. There is no report on a reaction of an alkylallyl substrate.

## 5 O-Nucleophiles

### 5.1 Phenolates as nucleophiles

The early work with phenolates as nucleophiles (Scheme 28) was carried out with a Ir/phosphorus amidite catalyst not

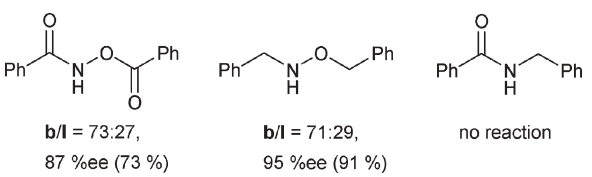
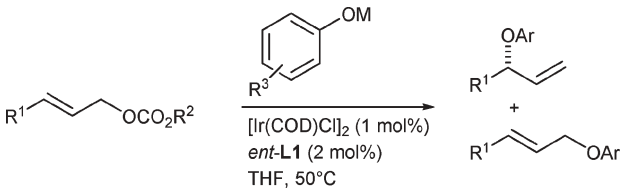



**Fig. 8** Selected pronucleophiles probed with cinnamyl diethyl phosphate as substrate and **Ph-Pybox** as ligand (*cf.* Scheme 27).




**Scheme 28** Allylic substitutions with phenolates as nucleophiles.

activated deliberately (Table 7).[46] Likely, cyclometallation occurred *in situ*, if not induced by phenolate, then by the alkoxide ion generated from the leaving group. Selectivities and yields were found to strongly depend on the base used to generate the phenolate. Alkali phenolates gave much better results then ammonium phenolates, which were preferably generated with $NEt_3$ (entry 1). Use of a sodium phenolate in combination with a methyl carbonate gave rise to transesterification as side reaction (entry 2). Better results were obtained with ethyl carbonates (entry 3) or lithium phenolates (entry 4). Typically, carbonates with $R^1$ = aryl gave better results than those with $R^1$ = alkyl (entry 5). The solvent was found to influence reaction rate and selectivity. Once again, the best results were obtained with THF.

**Table 7** Allylic substitutions with phenolates as nucleophiles (refs. 46, 47)

| Entry | $R^1$ | $R^2$ | $R^3$ | M | Time/h | Yield[a] (%) | **b** : **l** | Ee (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | Ph | Me | H | $NEt_3H$ | 15 | 76 | 93 : 7 | 84 |
| 2[b] | Ph | Me | H | Na | 22 | 40 | 97 : 3 | 92 |
| 3[b] | Ph | Et | H | Na | 35 | 76 | 99 : 1 | 94 |
| 4 | Ph | Me | H | Li | 20 | 86 | 96 : 4 | 96 |
| 5 | *n*-Pr | Me | *p*-OMe | Li | 14 | 73 | 90 : 10 | 85 |
| 6[c] | *n*-Pr | Me | *p*-OMe | Li | 14 | 95 | 93 : 7 | 94 |

[a] Yield of b + l. [b] Reaction temp. = 23 °C. [c] Catalyst activation by heating at 50 °C with propylamine for 20 min.

Later an activated catalyst was employed, formed by use of procedure C (*cf.* section 2.3.2). Yield and selectivities were distinctly improved (*cf.* entries 5 and 6).[47]

In the phenolate part (*cf.* Fig. 9), donor substituents including halogen were tolerated. Sterically hindered lithium phenolates were remarkably reactive. Phenolates with moderately strong electron-withdrawing substituents gave good

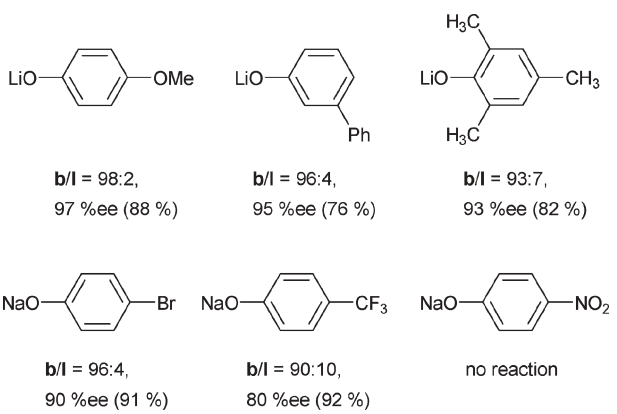
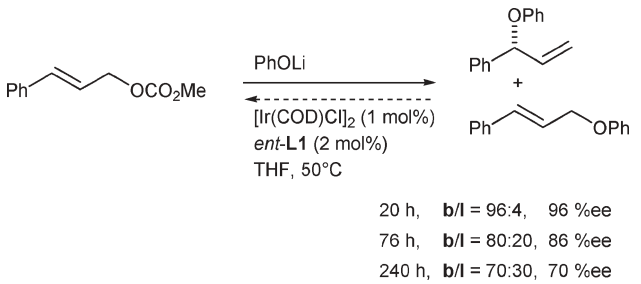



**Fig. 9** Various phenolates in the allylic substitution according to Scheme 28 ($R^1$ = Ph, $R^2$ = Me in the upper, $R^2$ = Et in the lower row).

results when their sodium salts in combination with ethyl carbonates were used. However, 4-nitro- and 4-cyanophenolates failed to react.

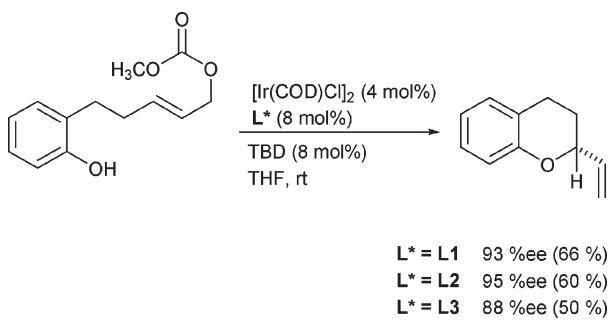
Reaction times significantly exceeding 20 h gave rise to a drop of regio- and enantioselectivity, which indicates reversibility of the reaction (Scheme 29).




**Scheme 29** Reversibility of allylic substitutions with phenoxide as nucleophile.

The etherification with a phenolate was also realised as intramolecular substitution. An example is the preparation of a chromane derivative described in Scheme 30.[30a] The catalyst was activated with the base TBD.

As mentioned in section 3, phenolates were used successfully as nucleophiles for kinetic resolutions by Carreira and coworkers[35] A catalyst prepared from $[Ir(COE)_2Cl]_2$ and a chiral bicyclo[2.2.2]octadiene was employed.

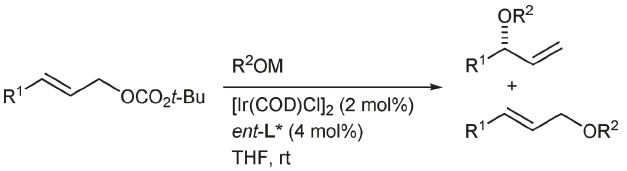



**Scheme 30** Intramolecular allylic etherification.

### 5.2 Alkoxides as nucleophiles

Alkali alkoxides are notoriously difficult nucleophiles. Superior results were obtained in allylic substitutions with Zn-alkoxides (achiral Ir-catalysts) by Roberts and Lee[48] and Cu-alkoxides (achiral Rh-catalyst with chiral substrates) by Evans and Leahy.[49] Shu and Hartwig successfully probed these compounds in the allylic substitution with Ir/phosphorus amidite catalysts.[50]

The exploratory work according to Scheme 31 established Cu- as better suited than Zn-alkoxides. Catalysts prepared from $[Ir(COD)Cl]_2$ and **L1** or **L3** without explicit base activation (procedure A, section 2.3.2) were employed. Methyl cinnamyl carbonate underwent transesterification, *tert*-butyl cinnamyl carbonate gave good results. Aryl and alkyl groups $R^1$ were tolerated in the allylic carbonate.




| $R^2OM$ | L* | $R^1$ | Yield (%) | b/l | Ee (%) |
|---|---|---|---|---|---|
| LiOBn + CuCl | **L1** | Ph | 70 | 92:8 | 56 |
| LiOBn + CuI | **L1** | Ph | 68 | 95:5 | 93 |
| LiOBn + CuI | **L3** | Ph | 92 | 99:1 | 94 |
| LiOBn + CuI | **L3** | Me | 80 | 95:5 | 97 |

**Scheme 31** Alkoxides as nucleophiles.

The allylic etherification was applied to a wide variety of alkoxides, using optimised conditions according to entries 3 and 4 of Scheme 31. Excellent results were obtained with alkoxides derived from primary and secondary alcohols (Fig. 10). Reactions with tertiary alkoxides gave excellent regioselectivities and yields, however, enantioselectivities were comparatively low. Further examples and applications of the method are presented in section 6.

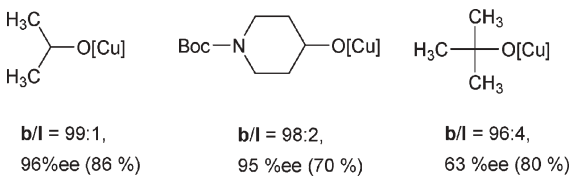
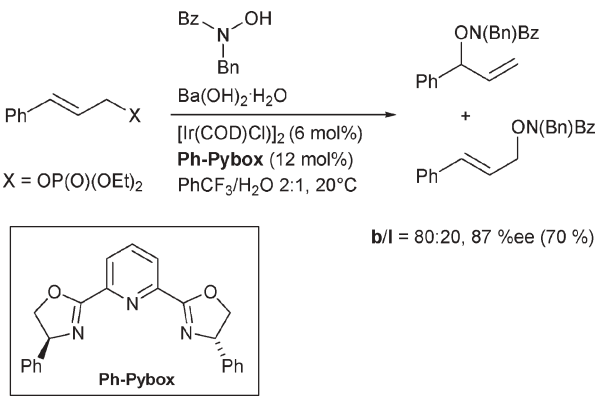



**Fig. 10** Results with selected Cu alkoxides according to Scheme 31 (conditions: entry 3, $R^1$ = Ph).

### 5.3 Hydroxylamine derivatives as O-nucleophiles

Hydroxylamine derivatives were already presented as N-nucleophiles (section 4.4). In this section, examples for the use of N-protected hydroxylamines as O-nucleophiles are described. Until now, only **Ph-Pybox** has been used as ligand; moderate to high enantio- and regioselectivities have been reached. As nucleophiles hydroxamic acid derivatives and oximes have been reported.[44]

An example for the reactions of hydroxamic acid derivatives is described in Scheme 32.[51] 3-Arylallyl phosphates were used

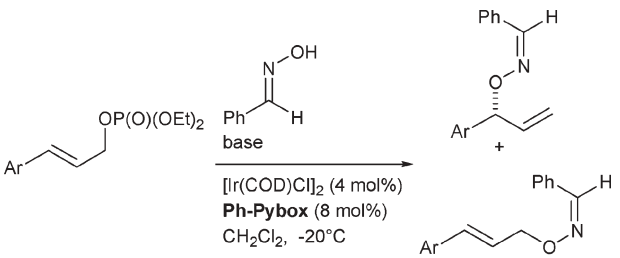



**Scheme 32** Allylic substitution with a hydroxamic acid as pronucleophile.

as allylic substrates, and the solvent was a biphasic 2 : 1 mixture of $PhCF_3$ and water. Reactivity, regio- and enantioselectivity were strongly influenced by base; $Ba(OH)_2$ was the generally most effective one.

Oximes are useful O-nucleophiles because their substitution products can be readily cleaved to give the corresponding alcohols. The Ir/**Ph-Pybox** catalyst worked well in $CH_2Cl_2$ at −20 °C, with phosphates as the most suited substrates (Scheme 33).[34,44] Again, selectivities strongly depended on the base used for activation of the oxime; $Ba(OH)_2{\cdot}H_2O$ gave the best results (Scheme 33). As substrates, only allylic phosphates containing an electron-rich aryl substituent have been reported.




| Base | Ar | Yield (%) | b/l | Ee (%) |
|---|---|---|---|---|
| *n*-BuLi | Ph | 40 | 66:34 | 80[a] |
| $K_2CO_3$ | Ph | 64 | 89:11 | 73[a] |
| $Ba(OH)_2{\cdot}H_2O$ | Ph | 87 | 90:10 | 95 |
| $Ba(OH)_2{\cdot}H_2O$ | α-Naphthyl | 83 | 94:6 | 90 |
| $Ba(OH)_2{\cdot}H_2O$ | *p*-$(CH_3)C_6H_4$ | 84 | 83:17 | 90 |

**Scheme 33** Oximes as O-nucleophiles ([a]20 °C).

Reactions of various types of oximes with diethyl cinnamyl phosphate are presented in Fig. 11. Oximes bearing two aromatic residues or containing an electron-withdrawing group were suitable pronucleophiles. The oxime derived from cyclohexanone gave inferior results.

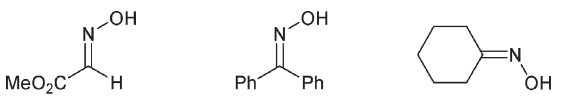
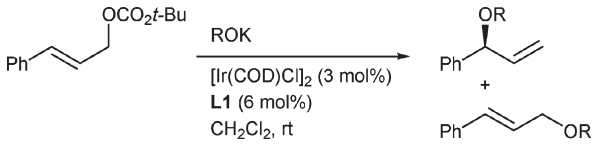



**Fig. 11** Selected oximes as O-nucleophiles in the allylic substitution with diethyl cinnamyl phosphate.

### 5.4 Silanolates as nucleophiles

Silanolates were introduced as nucleophiles by Carreira and co-workers very recently.[52] Cleavage of the resultant silyl ethers under mild conditions makes allylic alcohols accessible *via* Ir-catalysed allylic substitution.

Substitutions were carried out with an activated catalyst (procedure C, using *n*-propylamine, *cf.* section 2.3.2) formed from $[Ir(COD)Cl]_2$ and ligand **L1** (Scheme 34). THF was used

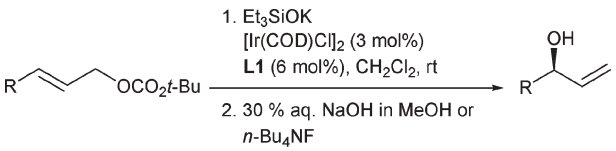



| R | Solvent | Yield (%) | b/l | Ee (%) |
|---|---|---|---|---|
| $SiEt_3$ | THF | 39 | 75:25 | 96 |
| $SiEt_3$ | $CH_2Cl_2$ | 90 | 99:1 | 97 |
| $SiMe_3$ | $CH_2Cl_2$ | 30 | n.d. | 94 |
| Si(*t*-Bu)$Me_2$ | $CH_2Cl_2$ | 79 | 97:3 | 98 |
| Si(*i*-Pr)$_3$ | $CH_2Cl_2$ | 64 | 86:14 | 99 |

**Scheme 34** Silanolates as nucleophiles.

as solvent for catalyst preparation; change to $CH_2Cl_2$ was required for the substitution reaction. As allylic substrates *tert*-butyl carbonates were found to be superior to methyl carbonates, which underwent transesterification as side reaction, and acetates, which yielded only the linear products.

The reaction tolerates allylic substrates with R being electron-rich and electron-poor aryl groups, heteroaryl groups (furyl, thienyl), alkenyl and alkyl groups (Scheme 35). The silyl ethers were transformed into allylic alcohols in standard manner.




| R | Yield (%) | Ee (%) |
|---|---|---|
| Aryl | 64-88 | 92-98 |
| Heteroaryl | 50-67 | 97-99 |
| Alkenyl | 65 | 97 |
| Alkyl | 65 | 95 |

**Scheme 35** Preparation of allylic alcohols *via* Ir-catalysed allylic substitution.

## 6 Combining allylic substitution and ring closing metathesis: an avenue to biologically active compounds

The Ir-catalysed allylic substitution has become a reliable, highly selective method only recently. Accordingly, only a few applications have been reported. In all cases a combination of the allylic substitution with a ring closing metathesis[53] reaction has been employed. This strategy had already been used for allylic substitutions catalysed by other transition metals (Fig. 12). It was pioneered by Evans *et al.* using Rh-catalysed allylic amination and etherification.[5e,54] Alexakis and Polet demonstrated the power of this concept for Cu-catalysed[55] and Trost and Jiang for Pd-catalysed allylic alkylations.[56]

The synthesis of the prostaglandin analogue *TEI-9826* is an example for the use of the Ir-catalysed allylic alkylation

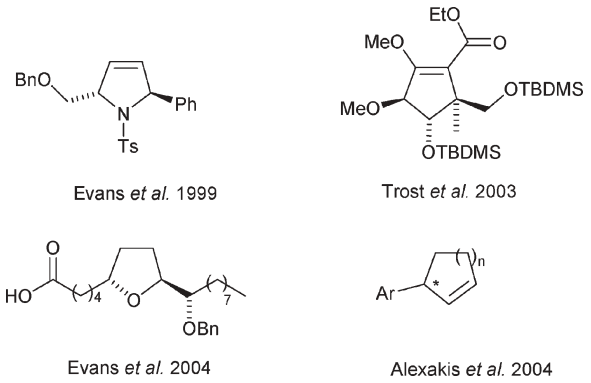
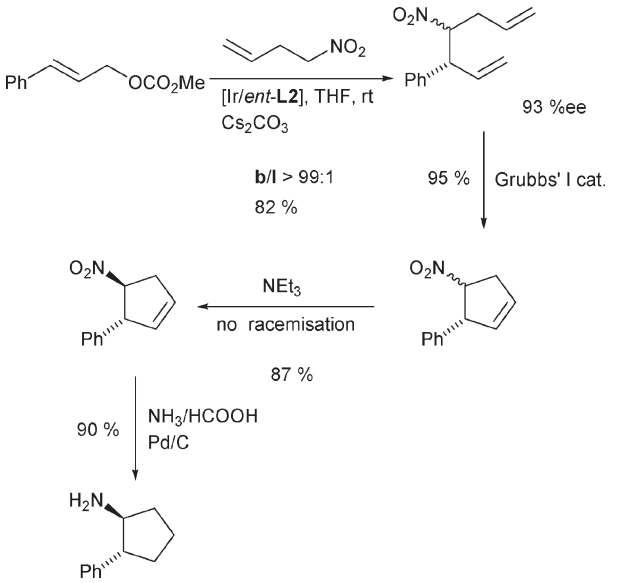



**Fig. 12** Examples of compounds prepared *via* combination of an allylic substitution and RCM.

(Scheme 36).[36] Allylic alkylation with a malonic amide of the Weinreb-type as pronucleophile proceeded with high selectivity of 96 %ee and up to 89% yield upon use of **L1** as ligand; with ligand **L2** the ee was improved to 99%. Subsequent saponification/decarboxylation of the material with 96 %ee furnished an amide (88%), which was reacted with vinyl magnesium chloride to give an enone (82%). RCM of this using Grubbs' II catalyst yielded 4-(*n*-octyl)cyclopent-2-enone (70%) without racemisation. Finally, aldol condensation gave the prostaglandin analogue *TEI-9826* in 45% yield over three steps.

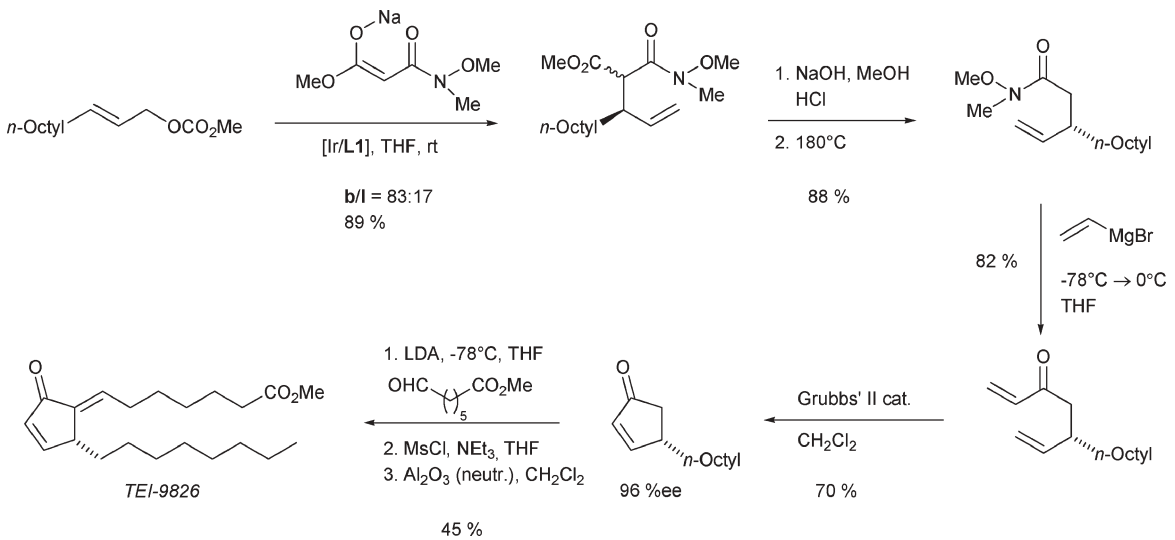
An Ir-catalysed alkylation also found application in a synthesis of (1*S*,2*R*)-*trans*-2-phenylcyclopentanamine, a compound displaying antidepressant activity (Scheme 37).[37] Alkylation of cinnamyl methyl carbonate, using 4-nitro-1-butene as pronucleophile gave the substitution product with 93 %ee in 82% yield. Subsequent RCM using Grubbs' I catalyst and epimerisation with $NEt_3$ yielded a *trans*-cyclopentene in 83% yield over two steps. Careful control showed that the epimerisation was not accompanied by racemisation. Finally, reduction of both the double bond and the nitro group with ammonium formate in methanol, using Pd/C as catalyst, gave the target compound in 90% yield.




**Scheme 37** Synthesis of (1*S*,2*R*)-*trans*-2-phenylcyclopentanamine.

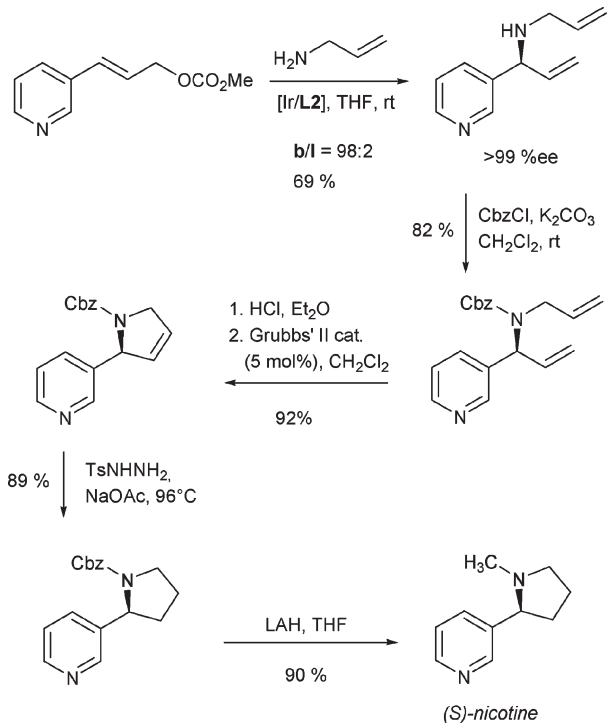
An example for the combination of an allylic amination and a RCM is illustrated by a synthesis of (*S*)-nicotine (Scheme 38).[57] Key step was the Ir-catalysed amination of methyl 3-(3-pyridyl)allyl carbonate with allylamine, which proceeded with up to >99 %ee and excellent regioselectivity. Then a Cbz derivative was prepared (82%) and its hydrochloride subjected to RCM, using Grubbs' II catalyst, to give a 2,5-dihydropyrrole in 92% yield. The double bond was reduced with diimide in order to exclude racemisation, which was observed in transition metal catalysed hydrogenation. Finally, reduction with LAH gave (*S*)-nicotine in 80% yield over two steps.

Primary chiral allylamines, prepared by Ir-catalysed allylic amination (*cf.* section 4.3), were used as nucleophiles for the synthesis of unsymmetrically 2,5-disubstituted 2,5-dihydropyrroles (Scheme 39).[43] The allylic amination was carried out with (*S*)-(1-phenylprop-2-enyl)amine and 3-propylallyl methyl




**Scheme 36** Synthesis of the prostaglandin analogue *TEI-9826*.

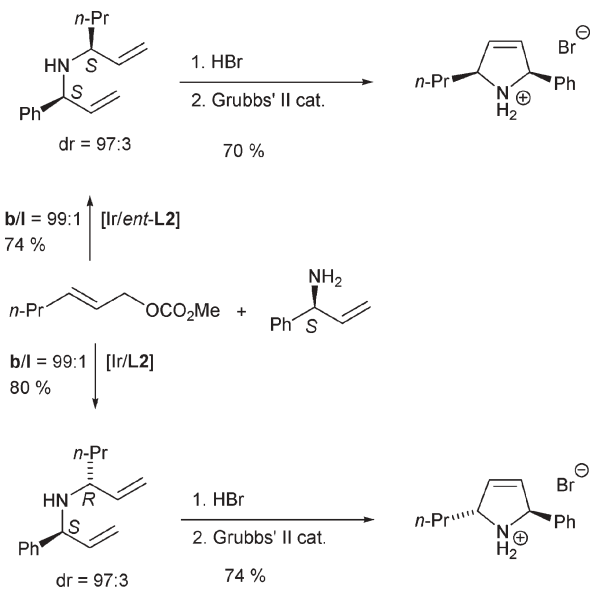
 



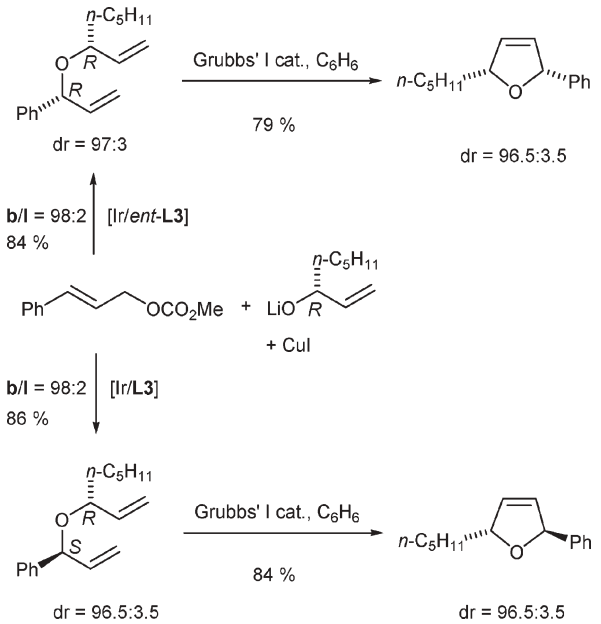

**Scheme 38** Synthesis of (*S*)-nicotine.

carbonate using ligands **L2** or *ent*-**L2** to furnish diastereoisomeric secondary amines with (*S*,*R*)- and (*S*,*S*)-configuration, respectively. In both directions excellent regio- and diastereoselectivity was achieved. This indicates that the substitution is mainly catalyst- rather than substrate-controlled. Protection of nitrogen by salt formation followed by RCM using Grubbs' II catalyst yielded *cis*- and *trans*-2,5-disubstituted 2,5-dihydropyrroles in 70 and 74% yield, respectively.

The approach used above to access dihydropyrroles was earlier used for the construction of corresponding dihydrofurans (Scheme 40) and disubstituted dihydropyrans.[50]




**Scheme 39** Synthesis of 2,5-disubstituted 2,5-dihydropyrroles.



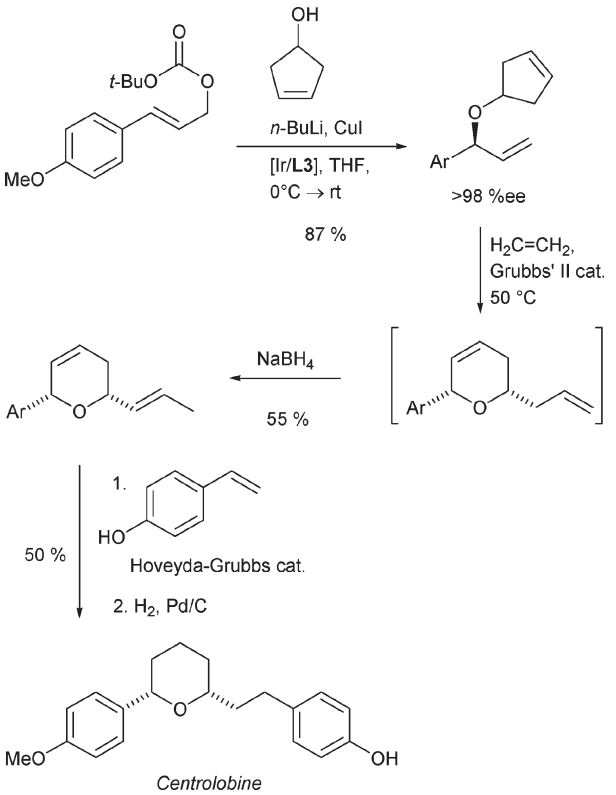

**Scheme 40** Synthesis of *cis*- and *trans*-2,5-disubstituted 2,5-dihydrofuran derivatives.

Ir-catalysed etherification of cinnamyl carbonate with the copper alkoxide derived from enantioenriched (*R*)-1-octen-3-ol gave diastereoisomeric ethers, depending on which enantiomer of the phosphorus amidite ligand was used with good yields and excellent selectivities. Subsequent RCM using Grubbs' I catalyst gave *cis*- and *trans*-2,5-disubstituted 2,5-dihydrofuran derivatives in 79 and 84% yield, respectively. Corresponding dihydropyran derivatives were similarly prepared.

Böhrsch and Blechert used an Ir-catalysed etherification in combination with ring rearrangement metathesis (RRM) for a synthesis of Centrolobine (Scheme 41).[58] Centrolobine is a tetrahydropyranic antibiotic that has shown activity against *Leishmania amazonensis promastigotes*, a health problem in Brazil. Ir-Catalysed allylation of the copper alkoxide of cyclopent-3-en-1-ol proceeded in 87% yield to give the allyl ether with >98 %ee. Subsequent RRM using Grubbs' II catalyst and then isomerisation of a terminal double bond with $NaBH_4$ followed by a one-pot cross metathesis/catalytic hydrogenation gave *Centrolobine* in good overall yield.

## Conclusions

We have described fundamentals and applications of the asymmetric Ir-catalysed allylic substitution. Broadly applicable catalysts can be obtained by combining $[Ir(COD)Cl]_2$ and phosphorus amidites followed by treatment with base to effect cyclometallation. The allylic substitution can be carried out with a variety of C-, N- and O-nucleophiles to give branched substitution products with high degrees of regio- and enantioselectivity. Applications in the synthesis of biologically active compounds include a prostaglandin analogue, alkaloids, an antibiotic and a variety of dihydropyrrole, dihydrofuran and -pyran derivatives, which are of interest in medicinal chemistry.




**Scheme 41** Synthesis of Centrolobine (Ar = *p*-(OMe)$C_6H_4$).

## Acknowledgements

Our work on Ir-catalysed allylic substitutions was supported by the Fonds der Chemischen Industrie, the Deutsche Forschungsgemeinschaft (SFB 623) and the EC (RTN HPRN-CT-2001-00172). We thank Prof. K. Ditrich, BASF AG, for generous donations of enantiomerically pure amines.

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