Carbocycles *via* enantioselective inter- and intramolecular iridium-catalysed allylic alkylations†

Stephane Streiff, Carolin Welter, Mathias Schelwies, Gunter Lipowsky, Nicole Miller and Günter Helmchen*

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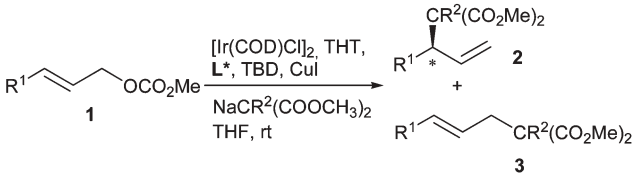
Carbocycles with > 90% ee were prepared *via* Ir-catalysed asymmetric allylic alkylation/ring closing metathesis sequences or enantioselective Ir-catalysed intramolecular allylic alkylations.

Asymmetric allylic substitutions have been studied with great intensity over the last decade.[1] Recently, reactions of monosubstituted allylic derivatives according to Scheme 1 have come into focus. In these reactions a very high increase of value can be created, if regioselectivity in favour of the branched, chiral product is achieved.

Recent work by us and others clearly shows that iridium complexes of electron poor ligands are useful catalysts, as only iridium catalysts have yielded uniformly good to excellent results in asymmetric alkylations,[2] aminations[3] and etherifications[4] of aryl- as well as alkylallyl derivatives. In addition, the price of iridium is low compared to most other precious metals.[5] In this report we describe improved reaction conditions for allylic alkylations, allylic alkylation/ring closing metathesis (RCM) sequences, and the first Ir-catalysed intramolecular allylic alkylations.

Complexes prepared from $[Ir(COD)Cl]_2$ and phosphorus amidites[6] derived from 2,2′-dihydroxybinaphthalene (BINOL) and 2-arylethylamines (Fig. 1) are probably the best suited catalysts until now.[7,8] However, success with these ligands requires close attention to catalyst preparation, because ligands can be altered by C–H activation 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. This procedure works well for aminations, in particular with ligand **L2**, which generally induces higher selectivity than **L1**.[2f,3a] (B) Procedure A and LiCl as additive. This procedure was worked out for alkylations using ligand **L1**,[2d,7] but gave superior results in conjunction with **L2** as was shown by Alexakis and Polet.[2e] (C) For *in situ* C–H activation of **L1** at the CH_3 group, the mixture according to A was treated with base (TBD[3a] or DABCO[3c])[9] in order to form an activated complex of type **K** (Fig. 2).[10] While this procedure yielded an excellent catalyst for aminations, results for alkylations using ligand **L1** were not satisfactory. (D) Finally, an optimal catalyst for alkylations was obtained by treating a mixture of $[Ir(COD)Cl]_2$, **L***, THT (tetrahydrothiophene) and THF with the base TBD for 2 h at rt, then the allylic substrate and subsequently CuI were added. In conjunction with ligand **L1** reaction times of 2 h at rt sufficed to generate products with reliably 96% ee for a broad spectrum of products (*cf.* Table 1).[2c]



1-3 **a** R^1 = Ph, R^2 = H
b R^1 = (*E*)-CH=CHPh, R^2 = H
c R^1 = CH_2CH_2Ph, R^2 = H
d R^1 = CH_2OSiPh_2t-Bu, R^2 = H
e R^1 = Ph, R^2 = $CH_2CH=CH_2$
f R^1 = Ph, R^2 = $(CH_2)_2CH=CH_2$

Scheme 1 Ir-catalysed allylic alkylation of carbonates **1**.

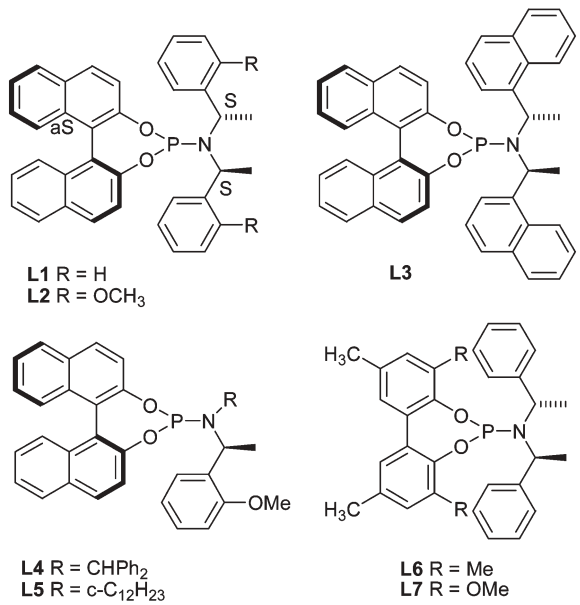


Fig. 1 Chiral phosphorus amidite ligands.

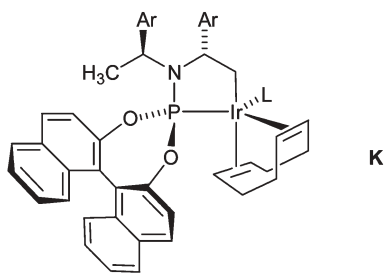


Fig. 2 Species generated by base activation.

† Electronic supplementary information (ESI) available: analytic data, general experimental procedures. See http://www.rsc.org/suppdata/cc/b5/b503713a/

*g.helmchen@urz.uni-heidelberg.de

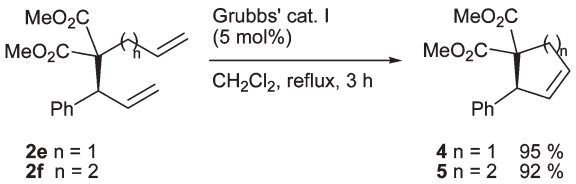
Table 1 Ir-catalysed allylic alkylations of carbonates **1** using phosphorus amidites as ligands (*cf.* Scheme 1)[a]

Entry	1–3	Ligand	Time (h)[b]	Yield[c] (%)	2/3[d]	Ee (%)[e]
1	**a**	**L1**	1	88	99 : 1	96
2	**a**	**L2**	0.5	92	> 99 : 1	98
3[f]	**a**	**L2**	3	84	98 : 2	98
4[g]	**a**	**L2**	120	83	96 : 4	95
5	**a**	**L3**	0.75	88	99 : 1	96
6	**a**	**L6**	16	70	97 : 3	79
7	**a**	**L7**	1.5	81	99 : 1	86
8	**b**	**L1**	1.5	92	98 : 2	96
9	**b**	**L2**	1	80	99 : 1	98
10	**b**	**L3**	0.5	89	98 : 2	95
11	**c**	**L1**	2	92	81 : 19	96
12	**c**	**L2**	0.5	93	91 : 9	98
13[h]	**c**	**L2**	12	87	86 : 14	96
14	**c**	**L3**	1	70	80 : 20	97
15	**c**	**L4**	3	88	88 : 12	88
16	**c**	**L5**	2	90	88 : 12	94
17	**c**	**L6**	24	74	82 : 18	94
18	**c**	**L7**	< 20	82	71 : 29	72
19	**d**	**L1**	2	88	88 : 12	97
20	**d**	**L2**	2	68	70 : 30	96
21	**e**	**L1**	3	85	⩾ 98 : 2[i]	89
22	**e**	**L2**	1	74	96 : 4	97
23	**f**	**L1**	4	71	92 : 8	88
24	**f**	**L2**	2	78	93 : 7	92

[a] If not stated otherwise, reactions were carried out on a 1 mmol scale of **1** using conditions D with 2 mol% of $[Ir(COD)Cl]_2$, 4 mol% of ligand, 20 mol% of THT, 8 mol% of TBD (activation for 2 h) and 20 mol% of CuI. For preparative procedures and absolute configurations of the products see ESI. Entries 1, 8, 11 and 19 are taken from ref. 2*c* for comparison. [b] Reaction time. [c] Yield of the isolated product. [d] Determined by ^{1}H NMR spectroscopic analysis of the crude product. [e] Determined by HPLC, see ESI. [f] Reaction performed with 0.2 mol% of $[Ir(COD)Cl]_2$, 0.4 mol% of **L2**, scale: 6 mmol of substrate. [g] Reaction performed with 0.05 mol% of $[Ir(COD)Cl]_2$, 0.1 mol% of **L2**, scale: 6 mmol of substrate. [h] Reaction using conditions C. [i] Isomer **3e** was not found.

We were particularly interested in probing the effectiveness of ligand **L2** under conditions D, hoping to gain further increase of reactivity and regioselectivity. In addition to the privileged substrate **1a** (*cf.* Table 1) a range of more significant substrates, **1b–1f**, were investigated. Furthermore, the known ligands **L1–L3** were supplemented by new phosphorus amidites **L4–L7** derived from non-symmetric amines or 2,2′-dihydroxybiphenyl derivatives (Fig. 1).

From the results presented in Table 1 the following main conclusions are drawn: (a) Except in the case of substrate **1d**, ligand **L2** induces the highest degrees of regio- as well as enantioselectivity. The basis for its superiority is perhaps a quantitative (steric bulk) rather than a qualitative effect (hemilability[2*e*]). As a working hypothesis we assume that increase of the steric bulk of **L** leads to enhanced liberation of **L** from complex **K**, thus formation of a reactive 16 VE complex is favoured. (b) Catalyst activation with base is important (*cf.* entry 13). With an optimal catalyst (procedure D) s/c ratios of up to 1000 : 1 are possible (entries 3,4). (c) Selectivities are higher for systems with sp^2-bound (entries 1–10) than with sp^3-bound substituents (entries 11–20). (d) Ligands **L4** and **L5** were devised in order to replace the residual chiral arylethyl group of **K** by an achiral group. These ligands are clearly inferior to **L1–L3**. (e) Ligands **L6** and **L7** are the least efficient (*cf.* entries 4,5,17,18). In fact, according to stereo models of complexes



Scheme 2 RCM using Grubbs' catalyst I.

analogous to **K**, there is considerable interaction of one of the substituents R with the COD moiety.

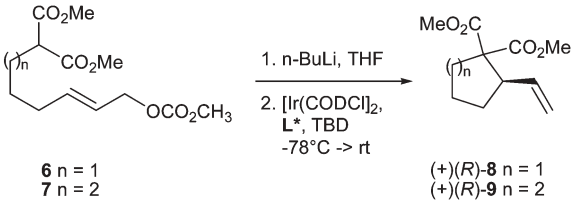
As a first approach towards carbocycles, the combination of allylic alkylation and ring closing metathesis according to Scheme 2 was probed.[11] Gratifyingly, the crucial Ir-catalysed alkylations of 2-allyl- and 2-(buten-4-yl)-malonates proceeded with high degrees of regioselectivity to give the branched products **2e** and **2f**, respectively, in good yield (Table 1, entries 21–24). Again, ligand **L2** gave superior results, *i.e.* regioselectivities > 13 : 1 in favour of the branched product and enantiomeric excess of 92–97% ee. Diene **2e** was also prepared in 82% yield by alkylation of the sodium enolate of **2a** with allyl bromide.

Dienes **2e** and **2f** were subjected to RCM, using Grubbs' catalyst I,[12] which furnished the cyclisation products **4** and **5** in yields > 90%. The cyclohexene derivative **5** was obtained enantiomerically pure after recrystallization (> 99% ee). These examples demonstrate that the combination of Ir-catalysed allylic alkylation and RCM constitutes a powerful method for construction of carbocycles.

After having established the feasibility of generating products with quaternary carbon, extension of our work to intramolecular allylic cyclisations according to Scheme 3 was studied. The results are described in Table 2.

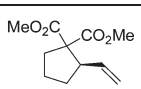
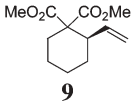
Initial experiments using procedure C,[13] previously worked out for intramolecular aminations,[3*a*] suffered from low reproducibility.

It turned out that the base initially used for generation of malonate anion, NaH at a reaction temperature of −20 °C, was not well suited because of competing non-catalysed cyclisation, which could not be suppressed. Accordingly, the anion was prepared at low temperature by addition of *n*-butyl lithium at −78 °C and the cyclisation run at both lower temperature (−78 °C → rt) and concentration (0.25 M) than the intermolecular reaction. Although longer reaction times were required, yields and enantioselectivities were excellent. Once again, optimal results were obtained with ligand **L2** (*cf.* Table 2, entries 2 and 7). A similar dependence on ligand structure was observed as for intramolecular aminations.[14] Cyclisations according to Scheme 3 were previously studied with (PHOX)Pd catalysts,[15] which were generally less effective than the Ir-catalysts described here. In the course of the previous work, absolute configurations of carbocycles **8** and **9** were determined by chemical correlation.[16]



Scheme 3 Intramolecular Ir-catalysed allylic alkylations.

Table 2 Intramolecular Ir-catalysed allylic alkylations of carbonates **6** and **7** according to Scheme 3[a]

Entry	Substrate	Ligand	Product	Yield[b] (%)	Ee (%)[c] (Abs. Conf.)
1	**6**	**L1**		68	85 (*R*)
2		**L2**		77	96 (*R*)
3		**L3**		81	93 (*R*)
4		**L4**	**8**	74	91 (*R*)
5		**L5**		78	86 (*R*)
6	**7**	**L1**		71	89 (*R*)
7		**L2**		79	97 (*R*)
8		**L3**		83	95 (*R*)
9		**L4**	**9**	73	95 (*R*)
10		**L5**		67	87 (*R*)

[a] All reactions were carried out on a 0.5 mmol scale using conditions C with 2 mol% of $[Ir(COD)Cl]_2$, 4 mol% of ligand and 2 h of activation with TBD (8 mol%). See ESI for experimental procedures. [b] Yield of isolated product. [c] Determined by GC (Chrompack permethyl β-cyclodextrin, Cp-Cyclodextrin-B-236-M-19 (25 m × 0.25 mm), 120 °C isothermal, injection temp. 200 °C, t_R[(*S*)-**8**] = 11.2 min, t_R[(*R*)-**8**] = 11.5 min, t_R[(*S*)-**9**] = 18.5 min, t_R[(*R*)-**9**] = 19.2 min).

In conclusion, improved reaction conditions for Ir-catalysed allylic alkylations based on the use of known and new phosphorus amidite ligands derived from 1-(2-methoxyphenyl)ethylamine were developed. Unsaturated carbocycles were prepared *via* allylic alkylation with sodioalkenylmalonates followed by ring closing metathesis. In addition, the first Ir-catalysed intramolecular allylic alkylations are reported.

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Stephane Streiff, Carolin Welter, Mathias Schelwies, Gunter Lipowsky, Nicole Miller and Günter Helmchen*
Organisch-Chemisches Institut der Ruprecht-Karls-Universität Heidelberg, Im Neuenheimer Feld 270, 69207, Heidelberg, Germany. E-mail: g.helmchen@urz.uni-heidelberg.de; Fax: +49 6221 544205; Tel: +49 6221 548401

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