

Highly Enantioselective Syntheses of Heterocycles via Intramolecular Ir-Catalyzed Allylic Amination and Etherification

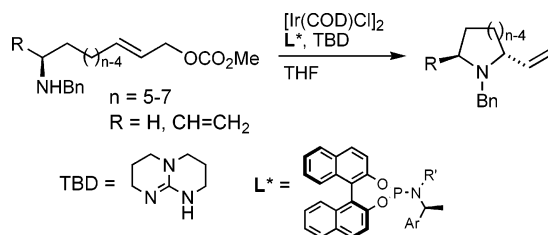
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Received December 23, 2004

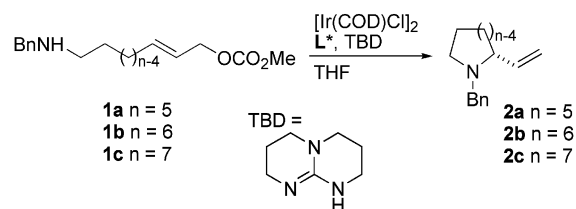
ABSTRACT



Enantioselective Ir-catalyzed intramolecular allylic aminations and etherifications are described. Up to 97% ee was achieved using catalysts prepared by in situ activation of mixtures of phosphorus amidites and $[\text{Ir}(\text{COD})\text{Cl}]_2$. Sequential aminations of bis-allylic carbonates, involving an inter- followed by an intramolecular reaction, gave *trans*-N-benzyl-2,5-divinylpyrrolidine and *trans*-N-benzyl-2,6-divinylpiperidine with $\geq 99\%$ ee. New phosphorus amidites as well as improved conditions for intermolecular aminations are reported.

Ir-catalyzed asymmetric allylic substitutions at 3-monosubstituted 2-propenol derivatives have been studied with great success over the past few years.¹ To probe the potential of these reactions for the preparation of medicinally interesting N-heterocycles, the intramolecular amination of amine **1b** to give the piperidine derivative **2b** was studied (Scheme 1).² Enantiomeric excess of up to 91% ee was achieved. We have now developed an improved Ir catalyst and extended the scope of the cyclization **1** \rightarrow **2** to include as products pyrrolidine and azepane derivatives. Furthermore, due to double stereoselection, essentially complete enantio- and

Scheme 1. Ir-Catalyzed Allylic Cyclizations of Substrates **1a–c**



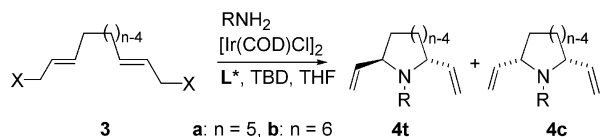
diastereoselectivity could be achieved for the reaction **3** \rightarrow **4**, involving sequential allylic aminations (Scheme 2). This finding extends the work of Takemoto et al.,³ who have accomplished cyclizations by sequential reactions of branched

(1) (a) Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595. (b) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, 3529. (c) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426. (d) Shu, C.; Leitner, A.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4797. (e) Shu, C.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4794. (f) Fischer, C.; Defieber, C.; Suzuki, T.; Carreira, E. M. *J. Am. Chem. Soc.* **2004**, *126*, 1628.

(2) Welter, C.; Koch, O.; Lipowsky, G.; Helmchen, G. *Chem. Commun.* **2004**, 896.

(3) Miyabe, H.; Yoshida, K.; Kobayashi, Y.; Matsumura, A.; Takemoto, Y. *Synlett* **2003**, 1031.

Scheme 2. N-Heterocycles via Sequential Ir-Catalyzed Allylic Aminations



bis-allylic substrates with primary amines; they used an achiral catalyst and obtained mixtures of *cis*- and *trans*-isomers.

Ir catalysts for the allylic substitution are usually prepared by combining $[\text{Ir}(\text{COD})\text{Cl}]_2$ with an electron-poor ligand in a 1:2 molar ratio. Since 1999,⁴ phosphorus amidites⁵ have been the preferred ligands (Figure 1). Previously, ligand **L1** was mostly used. Very recently, slightly superior results with respect to enantioselectivity have been obtained with **L2**^{1b,c} and **L3**.^{1e}

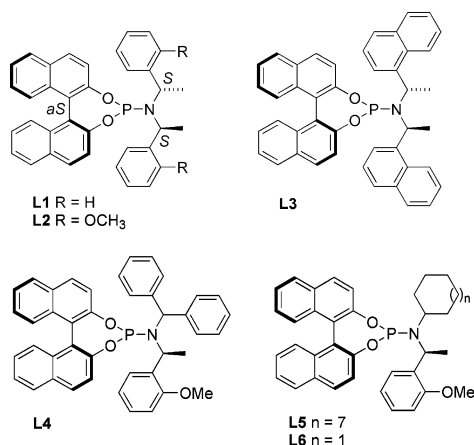
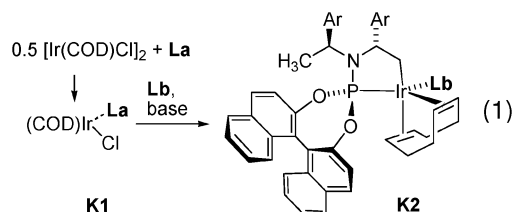


Figure 1. Ligands used in this work.

A very important aspect of Ir-catalyzed allylic substitutions is catalyst preparation. Hartwig's and this group have demonstrated that the most active catalysts are formed by C–H activation (eq 1), which is induced by base.⁶ By treatment of a solution of $[\text{Ir}(\text{COD})\text{Cl}]_2$ and ligand (molar ratio 1:2) in THF with TBD² (Scheme 1) or DABCO^{1d} a particularly active catalyst of type **K2** (**La** = **Lb** = phosphorus amidite) (eq 1) is generated in situ.

In the crystal structure of a complex **K2** with **Lb** = **PPh**₃ the residual 1-arylethyl group is located remote from the Ir center.^{6b} Accordingly, the chirality of this group does not appear to be important, and we have therefore prepared a new series of ligands (Figure 1, **L4**–**L6**)⁷ containing a bulky achiral substituent at nitrogen.⁸



Using the phosphorus amidite **L1** as ligand, the intramolecular allylic amination of carbonate **1b** according to Scheme 1 under standard conditions (4 mol % of iridium, 4 mol % of ligand, 8 mol % of TBD) gave (*R*)-*N*-benzyl-2-vinylpiperidine (**2b**) in 93% yield and an enantiomeric excess of 91% ee (Table 1, entry 7).²

Table 1. Ir-Catalyzed Allylic Cyclizations of Substrates **1a**–**c** According to Scheme 1 Using Phosphorus Amidites **L1**–**L6** as Ligands (Solvent: THF, Concentration: 1 M, rt)^a

entry	substrate	ligand	time ^b (h)	product	yield ^c (%)	% ee ^d
1	1a	L1	1	2a	89	92
2	1a	L2	0.5	2a	70	97
3	1a	L3	0.3	2a	94	97
4	1a	L4	1	2a	95	95
5	1a	L5	1	2a	86	96
6	1a	L6	1	2a	89	85
7	1b	L1	1	2b	93	91
8	1b	L2	0.75	2b	99	94
9	1b	L3	0.25	2b	64	97
10	1b	L4	3.5	2b	83	90
11	1b	L5	1	2b	92	96
12	1b	L6	0.75	2b	87	84
13	1c	L1	4	2c	76	93 ^e
14	1c	L2	1	2c	69	97 ^e
15	1c	L3	1	2c	74	97 ^e

^a All reactions were carried out on a 0.5 mmol scale using 2 mol % of $[\text{Ir}(\text{COD})\text{Cl}]_2$, 4 mol % of ligand, and 2 h of activation with TBD (8 mol %). ^b Reaction time. ^c Yield of isolated product. ^d Determined by HPLC (column: Daicel Chiralcel OD-H, eluent: *n*-hexane/*i*-PrOH 99.9:0.1, 250 × 4.6 mm, 5 μm, + guard cartridge 10 × 4 mm, 5 μm, flow: 0.5 mL/min), *t*_R[(*S*)-**2a**] = 11 min, *t*_R[(*R*)-**2a**] = 28 min, *t*_R[(*S*)-**2b**] = 11 min, *t*_R[(*R*)-**2b**] = 14 min. ^e Determined by GC (Chrompack permethyl β-cyclodextrin, Cp-cyclodextrin-B-236-M-19 (25 m × 0.25 mm), 120 °C isotherm, injection temperature 200 °C, *t*_R[(*S*)-**2c**] = 54 min, *t*_R[(*R*)-**2c**] = 56 min).

The rate of the cyclization was similar to that of a comparable intermolecular amination (Table 3, entry 1). Under otherwise identical reaction conditions, increased enantiomeric excess of up to 97% ee was obtained using ligands **L2**–**L6** (Table 1, entries 7–12). It is apparent that an increase of steric bulk of the ligand leads to an increase of selectivity. With respect to assessment of reaction rates, caution is required because catalysts are not stable under the reaction conditions; i.e., decrease of reaction time might be a consequence of enhanced catalyst activity or catalyst stability.

(4) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741.

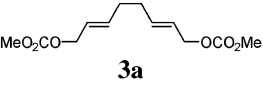
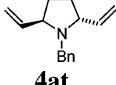
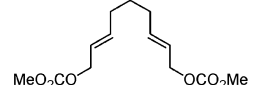

(5) Feringa, B. *Acc. Chem. Res.* **2000**, 33, 346.

(6) (a) Bartels, B.; García-Yebra, C.; Rominger, F.; Helmchen, G. *Eur. J. Inorg. Chem.* **2002**, 2569. (b) Kiener, C. A.; Shu, C.; Incavito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, 125, 14272.

(7) Ligands were prepared according to standard procedures; **L2**: Tissot-Croset, K.; Polet, D.; Gille, S.; Hawner, C.; Alexakis, A. *Synthesis* **2004**, 2586.

(8) Cf. also Leitner, A.; Shu, C.; Hartwig, J. F. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, 101, 5830.

Table 2. Ir-Catalyzed Sequential Allylic Amination/Cyclization Reactions Using Phosphorus Amidites **L1**–**L6** as Ligands (Solvent: THF, Concentration: 0.5 M, rt)^a

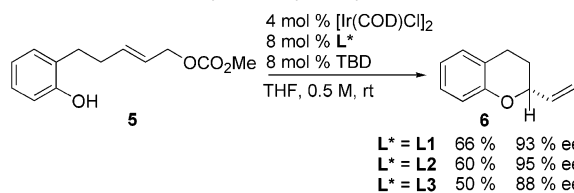
entry	substrate	ligand	additive	time (h)	product	yield ^b (%)	dr ^c	% ee ^d
1	 3a	L1	none	9	 4at	79	91:9	99
2		L1	Pb(OAc) ₂ , THT	2		82	92:8	99
3		L2	none	2		76	95:5	>99
4		L3	none	0.5		57	95:5	>99
5		L4	none	1		50	96:4	>99
6	 3b	L5	none	1	 4bt	59	97:3	>99
7		L1	none	1.5		66	94:6	>99
8		L2	none	0.5		73	97:3	>99
9		L3	none	0.5		77	96:4	>99
10		L4	none	0.5		61	95:5	>99
11		L5	none	0.5		67	96:4	>99
12		L6	none	3.5		62	88:12	>99

^a All reactions were carried out on a 0.5 mmol scale using 1.3 equiv of nucleophile, 4 mol % of [Ir(COD)Cl]₂, 8 mol % of ligand, and 2 h of activation with TBD (16 mol %). ^b Combined yield of isolated products. ^c Ratio of isomers **4t** and **4c**, determined by ¹H NMR analysis of crude reaction mixtures. ^d Determined by HPLC (column: Daicel Chiralcel OD-H, eluent: *n*-hexane/*i*-PrOH 99:1 (**4at**) or 99.9:0.1 (**4bt**), 250 × 4.6 mm, 5 μm, + guard cartridge 10 × 4 mm, 5 μm, flow 0.5 mL/min) *t*_R[(+)-**4at**] = 7.1 min, *t*_R[(−)-**4at**] = 8.1 min, *t*_R[(+)-**4bt**] = 8.5 min, *t*_R[(−)-**4bt**] = 11.0 min.

Cyclizations yielding pyrrolidine **2a** and azepane **2c** also proceeded smoothly (Table 1).⁹ For both reactions, results with ligands **L2** and **L3** were practically identical and superior to those achieved with **L1**. All cyclizations could be run at a high concentration of 1 M.

Furthermore, good results were obtained for an intramolecular etherification (Scheme 3). Thus, the chromane derivative (−)-(*R*)-**6** (Scheme 3) was obtained from the carbonate **5** with up to 95% ee.¹⁰ In this case, ligand **L2** performed significantly better than ligand **L3**.

Scheme 3. Ir-Catalyzed Allylic Cyclization of Substrate **5**



Next sequential inter- and intramolecular aminations of bisallylic substrates **3** according to Scheme 2 were studied (cf. Table 2).¹¹ Under the conditions described in Table 1 (4 mol % of catalyst per allylic moiety, THF, rt), the *trans*-products **4t** were formed with fairly high diastereoselectivity

(9) The absolute configuration of products **2a** and **2b** was determined by chemical correlation: ref 2 and: Koch, O. Dissertation, Universität Heidelberg, 2000. The absolute configuration of **2c** is assigned on the basis of analogy.

(10) This reaction has also been carried out using Pd catalysts: Trost, B. M.; Shen, H. C.; Dong, L.; Surivet, J.-P. *J. Am. Chem. Soc.* **2003**, *125*, 9276. Absolute configuration of **6**: Labrosse, J.-R.; Poncet, C.; Lhoste, P.; Sinou, D. *Tetrahedron: Asymmetry* **1999**, *10*, 1069.

(11) The absolute configurations of the products **4** are assigned on the basis of analogy to the reactions leading to amines **2a** and **2b** (cf. ref 9).

of >90:10. The extremely high enantiomeric excess of the products is a consequence of double stereoselection; i.e., both steps are controlled by the catalyst.¹² Ligand **L2** gave the best results with respect to rate and enantio- and diastereoselectivity.

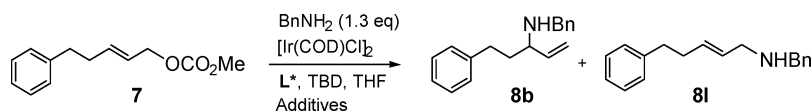
In an effort to further improve the catalysts, we applied a concept that was successful for alkylations.^{1a} We have shown that a combination **La** = **L1** and **Lb** = tetrahydrothiophene (THT) (cf. eq 1) with additional CuI yielded an extremely active catalyst for allylic alkylations.^{1a} Use of these additives was motivated by the idea to induce removal of a soft P- or S-ligand **Lb** from **K2**, necessary for oxidative addition of an allylic substrate, with a soft metal ion. While Cu(I) is suited for alkylations, it is not effective in aminations because of coordination to the amine. Therefore, effects of further salts of soft metal ions were investigated. Pb(II) salts in combination with tetrahydrothiophene (THT) were found to be most efficient in enhancing reaction rate. The results are described in Table 3.¹³ As a substrate likely to be generally representative, the allyl carbonate **7** with an arylalkyl substituent was chosen.

The effect of the Pb(II) salt was not pronounced for reactions run under standard conditions, except for a small increase of regioselectivity (entries 1–3). However, upon either decrease of catalyst loading (entries 4, 5) or concentration (entries 6, 7) beneficial effects became apparent. The effects were similar for reactions using **L1**, **L2**, and **L3**. In general, Pb(II) salts improve reaction rate and regioselectivity but give rise to small decrease of enantioselectivity.

In conclusion, we have demonstrated that asymmetric Ir-catalyzed intramolecular aminations and etherifications pro-

(12) Cf. Rieck, H.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2687.

(13) The following additional salts were investigated: SnCl₂, BiCl₃, CeCl₃, and PbCl₂.

Table 3. Optimization of Reaction Conditions of Ir-Catalyzed Intermolecular Aminations (Solvent: THF, rt)^a

entry	additive	mol % of [Ir(COD)Cl] ₂	ligand	conc (M)	time (h)	yield ^b (%)	8b/8l ^c	% ee ^d
1	none	4	L1	1	1.5	74	81:19	94
2	THT, 4 mol % of Pb(NO ₃) ₂	4	L1	1	0.75	77	84:16	91
3	THT, 4 mol % of Pb(OAc) ₂	4	L1	1	0.75	84	85:15	92
4	none	0.4	L1	1	168	0 ^e		
5	THT, 0.4 mol % of Pb(NO ₃) ₂	0.4	L1	1	72	83	81:19	95
6	none	4	L1	0.2	24	72	83:17	94
7	THT, 4 mol % of Pb(NO ₃) ₂	4	L1	0.2	1	71	83:17	94
8	none	4	L2	1	0.5	73	89:11	98
9	none	4	L2	0.2	3	72	86:14	95
10	THT, 4 mol % of Pb(NO ₃) ₂	4	L2	0.2	1.5	88	85:15	94
11	none	4	L3	1	0.75	65	86:14	98
12	THT, 4 mol % of Pb(NO ₃) ₂	4	L3	1	0.15	75	87:13	96
13	none	4	L3	0.2	5	83	84:16	98
14	THT, 4 mol % of Pb(NO ₃) ₂	4	L3	0.2	0.3	73	86:14	97
15	none	4	L4	1	1.5	73	88:12	98

^a Catalyst preparation according to Table 1. ^b Combined yield of the isolated regioisomeric products. ^c Determined by ¹H NMR analysis of the crude reaction mixture. ^d Determined by HPLC (columns: Daicel Chiralcel OD-H, eluent: *n*-hexane/*i*-PrOH 99:1, 250 × 4.6 mm, 5 μm, + guard cartridge 10 × 4 mm, 5 μm, flow 0.5 mL/min) *t*_R[(-)-**8b**] = 21 min, *t*_R[(+)-**8b**] = 24 min. ^e No conversion detected by ¹H NMR analysis of the crude reaction mixture.

ceed with very high yields and enantioselectivities, using in situ prepared Ir complexes of P,C-ligands derived from phosphorus amidites. Intermolecular and sequential inter- and intramolecular aminations yielding heterocycles with >99% ee are also described.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft (SFB 623) and by the Fonds der Chemischen Industrie. We thank Markus Krauter, Carola Berthold, and Sascha Trumm for competent experi-

mental assistance, Degussa AG for iridium salts, Dr. G. Egri (Reuter Chemischer Apparatebau KG) for (*S*)-BINOL, and Dr. K. Ditrach (BASF AG) for enantiomerically pure 2-arylethylamines.

Supporting Information Available: Experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL047351T