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Effects of Catalyst Activation and Ligand Steric Properties on the Enantioselective Allylation of Amines and Phenoxides

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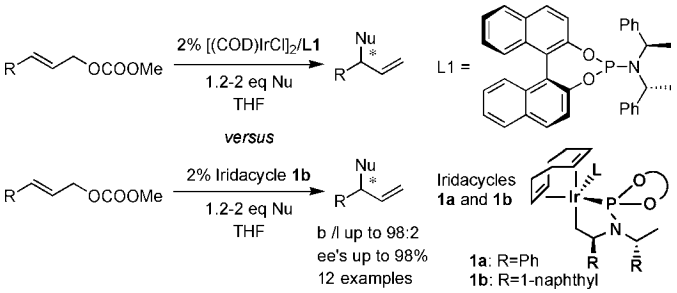
ABSTRACT



The yields, enantioselectivities, and regioselectivities of the reactions of amines and phenoxides with allylic carbonates in the presence of a metallacyclic iridium catalyst were compared. These data show that both preactivation of the catalyst and the size of the ligand affect the yield, enantioselectivity, and regioselectivity. With the activated catalyst containing a bis-naphthethylamino group, the allylic amination and etherification of a broad range of allylic carbonates occurred in high yields and with high regioselectivities and enantioselectivities.

Allylic amines and ethers with stereocenters α to a heteroatom are valuable synthetic building blocks. A large number of single enantiomer drug candidates and biologically active molecules can be derived from these materials because of the combination of heteroatom and olefinic functional groups. A prominent method to prepare these compounds is transition metal-catalyzed allylic substitution.[1]

Allylic substitution of acyclic, monosubstituted allylic electrophiles catalyzed by complexes of Ru,[2] Rh,[3] and Ir[4−12] often generate the more hindered, chiral, branched allylic amine or ether products from either linear or branched allylic carbonates or both. Recently, we reported the first highly enantioselective, iridium-catalyzed allylation of amines and alkoxides.[7−12] Achiral linear allylic carbonates reacted with high enantioselectivity when the iridium catalyst was gener-

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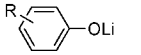
Table 1. Effect of Catalyst Activation and Ligand Steric Properties on the Yield, Enantioselectivity, and Regioselectivity of the Amination and Etherification of Allylic Carbonates[a]

entry	R	Nu	original catalyst			catalyst **1a** from **L1**			catalyst **1b** from **L2**		
			yield[b]	ee	b/l	yield[b]	ee	b/l	yield[b]	ee	b/l
1	C_3H_7	$BnNH_2$	66	95	88:8:4[d]	56	95	94:6	68	98	94:6
2[c]	*p*-$NO_2C_6H_4$	$BnNH_2$	80	93	85:9:6[d]	75	96	83:17	82	96	94:6
3[e]	C_3H_7	 R=*o*-Me	86	90	87:13	79	94	92:8	90	98	94:6
4[e]	C_3H_7	R=*p*-OMe	73	85	90:10	95	94	93:7	94	97	95:5

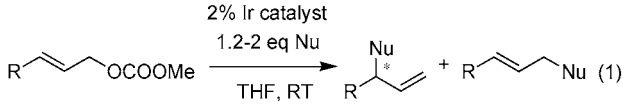
[a] Reactions were conducted at room temperature on a 1.0 mmol scale in THF (0.5 mL) with relative mole ratios of carbonate:amine:catalyst of 100:120:2. [b] Isolated yields out of two independent runs. [c] Reactions were conducted with relative mole ratios of carbonate:amine:catalyst of 100:120:4. [d] Ratio of linear:branched:diallylation product. [e] Reactions conducted with 2 equiv of aryloxide.

ated in situ from commercially available $[Ir(COD)Cl]_2$ and a phosphoramidite ligand **L1**.[8,10−12] This ligand was originally prepared and applied to copper-catalyzed processes by Feringa and de Vries.[13]

We showed that the square planar [Ir(COD)(Cl)(**L1**)], which was generated from **L1** and $[Ir(COD)(Cl)]_2$, reacts with aliphatic amines or other basic nucleophiles to generate a metallacyclic complex **1a** in which the monodentate ligand has become bidentate.[5,10,14,15] Complex **1a** appears to generate the active catalyst by dissociation of the second monodentate phosphoramidite.

We have published our use of this activated catalyst and its analogues to improve the scope of the reactions. We showed that the reactions of arylamines, which did not occur with the combination of $[Ir(COD)Cl]_2$ and phosphoramidite ligand **L1**, occurred with broad scope and in high yield and enantioselectivity if an aliphatic amine was added to the system to induce the cyclometalation.[8] We also showed that a catalyst generated from the bis-naphthethyl analogue of **L1**, phosphoramidite **L2**,[16] formed an iridium complex that catalyzed the first highly enantioselective allylation of alkoxides.[7]

Considering that activation of the catalyst with amine prior to addition of the nucleophile improved one set of reactions (those of aromatic amines) and that use of the naphthethyl ligand **L2** instead of **L1** improved another set of reactions (those of alkoxides), we have conducted a study to reevaluate the effect of catalyst activation with ligand **L2** on the reactions of amine and phenoxide nucleophiles we published initially. We conducted these further studies both to determine if these two changes to the catalyst would improve some of the less selective reactions of these two types of nucleophiles and to determine whether one of the two changes was more important than the other. We report that these reactions occur with a combination of faster rates, higher yields, increased regioselectivities, or increased enantioselectivities as a result of these changes to the catalyst and that both catalyst activation and changes to the ligand structure contribute to these improvements.



(1)

We initially studied four reactions to determine if the combination of the catalyst activated by cyclometalation prior to the addition of the reagents and the use of ligand **L2** to generate the activated catalyst would improve the yields, regioselectivities, and enantioselectivities of the allylation processes (eq 1 and Table 1). These four reactions were (1) the addition of amines to aliphatic allylic methyl carbonates, which occurred with high enantioselectivities with the original catalyst but lower yields and regioselectivities than reactions of cinnamyl carbonates;[12] (2) reaction of benzylamine with methyl *p*-nitrocinnamyl carbonate, which occurred with modest enantioselectivity and regioselectivity under the original conditions;[12] and (3) two reactions of aryloxides with an aliphatic methyl carbonate, which occurred with modest to good regioselectivities and enantioselectivities with the original catalyst.[11] Table 1 summarizes the reactions we published originally, the reactions conducted by addition of the reagents after activation of the catalyst generated from **L1**, and the reactions conducted by adding the reagents after activation of the catalyst containing ligand **L2**. The catalyst

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(14) Helmchen and co-workers mentioned in ref 5 the potential that cyclometalation of triphenyl phosphite leads to the active catalyst upon addition of nucleophiles to the related [Ir(COD)(L)Cl] complex with L = triphenyl phosphite. See also: Lipowsky, G.; Miller, N.; Helmchen, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 4595.

(15) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 2426. The authors report reactions with a phosphoramidite ligand with an anisyl group, which could be hemilabile, and which generates an Ir catalyst for allylic amination with cinnamyl methyl carbonate and alkylamines with rates and regio- and enantioselectivities that are similar to those of the catalyst in ref 10.

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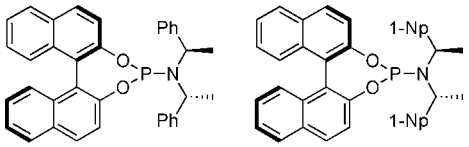

(R_a, R_c, R_c) **L1** (R_a, R_c, R_c) **L2**

Figure 1. Phosphoramidites used to generate catalysts **1a** and **1b**.

was "activated" by heating $[Ir(COD)Cl]_2$ and **L1** or $[Ir(COD)Cl]_2$ and **L2** with propylamine at 50 °C for 20 min to generate the metallacyclic core structure, followed by evaporation of the volatile materials before the addition of the reaction solvent and the two reagents.[8]

An evaluation of the results in Table 1 shows that both activation of the catalyst and a change in the steric properties of the ligand led to improvements in yields, regioselectivities, and enantioselectivities. For example, the branched-to-linear regioselectivity of the reaction of benzylamine with the linear aliphatic allylic carbonate in entry 1 was improved by generating the activated catalyst prior to the addition of the substrates, and the enantioselectivity was improved by increasing the size of the arylethyl group. In contrast, the enantioselectivity of the reaction of benzylamine with the electron-poor cinnamyl substrate in entry 2 was improved by activation of the catalyst prior to addition of the reagents, and the regioselectivity was improved by increasing the size of the arylethyl group. In contrast to each of these results, both the enantioselectivity and the regioselectivity of the reactions of the phenoxides were improved incrementally by activation of the catalyst before addition of the reagents and by increasing the size of the amino group.

With the information that both the activation of the catalyst and increased size of the amino group improve rates, yields, and selectivity, we assessed the scope of the reactions of amines and phenoxides with this catalyst system. A comparison of the yield, enantiomeric excess, and branched-to-linear regioselectivity of reactions with the activated catalysts containing ligands **L1** and **L2** is shown in Table 2. These data show that yield, enantioselectivity, or branched-to-linear regioselectivity is improved with the catalyst containing **L2** over the values obtained with the catalyst containing **L1**.

For example, entries 1−3 of Table 2 show that the reactions of a simple, unhindered aliphatic allylic carbonate occurred in good to excellent yields, enantioselectivities, and regioselectivities with benzylic and heteroarylmethylamines in the presence of the activated catalyst generated from ligand **L2**. Although none of the reactions of this allylic carbonate occurred in poor yield or with selectivities, with ligand **L1** either yield or selectivity was improved substantially by the generation of the catalyst from **L2**. The reaction of benzylamine with the linear aliphatic carbonate occurred in higher yield and with measurably higher enantioselectivity (entry 1), while reactions of the heteroarylmethylamines occurred with higher yields, enantioselectivities, *and* regioselectivities (entries 2 and 3) than did reactions with the catalyst generated from **L1**. The change from ligand **L1** to **L2** also improved reactions of benzylamine with more hindered aliphatic allylic carbonates. For example, the yield of the reaction of the allylic carbonate in entry 4, which contains a branch point α to the allyl unit, occurred in only 66% yield, 89% ee, and roughly 10:1 branched-to-linear regioselectivity with the catalyst derived from **L1**, but it occurred in 90% yield, 94%

Table 2. Comparison of the Yields and Selectivities of the Activated Catalysts Derived from Ligands **L1** and **L2**[a]

entry	carbonate	amine	catalyst derived from **L1**				catalyst derived from **L2**			
			yield[b] %	time (h)[c]	ee %	b/l	yield[b] %	time (h)[c]	ee %	b/l
1	C_3H_7 OCOOMe	$BnNH_2$	58	3	95	94:6	67	0.5	98	94:6
2		X=O	61	3	94	92:8	78	0.5	98	94:6
3		X=S	72	3	94	91:9	86	0.5	98	93:7
4	OCOOMe	$BnNH_2$	66	12	89	92:8	90	12	94	95:5
5[d]	OCOOMe		59	15	96	80:20	76	3	97	91:9
6[d]			63	15	92	82:18	71	3	98	92:8
7[d]		R=H	78	15	97	71:29	81	3	95	97:3
8[d]		R=SMe	73	15	93	93:7	93	3	98	99:1
9	*p*-NO_2Ph OCOOMe	$BnNH_2$	75[e]	14	96	83:17	82[e]	4	96	94:6
10	OCOOMe	$BnNH_2$	41	1	95	84:16	81	0.5	98	91:9
11[f]	C_3H_7 OCOOMe	R=*o*-Me	79	14	94	92:8	90	2	98	94:6
12[f]		R=*p*-OMe	95	14	94	93:7	94	2	97	95:5

[a] Reactions were conducted at room temperature on a 1.0 mmol scale in THF (0.5 mL) with a relative mole ratio of carbonate/nucleophile/catalyst of 100:120:2. [b] Isolated yields are an average from two independent runs. [c] Room temperature; reaction times were not optimized. [d] Catalyst was activated in situ with DABCO; relative mole ratio of carbonate:amine:DABCO/$[Ir(COD)Cl]_2$/L was 100:120:10:1:2. [e] Performed with 4% catalyst. [f] Performed with 2 equiv of nucleophile.

ee, and nearly 20:1 branched-to-linear regioselectivity with the catalyst from **L2**.

The reactions of dienyl carbonates to give optically active amines with two different olefinic units have been reported by us with anilines and by Helmchen et al.[6] with benzylamine. Although reactions catalyzed by complexes generated from ligand **L1** occurred with good enantioselectivity, the yields were modest and the branched-to-linear regioselectivities of reactions of the aliphatic dienyl carbonate were lower than that of the reaction of the analogous phenyl-substituted dienyl carbonate. In contrast, the reactions with the catalyst generated from ligand **L2** occurred with uniformly high regioselectivities, enantioselectivities, and yields (entries 5−8). For example, the regioselectivity of the reactions of furylmethylamine and thienylmethylamine were improved from 4:1 to greater than 10:1, and the enantioselectivity of the reaction of thienylmethylamine improved from 92 to 98%. Although the reactions of anilines occurred with high enantioselectivities with the catalyst generated from ligand **L1**, the regioselectivity was improved from roughly 4:1 to over 30:1 by generating the catalyst from **L2**.

Most reactions of cinnamyl carbonates with aliphatic and benzylic amines occurred with high regio- and enantioselectivity with ligand **L1**, but reaction of the strongly electron-poor cinnamyl carbonate with a *p*-nitro group occurred with low regioselectivity, even with the activated catalyst. In contrast, the reaction of benzylamine catalyzed by the complex derived from ligand **L2** occurred in high yield, ee, and regioselectivity (entry 9).

One might wonder whether reactions of basic nucleophiles conducted with a mixture of $[Ir(COD)Cl]_2$ and ligand **L2** without activation prior to addition of the reagents are as effective as reactions of the same nucleophiles conducted with the preformed metallacyclic catalyst derived from **L2**. Although the selectivities and yields may be equally high with or without activation prior to addition of the reagents, the rates are not. To avoid a long induction period, the cyclometalation process must occur on the time scale of minutes, and cyclometalation at room temperature requires hours. Thus, reactions without activation of the catalyst prior to addition of the reagents occur with an induction period and without the full concentration of active catalyst. Consistent with this analysis, the reaction of benzylamine with the carbonate derived from (*E*)-2-hexen-1-ol (Table 2, entry 1) without activation of the catalyst required 10 h to proceed to completion, while the reaction with initial activation with propylamine occurred within 2 h.

In summary, we have shown that a combination of generation of the metallacyclic catalyst prior to addition of the reagents and a change in the bis-arylethylamino group on the phosphoramidite from the bis-phenethylamino group in **L1** to the bis-naphthethylamino group in **L2** improves the rates, yields, regioselectivity, and enantioselectivity of many reactions of allylic carbonates with amines and phenoxides. Both preactivation of the catalyst and a change in the steric properties of the ligand improve these reactions. Structural information on the allyl intermediates would help to explain the changes in selectivity, and the synthesis of such a complex is one goal of our future work.

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Supporting Information Available: Experimental section containing reaction procedures and characterization of reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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