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Enantioselective Iridium-Catalyzed Allylic Amination of Ammonia and Convenient Ammonia Surrogates

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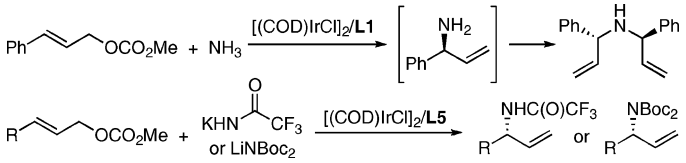
ABSTRACT



Iridium-catalyzed, asymmetric allylation of ammonia as a nucleophile occurs with stereoselectivity to form a symmetric diallylamine, and related allylation of the inexpensive ammonia equivalent potassium trifluoroacetamide or the highly reactive ammonia equivalent lithium di-*tert*-butyliminodicarboxylate forms a range of conveniently protected, primary, α-branched allylic amines in high yields, high branched-to-linear regioselectivities, and high enantiomeric excess. The reactions of ammonia equivalents were conducted with a catalyst generated from a phosphoramidite containing a single stereochemical element.

Cyclometalated iridium−phosphoramidite complexes[1] catalyze the enantioselective amination of linear allylic electrophiles to form branched allylic amines in high yield with high branched-to-linear ratios and high enantiomeric excess.[2−6] The regioselectivity of these reactions contrasts with the regioselectivity of palladium-catalyzed allylations that typically yield linear products.[7]

Published examples of asymmetric allylic amination have been conducted with alkylamines, arylamines, or ammonia equivalents. The direct enantioselective allylation of ammonia has not been reported with catalysts derived from any metal.[8] The use of ammonia as a nucleophile is desirable because it is inexpensive and avoids the use of protecting groups. The direct allylation of ammonia has been a challenge, presum-

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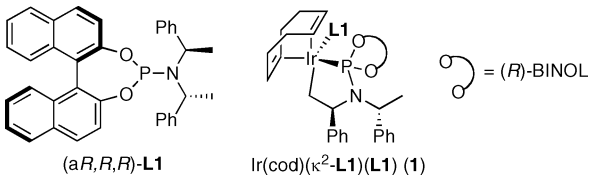
ably because ammonia poisons the catalyst or displaces the chiral ligands to generate an achiral catalyst.

Because of the challenge of conducting the allylation of ammonia, asymmetric allylations of many ammonia equivalents have been studied. Many of the ammonia equivalents studied for the iridium-catalyzed process are either relatively expensive or difficult to deprotect. Ir-catalyzed allylic aminations with the most convenient ammonia equivalents, such as amides or carbamates, have been achieved only by tethering the amide to the allyl group in the form of an imidodicarbonate.[9] Inexpensive sulfamic acid has been shown recently to convert allylic alcohols to allylamines, but only one enantioselective reaction of this type (70% ee) has been reported so far.[10] Ir-catalyzed allylations of one of the more convenient ammonia equivalents, di-*tert*-butyliminodicarboxylate ($HNBoc_2$), have been studied, but reactions with only two allylic carbonates were reported.[5,6]

We report the allylation of ammonia and of easily deprotected ammonia equivalents catalyzed by cyclometalated iridium phosphoramidite complexes. First, we show that the allylation of ammonia forms a diallylamine with high regio- and stereoselectivity. Second, we show that the potassium salt of the inexpensive trifluoroacetamide undergoes allylation with high enantioselectivity to form products that are readily deprotected.[11] Third, we show that the lithium salt of di-*tert*-butyliminodicarboxylate ($LiNBoc_2$) reacts with a broader scope of allylic carbonate than had been reported previously.[12] Moreover, we show that the reactions of $LiNBoc_2$ and potassium trifluoroacetamide occur in high yield, regioselectivity, and enantioselectivity in the presence of a catalyst derived from a phosphoramidite containing a single resolved stereocenter.[13]

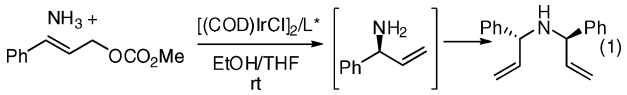
Allylic aminations catalyzed by iridium complexes of phosphoramidite **L1** occur after cyclometalation of the phosphoramidite ligand by a basic reagent or additive to generate the metallacyclic species [Ir(COD)(κ^2-**L1**)(**L1**)] (**1**) in Figure 1. The reactions of ammonia were conducted with



(a*R,R,R*)-**L1** Ir(cod)(κ^2-**L1**)(**L1**) (**1**)

Figure 1. Structure of phosphoramidite ligand **L1** and the cyclometalated, activated catalyst (**1**).

the catalyst generated by heating $[Ir(COD)Cl]_2$, **L1**, and propylamine at 50 °C for 30 min to induce cyclometalation, followed by separation of the iridium species from the $PrNH_3$-Cl salt. Ammonia was added as a 2 M solution in EtOH, and the reaction was run in a 1:1 mixture of EtOH and THF.



Equation 1 summarizes the reaction of ammonia with methyl cinnamyl carbonate. Despite the challenges in conducting the asymmetric allylation of ammonia, this reaction fully consumed the allylic carbonate to form the symmetrical diallylamine in 93% yield, 94:6 dr, and 99% ee. Apparently, the primary amine product of this reaction is sufficiently more reactive than ammonia that the diallylation product was formed exclusively. No monoallylation product was observed during the reaction. Related reactions of linear aliphatic carbonates formed mixtures of products during preliminary experiments.

C_2-symmetric pyrrolidines containing stereocenters in the 2- and 5-positions have been used recently as catalysts for the α-halogenation of aldehydes.[14] These materials are now accessible by allylation of cinnamyl carbonate with ammonia, followed by known ring-closing metathesis and hydrogenation.[6,15,16]

In parallel with this work on the direct allylation of ammonia, we have sought to identify ammonia equivalents that give rise to conveniently protected primary allylic amines. We sought a reagent that would be low in cost, that would possess a relatively low molecular weight, that would react with a broad scope of allylic carbonates with high enantioselectivity, and that would release the protective group under mild conditions. A number of ammonia equivalents are commercially available, but many, such as *p*-methoxybenzylamine, tosylamide, and phthalimide, require harsh conditions for deprotection. Others, such as nosylamide, are relatively expensive, and still others, such as $Bu^tOC(O)N(CHO)$,[6] are not commercially available.

After surveying reactions of lithium hexamethyldisilazide, benzophenone imine, *O*-benzylhydroxylamine, tritylamine, and the alkali metal salts of trichloroacetamide in the presence of the iridium catalyst generated from $[Ir(COD)Cl]_2$, **L1**, and propylamine to induce cyclometalation, we found that reactions of the alkali metal salts of trifluoroacetamide formed the protected allylic amine in acceptable yield, with high branched-to-linear regioselectivity and enantiomeric excess. To our knowledge, the base-labile trifluoroacetamide has not been used as an ammonia equivalent in allylic substitution catalyzed by any metal. Trifluoroacetamide is inexpensive[17] and undergoes facile deprotection under mildly basic conditions.[11]

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(17) $0.78/g from Aldrich.

Initial studies indicated that the potassium salt of trifluoroacetamide was most suitable for the allylic amination process. The lithium and sodium salts both reacted with methyl cinnamyl carbonate at room temperature in the presence of the cyclometalated catalyst, but the yields of these reactions (44% and 53% isolated yields, respectively) were lower than that for the potassium salt. The potassium salt of trifluoroacetamide reacted with cinnamyl carbonate in the presence of **L1** to form the allylation product in 68% yield and 96% ee after 18 h (eq 2).[18]

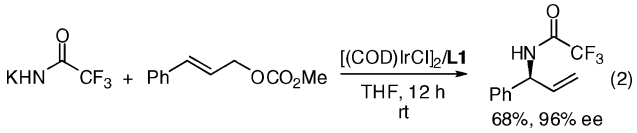
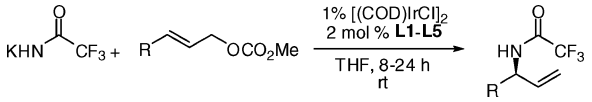


Table 1 shows the reaction of potassium trifluoroacetamide (K-TFAc) with cinnamyl methyl carbonate, using the different phosphoramidite ligands shown in Figure 2. These ligands include the original ligand we used in allylic amination (**L1**),[2,19] the naphthyl (**L2**) and *o*-anisyl (**L3**)[20] analogues of **L1**, and two phosphoramidites of the type developed recently in our laboratory for allylic amination possessing a single stereochemical element. One of these simplified ligands contains a biphenylate group on phosphorus, a cyclododecyl group on nitrogen, and a phenethyl group on nitrogen (**L4**)[13] while the second (**L5**) is an *o*-anisyl analogue of the simplified ligand **L4**. The reactions were conducted after cyclometalation of the precatalyst by added propylamine to form the structure in Figure 1.[13]

Table 1. Allylation of Potassium Trifluoroacetamide Catalyzed by Ir Complexes of Various Phosphoramidite Ligands[a]



entry	ligand	yield[b] (%)	time (h)	ee (%)
1	**L1**	68	18	96
2	**L2**	67	24	94
3	**L3**	74	24	97
4	**L4**	69	18	93
5	**L5**	68	8	94

[a] Reactions were conducted at room temperature on a 0.5 mmol scale in THF (0.5 mL) with a relative mole ratio of carbonate/nucleophile/[Ir(COD)Cl]$_2$/L of 100:120:1:2 unless otherwise noted. The catalyst was preactivated with $PrNH_2$ at 50 °C for 30 min. [b] Isolated yields of branched product.

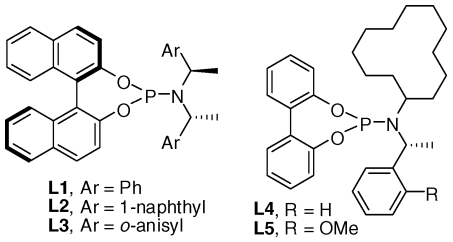
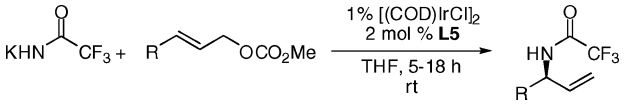


Figure 2. Ligands studied for the Ir-catalyzed allylation of potassium trifluoroacetamide.

As shown in Table 1, the yields from reactions with catalysts generated from the different ligands varied only slightly, but use of simplified anisyl ligand **L5** resulted in rates that were faster than those observed when using ligands **L1**−**L4**. In addition, the enantioselectivity was high for reactions conducted with ligand **L5**. Thus, studies on the scope of the allylation of potassium trifluoroacetamide were conducted with this phosphoramidite.

The scope of the allylation of potassium trifluoroacetamide is summarized in Table 2. These reactions occurred with para-substituted cinnamyl carbonates and aliphatic allylic carbonates to give a variety of pure branched, trifluoroacetate-protected primary allylic amines in 59−87% yields and 92−98% enantiomeric excess. Electron-neutral (entries 1 and 2), electron-rich (entry 3), and electron-poor (entries 4 and 5) cinnamyl carbonates, as well as aliphatic carbonates both with and without branching α to the allyl unit (entries 7 and

Table 2. Yields and Selectivities for the Allylations of Potassium Trifluoroacetamide[a]



entry	R	yield[b] (%)	time (h)	ee (%)
1	Ph	68	8	94
2	*p*-MeC_6H_4	74	5	96
3	*p*-MeOC_6H_4	93	12	98
4	*p*-ClC_6H_4	64	12	94
5	*p*-BrC_6H_4	59	18	92
6	*o*-FC_6H_4	47	18	85
7	*n*-heptyl	65	12	94
8[c]	cyclohexyl	79	18	96

[a] Reactions were conducted under the conditions described in Table 1. [b] Isolated yields of pure branched product are an average from two independent runs. [c] Conducted with 2 mol % of [Ir(COD)Cl]$_2$ and 4 mol % of **L5**.

(18) The linear monoallylation product could not be observed clearly in the ^{1}H NMR spectrum, and could not be quantified. Thus, we do not report branched-to-linear selectivities for these reactions. Several signals corresponding to a majority of the mass balance were observed in the region of the ^{1}H NMR spectrum in which the allylic hydrogens of linear products resonate, perhaps from formation of regioisomeric diallylation products. Nevertheless, these side products were easily removed from the branched product by flash chromatography, and good yields of the pure branched product were obtained. A larger excess of potassium trifluoroacetamide (2.4 equiv) increased the reaction rate and lowered the intensity of the resonances proposed to result from regioisomeric side products; however, it also increased the rate of decomposition of the carbonate to alcohol and did not measurably improve the overall yield.

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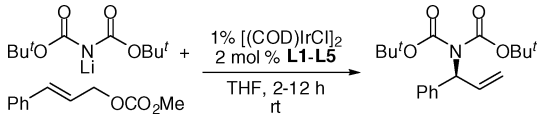
8), all reacted with potassium trifluoroacetamide. The reaction of an ortho-substituted cinnamyl carbonate (entry 6) occurred with lower enantioselectivity, but the same lower enantioselectivity has been observed for iridium-catalyzed allylic substitutions of ortho-substituted cinnamyl carbonates with all nucleophiles.[2,4,21]

In parallel with these studies on the allylation of potassium trifluoroacetamide, we showed that the lithium salt of di-*tert*-butyliminodicarboxylate ($LiNBoc_2$) reacts with allylic carbonates to form conveniently protected allylic amines. This reagent is much less atom-economical and is more expensive than trifluoroacetamide. However, it is well-established that *N*-alkyl di-*tert*-butyliminodicarboxylates undergo selective deprotection to form either the allylic carbamate or the primary allylic amine.[22] During the course of this work, reactions of this nucleophile with two allylic carbonates were reported with use of cyclometalated iridium catalysts like those we developed for allylic amination.[5,6] Here we more fully map the scope and limitations of this reagent and show that the simplified catalyst generated from phosphoramidite **L5** leads to high yields, regioselectivities, and enantioselectivities.

Studies on the allylation of $LiNBoc_2$ with a series of phosphoramidite ligands are summarized in Table 3. As has been reported for amination with alkylamines,[20] catalysts generated from the anisyl ligand **L3** reacted faster than those generated from the aryl and naphthyl analogues **L1** and **L2**. However, reactions conducted with the catalyst containing simplified ligand **L5** occurred at rates similar to those conducted with the more stereochemically complex ligand **L3** and with acceptable enantioselectivity. Thus, studies on the scope of the reactions of $LiNBoc_2$ were conducted with **L5**.

Table 3. Amination of Cinnamyl Methyl Carbonate with $LiNBoc_2$[a]

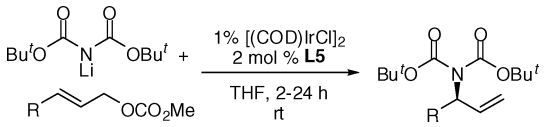


entry	ligand	yield[b] (%)	time (h)	b/l[c]	ee (%)
1	**L1**	84	6	96/4	94
2	**L2**	82	12	95/5	90
3	**L3**	84	1.5	98/2	98
4	**L4**	81	12	98/2	93
5	**L5**	82	2	93/7	93

[a] Reactions were conducted at room temperature on a 0.5 mmol scale in THF (0.5 mL) with a relative mole ratio of carbonate/nucleophile/$[Ir(COD)Cl]_2$/**L5** of 100:120:1:2 unless otherwise noted. The catalyst was preactivated with $PrNH_2$ at 50 °C for 30 min. [b] Isolated yields of branched product. [c] Branched-to-linear ratio.

The scope of the allylation of $LiNBoc_2$ with the catalyst derived from **L5** is summarized in Table 4. In general, the reactions of electron-neutral, electron-rich, and electron-poor cinnamyl carbonates occurred in good yield with high regioselectivity and enantioselectivity. In addition, the reactions of aliphatic carbonates occurred with high regioselectivity and enantioselectivity. Reactions of the linear, aliphatic allylic carbonate (entry 6) occurred in high yield, regioselectivity, and enantioselectivity. The reaction of an aliphatic allylic carbonate with branching α to the allyl group (entry 7) occurred more slowly and in lower yield, but with a high branched-to-linear ratio and enantioselectivity. In one case (entry 7), the reaction occurred with higher branched-to-linear ratios with the ligand **L1** than with **L5**.

Table 4. Amination of Allylic Carbonates with $LiNBoc_2$[a]



entry	R	ligand	yield[b] (%)	time (h)	b/l[c]	ee (%)
1	Ph	**L5**	82	2	93/7	93
2	*p*-$MeOC_6H_6$	**L5**	83	6	93/7	93
3[d]	*p*-$CF_3C_6H_6$	**L5**	76	4	85/15	92
4	*p*-BrC_6H_6	**L5**	78	10	90/10	94
5[e]	Pr	**L5**	77	24	93/7	95
6	*i*-Pr	**L5**	45	12	89/11	97
7	2-furyl	**L1**	62	5	79/21	92

[a] Reactions were conducted under the same conditions described in Table 3. [b] Isolated yields of branched product are an average from two independent runs. [c] Branched-to-linear ratio. [d] Conducted with 1.5 mol % of $[Ir(COD)Cl]_2$ and 3 mol % of **L5**. [e] Conducted with 2 mol % of $[Ir(COD)Cl]_2$ and 4 mol % of **L5**.

In summary, we have shown that the direct allylation of ammonia occurs enantioselectively to form the product from diallylation when catalyzed by the metallacyclic iridium complex generated from $[Ir(COD)Cl]_2$ and a common phosphoramidite ligand. In addition, we have shown that monoallylation products form with high enantioselectivity when using trifluoroacetamide as an inexpensive, easily deprotected ammonia equivalent. Finally, we have shown that di-*tert*-butyliminodicarboxylate reacts with a variety of aromatic and aliphatic allylic carbonates with high regioselectivity and high enantioselectivity. Reactions of both potassium trifluoroacetamide and lithium di-*tert*-butyliminodicarboxylate occur with high regioselectivities and enantioselectivities when the catalyst is generated from a phosphoramidite developed in our laboratory containing a single resolved stereochemical element.

Acknowledgment. We thank the NSF (CHE-0414542) for support and Johnson-Matthey for iridium.

Supporting Information Available: 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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