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Enantioselective, Iridium-Catalyzed Monoallylation of Ammonia

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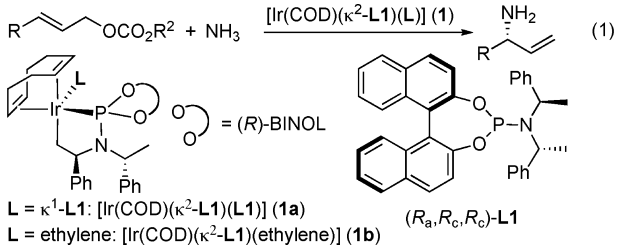
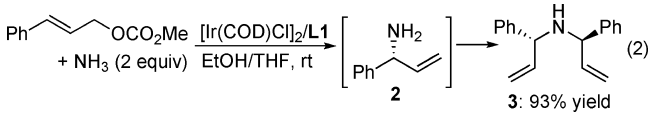
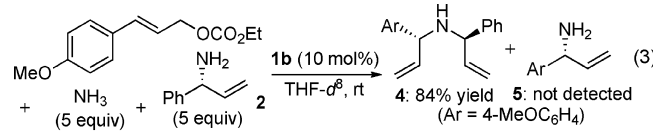
Enantioselective allylic substitution with metalacyclic iridium-phosphoramidite catalysts[1] has become a convenient method to prepare a variety of allylic amines from achiral allylic carbonates in high yield, branched-to-linear selectivity, and enantiomeric excess.[2] Although these reactions encompass a wide variety of amine nucleophiles, reactions of the simplest and most abundant nitrogen nucleophile, ammonia, have not been reported to form primary allylic amines in the presence of iridium catalysts, such as **1** (eq 1). Instead, enantioselective, iridium-catalyzed allylic substitution to form primary allylic amine derivatives has been conducted with ammonia equivalents, such as trifluoroacetamide,[3] imides,[3,4] and sulfonamides.[4−6] More generally, the enantioselective allylation of ammonia with any catalyst is limited to just one example.[7] This reaction was conducted with a palladium catalyst and the widely explored 1,3-diphenylallyl acetate electrophile, and it occurred with modest enantioselectivity (87% ee).

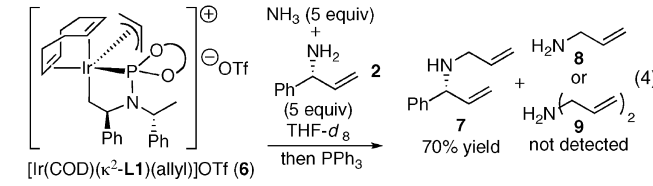


The development of a more general, asymmetric monoallylation of ammonia presents a series of challenges. Ammonia can form stable metal complexes that may be catalytically inactive or, if chiral ligands are displaced, generate achiral catalysts. Moreover, the selective monoallylation of ammonia is difficult to achieve because the allylic amine product is more nucleophilic than ammonia. Here, we describe iridium-catalyzed monoallylations of ammonia with achiral allylic esters that occur with excellent enantioselectivity with a series of allylic carbonate electrophiles to form the branched allylic amine products. This process was made possible by the recent development of a single-component,[8] metalacyclic catalyst, which we show to be stable to high concentrations of ammonia.



In previous work,[3] we demonstrated that the allylation of ammonia could be conducted with the metalacyclic iridium catalyst **1a** in eq 1 generated from $[Ir(COD)Cl]_2$ and **L1**, but the diallylamine **3** was the only amine product detected (eq 1). To assess directly the relative nucleophilicity of ammonia versus the monoallylamine **2**, which we presumed to be the initial product, we conducted the reaction of ethyl *p*-methoxycinnamyl carbonate with a mixture of ammonia and 1-phenylprop-2-en-1-amine **2** in the presence of iridium catalyst **1b** (eq 1). This reaction formed diallylamine **4** in 84% yield as determined by ^{1}H NMR spectroscopy; no 1-(4-methoxyphenyl)prop-2-en-1-amine **5** was detected. In addition, we conducted a competition between ammonia and **2** for reaction with the recently reported, discrete iridium-allyl complex **6**.[9] This reaction formed *N*-(1-phenylallyl)prop-2-en-1-amine **7** in 70% yield, as determined by ^{1}H NMR spectroscopy; allylamine **8** and diallylamine **9** were not detected (eq 4).





The results from these competition experiments imply that the selective monoallylation of ammonia with this catalyst requires a large excess of ammonia. The metalacyclic catalyst [Ir(COD)(κ^2-**L1**)(**L1**)] (**1a**) previously studied for iridium-catalyzed allylation reactions requires an additive, such as $[Ir(COD)Cl]_2$, to bind the liberated κ^1-phosphoramidite ligand and to promote formation of the catalytically active 16-electron intermediate.[8] Although **1a** is stable to the large excess of ammonia, $[Ir(COD)Cl]_2$ reacts with ammonia to precipitate an unidentified species that did not bind the κ^1-phosphoramidite ligand. Consistent with this observation, the reaction of ammonia with ethyl cinnamyl carbonate catalyzed by 2 mol % **1a** with 1 mol % added $[Ir(COD)Cl]_2$ occurred to only 76% conversion and formed **2** in 45% yield (Table 1, entry 1).

To avoid this need for a Lewis acid, we studied reactions catalyzed by the ethylene complex [Ir(COD)(κ^2-**L1**)(ethylene)] (**1b**) that operates without additives.[8] Although ammonia might be expected to displace ethylene from **1b**, complex **1b** is stable to 2000 equiv of ammonia, as determined by ^{31}P NMR spectroscopy. Thus, a selective reaction with ammonia might be achieved by simply conducting the allylation process with a large excess of ammonia and **1b** as the catalyst precursor.

Indeed, the monoallylation product **2** was increasingly favored with increasing amounts of ammonia, and the catalyst remained active under these conditions. The reaction of methyl cinnamyl carbonate with 16 equiv of ammonia formed a 65:35 ratio of mono- to diallylation products (**2**/**3**) and a 59% yield of the primary allylic amine **2** (entry 2) as determined by ^{1}H NMR spectroscopy of the reaction mixture. Reaction with 100 equiv of ammonia formed a higher 90:10 ratio of the monoallylation product **2** to diallylation product **3** (entry 3). Reactions of ethyl carbonates, rather than methyl carbonates, formed less side products and formed **2** in higher yields (entry 4). In addition,

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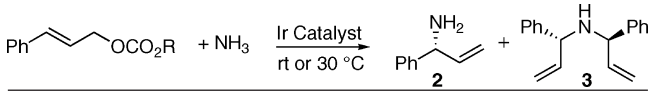
reactions at 30 °C in THF occurred with even higher selectivity for the monoallylation product (92:8 **2**/**3**, entry 5) and yield of **2** (81%).

Table 1. Development of Reaction Conditions for the Iridium-Catalyzed Monoallylation of Ammonia[a]

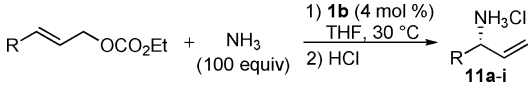


entry	R	Ir cat. (mol %)	equiv of NH_3	*T* (°C)	time (h)	yield (%)[b]	**2**:**3**[b]
1	Et	**1a** (2) + $[Ir(COD)Cl]_2$ (1)	100	30	15	45	94:6
2	Me	**1b** (4)	16	rt	24	59	65:35
3	Me	**1b** (4)	100	rt	24	63	90:10
4	Et	**1b** (4)	100	rt	48	66	91:9
5[c]	Et	**1b** (4)	100	30	15	81	92:8

[a] Reactions were conducted in 1:1 THF-d_8/ethanol-d_6 in a medium-wall NMR tube with 4.0 mol % Ir catalyst, 0.15 mmol of cinnamyl carbonate, and hexamethylbenzene or mesitylene as an internal standard. [b] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [c] Performed in THF-d_8.

The results of reactions of ammonia with a series of ethyl allylic carbonates under the conditions of entry 5 in Table 1 are shown in Table 2. The ammonium salts **11** were isolated and characterized after protonation of the primary amine products in situ with HCl. The reactions of ammonia with electron-neutral, -rich, and -poor cinnamyl carbonates occurred in moderate to good yield and with excellent enantioselectivity (entries 1−6). Furthermore, the reactions of aliphatic allylic carbonates as well as dienyl carbonates occurred with high enantioselectivity (entries 7−9). Reaction of ammonia with the trityloxy-substituted allylic carbonate (entry 8) generated a product containing a conveniently protected 1,2-aminoalcohol in high ee.

Table 2. Ir-Catalyzed Allylic Amination with Ammonia[a]

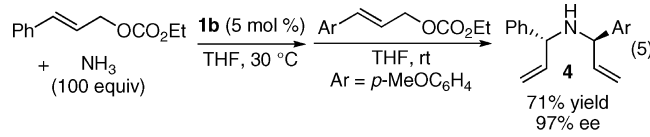


entry	R	**11**	yield (%)[b]	time (h)	ee (%)[c]
1	C_6H_5	**11a**	73	4	97
2	*p*-MeC_6H_4	**11b**	63	4	99
3	*p*-$MeOC_6H_4$	**11c**	58	14	98
4	*p*-BrC_6H_4	**11d**	57	12	99
5	*p*-$CF_3C_6H_4$	**11e**	51	12	99
6	*m*-$MeOC_6H_4$	**11f**	66	12	98
7[d]	*n*-heptyl	**11g**	49	24	96
8[e]	$TrOCH_2$	**11h**	53	5	97
9[f]	1-cyclohexenyl	**11i**	57	12	99

[a] Reactions were conducted on a 0.5 mmol scale in THF (0.5 mL) in a 10 mL pressure vessel with a vacuum side arm. Yields and enantioselectivities are averages from two independent runs. Products were characterized as their HCl salts. [b] Isolated yields of branched monoallylation products **11**. [c] Determined by chiral HPLC. [d] Conducted at room temperature. [e] Isolated as the free amine. [f] Conducted with 5 mol % **1b**.

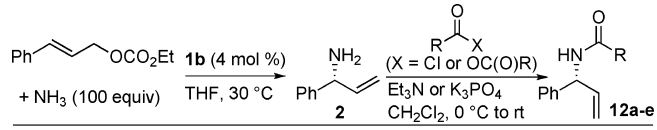
This direct access to primary allylic amines allowed the development of sequential reactions of allylic carbonates without blocking or protective groups. For example, two sequential allyations of ammonia form a chiral, unsymmetrical diallylamine with high enantio- and diastereoselectivity. After venting the ammonia from the reaction of ethyl cinnamyl carbonate in the presence of 5 mol % **1b** and addition of ethyl *p*-methoxycinnamyl carbonate, the heterodiallylation product **4** was isolated in 71% yield as a single diastereomer in 97% ee (eq 3).

The monoallylation of ammonia also provides access to allylic amine derivatives that are not directly accessible by Ir-catalyzed allylic substitution. The allylation of ammonia with a linear allylic carbonate, followed by quenching the product with an acid chloride or anhydride, represents a simple, one-pot process to synthesize



enantiomerically enriched *N*-allylamides that are inaccessible by direct reaction of an amide (Table 3). After venting the excess ammonia from the reaction of ethyl cinnamyl carbonate, acylation of the product with 4-chlorobenzoyl chloride, trimethylacetyl chloride, or phenylacetyl chloride in the presence of triethylamine or K_3PO_4 base formed the *N*-allylamides **12a**−**c** in 63−75% yield and 98% ee (entries 1−3). Enantioenriched α,β-unsaturated *N*-allyl amides were synthesized by an analogous procedure. Monoallylation, followed by acylation with methacryloyl anhydride or crotonic anhydride in the presence of triethylamine, formed the α,β-unsaturated amides **12d** and **12e** in 72% and 65% yield, respectively, and in 98% ee (entries 4 and 5).

Table 3. One-Pot Allylation and Acylation To Form Chiral *N*-Allylamides[a]



entry	R	base	**12**	yield (%)[b]	ee (%)[c]
1	*p*-Cl−C_6H_4	Et_3N	**12a**	63	98
2	*t*-Bu	Et_3N	**12b**	72	98
3[d]	Bn	K_3PO_4	**12c**	75	98
4	$C(CH_3)$=CH_2	Et_3N	**12d**	72	98
5	(*E*)-CH=$CHCH_3$	Et_3N	**12e**	65	98

[a] For experimental details see the Supporting Information. [b] Yields are for isolated amides **12a**−**e**. [c] Enantiomeric excess was determined by chiral HPLC. [d] The solvent for the acylation reaction was THF.

In summary, we have demonstrated the first series of monoallylations of ammonia to form primary allylic amines with high enantioselectivity. This process is enabled by the use of a recently prepared iridium precursor that is stable toward excess ammonia, presumably due to chelation of the COD ligand and the metalacyclic nature of the chiral ligand. This process allows for formation of primary amines, as well as derivatives of primary amines that are inaccessible by direct *N*-allylation.

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Supporting Information Available: Experimental 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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