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Enantioselective, Iridium-Catalyzed Monoallylation of Ammonia

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Abstract

Highly enantioselective, iridium-catalyzed monoallylations of ammonia are reported. These reactions occur with electron-neutral, -rich, and -poor cinnamyl carbonates, alkyl and trityloxy-substituted allylic carbonates, and dienyl carbonates in moderate to good yields and excellent enantioselectivities. This process is enabled by the use of an iridium catalyst that does not require a Lewis acid for activation and that is stable toward a large excess of ammonia. This selective formation of primary allylic amines allows for one-pot syntheses of heterodiallylamines and allylic amides that are not otherwise accessible via iridium-catalyzed allylic amination without the use of blocking groups and protective group manipulations.

Enantioselective allylic substitution with metalacyclic iridium-phosphoramidite catalysts¹ 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 amination to form primary allylic amine derivatives has been conducted with ammonia equivalents, such as trifluoroacetamide,³ imides,^{3,4} and sulfonamides.^{4,5,6} 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, the widely explored 1,3-diphenylallyl acetate electrophile, and occurred with modest enantioselectivity (87% ee).

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Supporting Information Available. Experimental procedures and characterization of reaction products. This information is available free of charge via the Internet at www.pubs.acs.org.

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.

(2)

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 $[\text{Ir}(\text{COD})\text{Cl}]_2$ and **L1**, but the diallylamine **3** was the only amine product detected (eq 2). 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 4-methoxycinnamyl carbonate with a mixture of ammonia and 1-phenylprop-2-en-1-amine **2** in the presence of iridium catalyst **1b** (eq 3). This reaction formed diallylamine **4** in 84% yield as determined by $^1\text{H-NMR}$ spectroscopy; no 1-(4-methoxyphenyl)prop-2-en-1-amine **5** was detected. In addition, we conducted a competition between ammonia and **2** 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 $^1\text{H-NMR}$ spectroscopy; allylamine **8** and diallylamine **9** were not detected (eq 4).

(3)

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 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 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 ³¹P 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 equivalents 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 ¹H-NMR spectroscopy of the reaction mixture. Reaction with 100 equivalents 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, reactions at 30 °C in THF occurred with even higher selectivity for the branched product (92:8 **2/3**, entry 5) and yield of **2** (81%).

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, electron-rich, and electron-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.

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 allylations 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 4-methoxycinnamyl carbonate, the heterodiallylation product **4** was isolated in 71% yield as a single diastereomer in 97% ee (eq 5).

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

(5)

carbonate, followed by quenching the product with an acid chloride or anhydride represents a simple, one-pot process to access 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*-allylamides 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 *N*-allylamides **12d** and **12e** in 72% and 65% yield, respectively, and in 98% ee (entries 4 and 5).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1
Development of Reaction Conditions for the Iridium-Catalyzed Monoallylation of Ammonia^a

entry	R	Ir Cat. (mol %)	equiv NH ₃	°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 cinnamyl carbonate, and hexamethyl benzene or mesitylene as an internal standard.

^b Determined by ¹H NMR spectroscopy of the reaction mixture.

^c Performed in THF-*d*₈.

Table 2

Ir-Catalyzed Allylic Amination with Ammonia^a

$ \begin{array}{c} \text{R} \text{---} \text{CH=CH} \text{---} \text{CH}_2 \text{---} \text{OCO}_2\text{Et} + \text{NH}_3 \xrightarrow[\text{THF, 30 } ^\circ\text{C}]{\text{1) } \mathbf{1b} \text{ (4 mol \%)} \quad \text{2) HCl}} \text{R} \text{---} \text{CH=CH} \text{---} \text{CH}_2 \text{---} \text{NH}_2 \quad \mathbf{11a-i} \\ \text{(100 equiv)} \end{array} $					
entry	R	11	yield (%) ^b	time (h)	ee (%) ^c
1	C ₆ H ₅	11a	73	4	97
2	<i>p</i> -MeC ₆ H ₄	11b	63	4	99
3	<i>p</i> -MeOC ₆ H ₄	11c	58	14	98
4	<i>p</i> -BrC ₆ H ₄	11d	57	12	99
5	<i>p</i> -CF ₃ C ₆ H ₄	11e	51	12	99
6	<i>m</i> -MeOC ₆ H ₄	11f	66	12	98
7 ^d	<i>n</i> -heptyl	11g	49	24	96
8 ^e	TrOCH ₂	11h	53	5	97
9 ^f	1-cyclohexenyl	11i	57	12	99

^aReactions 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.

^bIsolated yields of branched monoallylation products **11**.

^cDetermined by chiral HPLC.

^dConducted at room temperature.

^eIsolated as the free amine.

^fConducted with 5 mol % **1b**.

Table 3
One-pot Allylation and Acylation to form Chiral *N*-Allylamides^a

entry	R	base	12	yield ^b	ee ^c
1	<i>p</i> -Cl-C ₆ H ₄	Et ₃ N	12a	63%	98%
2	<i>t</i> -Bu	Et ₃ N	12b	72%	98%
3 ^d	Bn	K ₃ PO ₄	12c	75%	98%
4	C(CH ₃)=CH ₂	Et ₃ N	12d	72%	98%
5	(<i>E</i>)-CH=CHCH ₃	Et ₃ N	12e	65%	98%

^aFor experimental details see the Supporting Information.

^bYields are for isolated amides **12a–e**.

^cEnantiomeric excess was determined by chiral HPLC.

^dThe solvent for the acylation reaction was THF.