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Iridium-Catalyzed, Asymmetric Amination of Allylic Alcohols Activated by Lewis Acids

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Enantioselective substitution of allylic esters by carbon and heteroatom nucleophiles has become a classic catalytic asymmetric transformation,[1] but enantioselective substitution of allylic alcohols is more challenging. Because allylic esters are typically prepared from allylic alcohols, the use of allylic alcohols in asymmetric allylic substitution would streamline synthetic sequences and would be more atom economic.

The poor leaving-group ability of a hydroxyl group causes the substitutions of allylic alcohols typically[2] to require high temperatures, neat conditions,[3] or an activator.[4−6] Thus far, most published reactions of allylic alcohols form achiral products. Direct asymmetric substitutions[7−10] of allylic alcohols have only recently been conducted with substantial enantiomeric excess,[8,9,11] and only one enantioselective substitution of a terminal allylic alcohol[9,10] to form preferentially the branched substitution product over the linear product (73:27 ratio, 81% ee) in substantial yield has been reported.

Using the catalyst we developed for enantioselective allylic amination of terminal allylic esters to form branched substitution products,[12,13] we sought to develop enantioselective aminations of allylic alcohols. We report enantioselective Ir-catalyzed aminations of terminal allylic alcohols activated with a niobium alkoxide and enantioselective aminations of terminal allylic alcohols activated with catalytic amounts of triphenylborane. A series of these reactions form branched allylic amine products with high regioselectivity and enantioselectivity.

We began our investigation of the amination of allylic alcohols by studying the reaction of cinnamyl alcohol **1a** with aniline **2a** to form the branched and linear substitution products **3** and **4** in the presence of the cyclometalated iridium catalysts prepared in situ from the chiral phosphoramidite ligands **5a** and **5b**.[12] This catalyst was generated from $[Ir(COD)Cl]_2$ and **5a** or **5b** by heating with propylamine, as described previously.[13,14] Reactions conducted without any activator of the allylic alcohol formed only trace amounts of the allylic amine, even in refluxing THF. Thus, we studied reactions in the presence of Lewis acid activators of the hydroxyl group. Although the activation of allylic alcohols has precedent,[4,5] a strong Lewis acid could affect the reactivity and selectivity of a late metal catalyst, particularly one containing P−O, P−N, and M−C bonds.

Table 1 summarizes studies with a variety of early metal activators. Although titanium alkoxides have been used to activate allylic alcohols for Pd-catalyzed aminations to form linear allylic amines,[5] Ir-catalyzed reactions conducted with $Ti(O^iPr)_4$ or $Ti(O^tBu)_4$ occurred with low conversions, albeit with substantial selectivities (Table 1, entries 1 and 2), even after extensive experimentation (Table S1 of Supporting Information).

Experiments conducted with a variety of related Lewis acids (Table S2) showed that reactions with Ta and Nb alkoxides occur with moderate to high conversion of allylic alcohol (Table 1, entries 3 and 4). High yield of the allylic amine was obtained from reactions containing niobium ethoxide ($Nb(OEt)_5$), and these reactions also occurred with high branched-to-linear selectivity (entry 4). $Nb(OEt)_5$ has not been used previously to activate allylic alcohols.[15]

Table 1. Ir-Catalyzed Asymmetric Allylic Amination in the Presence of Lewis Acids[a]

entry	activator (equiv)	yield[b] (%)	**3**/**4**[c]	ee (%)
1	$Ti(O^iPr)_4$ (1.2)	16	89/11	81
2	$Ti(O^tBu)_4$ (1.2)	30	94/6	89
3	$Ta(OEt)_5$ (1.2)	62	96/4	81
4	$Nb(OEt)_5$ (1.2)	82	98/2	92
5[d]	$Nb(OEt)_5$ (1.2)	47	91/9	92
6	$Nb(OEt)_5$ (0.5)	64	84/16	63
7[e]	$Nb(OEt)_5$ (1.2)	85	97/3	92
8[f]	$Nb(OEt)_5$ (1.2)	64	98/2	94
9[e,g]	$Nb(OEt)_5$ (1.2)	42	98/2	95

[a] The reaction was performed with cinnamyl alcohol (1.0 mmol) and aniline (1.2 mmol) in THF (0.5 mL) at 50 °C for 24 h, and the Ir complex (2 mol %) prepared from $[Ir(COD)Cl]_2$ (0.010 mmol) and **5a** (0.020 mmol), Lewis acid activator, and powdered 4 Å molecular sieves (4 Å MS, 50 mg) were used unless otherwise noted. [b] Isolated yield of branched product **3**. [c] Ratio of **3**:**4** determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Without 4 Å MS. [e] 1.5 mmol of aniline was used. [f] Ligand **5b** was used. [g] Conducted at room temperature.

Further studies on reaction conditions with $Nb(OEt)_5$ as activator showed that the identity of the solvent (toluene, DME, TBME, 1,4-dioxane) had little effect on yield and selectivities, but that omission of the 4 Å molecular sieves (4 Å MS) led to a decrease in reaction yield (entry 5). Reactions conducted with substoichiometric amounts of $Nb(OEt)_5$ occurred with lower conversions and selectivities (entry 6) than those with 1.2 equiv of $Nb(OEt)_5$. However, reactions with larger quantities of aniline occurred in higher yields based on the allylic alcohol (entry 7).

A comparison of reactions conducted with the catalyst formed from ligands **5a** and **5b** showed that the rate was faster with the catalyst generated from **5a**, but that the enantioselectivity was slightly higher with the catalyst generated from **5b** (entry 8). Reactions catalyzed by the complex generated from **5a** occurred even at room temperature, although slowly (entry 9).

The scope of the reaction under the conditions of entry 7 of Table 1 is summarized in Table 2. Reactions of arylamines containing electron-donating and electron-withdrawing substituents occurred in high yield and with high regioselectivities and enantioselectivities. Slightly lower yields were obtained from reactions of haloanilines (entries 5 and 6) and ortho-substituted anilines (entry 3). Even reactions of benzylic and aliphatic amines occurred (entries 7−9), despite their greater Lewis basicity. Substituted cinnamyl and 3-substituted aliphatic allylic alcohol derivatives reacted with aniline in the presence of the chiral Ir catalyst to afford the desired branched product **3** with high enantioselectivities.

Our success using a combination of allylic alcohol and stoichiometric amounts of Lewis acid as electrophile led us to develop conditions for the reactions of allylic alcohols with aromatic amines in the presence of a catalytic amount of Lewis acid. After exploring a series of Lewis acids in different solvents, we found that reactions conducted with a catalytic amount of triphenylboron (BPh_3) as an

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Table 2. Ir-Catalyzed Asymmetric Allylic Amination of Allylic Alcohols in the Presence of $Nb(OEt)_5$[a]

entry	**1**, R^1 =	**2**[b], R^2 =	yield[c] (%)	**3**/**4**[d]	ee[e] (%)
1	Ph	*p*-MeC_6H_4	85	>96/<4[f]	92
2	Ph	*p*-$MeOC_6H_4$	84	96/4[f]	89
3	Ph	*o*-$MeOC_6H_4$	66	>96/<4[f]	92
4	Ph	*m*-$MeOC_6H_4$	83	96/4[f]	81
5[g,h]	Ph	*p*-IC_6H_4	79	95/5	86
6[g,h]	Ph	*p*-ClC_6H_4	82	96/4	87
7[g]	Ph	Bn	72	96/4	93
8[g]	Ph	*p*-$MeOC_6H_4CH_2$	66	93/7	90
9	Ph	**2**=morpholine	90	98/2	94
10	*p*-$MeOC_6H_4$	Ph	85	98/2	89
11	*o*-$MeOC_6H_4$	Ph	78	99/1	70
12[i]	2-furyl	Ph	70	81/19	92
13	propyl	Ph	70	92/8	90
14[j]	isopropyl	Ph	45	88/12[f]	82
15	1-propenyl	Ph	67	79/14/7[k]	89

[a] The reaction was performed with **1** (1.0 mmol) and **2** (1.5 mmol) in THF (0.5 mL) at 50 °C for 24 h in the presence of 2 mol % of catalyst prepared from $[Ir(COD)Cl]_2$ (0.010 mmol), and **5a** (0.020 mmol), $Nb(OEt)_5$ (1.2 mmol), and 4 Å MS (50 mg) were used unless otherwise noted. [b] Except entry 10, R^3 = H. [c] Isolated yield of branched product **3**. [d] Ratio of **3** and **4** was determined by ^1H NMR analysis of the crude reaction mixture. [e] Enantiomeric excess of **3**. [f] Determined after isolation. [g] The Ir catalyst (3 mol %) was used. [h] **2** (2.0 mmol) was used. [i] The reaction was carried out at 40 °C. [j] The Ir catalyst (5 mol %) and aniline (2.0 mmol) were used. [k] Branched/5-phenylamino-1,3-hexadiene/linear.

Scheme 1

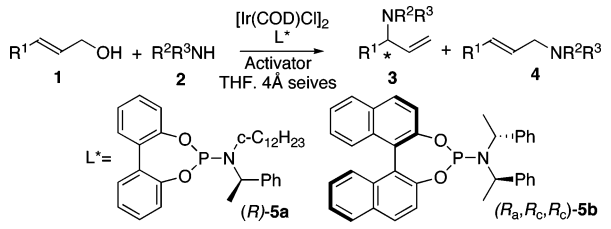

Table 3. Ir-Catalyzed Asymmetric Allylic Substitutions of **1** with **2** in the Presence Catalytic BPh_3[a]

entry	**1**, R^1 =	**2**, R^2 =	yield[b] (%)	**3**/**4**[c]	ee (%)
1	Ph	*p*-MeC_6H_4	74	97/3	88
2	Ph	*p*-$MeOC_6H_4$	72	94/6	93
3	Ph	*o*-$MeOC_6H_4$	52[d]	95/5	94
4	Ph	*p*-ClC_6H_4	53	>94/<6	92
5	*p*-$MeOC_6H_4$	*p*-MeC_6H_4	72	96/4	92
6	*p*-$MeOC_6H_4$	*m*-$MeOC_6H_4$	61	>97/<3	83
7	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	66	95/5	93
8	*p*-MeC_6H_4	*p*-MeC_6H_4	66[d]	>95/<5	94
9	*p*-BrC_6H_4	*p*-MeC_6H_4	61	>92/<8	87

[a] The reaction was performed by using **1** (1.5 mmol) and **2** (1.0 mmol) in dioxane (2.0 mL) at 50 °C for 24 h in the presence of a chiral Ir complex (5 mol %) prepared from $[Ir(COD)Cl]_2$ (0.025 mmol) and **5a** (0.050 mmol), BPh_3 (0.08 mmol), and 4 Å MS (300 mg) unless otherwise noted. [b] Isolated yield of branched product **3**. [c] Ratio of **3** and **4** was determined by GC analysis of the crude reaction mixture. [d] The reaction was conducted for 40 h.

activator in dioxane solvent containing 4 Å molecular sieves (Scheme 1, "activator" = BPh_3) formed branched allylic alcohols in moderate to excellent yields with excellent regioselectivities and enantioselectivities.

The scope of the reactions containing catalytic amounts of BPh_3 is summarized in Table 3. The reactions of substituted cinnamyl alcohols with various anilines proceeded in moderate to good yield with excellent regioselectivities and good to excellent enantioselectivities in the presence of the catalyst generated from $[Ir(COD)Cl]_2$ and ligand **5a** developed in our laboratory for iridium-catalyzed allylic substitution.[13] Reactions conducted with the more common phosphoramidite ligand **5b**[16] occurred with much lower conversions. The reactions occurred in acceptable yields with the parent cinnamyl alcohol (entries 1−4), and the highest yields were observed from reactions of the electron-rich *p*-methoxy-substituted cinnamyl alcohol. Arylamines bearing substituents in the 2-, 3-, and 4-position reacted, and anilines containing *p*-chloro groups reacted without cleaving the C−Cl bond. The major competing process was formation of diallyl ethers; thus, the reactions were conducted with 1.5 equiv of the alcohol. These reactions constitute a rare example of the activation of allylic alcohols using a catalytic amount of transition metal complex, as well as a catalytic amount of Lewis acid.

In summary, two procedures have been developed for iridium-catalyzed allylic amination of allylic alcohols to form branched allylic amine products with high regio- and enantioselectivity. $Nb(OEt)_5$ was found to serve as an activator of the allylic alcohol in situ, and BPh_3 was found to act as an activator in catalytic amounts. Further investigation of the scope and mechanism of this process is ongoing.

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Note Added after ASAP Publication. Table 1, foonote *a* was corrected on May 29, 2007.

Supporting Information Available: Experimental procedures and spectroscopic data of the reaction products (PDF). This material is available free of charge via Internet at http://pubs.acs.org.

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