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Stereospecific Substitution of Allylic Alcohols To Give Optically Active Primary Allylic Amines: Unique Reactivity of a (P,alkene)Ir Complex Modulated by Iodide

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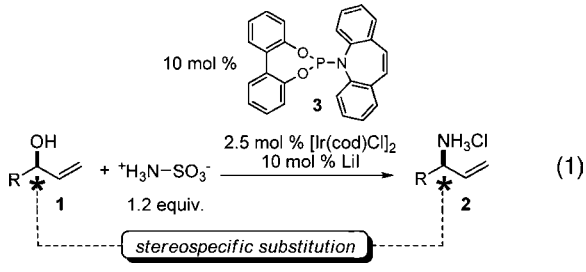
Abstract: A stereospecific allylic amination of unactivated secondary (2°)-allylic alcohols is reported. The primary (1°)-allylic amine can be isolated directly or protected in situ. Spectroscopic studies have shed light on the structure of the catalytically active Ir•(P,olefin)2I complex.

Allylic amines are versatile building blocks in organic synthesis in both academia and industry.[1] Two common methods have emerged for their enantioselective preparation. These include the addition of organometallic reagents to imines[2] and the displacement of allylic esters,[3a,b] alcohols,[3c] or carbonates[3d−m] with amines through enantioselective allylic substitution. An alternative strategy involves stereospecific substitution of optically active carbonates,[4a] imidodicarboxylates,[4b] and alcohols[4c] by amine nucleophiles. Indeed, numerous catalysts and approaches have been reported for the asymmetric synthesis of optically active secondary (2°)-allylic alcohols, such as the addition of vinyl-metal reagents to aldehydes,[5] ketone reductions,[6] allylic substitution of primary (1°)-allylic carbonates,[7] and lipase resolution.[8] However, methods involving the direct displacement of chiral alcohols by ammonia are altogether absent from the literature. Herein, we report the direct stereospecific displacement of unactivated 2°-allylic alcohols to afford optically active 1°-allylic amines (eq 1). The reaction is effected by treatment of optically active alcohol substrates, accessed by biocatalysis, with sulfamic acid in the presence of a catalyst generated from Ir(I) and achiral phosporamidite-olefin ligand **3** in the presence of LiI. In addition we provide an X-ray crystal structure of an Ir•(P,olefin)$_2$I complex that is catalytically competent.

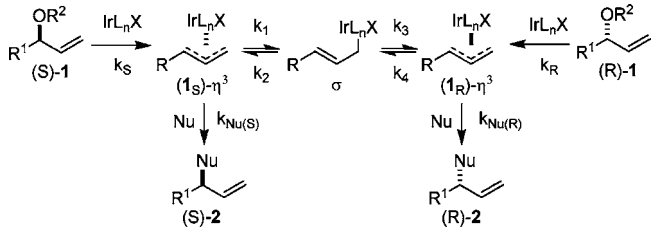


(1)

Much progress has been made recently in catalytic enantioselective allylic amination. In general, the starting materials for such processes are linear or branched allylic alcohols activated as the corresponding carbonates or esters. The products from the substitution reactions typically furnish 2°-amines or protected amines. There have been recent reports on the use of ammonia in the displacement reaction of 1°-allylic carbonates, which in order to avoid formation of secondary amines prescribe excess ammonia (100 equiv) or high dilution.[9] However, direct, enantiospecific transformation of easily accessible, optically active unactivated allylic alcohols to unprotected 1°-allylic amines has not been reported. In recent work we have documented the use of sulfamic acid as an inexpensive, easily handled ammonia equivalent that participates in displacement reactions in the presence of a unique catalyst incorporating a P-alkene ligand.[10] In light of the easy access to optically pure 2°-allylic alcohols, we sought to investigate whether an amination protocol could be developed involving stereospecific substitution of optically active allylic alcohols.

In 1999 Helmchen reported that a chiral Ir(I)-phosphoramidite complex catalyzed the displacement reaction of a racemic allylic acetate by sodium malonate, leading to product in 86% ee and 83% yield.[11] This observation suggests that in the Ir(I)-catalyzed displacement reactions of allylic nucleofuges equilibration of diastereomeric Ir-allyl intermediates occurs faster than nucleophilic attack (Scheme 1: (**1**$_S$)-η^3 ⇆ (**1**$_R$)-η^3 faster than $k_{Nuc(S)}$ or $k_{Nuc(R)}$). In that work, it was noted that the use of enantioenriched starting acetate (91% ee) with a catalyst incorporating $P(OPh)_3$ as ligand afforded product with 51% ee, which the authors suggested was indicative that the absolute rate of isomerization of allyl-Ir intermediates was slow.[12] In recent work, Hartwig has documented the stereospecific substitution of an allylic benzoate (98% ee) by phenoxide mediated by a chiral metallacyclic Ir-phosphoramidite catalyst to the corresponding ether (98% ee).[13] Our report of a case in which a racemic allylic alcohol is enantioselectively converted into an optically active amine underscores that, in the process with sulfamic acid, fast equilibration relative to substitution (or alkylation) is operative.[10] Helmchen and P. A. Evans have demonstrated with Ir[14] and Rh,[15] respectively, that the isomerization process can be inhibited by the proper selection of ligand with phosphites giving rise to stereospecific alkylation processes. At the outset of our studies however, we were concerned because the direct displacement reaction of alcohols by sulfamic acid had been noted to have strict requirements for a phosphoramidite-olefin ligand,[10] limiting potential variations of this parameter.

Scheme 1. Stereospecific Amination of Allylic Alcohols



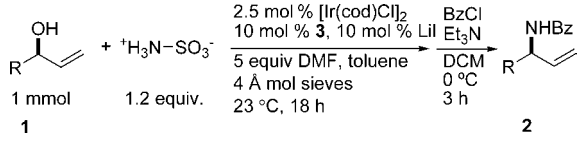
We first examined the simple, achiral phosphoramidite-olefin ligand **3** for the stereospecific substitution reaction of (*S*)-phenyl vinyl carbinol as a test substrate. In the typical experiment, alcohol, 1.2 equiv of sulfamic acid, [Ir(cod)Cl]$_2$, ligand, and 5 equiv of DMF

Table 1. Optimization of the Stereospecific Allylic Amination of (*S*)-Phenyl Vinyl Carbinol with Sulfamic Acid[a]

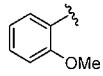
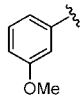
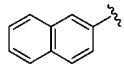
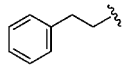
Entry	Ligand	Conditions	e.s. [%][b]	Yield [%]
1	**3**	THF	48	60
2	**3**[c]	THF	41	20
3	$P(OPh)_3$	THF	0	13
4	$P(2\text{-Fur})_3$	THF	0	13
5	**3**/$P(OPh)_3$[d]	THF	46	11
6	**3**	$^{i}Pr_2O$	66	33
7	**3**	CCl_4	57	19
8	**3**	PhMe	80	61
9	**3**	PhMe, LiI	90	65
10	**3**	PhMe, LiCl[e]	94	45
11	**3**	PhMe, LiBr[e]	89	26
12	**3**	PhMe, NaI[e]	>98	43
13	**3**	PhMe, KI[e]	>98	44
14	**3**	PhMe, CsI[e]	>98	46
15	**3**	PhMe, Bu_4NI[e]	>98	65
16	**3**	PhMe, $AgPF_6$[e]	–	0[f]
17	**3**	PhMe, LiI[e]	>98	70

[a] Reaction conditions: **1a** (0.5 mmol), $[Ir(cod)Cl]_2$ (2.5 mol %), ligand **3** (11 mol %), sulfamic acid (1.2 equiv), additive (10%), solvent (1 mL), DMF (5 equiv), 23 °C, 20 h. [b] Determined by chiral HPLC; absolute configuration determined by comparison with $[\alpha]_D$ values of known compounds. [c] $[Rh(cod)Cl]_2$ (2.5 mol %). [d] 5.5 mol % of each ligand. [e] 100 mg of 4 Å mol sieves added. [f] Starting material reisolated.

Table 2. Stereospecific Allylic Amination of Aromatic Allylic Alcohols



1 mmol 1.2 equiv. **1** **2**

Entry	Substrate (er)	R	Product er	e.s. [%][a]	Yield [%][b]
1	**1a** (95:5)		95:5	>98	70
2	**1b** (81:19)		81:19	>98	64
3	**1c** (99:1)		96:4	94[c]	64[d]
4	**1d** (62:28)		62:28	>98	61
5	**1e** (97:3)		96:4	97	60
6	**1f** (96:4)		96:4	>98	70
7	**1g** (99:1)		99:1	>98	63[d]
8	**1h** (95:5)		93:7	96[c]	63[c]
9	**1i** (99:1)		92:8	84[c]	46[c]
10	**1j** (96:4)		84:16	74[c]	52[d,e]

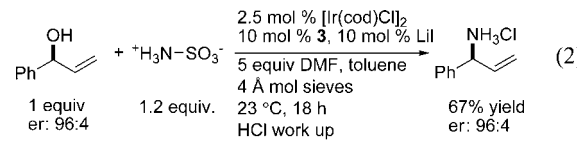
[a] Determined by chiral HPLC; absolute configuration determined by comparison with $[\alpha]_D$ values of known compounds. [b] Yield of isolated product. [c] *R*-enantiomer used. [d] Conducted on 0.5 mmol scale. [e] Conducted at 50 °C.

were employed. For ease of workup and analysis of enantiospecificity (e.s. = $(ee_{product}/ee_{substrate}) \cdot 100$),[16] it was convenient to protect the amine products as benzamides. As shown in entry 1 (Table 1) the displacement reaction proceeds with poor e.s. (48%) when ligand **3** was employed. A catalyst prepared *in situ* from $[Rh(cod)Cl]_2$ and ligand **3** provided product in only 41% e.s. and 20% yield (entry 2). Subsequent examination of other P-ligands that are good π-acceptors in the iridium catalyzed transformation, such as $(PhO)_3P$ and $(2\text{-Fur})_3P$, led to racemic product (entries 3 and 4).

On the basis of recent work by Reetz,[17] we also examined the combination of **3** and $P(OPh)_3$; however, product was isolated from the experiment in comparable 46% e.s. and lower yield (entry 5). The use of nonpolar solvents such as $i\text{-}Pr_2O$ or CCl_4 led to 66% and 57% e.s., respectively (entries 6 and 7). A promising result was obtained when toluene was employed, resulting in an increase in e.s. to 80% (entry 8). In order to further improve the process, we examined the use of various salts along with molecular sieves as additives (entries 9−17). As shown in Table 1, the presence of iodide (LiI, NaI, KI, CsI, Bu_4NI) uniformly leads to an increase in the optical purity of the isolated product. The combination of LiI (10 mol %) and powdered 4 Å mol sieves provides modest improvement in product yield (70%) and a dramatic increase in stereospecificity (>98% e.s., Table 1, entry 17). The generality of the stereospecific substitution process was then investigated (Table 2).

The allylic amination of alcohols with sulfamic acid proceeds with complete regioselectivity, and no di- or triallylated amines are observed.[8] As we have noted previously, the chemistry of (P,olefin)•Ir complexes with ligand **3** is complementary to that observed for phosphoramidite•Ir catalysts. Thus, for the enantioselective synthesis of amines and their derivatives (amides and urethanes) the latter prescribe 1°-allylic alcohols (activated as esters or carbonates) as substrates.[3,7,8] However, the single case reported for the enantioselective synthesis of a 1°-amine with sulfamic acid[10] requires the use of the isomeric 2°-allylic alcohol as substrate.

The allylic alcohols that may be employed as starting materials to give the corresponding amine can incorporate various aromatic substituents; these include electron-rich arenes (Table 2, entries 2 and 3), *o*-tolyl (entry 4), and heteroarenes (entries 6 and 7). The aromatic substrates gave good yields (60%−70%) and excellent enantiospecificity (e.s. 94% to >98%). For aliphatic substrates, it was found that the reaction of 5-phenylpent-1-en-3-ol (**1h**) goes to full conversion only if the reaction mixture was heated to 50 °C. At this temperature the product was isolated in good yield and excellent e.s. (entry 8). Other aliphatic substrates gave moderate yields and good stereospecificity (entries 9 and 10). To demonstrate the scalability of the procedure the reaction was conducted on preparative scale (6 mmol), from which the hydrochloride salt of the free amine was isolated (eq 2) in comparable stereospecificity and yield.



1 equiv er: 96:4 1.2 equiv. 67% yield er: 96:4 (2)

1a

In order to gain insight into the nature of the active catalyst, we carried out several spectroscopic investigations that include studies by one-dimensional and two-dimensional ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy, high-resolution mass spectrometry, and X-ray diffraction. Upon dissolution of $[Ir(cod)Cl]_2$ and 2 equiv each of

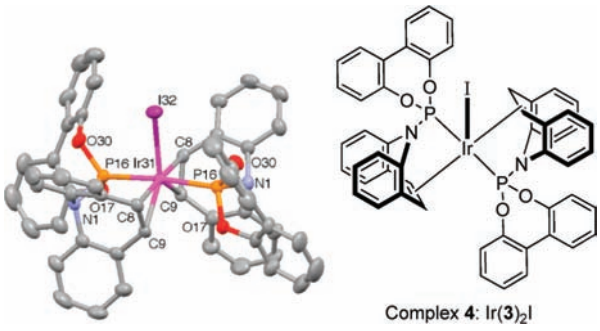


Figure 1. Crystallographic representation of iridium complex **4** and schematic ChemDraw structure.

phosphoramidite **3** and LiI (relative to Ir(I)) in $CDCl_3$, a color change was observed from orange/red to yellow over the course of 15 min. At this time point, no free ligand or unreacted $[Ir(cod)Cl]_2$ was noted by ^1H and ^{31}P NMR (see Supporting Information). The most prominent features of the newly formed complex were a single peak at 136.8 ppm in the proton decoupled ^{31}P spectrum and the diastereotopic H-Csp^2 signals at 4.9 and 4.2 ppm in the ^1H NMR, indicating *trans*-complexation of two phosphoramidite ligands **3** via both the phosphorus and the double bond. Layering the crude mixture of complex **4** with hexane led to crystals suitable for X-ray analysis. The obtained crystal structure verified the proposed *trans*-arrangement of ligands (see Figure 1) which is in contrast to related structures reported by Grützmacher and Dorta.[18] The bond lengths of the complexed alkenes are elongated to 1.44 Å, compared to 1.32 Å in iminostilbene,[19] and the Ir−C distances involving the alkene carbons are 2.189 and 2.194 Å. The iridium−phosphorus bonds are 2.28 Å long and together with the two Ir−C(8) bonds form a nearly perfect plane orthogonal to the Ir−I bond. The other alkene carbons, C(9), lie below this iridium−phosphorus−C(8) plane (additional details for **4** may be found in the Supporting Information).

Complex **4** is stable in solution ($CDCl_3$) for 2 days and could be purified by chromatography on silica gel with hexanes/diethyl ether as eluent under standard isocratic conditions. The off-white complex isolated may be employed in the reactions described in Table 2. For example, when **4** is employed for the reaction of substrate **1a**, product **2a** was isolated with excellent stereospecificity (>98% e.s.; compare with entry 1, Table 2: >98% e.s.) and comparable yield (65%; compare with entry 1, Table 2: 70%), confirming that **4** is catalytically competent. It is comparable to the complex formed *in situ* ($[Ir(cod)Cl]_2$, **3**, and LiI) as judged by ^{31}P NMR spectroscopy in $CDCl_3$: the complex prepared in situ δ 136.920 versus a solution of **4** δ 136.825.

In summary we have demonstrated the first general Ir-catalyzed stereospecific allylic amination of optically active, unactivated, allylic alcohols. The 1°-allylic amine can be isolated directly or protected *in situ* as part of the workup. The reaction is made possible because of the unique reactivity of a complex generated from Ir(I) and 2 equiv of a phosphoramidite-alkene ligand whose reactivity is modulated in the presence of LiI. Given the availability of optically active allylic alcohols through a variety of methods, the transformation we describe provides rapid entry to optically active allylic amines. Spectroscopic studies have shed light on the catalyst structure. Further studies are underway to clarify the pathway from substrate to allylic amine product, which will be reported as results become available.

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Supporting Information Available: Experimental procedures and spectral data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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