Enantioselective Allylic Amination

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Direct, Enantioselective Iridium-Catalyzed Allylic Amination of Racemic Allylic Alcohols**

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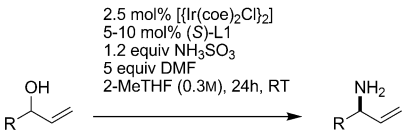
In memory of Keith Fagnou

Transition-metal-catalyzed asymmetric allylic substitution reactions constitute one of the most convenient approaches for the generation of optically active allylic amines.[1] The best solutions for the enantioselective synthesis of optically active amines from precursor allylic alcohols to date involve the use of primary allylic esters,[2a,b] carbonates,[2c–l] and phosphates[2m] as substrates. Substitution of a racemic mixture of secondary allylic alcohols to afford optically active amines has not been achieved to date.[3] This is a shortcoming given that these starting substrates are conveniently accessed by the addition of vinylorganometallic reagents to aldehydes. Herein, we document for the first time the enantioselective displacement of secondary racemic allylic alcohols with sulfamic acid to give directly primary amines in a reaction catalyzed by an optically active Ir-(P,alkene) complex [Eq. (1)].



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The use of allylic alcohols as substrates in allylic aminations has been limited by the poor aptitude of the hydroxy group as a leaving group. Several protocols which rely on high temperatures,[4] Lewis acids, or Brønsted acids[3a,5] have been developed. For example, Hartwig and co-workers reported the asymmetric amination of primary allylic alcohols activated by Lewis acids.[6] In the context of iridium-catalyzed allylic displacements, the use of branched secondary allylic alcohols as substrates has been limited, however, as they afford product amines in low enantioselectivity.[7] This can be circumvented through the implementation of a sequential Pd-catalyzed isomerization/Ir-catalyzed allylic substitution process.[8] Han and Singh have developed an iridium-catalyzed stereospecific decarboxylative allylic amidation of chiral branched benzyl allyl imidodicarboxylates.[9] However, absent from the reported work in this area is the use of racemic secondary allylic alcohols as the starting point for the preparation of optically active amines through an enantioconvergent process.

Recent reports on the use of ammonia as a nucleophile represent a significant advance, but overalkylation with accompanying formation of secondary amine products can be problematic.[10] In order to circumvent this, Kobayashi and Nagano have prescribed high catalyst loading and high dilution (0.03–0.04 M).[10c] Consequently, much attention has been devoted to the use of ammonia surrogates in the form of amides or imides.[1,10a,11]

We have been interested in this problem following our observation that sulfamic acid can serve as an ammonia surrogate in the direct displacement of secondary allylic alcohols to afford optically active primary amines.[12,13] Our disclosure described the direct displacement of allylic alcohols by sulfamic acid to produce racemic amines. We have documented a single case in which the racemic alcohol could be converted to the optically active amine in 70% *ee* using a catalyst generated from a 1:1 mixture of a P,alkene ligand and Ir.[12a]

Because the conversion of secondary allylic alcohols to afford optically active amines in an enantioconvergent manner is an unsolved problem,[14] we have opted to re-evaluate the reaction. We have chosen phenyl vinyl carbinol **1a** as a substrate in a variety of test reactions in which various ligands were examined with Ir^I (Table 1). In order to facilitate analysis, products were protected in situ as the corresponding benzamides. Following our previously reported conditions (2.5 mol% $[\{Ir(coe)_2Cl\}_2]$ (coe = cyclooctene, 5 mol% ligand (*S*)-L1 (Scheme 1), 1.2 equiv sulfamic acid in dimethylformamide (DMF) at room temperature for 24 h), product **2a** was isolated in 69% yield and 76% *ee* (Table 1, entry 1), consistent with the modest results previously reported.

Interestingly, however, we observed that increasing ligand loading was beneficial, leading to dramatic improvement in the enantioselectivity of the reaction process. Thus, under otherwise identical conditions, the use of 10 mol% (*S*)-L1 and 5 mol% Ir^I (ligand/Ir 2:1) furnished product **2a** in 96% *ee* and in 52% yield (Table 1, entry 2). In our initial report we had employed DMF as the reaction solvent, which is a suboptimal reaction medium in terms of potential preparative-scale applications. We thus examined the use of DMF as a cosolvent in combination with common organic solvents. To our delight, the use of 5 equiv of DMF was sufficient to obtain full

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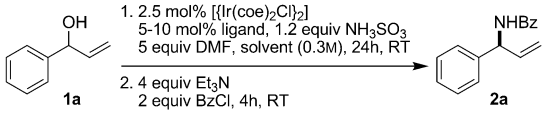
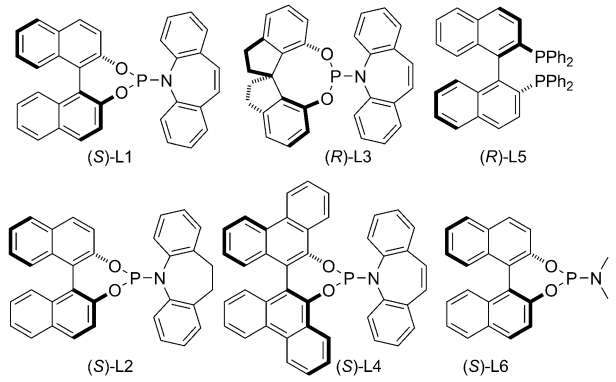
Table 1: Investigation of the enantioselective, Ir-catalyzed direct allylic amination reaction.



Entry	Ligand	Solvent	Yield [%][a]	*ee* [%][b]
1	(*S*)-L1 (5 mol%)	DMF	69	76
2	(*S*)-L1 (10 mol%)	DMF	52	96
3	(*S*)-L1 (10 mol%)	MeCN	64	90
4	(*S*)-L1 (10 mol%)	toluene	73	88
5	(*S*)-L1 (10 mol%)	acetone	53	98
6	(*S*)-L1 (10 mol%)	*i*PrOAc	75	97
7	(*S*)-L1 (10 mol%)	DCE	88	99
8	(*S*)-L1 (10 mol%)	CH_2Cl_2	58	97
9	(*S*)-L1 (10 mol%)	$CHCl_3$	89	99
10	(*S*)-L1 (10 mol%)	1,4-dioxane	83	95
11	(*S*)-L1 (10 mol%)	Et_2O	59	82
12	(*S*)-L1 (10 mol%)	THF	80	99
13	(*S*)-L1 (10 mol%)	2-MeTHF	77	99
14	(*S*)-L2 (10 mol%)	2-MeTHF	<5[c]	–
15	(*S*)-L3 (10 mol%)	2-MeTHF	30[d]	70
16	(*S*)-L4 (10 mol%)	2-MeTHF	33[d]	67
17	(*S*)-L5 (10 mol%)	2-MeTHF	<5[c]	–
18	(*S*)-L6 (10 mol%)	2-MeTHF	12[d]	93
19	(*S*)-L1 (2 mol%)	2-MeTHF	62[e]	99

[a] Yield of isolated product after purification by chromatography after 2 steps; Regioselectivity was >99:1 as shown by the ^{1}H NMR spectrum of the unpurified reaction mixture. [b] *ee* was determined by HPLC. [c] Recovered starting material. [d] Incomplete conversion. [e] Reaction was performed using 0.5 mol% $[Ir(coe)_2Cl]_2$.



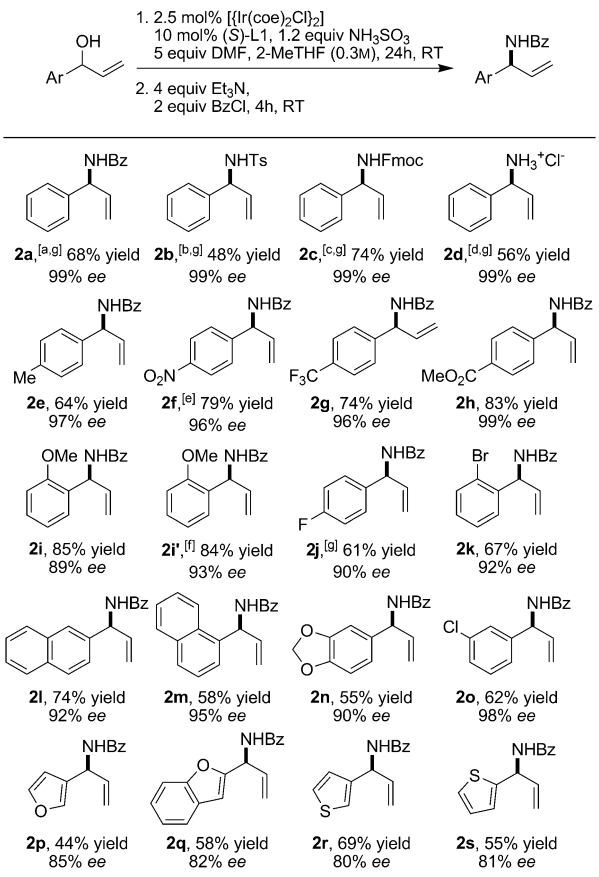
Scheme 1. Selected ligands examined for the enantioselective, iridium-catalyzed direct allylic amination of allylic alcohols with sulfamic acid.

conversion to the allylic amine with a wide range of cosolvents. As can be seen in Table 1, with the exception of diethyl ether and toluene, the reaction enantioselectivity is relatively insensitive to the nature of the media employed (entries 3–13). When the substitution reactions were conducted in acetonitrile or acetone, the product was obtained with high enantioselectivity, albeit in moderate yields (Table 1, entries 3 and 5). Better results were obtained with chlorinated solvents (1,2-dichloroethylene (DCE), CH_2Cl_2, $CHCl_3$), 1,4-dioxane, and THF (Table 1, entries 7–10 and 12). Industry-preferred solvents such as isopropyl ethyl acetate and 2-methyltetrahydrofuran (2-MeTHF) were also suitable cosolvents, giving the product in 75% yield, 97% *ee* and 77% yield, 99% *ee*, respectively (Table 1, entries 6 and 13). We opted to employ the environmentally friendly 2-methyltetrahydrofuran[15] as our preferred solvent in establishing the scope of the process.

With the optimized conditions for the conversion of secondary alcohols to amines in hand, we evaluated a collection of optically active ligands for Ir^I, in order to establish whether (*S*)-L1 was particularly unique. Consistent with our previous observations with this class of P,alkene ligands,[16] we found that the use of ligand (*S*)-L1 provided the product with the highest selectivity and yield. When the saturated analogue (*S*)-L2 was employed, only trace amounts of the products were observed (Table 1, entry 14). The results are consistent with the alkene acting as a donor group; we surmise that it is labile and following exchange with substrate, alkene ionization is initiated to give rise to an allyl iridium intermediate.[12b] Investigation of a variety of analogous ligands incorporating a substituted BINOL scaffold resulted only in slower reaction rates and diminished enantioselectivity. Employing phosphoramidites prepared from (*R*)-SPINOL[17] ((*S*)-L3) as well as the more bulky (*S*)-10,10′-dihydroxy-9,9′-biphenanthryl[18] ((*S*)-L4), we observed moderate reaction rates and modest enantioselectivity (Table 1, entries 15–16). The use of Ir complexes derived from (*S*)-BINAP ((*S*)-L5) or (*S*)-Monophos ((*S*)-L6) afforded only traces of products (Table 1, entries 17 and 18). Finally, we note that the reactions may be conducted with 0.5 mol% catalyst loading ([$\{Ir(coe)_2Cl\}_2$]) furnishing product in 62% yield and 99% *ee* (Table 1xtabr1 > , entry 19). It is worth noting that all reactions proceeded with complete regioselectivity and with formation of the monoallylated amines exclusively. The reaction was performed on a one-gram scale to give the isolated product in 68% yield and 99% *ee* (Scheme 2, **2a**). The free amine could be protected in situ as 9-fluorenylmethoxycarbonyl (Fmoc), *N*-tosyl, and hydrochloride salt derivatives[12b,19] in 74, 48, and 56% yield, respectively (**2b–d**). The scope of the allylic substitution reaction with respect to aromatic allylic alcohols is summarized in Scheme 2. A wide range of electron-rich and electron-deficient aromatic allylic alcohols were all found to be suitable substrates giving rise to the product in moderate to good yields and good to high enantioselectivity. The enantioselectivity of the product formed could be fine-tuned by employing different cosolvents as demonstrated with **2i** and **2i′** (89% *ee* in 2-MeTHF vs. 93% *ee* in $CHCl_3$).

Under the conditions described above with generation of the catalyst in situ and a ligand/Ir ratio of 2:1, aliphatic allylic alcohols reacted sluggishly giving the products in good enantioselectivity, albeit in low yield.[20] However, the use of a protocol prescribing a ligand/Ir ratio of 1:1 provides products in good to high selectivity and synthetically useful yields, as shown in Scheme 3.

In summary, we report the direct enantioselective iridium-catalyzed substitution of racemic secondary allylic alcohols using sulfamic acid to give optically active primary amines. The salient features of the method include the preparation of amine products through the displacement of the alcohols without the need for prior activation and without resorting to high dilution or use of a protected amine. Additionally, the

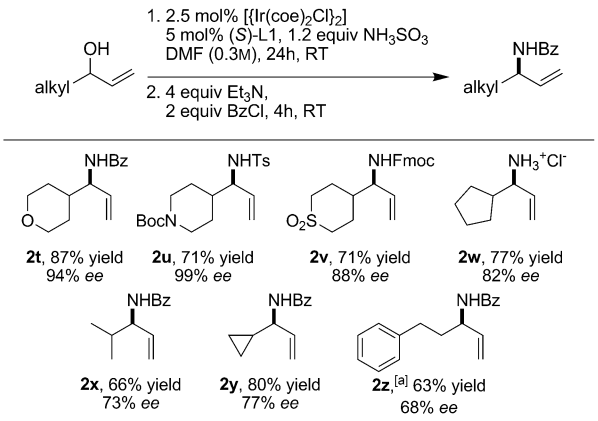


Scheme 2. Scope of the direct, enantioselective, allylic amination of aromatic racemic allylic alcohols. Yield of the isolated product after purification by chromatography after 2 steps; regioselectivity was >99:1 as shown by the ^{1}H NMR spectrum of the unpurified reaction mixture after full consumption of starting material **1**; the *ee* value was determined by HPLC. [a] Reaction performed on 1 g scale. [b] Protection was performed with 4 equiv NEt_3 and 2 equiv of TsCl. [c] Protection was performed with 4 equiv NEt_3 and 2 equiv of FmocCl. [d] Generated upon treatment of amine with 2 M HCl in Et_2O. [e] Generated upon treatment of amine with 1.2 equiv of NaH and 1.2 equiv of BzCl. [f] Reaction performed in $CHCl_3$ as cosolvent. [g] Absolute configuration assigned by comparison with known compounds.

use of the racemic branched allylic alcohols as starting materials is convenient as a consequence of their ease of synthesis. The study also illustrates intriguing effects of the ligand/Ir ratio on the Ir catalyst. Further investigations are ongoing in order to understand the mechanism of activation and to identify a wider range of suitable nucleophiles for the intermediate putative allylyridium species generated directly from racemic allylic alcohols.

Experimental Section

General procedure: [{Ir(coe)$_2$Cl}$_2$] (11.2 mg, 13.0 μmol), ligand (*S*)-L1 (26.0 mg, 50.0 μmol), and sulfamic acid (60.0 mg, 0.610 mmol, 1.20 equiv) were placed in a screw-capped vial (2.00 mL) or round-bottom flask with a magnetic stir bar. The reaction vessel was purged with argon. Dimethylformamide (5.00 equiv, 0.200 mL) was added followed by 2-methyltetrahydrofuran (1.00 mL). The reaction mixture was stirred vigorously for 10 min during which time the solution turned dark red. Allylic alcohol **1** (0.500 mmol, 1.00 equiv) was added as a solution in 2-methyltetrahydrofuran (0.500 mL) to the reaction mixture which resulted in a yellow solution. The reaction mixture was stirred at room temperature for 24 h. Triethylamine (0.300 mL, 2.00 mmol) was then added followed by benzoyl chloride (0.110 mL, 1.00 mmol), and the resulting mixture was stirred at room temperature for 4 h. The product was obtained by flash chromatography of the reaction mixture diethyl ether/hexane.



Scheme 3. Scope of enantioselective, direct, allylic amination of aliphatic allylic alcohols. Yield of the isolated product after purification by chromatography after 2 steps; regioselectivity was >99:1 as shown by the ^{1}H NMR spectrum of the unpurified reaction mixture; *ee* was determined by HPLC. [a] Absolute configuration was assigned by comparison with reported compounds.

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[20] Incomplete conversion with concomitant formation of elimination reaction to form the diene as a by-product was observed.

