

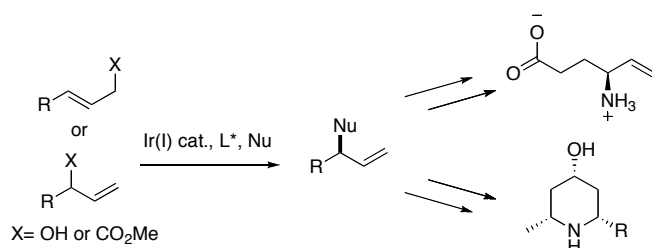
Recent Advances in Ir-Catalyzed Allylic Substitution: Strides Toward Atom Economy and Applications in Synthesis

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ABSTRACT



Ir-catalyzed allylic substitution reactions have emerged as the premier methodology for forming α allyl compounds. The generality of this method for affording desirable branched products with high regio- and stereoselectivity using a new class of N- and O- nucleophiles, as well as the use of the alcohols as leaving groups has been recently illustrated. Advances toward a more robust catalyst system as well as strides towards atom economy and applications in recent total synthesis will be highlighted.

Iridium-catalyzed enantioselective allylic substitutions have developed as the method of choice for the construction of chiral α -branched allylic compounds. These reactions involve S_N2' nucleophilic attack on a Ir-allyl intermediate most commonly formed from a linear carbonate or ester (Figure 1). The mechanism of these reactions involves an iridium I/III catalytic cycle. As shown in Scheme 1, the Ir(I) catalyst **I** nucleophilically attacks an allylic substrate to eliminate the leaving group X and form an Ir(III) allylic intermediate **II**. An external nucleophile attacks in an S_N2' fashion on the coordinated allyl to generate the olefin-coordinated Ir(I) complex **III**. Finally, dissociation of the olefin from iridium completes the catalytic cycle and regenerates the catalyst.

Some key advantageous features of these transformations are i) broad generality with respect to allylic ester substrates and nucleophiles, ii) complementarity to Pd-catalyzed allylic substitutions in terms of high branched to linear ratios (**b**:**l**), iii) simplicity and accessibility of effective chiral ligands, and iv) consistent high enantioselectivities. Since 2005, the scope

of various nucleophiles and new ligand frameworks for Ir-catalyzed allylic substitutions has been reviewed.¹

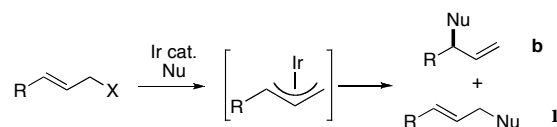
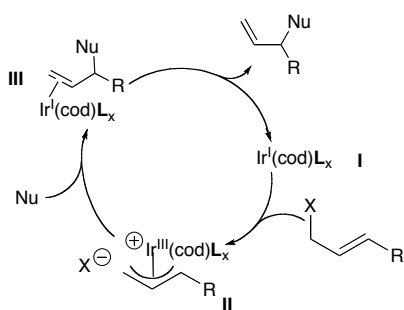


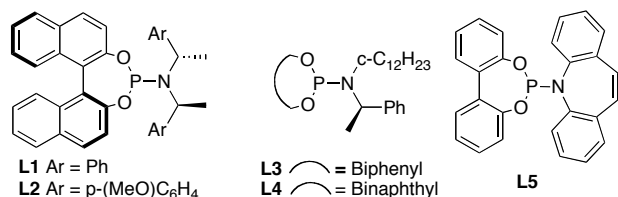
Figure 1. General Reaction for Ir-Catalyzed Substitutions.

However, advances toward a more robust catalyst system as well as strides towards atom economy and applications in recent total synthesis have not been highlighted, and hence are the subject of this review.

(1) a) Lu, Z.; Ma, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 258. b) Helmchen, G.; Dahnz, A.; Duebon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675. c) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, *20*, 3349. d) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, *11*, 1641.

Scheme 1. Catalytic Cycle for Allylic Substitutions

It has long been established that $[\text{Ir}(\text{cod})\text{Cl}]_2$ is an ideal metal precursor for this class of transformations in terms of generality and reactivity.² Many phosphorus-based ligands have been used to induce high chemoselectivity.³ The currently preferred catalyst system involves $[\text{Ir}(\text{cod})\text{L}]$ complexes with ligands **L** such as **L1-L4** shown in Figure 2 which were initially introduced by Feringa and coworkers (Figure 2). In these reactions the catalyst is typically generated in situ by addition of a base and an appropriate.⁴ However, in terms of stability, the $[\text{Ir}(\text{cod})\text{Cl}]_2$ precatalyst is prone to decomposition even in the presence of ligands via exposure to air due to the labilization of the cod ligand.

**Figure 2.** Ligands Utilized in Ir(I) Substitutions

Efforts toward a more robust Ir precatalyst was reported by Helmchen and coworkers in the design of a stable dibenzo[a,e]cyclooctatetraene (dbcot) Ir phosphoramidite complex (Table 1).⁵ The strong ligation of dbcot allows allylic substitutions to be run under ambient conditions. The regioselectivities of amination products using **L2** were found to be similar to those reported under inert conditions. Furthermore, substrates that were unreactive under ambient conditions reacted to afford products in high yields and chemoselectivity in the presence of the dbcot catalyst. Although the improved

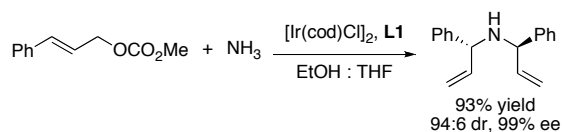
stability of $[\text{Ir}(\text{dbcot})\text{Cl}]_2$ allowed the reactions to be run in the presence of air without a significant change in regio- or enantioselectivity, the accompanying slight decrease in catalyst reactivity requires an increase in temperature to achieve short reaction times.

Table 1. “Open to Air” conditions for a robust Ir catalyst

| entry | substrate | x=precat. L | time (h) | yield | b:l ratio | ee % |
|-------|-----------|-------------|------------------|-------|-----------|------|
| 1 | 1a | cod | >70 | 0 | – | – |
| 2 | 1a | dbcot | 20 | 89 | 99:1 | 98 |
| 3 | 1a | dbcot | 3 ^a | 88 | 98:2 | 98 |
| 4 | 1b | cod | >70 | 0 | – | – |
| 5 | 1b | dbcot | 72 | 46 | 94:6 | 94 |
| 6 | 1b | dbcot | 3.5 ^a | 79 | 96:4 | 94 |

a) inert Ar gas conditions were used b) T = 50°C

Concomitant with the recent search for robust catalysts, significant research efforts have focused on increasing the atom economy of these Ir-catalyzed substitution reactions. Until recently, iridium-catalyzed amination relied on the use of amino surrogates such as *o*-nosylamines, phthalimides, trifluoroacetamides, and Boc-protected amines.⁶ While these reactions afforded secondary and tertiary allyl amines in high yields, they still required protected N- and O- nucleophiles, thereby requiring multiple synthetic steps for protection and deprotection. However, Hartwig and coworkers have shown that amination of allylic carbonates can be conducted using ammonia (Figure 3).⁷ While the initial goal of this methodology was to obtain primary allylic amines, the symmetrical diallylamine was instead formed in high yield and excellent ee. This is a rare example of the use of ammonia as a nucleophile in any type of metal catalyzed allylic substitution reaction.

**Figure 3.** Diallylation of Ammonia

These diallylamines are useful as they are easily transformed into chiral heterocycles by employing ring closing metathesis and subsequent hydrogenation. This

(2) See reference 1b and references therein.

(3) Polet, D.; Alexakis, A.; Tissot-Croset, K.; Corminboeuf, C.; Ditrich, D. *Chem. Eur. J.* **2006**, *12*, 3596-3609.

(4) Kiener, C. A.; Shu, C.; Incarvito, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14272.

(5) Spiess, S.; Welter, C.; Franck, G.; Taquet, J. P.; Helmchen, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 7652-7655

(6) Weihofen, R.; Tverskoy, O.; Helmchen, G.; *Angew. Chem. Int. Ed.* **2006**, *45*, 5546.

(7) Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949-3952

methodology has already been applied to the synthesis of natural products and organocatalysts.⁸

Furthermore, Hartwig and coworkers demonstrated the direct Ir-catalyzed allylic amination of linear alcohols, thereby eliminating the synthetic transformation of the linear alcohol to a carbonate.⁹ A stoichiometric amount of a Nb(OEt)₅ (a Lewis acid) was used to activate the alcohol, which allowed for the formation of various branched allylic amine products with high regio- and enantioselectivity. As shown in Table 2, these reactions were general with respect to the electronics on the amine and on the substituted olefin, affording allylamines in modest to good yields and high enantioselectivities. Alternatively, a substoichiometric amount of BPh₃ also afforded the products with similar chemoselectivity. The nucleophiles used for the transformation with BPh₃ were limited to aniline derivatives, although both aliphatic and aromatic substitution are tolerated on the olefin.

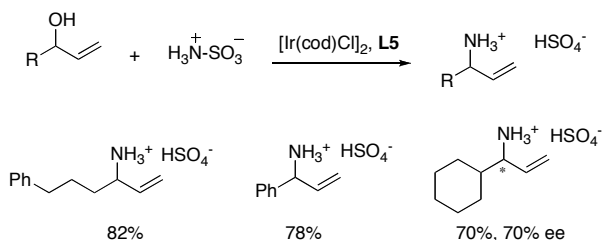
Table 2. Lewis Acid Activation of Allylic Alcohols

| R ₁ | R ₂ | Lewis Acid | yield (%) | b:l | ee (%) |
|----------------|------------------------------------|-----------------------------------|-----------|-------|--------|
| Ph | p-MeOC ₆ H ₄ | Nb(OEt) ₅ ^a | 84 | 96:4 | 89 |
| Ph | p-ClC ₆ H ₄ | Nb(OEt) ₅ ^a | 82 | 96:4 | 87 |
| Ph | Bn | Nb(OEt) ₅ ^a | 72 | 96:4 | 93 |
| propyl | Ph | Nb(OEt) ₅ ^a | 70 | 92:8 | 90 |
| Ph | p-MeOC ₆ H ₄ | BPh ₃ ^b | 72 | 94:6 | 93 |
| Ph | p-ClC ₆ H ₄ | BPh ₃ ^b | 53 | >94:6 | 92 |

a) Stoichiometric L.A. b) 8 mol% L.A.

Combining the atom economy of ammonia as a nucleophile and employment of the alcohol directly, Carreira and coworkers reported that sulfamic acids could react as ammonia equivalents with the unprotected alcohols (Scheme 2).

Scheme 2. Allylic Amination using Sulfamic Acid



(8) a) Spiess, S.; Berthold, C.; Weihofen, R.; Helmchen, G. *Org. Biomol. Chem.* **2007**, *5*, 2357. b) Lee, J. H.; Shin, S.; Kung, J.; Lee, S. *J. Org. Chem.* **2007**, *72*, 7443.

(9) Yamashita, Y.; Gopalarathnam, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7508-7509

This methodology transforms branched racemic α-alcohols exclusively into branched enantioenriched primary amines.¹⁰ The first example of enantioselective formation of a branched primary amine demonstrated with a cyclohexyl substrate required a chiral derivative of **L5**, however, this is the only enantioselective example reported. Development of a ligand system that will allow better stereoselection to primary amines would be complementary to Pd-catalyzed methodology that affords similar transformations for internal olefin substrates.^{1a}

The state of the art O-nucleophiles that are employed to Ir-catalyzed allylic substitutions are siloxanes that act as hydroxide equivalents. This is a significant advance over the previous methodology which afforded the chiral branched alcohols only through deprotection of benzyl ethers formed via alkoxide nucleophiles. The utility of Ir-catalyzed allylic alcohol formation was therefore limited as there are few methods for selective deprotection of benzyl ethers in the presence of terminal olefins. However, Carreira and coworkers demonstrated facile access to branched chiral alcohols upon mild deprotection of the resulting siloxanes with minimal stereoerosion of the formed chiral center (Table 3).¹¹ Development of conditions for water or hydroxide as nucleophiles would further improve atom economy for alcohol formation.

Table 3. Siloxanes as Hydroxide equivalents

| R | Nu | Yield (%) | b:l | ee |
|-------------------------------------|--------|-----------|-------|----|
| Ph | TBSOK | 79 | 97:3 | 98 |
| Ph | TIPSOK | 64 | 86:14 | 99 |
| p-OMe-C ₆ H ₅ | TESOK | 75 | 99:1 | 95 |
| n-propyl | TESOK | 65 | 99:1 | 95 |

Recently, allylic etherification was achieved through the use of a variety of aliphatic alcohols as nucleophiles forming ethers in excellent regio- and enantioselectivity (Table 4).¹² Hartwig and coworkers extended the scope of both alcohols and substituted olefins to include aliphatic as well as aryl substituents. The presence of a substoichiometric amount of alkyne is required to poison small amounts of an Ir species that facilitates isomerization of the products to the enol ether. Prior to this methodology, allylic etherification required use of zinc or alkali metal alkoxides in order to achieve modest yields and enantioselectivities.¹³

(10) Defieber, C.; Ariger, M.; Moriel, P.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 3139-3143

(11) Lyothier, I.; Defieber, C.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 6204.

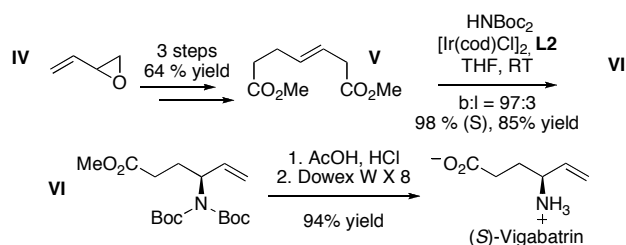
(12) Ueno, S.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2008**, *47*, 1928

(13) a) Roberts, J. P.; Lee, C. *Org. Lett.* **2005**, *7*, 2679. b) Lopez, F.; Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 3426.

Table 4. Allylic Etherification of Acetates

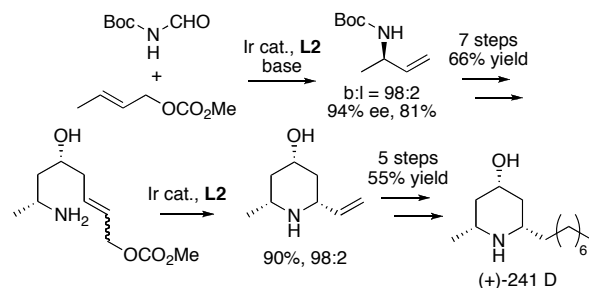
| R | time (h) | b:l | yield (%) | ee% |
|---------------------|----------|------|-----------|-----|
| Bn | 22 | 99:1 | 68 | 93 |
| n-hexyl | 40 | 99:1 | 71 | 91 |
| N-Boc-4-piperidinyI | 50 | 99:1 | 66 | 90 |
| TBDMS | 40 | 98:2 | 85 | 98 |

As discussed in the introduction, Ir-catalyzed allylic substitution is the leading method for formation of branched chiral allylic compounds. Not surprisingly, this methodology has recently been applied in the synthesis of a variety of biologically active molecules. Helmchen and coworkers demonstrated Ir-catalyzed allylic amination as a key transformation in the synthesis of (*S*)-Vigabatrin, an anti-epilepsy drug (Scheme 3).¹⁴ Employing vinyloxirane **IV** as a starting material and converting it to the linear carbonate **V** as previously reported, the allylic amination step proceeded in 85% yield with high regio- and enantioselectivity (97:3, 98%). The overall yield of (*S*)-Vigabatrin (**VI**) was 51% over five steps.

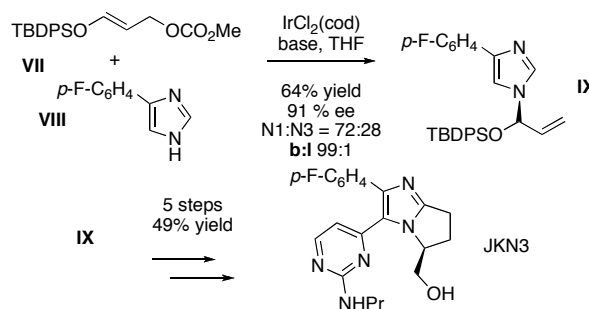
Scheme 3. Ir-Catalyzed Amination en route to (*S*)-Vigabatrin

In a synthesis of alkaloid (+)-241D, a potent inhibitor for nicotine receptors, Helmchen and coworkers again applied asymmetric allylic amination for both the initial construction of the stereocenter, as well as for the final ring closing step (Scheme 4).¹⁵ The first stereocenter was formed in good yield (81%) and excellent ee (94%). In the ring-closing step, either epimer could be obtained depending on ligand selection. For the synthesis of the desired (+)-241D alkaloid, use of the matched ligand afforded the intramolecular allylic amination product in 90% yield with good regioselectivity (98:2). This

example highlights the power of ligand-controlled regioselectivity for allylic amination.

Scheme 4. Synthesis of (+)-241D

Very recently the incorporation of less electron rich N-nucleophiles such as guanines, purines and other azoles has been developed for allylic amination.¹⁶ As depicted in Scheme 5 the synthesis of c-jun N-terminal kinase 3 (JKN3) inhibitor was completed using allylic amination of allylic ester **VII** with imidazole **VIII** as the nucleophile to form the allylated intermediate **IX** (Scheme 5). The imidazole was selectively allylated at N3 over N1, and the branched product was obtained with high selectivity and enantioselectivity. The formal synthesis of was completed over seven steps with an overall yield of 20%.

Scheme 5. Formal Synthesis of JKN3

In all, this review has highlighted recent improvements toward atom economy for Ir-catalyzed allylic amination and etherification reactions. Additionally, the design of air stable Ir catalysts allows these reactions to be conducted on the benchtop. Furthermore, efficient utilization of these transformations in a number of recent syntheses of biologically active compounds has been presented. As this methodology streamlines synthetic sequences for forming this class of chiral allylic olefins, it is expected to find increasing future applications in the synthesis of natural products.

(14) Gnamm, C.; Franck, G.; Miller, N.; Stork, T.; Broedner, K.; Helmchen, G. *Synthesis* **2008**, *20*, 3331.

(15) Gnamm, C.; Krauter, C. M.; Broedner, K.; Helmchen, G. *Chem. Eur. J.* **2009**, *15*, 2050.

(16) Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, ASAP