Regioselective Allylation

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Primary *tert*- and *sec*-Allylamines via Palladium-Catalyzed Hydroamination and Allylic Substitution with Hydrazine and Hydroxylamine Derivatives**

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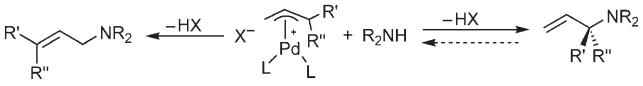
The challenge of controlling the regiochemistry of palladium-catalyzed allylic substitution by choice of ancillary ligand has a long history. Much attention has been focused on controlling regiochemistry because formation of the more substituted product could be developed into a mild route to *sec*- and even *tert*-alkylamines (Scheme 1). Åkermark and co-workers



Scheme 1.

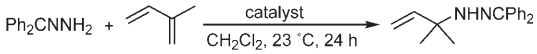
reported that attack can occur at the more substituted position of a prenyl complex, but that the reversibility of this attack ultimately leads to formation of the less substituted amine in many cases.[1] More recently, Hou and co-workers reported a ligand for palladium that causes benzylamine to add irreversibly to form secondary and tertiary *N*-alkyl *sec*-butylamines,[2] and Yudin and co-workers have shown that the attack by aziridine is irreversible and that *tert*-alkyl-substituted aziridines can be prepared by allylic substitution.[3,4]

During studies to develop the scope of the hydroamination of dienes,[5–7] we found that the reactions of hydrazine and hydroxylamine derivatives occur irreversibly at the more substituted position of both prenyl and crotyl palladium intermediates. We explored this transformation further because, unlike the products from additions of aziridines,[3,4] the products from addition of hydrazine and hydroxylamine derivatives could be readily transformed into primary *tert*-alkylamines or *sec*-alkylamines. The synthesis of primary amines containing tertiary alkyl groups is challenging because many of the conventional methods, such as nucleophilic substitution and additions to imines, are difficult to conduct at tertiary electrophiles and at ketimines,[8,9] and few catalytic reactions have been developed that form *tert*-alkyl-substituted amines.[10,11]

Herein we report our studies on the reactions of hydrazine and hydroxylamine derivatives to form allylamine products from reaction at the more hindered site of aliphatic dienes or allylic esters. This regioselectivity was observed in the presence of palladium catalysts bearing a range of bisphosphine ligands. Thus, this regioselectivity is controlled by the reagent and provides a versatile synthesis of *sec*- and *tert*-allylamines by palladium-catalyzed additions or substitutions, with subsequent N–N or N–O bond cleavage.

While studying the reactions of hydrazine derivatives with isoprene as an avenue to expand the scope of the hydroamination of dienes,[5–7] we found that these reactions formed the product in which the C–N bond is formed between the hydrazone group and the most substituted carbon atom of the diene. Table 1 shows these reactions catalyzed by palladium

Table 1: Effect of catalyst components on the hydroamination of isoprene with benzophenone hydrazone.[a]



Entry	Pd precursor	Ligand	Yield [%][b]
1	1% [{Pd(η³-allyl)Cl}₂]	2% xantphos	95
2	1% [{Pd(η³-allyl)Cl}₂]	2% dpephos	92
3	1% [{Pd(η³-allyl)Cl}₂]	2% binap	60
4	1% [{Pd(η³-allyl)Cl}₂]	2% dppf	77
5	2% $Pd(TFA)_2$	2% xantphos	79
6	1% $[Pd_2(dba)_3]\cdot CHCl_3$	2% xantphos	4
7	2% $[Pd(PPh_3)_4]$	–	3

[a] Reaction conditions: 0.5 mmol benzophenone hydrazone, 0.5 mmol isoprene, 0.5 mL CH_2Cl_2, 24 h at 23 °C. [b] GC yields. Ligand abbreviations: xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, dpephos = bis(2-diphenylphosphinophenyl)ether, dppf = 1,1′-bis(diphenylphosphino)ferrocene, binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl, TFA = trifluoroacetate, dba = *trans*,*trans*-dibenzylideneacetone.

complexes containing a series of bidentate phosphine ligands. Analysis of the crude reaction mixtures by ^1H NMR spectroscopy revealed that the less substituted *N*-prenyl regioisomer was typically formed in less than 3% yield, regardless of the identity of the ligand in the catalyst. This regioselectivity contrasts that obtained from reactions of arylamines, even with the same catalyst.[5]

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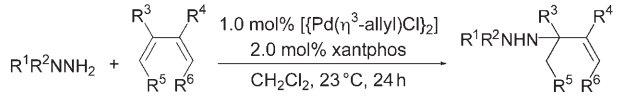
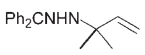
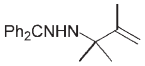
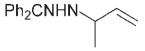
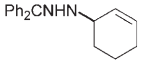
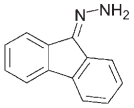
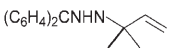
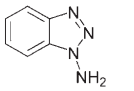
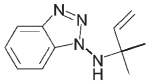
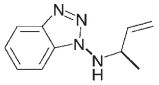
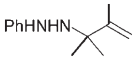
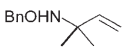
Consistent with the high activity of palladium–xantphos complexes as catalyst for the hydroamination of 1,3-dienes with arylamines,[5] the reaction of benzophenone hydrazone with isoprene occurred in the highest yields when catalyzed by the combination of [{Pd(allyl)Cl}$_2$] and xantphos. Nevertheless, this reaction catalyzed by palladium complexes of several other bisphosphines or generated from alternative precursors formed the hydroamination product in substantial yields. The addition of HCl as an acid cocatalyst had no significant impact on the activity or regioselectivity of the reaction.[12]

Studies on the scope of the hydroamination of dienes with benzophenone hydrazone and related nitrogen nucleophiles are summarized in Table 2. A variety of nucleophiles con-

Table 2: Palladium-catalyzed hydroamination of acyclic and cyclic 1,3-dienes with H_2NX (X = N, O) nucleophiles.[a]



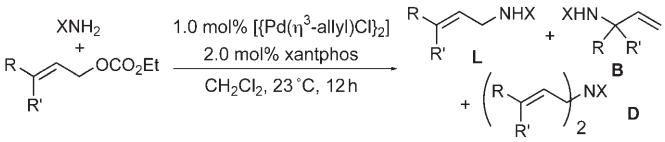
Entry	Nucleophile	1,3-Diene	Product	Yield [%][b]
1	Ph_2CNNH_2			95
2				90
3				89
4				98
5				96
6				97
7				88
8				78
9[c]	$BnONH_2$			76

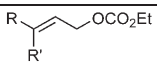
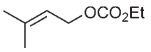
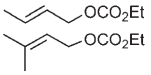
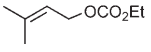
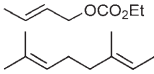
[a] Reaction conditions: 1.0 mmol H_2NX nucleophile, 1.0 mmol diene, 1.0 mL CH_2Cl_2. [b] Yield of isolated product (average of two runs). [c] THF and d*t*Bu-xantphos were used in the place of CH_2Cl_2 and xantphos.

taining an N–N or N–O bond underwent addition to 1,3-dienes to produce the branched addition product in excellent yields. Benzophenone hydrazone, fluorenone hydrazone, 1-aminobenzotriazole, and phenylhydrazine all reacted with acyclic 1,3-dienes to yield the corresponding branched monoallylation products in excellent yields. *O*-benzylhydroxylamine also reacted with isoprene to yield the branched monoallylation product. Reactions of this hydroxylamine conducted in dichloromethane or toluene yielded predominantly the diallylation product, but reactions in tetrahydrofuran occurred with excellent selectivity for the branched, monoallylation product. Because the catalyst generated from xantphos was poorly soluble in tetrahydrofuran, these reactions were conducted with the catalyst generated from 2,7-di-*tert*-butyl-9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene (d*t*Bu-xantphos).

Because catalytic amination of allylic esters is likely to occur through the same η^3-allylpalladium complexes as the hydroamination of dienes, we examined the addition of benzophenone hydrazone to ethyl 3-methylbut-2-enyl carbonate (Table 3). This substitution reaction formed only the branched regioisomer after 12 h at room temperature in the presence of the catalyst generated from xantphos and [{Pd-

Table 3: Palladium-catalyzed addition of H_2NX nucleophiles to allylic esters.[a]



Entry	XNH_2		Conv. [%][b]	b/l/d[c]	Yield [%][d]
1	Ph_2CNNH_2		100	98:2:0	98
2			100	83:17:0	77[e]
3	$BnONH_2$		100	95:5:0	90
4	Ph_3CONH_2		100	90:10:0	75
5			100	85:15:0	82
6			100	85:15:0	76

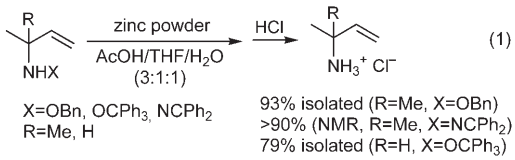
[a] Reaction conditions: 1.0 mmol benzophenone hydrazone or *O*-tritylhydroxylamine or 1.3 mmol *O*-benzylhydroxylamine, 1.0 mmol allylic carbonate, 1.0 mL CH_2Cl_2, 12 h at 23 °C. [b] Determined by GC. [c] Branched/linear/diallylation. [d] Yield of the isolated branched regioisomer (average of two runs). [e] Full conversion was observed after 2 h; the b/l ratio decreased with extended reaction times.

(allyl)Cl}$_2$]. Like the hydroamination of isoprene, this allylic substitution favored the branched isomer with catalysts generated from all ligands tested (dpephos, binap, dppf, dpppent, and xantphos; see the Supporting Information). The identity of the leaving group of the allylic ester did affect the regioselectivity. A comparison of the reactions of the two regioisomers of prenyl ethyl carbonate revealed some memory effect,[13,14] and significant amounts of linear product were observed from reactions of prenyl acetates and phosphates. Nevertheless, reactions of allylic carbonates formed the branched products selectively.

Table 3 shows the reactions of benzophenone hydrazone, *O*-benzylhydroxylamine, and *O*-tritylhydroxylamine with a selection of alkyl-substituted allylic carbonates to form the branched substitution products. Additions of all three nucleophiles to prenyl ethyl carbonate yielded the branched regioisomer in good to excellent yield of isolated product (Table 3, entries 1,3,4). Reactions of *O*-tritylhydroxylamine with phenyl ethyl carbonate, but-2-enyl ethyl carbonate, and geraniol ethyl carbonate also yielded the branched regioiso-

mer in good yield (Table 3, entries 4–6). Like the published reactions of aziridines, the regioselectivities of the reactions in Table 3 were independent of the reaction time.[4] By comparison, these reactions with morpholine formed the opposite regioisomeric products that result from substitution at the less hindered position of the allyl intermediate, just as reported with related bisphosphine ligands.[4] Reactions with cinnamyl carbonate catalyzed by [{Pd(η^3-allyl)Cl}$_2$] and xantphos in dichloromethane also formed the linear product.

Although hydroxylamine and hydrazine derivatives can be valuable for certain applications, we sought to exploit the regioselectivity from these N-allylations of hydrazine and hydroxylamine derivatives to generate the more common amine functionality. The reactions in Equation (1) show that



N-prenyl-*O*-benzylhydroxylamine, *N*-3-crotyl-*O*-tritylhydroxylamine, and *N*-prenyl benzophenone hydrazone all undergo cleavage to the primary amine with powdered Zn in acetic acid. The volatile amine products were isolated as the HCl salts.[15] Although cleavage of hydroxylamines and hydrazides by zinc is well-known,[16,17] cleavage of hydrazones under these conditions is less established.

In summary, we have demonstrated that the regioselectivity for the hydroamination of dienes and the amination of allylic esters with hydrazine and hydroxylamine derivatives favors formation of the branched *N*-allyl products. This process gains particular synthetic value because the benzophenone hydrazone and hydroxylamine products form secondary and tertiary carbinamines after N–X bond cleavage with zinc. Because the regioselectivity occurs for a wide variety of bisphosphines, this sequence provides opportunities to develop new classes of enantioselective amination, and studies on this process are ongoing.

Experimental Section

General procedure for the hydroamination of isoprene with benzophenone hydrazone (Table 1): In a drybox, [{Pd(allyl)Cl}$_2$] (1.9 mg, 0.0052 mmol), bisphosphine (0.010 mmol), isoprene (50 μL, 0.50 mmol), and benzophenone hydrazone (98 mg, 0.50 mmol) were placed into a small vial, dissolved in dichloromethane (0.50 mL), and sealed with a cap containing a PTFE septum. The reaction mixture was stirred at 23 °C for 24 h, and yields were determined by gas chromatography.

General procedure for the hydroamination of 1,3-dienes with H_2NX nucleophiles (Table 2): In a drybox, [{Pd(allyl)Cl}$_2$] (3.7 mg, 0.010 mmol), xantphos (11.6 mg, 0.020 mmol), 1,3-diene (1.0 mmol), the H_2NX nucleophile (1.00 mmol), and dodecane (10 μL, 0.044 mmol) as an internal standard were placed into a small vial, dissolved in dichloromethane (1.00 mL), and sealed with a cap containing a PTFE septum. The reaction mixture was stirred at 23 °C for 24 h. Upon completion, as determined by gas chromatography, the reaction mixture was purified by flash chromatography using a solvent gradient ranging from 3:97 v/v ethyl acetate/hexanes to 20:80 v/v ethyl acetate/hexanes.

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