Platinum-catalyzed hydrofunctionalization of unactivated alkenes with carbon, nitrogen and oxygen nucleophiles

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The transition metal-catalyzed addition of the X–H bond of a carbon, nitrogen or oxygen nucleophile across the C=C bond of an unactivated alkene (hydrofunctionalization) represents an attractive, atom-economical approach to the synthesis of carbocyclic and heterocyclic molecules and for the elaboration of ethylene and 1-alkenes. We have developed a family of Pt(II)-catalyzed protocols for the inter- and intramolecular hydrofunctionalization of unactivated alkenes with a range of H–X nucleophiles including β-diketones, indoles, amines, carboxamides and alcohols. These transformations display good functional group compatibility, low moisture sensitivity, and often good generality.

Introduction

Simple alkenes are one of the most versatile and important functional groups utilized in the synthesis of complex organic molecules.[1] Unactivated alkenes also constitute one of the most important carbon feedstocks employed in the synthesis of commodity chemicals.[2] For these reasons, the development of efficient and selective methods for the elaboration of unactivated alkenes remains an important challenge in both organic synthesis and homogeneous catalysis. Notable methods for the elaboration of unactivated alkenes in both small- and large-scale synthesis include oxidation to form carbonyl compounds, epoxides or diols,[2,3] metathesis to form acyclic, carbocyclic or heterocyclic alkenes,[4] and hydrofunctionalization to form functionalized alkanes.[2,5]

A particularly challenging subset of alkene hydrofunctionalization involves the addition of the H–X bond of a carbon or heteroatom nucleophile across the C=C bond of an unactivated alkene. Included in this group of H–X nucleophiles are activated methylene compounds, electron-rich arenes, amines and alcohols. Although hydrofunctionalization of alkenes with H–X nucleophiles has been achieved in the presence of radical initiators[6] or Lewis[7] or Brønsted acid-catalysts,[8] these transformations suffer from myriad limitations including poor selectivity, limited scope, and/or poor functional group compatibility. Rather, selective hydrofunctionalization of unactivated alkenes with H–X nucleophiles has traditionally required activation of the alkene with a stoichiometric amount of an electrophile such as Hg(II) followed by reduction in a subsequent step with an activated metal or metal hydride reagent.[9]

Transition metal catalysis represents a potential means to achieve the selective hydrofunctionalization of unactivated alkenes with H–X nucleophiles under mild conditions. However, at the time we began our investigation of Pt(II) chemistry (~2003), effective protocols remained scarce. For example, catalytic alkene hydroalkylation had been achieved only in the case of 3-butenyl- or 4-pentenyl ketones (see below)[10–13] or for activated C=C bonds such as allenes,[14] 1,3-dienes,[15] or alkylidenecyclopropanes.[16]

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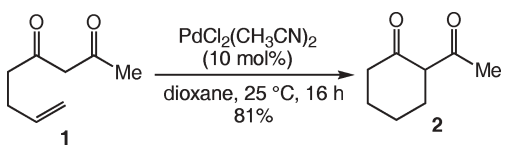
Catalytic hydroarylation of unactivated alkenes was restricted to arenes that possessed a suitable directing group or that were disposed to the formation of a stable metal–carbene intermediate.[17] The corresponding transformations employing unfunctionalized arenes typically required forcing conditions and/or a large excess of arene.[18] Although hydroamination of non-conjugated alkenes had been achieved under mild conditions employing d^0-lanthanide metallocene[19] or amido[20] catalysts,[21] the synthetic utility of these protocols was compromised by the excessive oxophilicity of the catalysts. Conversely, hydroamination catalyzed by late transition metal complexes required forcing conditions[22] or was restricted to conjugated alkenes[23,24] or allenes.[21,25] Similarly, catalytic alkene hydroalkoxylation was restricted to *o*-alkenyl phenols[26] or activated C=C bonds such as conjugated dienes[27] or allenes.[25]

In response to the limitations associated with alkene hydrofunctionalization, we initiated a program directed toward the development of late transition metal-catalyzed protocols for the hydrofunctionalization of unactivated alkenes with H–X nucleophiles. We targeted late transition metal complexes as catalysts due to the increased potential for good functional group compatibility and low moisture sensitivity. Although our initial efforts employed Pd(II) complexes as catalysts, simple Pt(II) complexes proved more effective and more general as catalysts for the hydrofunctionalization of unactivated alkenes. Here we provide an account of our efforts directed toward the transition metal catalyzed hydrofunctionalization of unactivated alkenes with H–X nucleophiles.

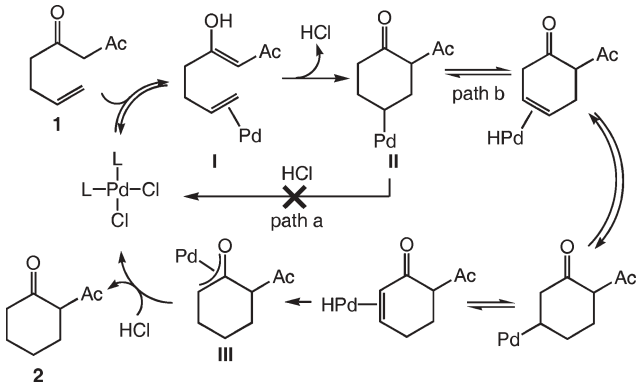
I Pd(II)-catalyzed hydroalkylation

In 2001, we reported the Pd(II)-catalyzed intramolecular hydroalkylation of 3-butenyl β-diketones to form cyclohexanones,[10] which represents the first example of the transition metal-catalyzed hydroalkylation of an unactivated alkene. As an example of this protocol, treatment of 7-octene-2,4-dione (**1**) with a catalytic amount of $PdCl_2(CH_3CN)_2$ (10 mol%) in dioxane at room temperature for 16 h led to isolation of 2-acetylcyclohexanone (**2**) in 81% yield (eqn (1)).



(1)

We initially envisioned a mechanism for the palladium-catalyzed conversion of **1** to **2** involving intramolecular, outer-sphere† attack of the pendant enol on the palladium-complexed olefin of intermediate **I** followed by loss of HCl to form the palladium cyclohexyl intermediate **II** (Scheme 1).[10,11] Protonation of the Pd–C bond of **II** with HCl generated in the formation of **II** could then release **2** and regenerate the active Pd(II) catalyst (Scheme 1, path a). However, subsequent experimentation revealed that Pd–C bond protonolysis was preceded by a series of rapid and reversible β-hydride elimination/addition steps during which the palladium atom of **II** migrates from the C(4) to the C(6) position of cyclohexyl ring to form palladium enolate complex **III** (Scheme 1, path b). Rapid Pd–C bond protonolysis of **III** with the HCl releases the



Scheme 1

cyclohexanone and regenerates the Pd(II) catalyst.[12] In hindsight, the rapid β-hydride elimination of **II** in preference to Pd–C bond protonolysis is not surprising given the high reactivity of Pd(II) alkyl complexes with respect to β-hydride.[28]

Subsequent experimentation extended the scope of palladium-catalyzed alkene hydroalkylation to include less reactive nucleophiles such as β-keto esters, α-aryl ketones and dialkyl ketones.[13] Unfortunately, catalytic hydroalkylation remained intolerant of substitution along the alkyl chain that tethered the alkene to the nucleophile, was restricted to the formation of six-membered rings, and often formed mixtures of products due to the presence of a competing oxidative alkylation pathway. We attributed these limitations at least in part to the presence of the non-productive β-hydride elimination/addition processes operative in the hydroalkylation reaction manifold. On the basis of this hypothesis, we directed our efforts toward the identification of a ''true'' hydroalkylation catalyst that would mediate the addition of the C–H bond of a carbon nucleophile across the C=C bond of an unactivated alkene without competitive β-hydride elimination.

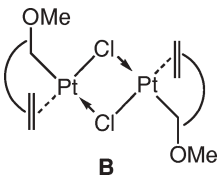
II Platinum-mediated activation of alkenes

As is the case with Pd(II) complexes, Pt(II) complexes activate alkenes toward outer-sphere† attack by nucleophiles. However, Pt(II) alkyl complexes are significantly less reactive toward β-hydride elimination than are the corresponding Pd(II) complexes. Because a vacant coordination site is required for β-hydride elimination,[29] the lower reactivity of Pt(II)–alkyl compounds relative to Pd(II) compounds with respect to β-hydride elimination presumably stems from the stronger M–L bonds of Pt(II) complexes as compared to Pd(II) complexes.[30]

The stoichiometric reactions of platinum alkene complexes with nucleophiles have been investigated for nearly a century. In 1908 Hofmann and von Narbutt reported that reaction of K_2PtCl_4 with dicyclopentadiene in aqueous methanol formed a complex of the formula $ClPt{\cdot}C_{10}H_{12}{\cdot}OCH_3$ (**A**).[31] Although a

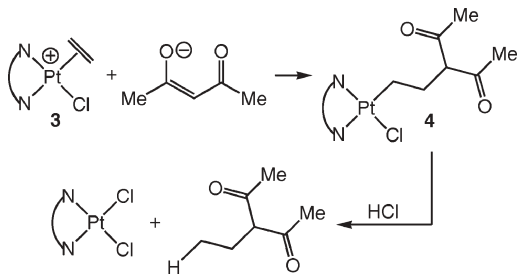
† The terms ''inner-sphere'' and ''outer-sphere'' refer to the two limiting mechanisms for the addition of a nucleophile to the alkene of a transition metal alkene complex. In the outer-sphere pathway, the nucleophile attacks the amine without prior binding to the metal center. In the inner-sphere mechanism, the nucleophile first attacks the metal and is then transferred to the alkene *via* β-migratory insertion.

specific structure was not assigned, the authors proposed that **A** contained a carbon-bound, as opposed to platinum-bound methoxy group, based largely on the sluggish reaction of **A** with HCl.[31] In 1957, Chatt *et al*. proposed that complex **A** was a chloride-bridged dimer, which he depicted as structure **B**, formed *via* addition of methoxide and platinum across a C=C bond.[32] This contention was subsequently corroborated by Stille *et al*.[33] and Venanzi and co-workers,[34] the latter unambiguously *via* a single-crystal X-ray diffraction study. In 1968 Orchin and co-workers obtained NMR evidence for reversible attack of pyridine on the ethylene ligand of $PtCl_2$(pyridine)-($H_2C{=}CH_2$).[35] Panunzi and co-workers subsequently performed more detailed investigations of the reactions of alkylamines with Pt(II) diene[36] and monoene[37] complexes. This work established the outer-sphere† nature of C–N bond formation and demonstrated that the platinum (β-ammonium)ethyl complexes formed *via* outer-sphere amination underwent Pt–C bond protonolysis in the presence of HCl.



B

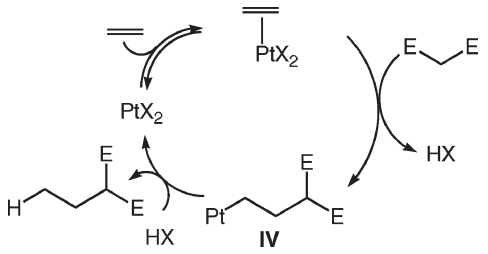
The stoichiometric reactions of platinum alkene complexes with carbon nucleophiles has also been documented. In 1992 Maresca and co-workers reported that the cationic platinum ethylene complex **3** reacted with the anion of 2,4-pentanedione to form the neutral platinum alkyl complex **4**, which was stable with respect to β-hydride elimination.[38] However, treatment of **4** with HCl led to Pt–C bond protonolysis to form 3-ethyl-2,4-pentadione (Scheme 2). In a similar manner, reaction of **3** with the electron-rich arene 1,8-bis(dimethylamino)naphthalene (Proton sponge) formed a stable platinum (β-aryl)ethyl complex that reacted with HCl to release 1,8-bis(dimethylamino)-4-ethylnaphthalene.[39]



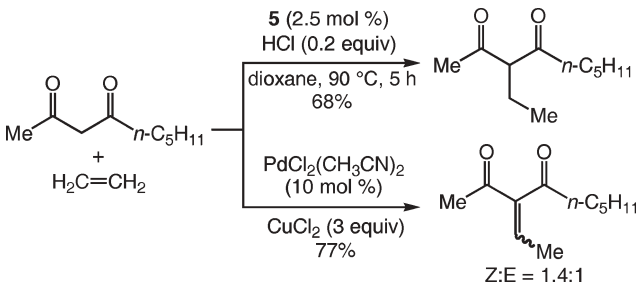
Scheme 2

III Platinum(II)-catalyzed hydroalkylation

On the basis of Maresca's work, we envisioned a catalytic cycle for alkene hydroalkylation involving outer-sphere attack of an activated methylene compound on a PtX_2(alkene) complex coupled with loss of HX to form the neutral platinum alkyl intermediate **IV** (Scheme 3). Subsequent Pt–C bond protonolysis would release the hydroalkylation product with regeneration of PtX_2 (Scheme 4). Troubling, however, was



Scheme 3



Scheme 4

that effective catalysis based on the electrophilic activation of alkenes by Pt(II) had not been previously demonstrated, presumably due to the high kinetic and thermodynamic stability of platinum σ-alkyl and π-alkene complexes.[40] Nevertheless, we initiated a program directed toward the application of platinum(II) complexes as catalysts for the hydroalkylation of unactivated alkenes.

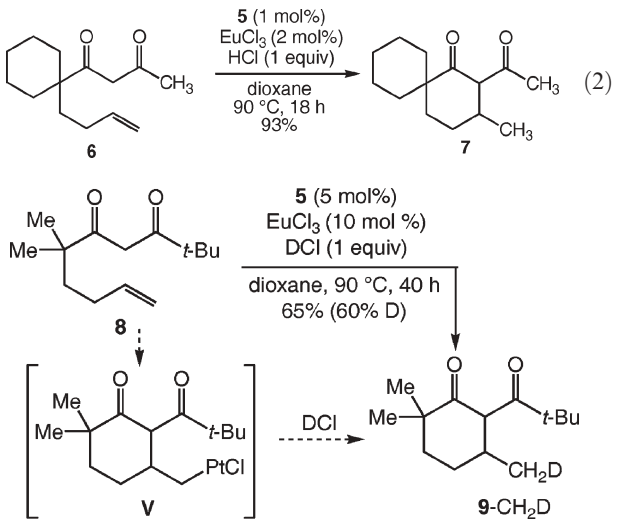
Intermolecular hydroalkylation

Simple Pt(II) complexes proved effective catalysts for the intermolecular hydroalkylation of ethylene with β-diketones. For example, treatment of 2,4-nonadione with ethylene (50 psi) and a catalytic mixture of $[PtCl_2(H_2C{=}CH_2)]_2$ (**5**) (2.5 mol%) and HCl (0.2 equiv) in dioxane at 90 °C for 5 h led to isolation of 3-ethyl-2,4-nonadione in 68% yield (Scheme 4).[41] The presence of a small amount of HCl was presumably required to facilitate protonolysis of the Pt–C bond of the initially formed platinum alkyl intermediate. Illustrative of the complementary reactivity of Pd(II) and Pt(II) complexes as catalysts for alkene alkylation, reaction of 2,4-nonadione with ethylene catalyzed by $PdCl_2(CH_3CN)_2$ (10 mol%) in the presence of a stoichiometric amount of $CuCl_2$ led to oxidative alkylation and isolation of 3-ethylidene-2,4-nonadione in 77% yield as a 1.4 : 1 mixture of *Z* : *E* isomers (Scheme 4).[41]

Intramolecular hydroalkylation

Complex **5** also catalyzed the intramolecular hydroalkylation of unactivated alkenes, provided that a stoichiometric amount of HCl and a catalytic amount of $EuCl_3$ were present in the reaction mixture.[42] The lanthanide salt presumably enhances the nucleophilicity of the β-diketone through transient formation of a β-diketonate complex.[43] As an example of this protocol, treatment of alkenyl β-diketone **6** with a catalytic 1 : 2 mixture of **5** (1 mol%) and $EuCl_3$ (2 mol%) in dioxane that contained HCl (1 equiv.) led to intramolecular

hydroalkylation to form cyclohexanone **7** in 93% isolated yield (eqn (2)).[42] Noteworthy was that Pt-catalyzed hydroalkylation of **8** in the presence of DCl led to isolation of **9**-CH_2D in 65% yield as the exclusive deuterated isotopomer, which points to direct protonation of the initially formed platinum alkyl complex **V** prior to β-hydride elimination (Scheme 5).



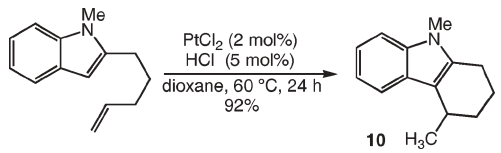
(2)

Scheme 5

IV Platinum(II)-catalyzed hydroarylation

Intramolecular hydroarylation

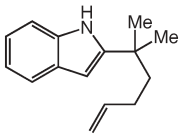
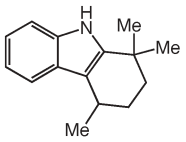
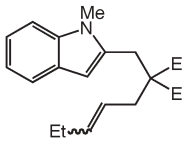
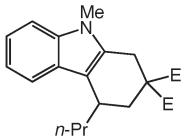
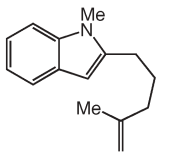
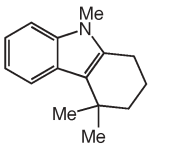
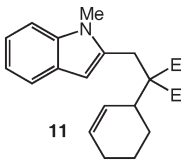
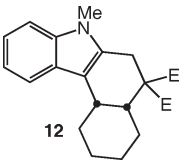
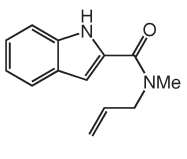
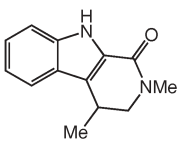
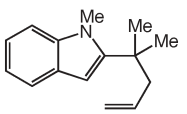
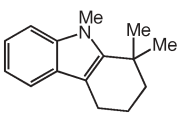
As was noted in the Introduction, effective catalytic methods for the hydroarylation of unactivated alkenes with electron-rich arenes have not been forthcoming.[17,18] Given the effectiveness of **5** as a catalyst for alkene hydroalkylation, we considered that platinum(II) complexes might also catalyze the hydroarylation of unactivated alkenes with electron-rich arenes. We initially focused our efforts on the intramolecular hydroarylation of 2-alkenyl indoles both because the resulting tetrahydrocarbazoles are an important class of naturally occurring molecules,[44] and because the C(3) position of an indole is highly nucleophilic. Indeed, treatment of 1-methyl-2-(4-pentenyl)indole with a catalytic mixture of $PtCl_2$ (2 mol%) and HCl (5 mol%) in dioxane at 60 °C for 24 h led to isolation of tetrahydrocarbazole **10** in 92% yield (eqn (3)).[45]



(3)

Platinum-catalyzed hydroarylation of 2-(4-pentenyl)indoles tolerated substitution at each position of the 4-pentenyl chain including the internal and *cis*- and *trans*-terminal alkenyl positions (Table 1). In a noteworthy example, Pt-catalyzed intramolecular hydroarylation of the cyclohexenyl-substituted indole **11** formed the cis-fused tetracycle **12** in 82% yield as a single diastereomer (Table 1). The protocol was also applicable to the synthesis of tetrahydro-β-carbolinones and was effective

Table 1 Intramolecular hydroarylation of 2-alkenyl indoles catalyzed by $PtCl_2$ (2 mol%) in dioxane that contained HCl (5 mol%) at 60 °C for 18–24 h

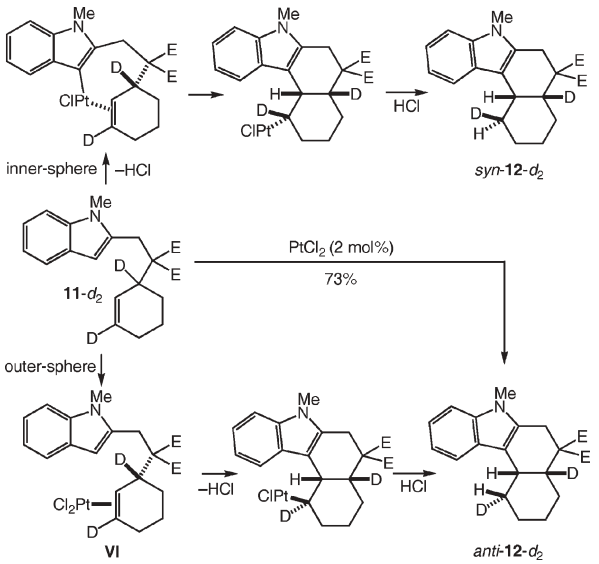
Alkenyl indole	Polycycle	Yield (%)
		87
		*cis* = 80 *trans* = 81
		91
		82 (≥50 : 1[a])
		90
		89

[a] Isomer ratio.

for cyclization of unprotected indoles (Table 1). In addition, 2-(3-butenyl)indoles underwent platinum-catalyzed hydroarylation with exclusive 6-*endo*-trig regioselectivity (Table 1).

Mechanism of hydroarylation

Although we initially envisioned an outer-sphere mechanism for platinum-catalyzed hydroarylation analogous to that depicted in Scheme 3, existing mechanistic studies of transition metal-catalyzed hydroarylation and oxidative arylation were, in each case, consistent with inner-sphere† arylation.[17a,46] We therefore sought to distinguish between inner-sphere and outer-sphere mechanisms for the Pt-catalyzed hydroarylation of alkenyl indoles. Our approach toward this goal exploited the different stereochemical outcomes of inner-sphere and outer-sphere hydroarylation and employed the doubly deuterated cyclohexenyl-substituted indole **11**-d_2. In the inner-sphere pathway, activation of the indole C–H bond followed by β-migratory insertion and Pt–C bond protonolysis with retention of stereochemistry[47] would form *syn*-**12**-d_2 (Scheme 6). In the outer-sphere pathway, attack of the indole on the platinum-complexed olefin of **VI** followed by Pt–C

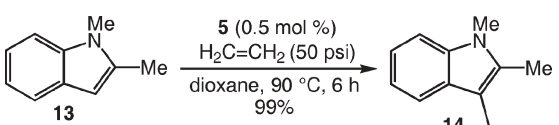


Scheme 6

bond protonolysis would form *anti*-**12**-d_2 (Scheme 6). In accord with our initial expectations, treatment of **11**-d_2 with a catalytic mixture of $PtCl_2$ and HCl led to isolation of *anti*-**12**-d_2 in 73% as the exclusive product with $\geqslant$98% isotopic purity (Scheme 6), which established hydroarylation *via* an outer-sphere mechanism.

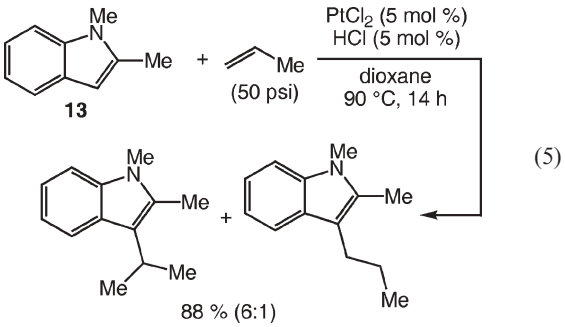
Intermolecular hydroarylation

We have extended the scope of platinum-catalyzed hydroarylation to include the intermolecular hydroarylation of unactivated alkenes with indoles. For example, reaction of 1,2-dimethylindole (**13**) with ethylene (50 psi) catalyzed by **5** (0.5 mol%) in dioxane at 90 °C for 6 h led to isolation of 3-ethyl-1,2-dimethylindole (**14**) in 99% yield (eqn (4)).[48] Intermolecular hydroarylation was highly efficient and up to 900 turnovers were obtained for the Pt-catalyzed conversion of **13** to **14**. 1-Alkenes also underwent Pt-catalyzed hydroarylation with indoles with predominant formation of the Markovnikov addition product. For example, reaction of **13** with propene (50 psi) and a catalytic 1 : 1 mixture of $PtCl_2$ and HCl (5 mol%) in dioxane at 90 °C for 14 h led to isolation of a 6 : 1 mixture of 3-isopropyl-1,2-dimethylindole and 3-*n*-propyl-1,2-dimethylindole in 88% combined yield (eqn (5)).



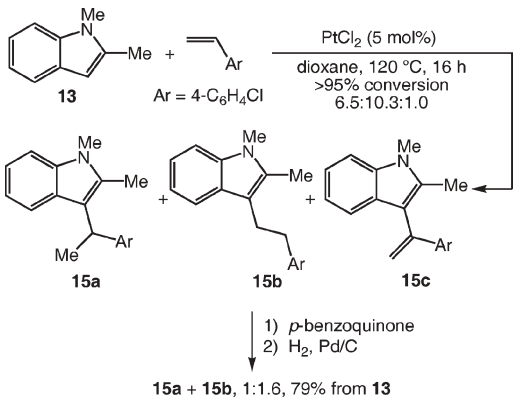
(4)

Vinyl arenes also underwent Pt-catalyzed hydroarylation with indoles although oxidative arylation competed with hydroarylation.[48] For example, reaction of **13** and *p*-chlorostyrene with a catalytic amount of $PtCl_2$ (5 mol%) in dioxane at 120 °C for 16 h led to >95% conversion to form a 6.5 : 10.3 : 1.0 mixture of Markovnikov adduct **15a**, anti-Markovnikov adduct **15b**, and oxidized Markovnikov product **15c** in 89% combined yield (GC, Scheme 7). Treatment of the crude



(5)

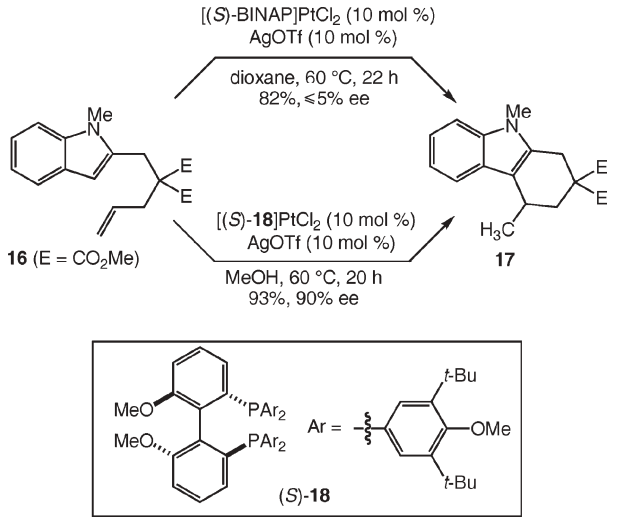
reaction mixture with 1,4-benzoquinone to consume unreacted 1,2-dimethylindole and hydrogenation to convert **15c** to **15a** followed by chromatography led to isolation of a 1 : 1.6 mixture of **15a** and **15b** in 79% combined yield (Scheme 7). The Markovnikov/anti-Markovnikov selectivity of Pt-catalyzed hydroarylation depended strongly on the electronic nature of the vinyl arene and decreased from 2.0 : 1 for the hydroarylation of *p*-methylstyrene to 1 : 5.8 for the hydroarylation of *p*-nitrostyrene.



Scheme 7

Enantioselective hydroarylation

General and efficient methods for the enantioselective hydroarylation of unactivated alkenes are exceedingly rare[49] and, for this reason, we sought to develop an effective platinum-catalyzed protocol for asymmetric hydroarylation. To this end, we targeted dicationic platinum bis(phosphine) dimers such as $[(BINAP)Pt(\mu\text{-}Cl)]_2(OTf)_2$ as catalysts for intramolecular asymmetric hydroarylation. In an initial experiment, reaction of alkenyl indole **16** with a 1 : 1 mixture of [(*S*)-BINAP]$PtCl_2$ and AgOTf at 60 °C in dioxane for 22 h led to isolation of tetrahydrocarbazole **17** in good yield, but the transformation occurred with no significant enantioselectivity (Scheme 8). Subsequent experimentation identified (*S*)-3,5-*t*-Bu-4-MeO-MeOBIPHEP [(*S*)-**18**] as an effective ligand and methanol as an effective solvent for Pt-catalyzed enantioselective hydroarylation. In this optimized protocol, treatment of **16** with a catalytic 1 : 1 mixture of [(*S*)-**18**]$PtCl_2$ and AgOTf (10 mol%) at 60 °C in methanol for 20 h led to isolation of tetrahydrocarbazole **17** in 93% yield with 90% ee (Scheme 8).[50]

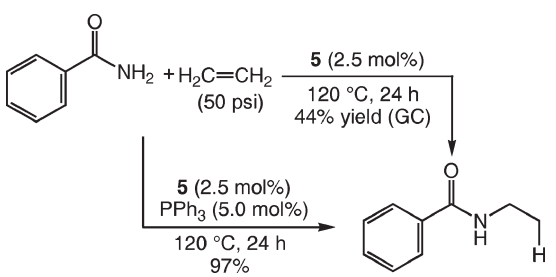


Scheme 8

V Platinum-catalyzed hydroamination

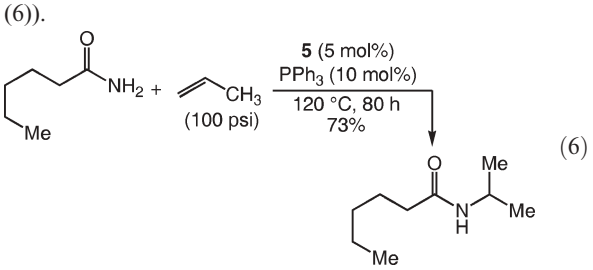
Intermolecular hydroamination

Successful demonstration of the Pt(II)-catalyzed hydroalkylation and hydroarylation of unactivated alkenes combined with the examples of the stoichiometric amination of platinum amine complexes[35–37] pointed to the potential of platinum(II)-catalyzed alkene hydroamination. Our efforts in this area initially focused on the intermolecular hydroamination of ethylene with carboxamides. When a dioxane solution of benzamide, ethylene (50 psi), and a catalytic amount of **5** (2.5 mol%) was heated at 90 °C for 24 h, 44% of the benzamide was consumed to form *N*-ethylbenzamide as the exclusive product with concomitant decomposition of **5** (Scheme 9).[51] The efficiency of the platinum-catalyzed hydroamination of ethylene with benzamide was evaluated as a function of exogenous phosphine on the assumption that the active hydroamination catalyst might be stabilized by phosphine ligation. From these experiments, PPh_3 emerged as an effective supporting ligand for platinum-catalyzed hydroamination. For example, reaction of benzamide with ethylene catalyzed by a 2 : 1 mixture of PPh_3 and **5** (P : Pt = 1 : 1) at 120 °C for 24 h led to complete consumption of benzamide and isolation of *N*-ethylbenzamide in 97% yield (Scheme 9).[51] Noteworthy was that treatment of a mixture of ethylene and benzamide with either a catalytic 4 : 1 mixture of PPh_3 and **5** (P : Pt = 2 : 1) or a catalytic amount of $(PPh_3)_2PtCl_2$ led to no detectable consumption of benzamide.



Scheme 9

The platinum-catalyzed hydroamination of ethylene was effective for a range of primary aryl carboxamides including *p*-methoxy, *p*-bromo and *p*-nitrobenzamide, *p*- and *o*-toluamide, and 1- and 2-napthylcarboxamide (Chart 1).[51] In addition to aryl carboxamides, primary alkyl amides, γ-valerolactam and 2-oxazolidone also underwent platinum-catalyzed hydroarylation with ethylene to form the corresponding *N*-ethylated derivatives in good yield (Chart 1). Propene also underwent platinum-catalyzed hydroamination with carboxamides although more forcing conditions were required. For example, reaction of valeramide with propene (100 psi) and a catalytic 1 : 2 mixture of **5** and PPh_3 at 120 °C for 80 h led to isolation of *N*-isopropylvaleramide in 73% as a single isomer (eqn (6)).



(6)

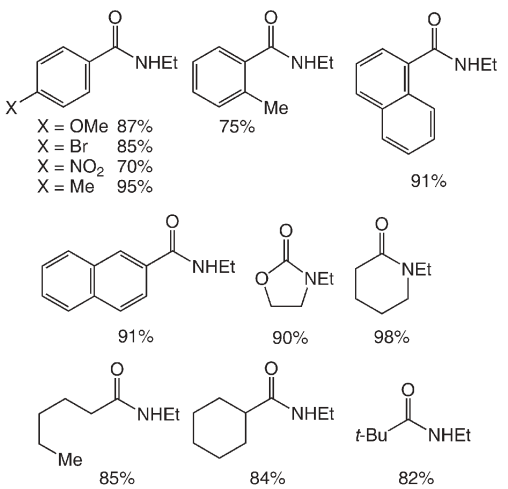
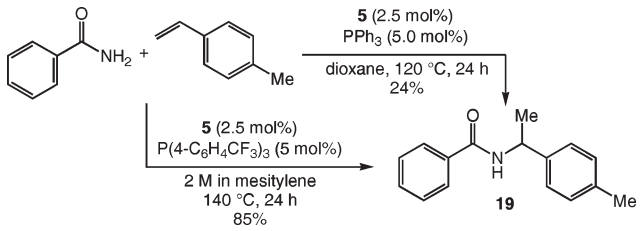


Chart 1 *N*-Ethyl carboxamide derivatives formed *via* the Pt-catalyzed hydroamination of ethylene.

In an effort to extend the scope of intermolecular hydroamination, we investigated the platinum-catalyzed hydroamination of vinyl arenes with carboxamides. Unfortunately, reaction of benzamide with 4-methylstyrene employing conditions optimized for the hydroamination of ethylene with carboxamides led to isolation of *N*-(1-*p*-tolylethyl)benzamide (**19**) in only 24% yield (Scheme 10).[52] However, subsequent optimization with respect to phosphine and solvent led to identification of more effective conditions for the intermolecular hydroamination of vinyl arenes. For example, reaction of a concentrated solution of benzamide and 4-methylstyrene in mesitylene catalyzed by a mixture of **5** and $P(4\text{-}C_6H_4CF_3)_3$ at 140 °C led to isolation of the Markovnikov addition product **19** in 85% yield as the exclusive (⩾50 : 1) regioisomer (Scheme 10).[52] Platinum-catalyzed intermolecular hydroamination of vinyl arenes tolerated electron-rich, electron-deficient, and sterically hindered vinyl arenes, electron-rich



Scheme 10

and electron-deficient aryl carboxamides, alkyl carboxamides and cyclic carbamates (Chart 2). The protocol tolerated a range of polar functionality including methoxy, bromo, trifluoromethyl, carbomethoxy, silyl ether and acetal groups (Chart 2).[52]

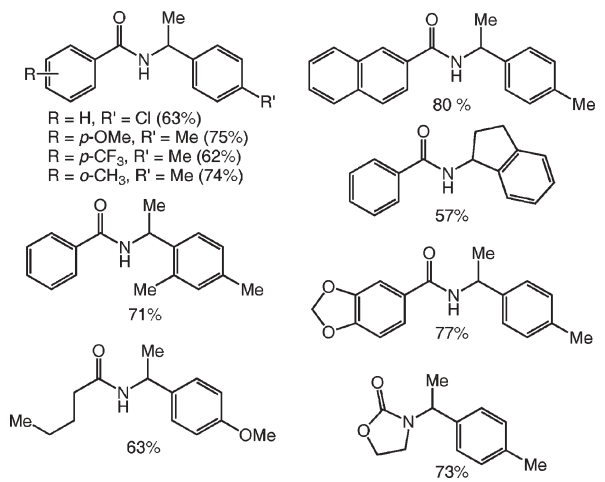
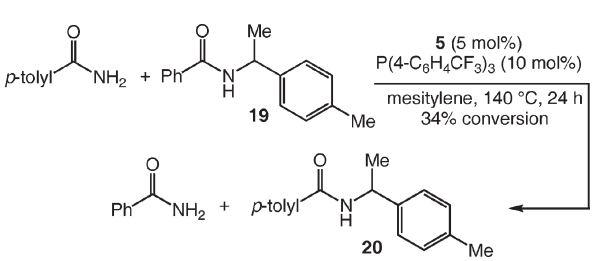


Chart 2 Benzyl carboxamide derivatives formed *via* the Pt-catalyzed hydroamination of vinyl arenes.

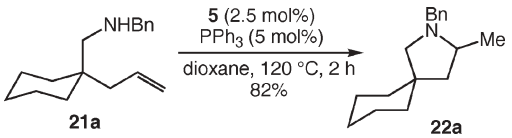
Using tabulated heats of formation data and entropy data from related transformations,[53] we estimated a free energy of reaction for the hydroamination of a vinyl arene with a carboxamide of $\Delta G \approx -1.5$ kcal mol^{-1} at 140 °C, which suggests that hydroamination is reversible under these conditions. To probe for reversibility in the platinum-catalyzed intermolecular hydroamination of vinyl arenes, a 1 : 1 mixture of *p*-toluamide and **19** was heated with a catalytic 1 : 2 mixture of **5** and P(4-$C_6H_4CF_3$)$_3$ at 140 °C. Analysis of the reaction mixture after 24 h revealed the presence of a ~2 : 2 : 1 : 1 mixture of *p*-toluamide, **19**, benzamide and *N*-(1-*p*-tolylethyl)*p*-toluamide (**20**), which confirmed the reversible nature of hydroamination under these conditions (Scheme 11).



Scheme 11

Intramolecular hydroamination

Intramolecular reactions are often faster than are the corresponding intermolecular reactions due to the more favorable entropy of activation associated with the former processes. For this reason, it was somewhat surprising that a mixture of **5** and PPh_3 proved ineffective as a catalyst system for the intramolecular hydroamination of alkenes with carboxamides. However, mixtures of **5** and PPh_3 catalyzed the intramolecular hydroamination of unactivated alkenes with secondary alkyl amines. For example, treatment of the 4-pentenyl amine **21a** with a catalytic mixture of **5** and PPh_3 in dioxane at 120 °C for 2 h led to isolation of pyrrolidine **22a** in 82% yield (eqn (7)).[54] This result was unexpected as the identification of effective late transition metal catalysts for the hydroamination of unactivated alkenes with alkyl amines represents one the most elusive goals in homogeneous catalysis. The difficulty of such a transformation presumably stems from the stronger binding of electrophilic late transition metal complexes to primary or secondary amines than to alkenes.



(7)

Although rather forcing conditions were required for the platinum-catalyzed hydroamination of 4-pentenyl amines, the protocol tolerated a range of polar functional groups including bromo, nitro and cyano groups, carboxylic esters, acetals, and benzyl and silyl ethers (Table 2). Platinum-catalyzed hydroamination of 4-pentenyl amines tolerated substitution at the C(2), C(3) or C(4) position of the 4-pentenyl chain and was effective for both primary and secondary *N*-bound alkyl groups (Table 2). *gem*-Dialkyl substitution at the C(2) position of the 4-pentenyl chain facilitated hydroamination, but was not required. Also noteworthy was that neither the rate nor yield of hydroamination was affected by the presence of water (0.5 equiv) in the reaction mixture.

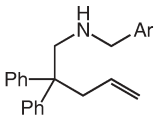
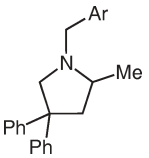
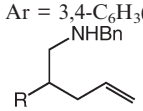
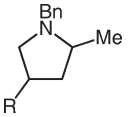
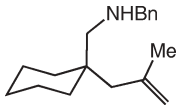
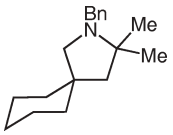
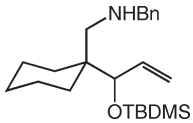
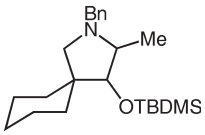
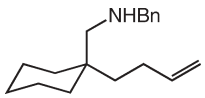
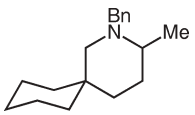
Mechanism of intramolecular hydroamination

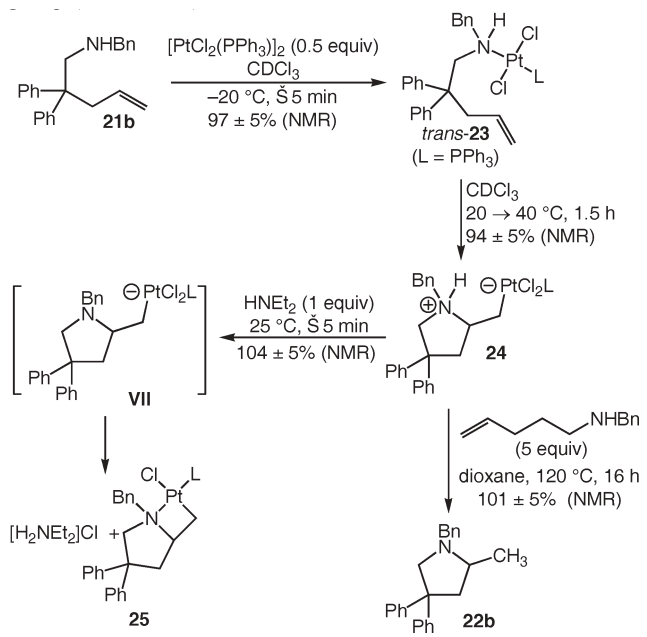
Variable temperature NMR experiments provided insight into the mechanism of the platinum-catalyzed intramolecular hydroamination of alkenyl amines. In one experiment, reaction of **21b** with a stoichiometric amount of the platinum phosphine dimer $[PtCl_2(PPh_3)]_2$‡ (0.5 equiv) in $CDCl_3$ at −20 °C for 5 min led to formation of the platinum amine complex *trans*-**23** in 97 ± 5% yield (^{1}H NMR) (Scheme 12).[54] The trans relationship of the amine and phosphine ligands of *trans*-**23** was established by the large phosphorus–nitrogen coupling constant (J_{PN} = 48 Hz) in the ^{31}P NMR spectrum of the ^{15}N-labelled isotopomer *trans*-**23**-(^{15}N). Warming a solution of *trans*-**23** at 20 °C for 1 h and 40 °C for 30 min led to rearrangement/cyclization to form the zwitterionic complex **24** in 94 ± 5% yield (^{1}H NMR) (Scheme 12).[54]

Heating a dioxane solution of **24** at 80 °C for 16 h led to decomposition without formation of **22b**. This observation

‡ The dimer $[PtCl_2(PPh_3)]_2$ was an active catalyst for the hydroamination of **21**.

Table 2 Intramolecular hydroamination of alkenyl amines catalyzed by a mixture of **5** (2.5 mol%) and PPh_3 (5 mol%) in dioxane at 120 °C for 6–40 h

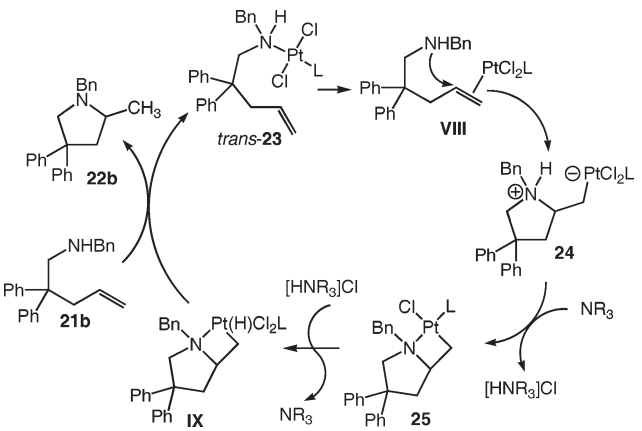
Alkenyl amine	Heterocycle	Yield (%)
		
Ar = 4-C_6H_4Br		70
Ar = 4-C_6H_4CN		64
Ar = 4-$C_6H_4NO_2$		72
Ar = 4-$C_6H_4CO_2Me$		77
Ar = 3,4-C_6H_3(–OCH_2O–)		71
 R = *p*-C_6H_4OMe		59 (1.5 : 1)
		79
		85 (3.5 : 1)
		57



Scheme 12

ruled out the direct conversion of **24** to **22b** and instead pointed to a mechanism involving intermolecular deprotonation followed by Pt–C bond protonolysis. Indeed, heating a solution of **24** and an excess of *N*-benzyl-4-pentenylamine§ at 120 °C for 16 h led to quantitative formation of **22b**. In a separate experiment, treatment of **24** with $HNEt_2$ (1 equiv.) at room temperature for 5 min led to formation of the heterobicyclic platinum amine complex **25** (Scheme 12),[54] presumably *via* initial formation of the anionic platinum pyrrolidine intermediate **VII** followed by intramolecular chloride displacement by the pendant amino group (Scheme 12).

The experiments described in the preceding paragraphs support a mechanism for the platinum-catalyzed hydroamination of **21b** initiated by a bridge-splitting reaction of the platinum phosphine dimer with amine to form platinum amine complex *trans*-**23** (Scheme 13). Associative, intramolecular displacement of the amine ligand with the pendant alkene moiety would form the unobserved platinum alkene complex **VIII**. Outer-sphere† attack of the pendant amine on the alkene of **VIII** would form the observed zwitterionic complex **24**,[54] which would react with free amine to form the heterobicyclic amine complex **25** (Scheme 13). Protonolysis of the Pt–C bond of **25** with $[HNR_3]Cl$, perhaps *via* the Pt(IV) hydride intermediate **IX**,[55] would release **22b** (Scheme 13).



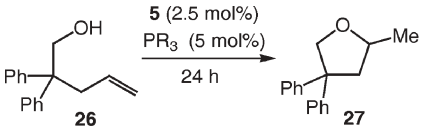
Scheme 13

VI Pt(II)-catalyzed hydroalkoxylation

Development of effective Pt(II)-catalyzed protocols for the hydrofunctionalization of unactivated alkenes with carbon and nitrogen nucleophiles suggested that Pt(II) might also catalyze the hydroalkoxylation of unactivated alkenes. Because saturated oxygen heterocycles are common components of a wide range of naturally occurring and biologically active molecules including the acetogenins[56,57] and polyether antibiotics,[56,58] we focused our efforts on the platinum-catalyzed intramolecular hydroalkoxylation of γ- and δ-hydroxyl alkenes. Unfortunately, attempted hydroalkoxylation of 2,2-diphenyl-4-penten-1-ol (**26**) employing the conditions optimized for

§ *N*-Benzyl-4-pentenylamine is unreactive with respect to platinum-catalyzed intramolecular hydroamination.

intramolecular C–C and C–N bond formation proved largely ineffective (Scheme 14).[59] However, subsequent optimization with respect to solvent and phosphine led to identification of an effective protocol for intramolecular alkene hydroalkoxylation. For example, reaction of **26** with a catalytic mixture of **5** (2.5 mol%) and P(4-$C_6H_4CF_3$)$_3$ (5 mol%) in $Cl_2CHCHCl_2$ at 70 °C for 24 h led to isolation of 2-methyl-4,4-diphenyltetrahydrofuran (**27**) in 82% yield as a single regioisomer (Scheme 14).[59]



PR_3	solvent	temp (°C)	yield (%)
none	dioxane	80	12
PPh_3	dioxane	80	42
P(4-$C_6H_4CF_3$)$_3$	$C_2H_2Cl_4$	70	82

Scheme 14

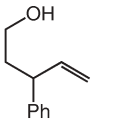
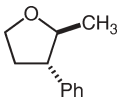
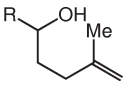
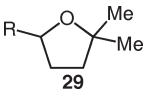
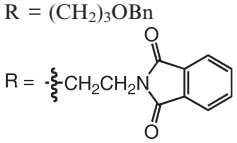
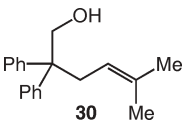
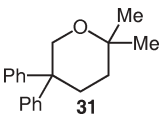
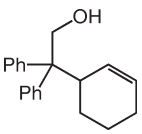
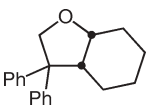
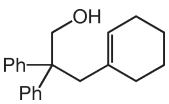
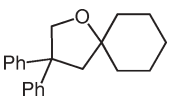
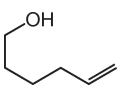
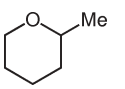
Platinum-catalyzed hydroalkoxylation of γ-hydroxy alkenes displayed good generality and tolerated a number of functional groups including acetate and pivaloate groups, carboxamides, and benzyl and silyl ethers. Platinum-catalyzed hydroalkoxylation tolerated substitution at the α-, β- or γ-position of the γ-hydroxyalkene and at the internal or terminal alkenyl positions. The regioselectivity of hydroalkoxylation was sensitive to alkenyl substitution. Whereas Pt-catalyzed hydroalkoxylation of **28** formed **29** in 91% yield *via* a 5-*exo* cyclization, Pt-catalyzed hydroalkoxylation of **30** led to exclusive formation of **31** in 98% yield *via* 6-*endo* cyclization (Table 3). Platinum-catalyzed hydroalkoxylation was also effective for the formation of fused and spirobicyclic ethers and for the 6-*exo* cyclization of δ-hydroxy alkenes (Table 3).[59]

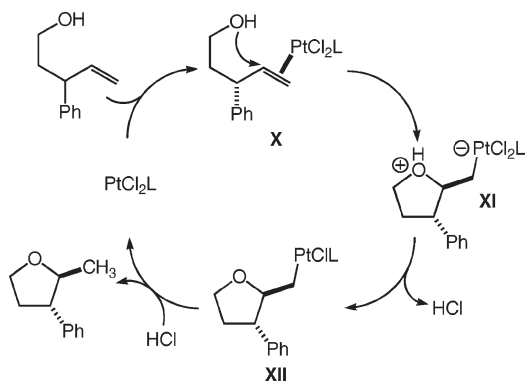
The regio- and stereoselectivity of platinum-catalyzed hydroalkoxylation mirrors that observed for the oxymercuration of γ- and δ-hydroxy alkenes.[9] On the basis of this relationship and by analogy to the mechanisms established for the platinum-catalyzed hydroarylation and hydroamination, we proposed a mechanism for platinum-catalyzed hydroalkoxylation involving outer-sphere† attack of the pendant hydroxyl group on the platinum-complexed alkene of **X** to form zwitterion **XI** (Scheme 15). Loss of HCl followed by protonolysis of the Pt–C bond of **XII** would release the oxygen heterocycle with regeneration of the Pt(II) catalyst (Scheme 15).

VII Related Pt-catalyzed hydrofunctionalization processes

In addition to the results described herein, a number of related platinum-catalyzed transformations have appeared recently. Tilley and co-workers have reported that (COD)Pt(OTf)$_2$ or mixtures of **5** and $AgBF_4$ catalyze both the hydroamination of unactivated alkenes with sulfonamides and the hydroamination of norbornene with electron deficient anilines.[60] Mixtures of **5** and $AgBF_4$ also catalyze the intermolecular hydroarylation of norbornene, 1-alkenes and cyclic alkenes.[61] Brunet has

Table 3 Hydroalkoxylation of γ- and δ-hydroxy alkenes catalyzed by a mixture of **5** (1 mol%) and P(4-$C_6H_4CF_3$)$_3$ (2 mol%) at 70 °C for 16–48 h

Alkenyl alcohol	Heterocycle	Yield (%)
		66 (8 : 1)
		
R = Bn (**28**)		91
R = $(CH_2)_2OH$		91
R = $(CH_2)_3OBn$		79
		73
		98
		87
		98
		92



Scheme 15

shown that $PtBr_2$ catalyzes the intermolecular hydroamination of ethylene and 1-alkenes with aniline at 150 °C in *n*-Bu_4PBr.[62] Sames and co-workers have reported that $PtCl_4$ catalyzes the intramolecular hydroarylation of alkynes with electron-rich arenes.[63] Vitagliano and co-workers have described the hydrovinylation of ethylene, 2-butene and 2-methyl-2-butene catalyzed by the dicationic platinum ethylene complex

$(PNP)Pt(H_2C{=}CH_2)^{2+}$ [PNP = 2,6-bis(diphenylphosphinomethyl)pyridine].[64] Gagné and co-workers have employed similar dicationic platinum complexes as catalysts for the cycloisomerization and asymmetric cycloisomerization of 1,6-dienes.[65]

Summary and outlook

The Pt(II)-catalyzed processes described in this Feature Article constitute only one of a number of approaches to the hydrofunctionalization of unactivated alkenes with H–X nucleophiles. This area of research has attracted considerable attention as of late and the past several years have witnessed important advances in the hydroalkylation,[66] hydroarylation,[67] hydroamination,[68–71] and hydroalkoxylation[72] of unactivated alkenes. Highlights include the development of an effective Rh(I)-catalyzed protocol for the intramolecular enantioselective hydroarylation of alkenes with aromatic imines,[49] the emergence of cationic Au(I) complexes as effective catalysts for alkene hydroamination,[69] the development of enantioselective alkene hydroamination protocols catalyzed by rare earth and group 4 complexes,[70] and the development of effective Ru- and Rh-catalyzed protocols for the anti-Markovnikov hydroamination of vinyl arenes with secondary alkyl amines.[71]

Despite our and others' efforts, the scope of catalytic alkene hydrofunctionalization remains limited. Transformations catalyzed by early transition metal complexes typically suffer from poor functional group compatibility and extreme air- and moisture- sensitivity,[19,20,21,70] while those catalyzed by late transition metal complexes often require forcing conditions and/or display limited scope. Furthermore, there remains a dearth of effective enantioselective hydrofunctionalization protocols; methods for enantioselective hydroarylation require either a suitable directing group[49] or are of limited scope,[50] enantioselective hydroamination requires either an early transition metal catalyst or a conjugated alkene,[70,73] and enantioselective alkene hydroalkoxylation has not been demonstrated. Similarly, whereas selective anti-Markovnikov hydrofunctionalization has been realized in the case of hydroarylation,[17,45] anti-Markovnikov hydroamination has been demonstrated only in the case of vinyl arenes,[21,24,71] and anti-Markovnikov alkene hydroalkoxylation remains unknown.[74] Therefore, the primary challenges in the area of alkene hydrofunctionalization are the development of selective, highly active catalyst systems for the hydrofunctionalization of unactivated alkenes that display good functional group compatibility and generality and the development of the corresponding enantioselective and anti-Markovnikov selective protocols.

It should be noted that outer-sphere attack of an H–X nucleophile on an η^2-alkene complex followed by protonolysis of the resulting metal alkyl species (Scheme 3) constitutes only one of several mechanisms documented for alkene hydrofunctionalization. Alternative modes of C–X bond formation include β-migratory insertion of an alkene into a M–X bond,[75] [2 + 2] cycloaddition of a C=C bond with an M=X bond,[76] and outer-sphere attack of an H–X nucleophile on an η^3-allyl or benzyl intermediate.[77] Although no one mechanism has proven superior to others with respect to generality, anti-Markovnikov selectivity or enantioselectivity, it appears likely that such a trend may emerge with continued experimentation. Furthermore, continued experimentation will likely lead to the identification of new mechanisms that may present new opportunities for alkene hydrofunctionalization. Toward this goal, Sanford and Groves has recently outlined a potential mechanism for the anti-Markovnikov hydrofunctionalization of an amino or hydroxyl alkene by demonstrating each step of the potential catalytic cycle under stoichiometric conditions employing a rhodium porphyrin hydride complex.[78] These steps consist of hydrometallation of the C=C bond to form a rhodium primary-alkyl intermediate, attack of the nucleophile on the rhodium-bound methylene carbon to release the heterocycle and form a rhodium anion, and protonation to regenerate the rhodium hydride species.

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