ORGANIC
LETTERS

2005
Vol. 7, No. 13
2635−2638

# Platinum-Catalyzed Intermolecular Hydroamination of Vinyl Arenes with Carboxamides

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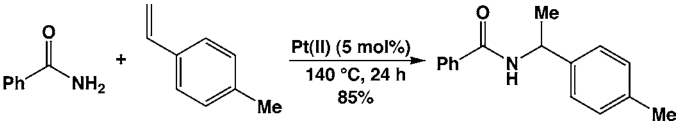
Received April 6, 2005

## ABSTRACT



**Reaction of benzamide with 4-methylstyrene catalyzed by a 1:2 mixture of $[PtCl_2(H_2C{=}CH_2)]_2$ and $P(4\text{-}C_6H_4CF_3)_3$ (5 mol %) in mesitylene at 140 °C for 24 h led to the isolation of *N*-(1-*p*-tolylethyl)benzamide in 85% yield. Electron-rich, electron-poor, and hindered vinyl arenes underwent Markovnikov hydroamination with a range of carboxamides and amide derivatives in moderate to good yield with excellent regioselectivity.**

The importance of amines and amine derivatives in the synthesis of pharmaceuticals and fine chemicals has stimulated considerable interest in catalytic olefin hydroamination as a route to nitrogen-containing molecules.[1] However, despite recent advances in this area,[3−8] the intermolecular hydroamination of unactivated olefins remains problematic. Although lanthanide metallocene,[2] bis(phosphine) Rh(I),[3] and bis(2-methylallyl) Ru(II)[4] complexes catalyze the anti-Markovnikov hydroamination of vinyl arenes with alkylamines, these protocols suffer from a number of limitations, including poor functional group compatibility, poor selectivity, and/or limited scope. Bis(phosphine) palladium(II) complexes employed in conjunction with triflic acid catalyze the Markovnikov hydroamination of vinyl arenes with both aryl-[5] and alkylamines,[6] but these protocols are also of limited scope and are not applicable to the employment of carboxamides and related derivatives as substrates.[7,8]

As part of a program directed toward the development of transition metal-catalyzed methods for the addition of carbon-[9,10] and heteroatom-nucleophiles[11−13] to unactivated olefins, we recently reported the Pt(II)-catalyzed intermolecular hydroamination of ethylene with carboxamides.[12] For example, reaction of benzamide and ethylene (50 psi) catalyzed

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[1] (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Bytschkov, I.; Doye, S. *Chem. Eur. J.* **2003**, 935.

[2] Ryu, J-. S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

[3] (a) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999**, *5*, 1306. (b) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 5608.

[4] Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702.

[5] Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546.

[6] Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286.

[7] Transition metal-catalyzed intermolecular hydroamination of ethylene,[7a,b] strained olefins,[7c] 1,3-dienes,[7d,e] and Michael acceptors[7f,g] is also known. (a) Coulson, D. R. *Tetrahedron Lett.* **1971**, *12*, 429. (b) Brunet, J.-J.; Cadena, M.; Chu, N. C.; Diallo, O.; Jacob, K.; Mothes, E. *Organometallics* **2004**, *23*, 1264. (c) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738. (d) Baker, R.; Onions, A.; Popplestone, R. J.; Smith, T. N. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1133. (e) Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. (f) Seligson, A. L.; Trogler, W. C. *Organometallics* **1993**, *12*, 744. (g) Gaunt, M. J.; Spencer, J. B. *Org. Lett.* **2001**, *3*, 25.

[8] Stahl has recently reported the catalytic intermolecular oxidative amination of aromatic[8a] and aliphatic[8b] α-olefins with amides. (a) Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 12996. (b) Brice, J. L.; Harang, J. E.; Timokhin, V. I.; Anastasi, N. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2005**, *127*, 2868.

[9] Indoles: (a) Liu, C.; Han, X.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 3700. (b) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250.

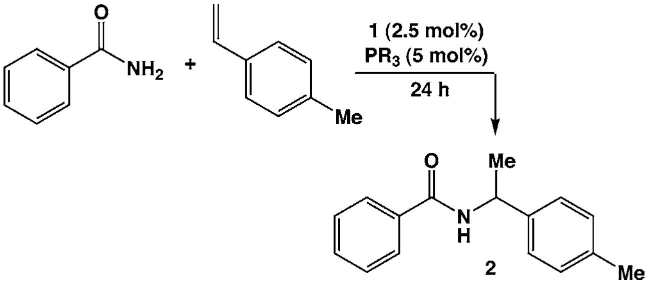
[10] Activated methylene compounds: (a) Widenhoefer, R. A. *Pure Appl. Chem.* **2004**, *76*, 671 and references therein. (b) Liu, C.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem. Eur. J.* **2004**, *10*, 6343. (c) Han, X.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem. Eur. J.* **2004**, *10*, 6333. (d) Wang, X.; Widenhoefer, R. A. *Chem. Commun.* **2004**, 660. (e) Qian, H.; Pei, T.; Widenhoefer, R. A. *Organometallics* **2005**, *24*, 287. (f) Liu, C.; Widenhoefer, R. A. *Tetrahedron Lett.* **2005**, *46*, 285.

[11] Alkylamines: Bender, C. F.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2005**, *127*, 1070.

[12] Carboxamides: Wang, X.; Widenhoefer, R. A. *Organometallics* **2004**, *23*, 1649.

10.1021/ol050745f CCC: $30.25

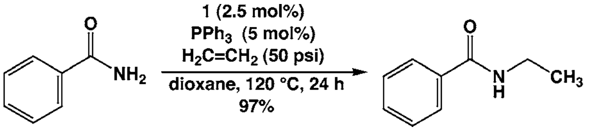
**Table 1.** Effect of Solvent, Phosphine, and Temperature on the Pt(II)-Catalyzed Reaction of Benzamide (2 M) with 4-Methylstyrene (4 Equiv)



| entry | $PR_3$ | temp (°C) | solvent | yield (%)[a] |
|---|---|---|---|---|
| 1 | $PPh_3$ | 120 | dioxane | 24 |
| 2 | none | 120 | dioxane | 71 |
| 3 | $P(4\text{-}C_6H_4CF_3)_3$ | 120 | dioxane | 72 |
| 4 | $P(4\text{-}C_6H_4CF_3)_3$ | 140 | dioxane | 77 |
| 5 | $P(4\text{-}C_6H_4CF_3)_3$ | 140 | toluene | 81 |
| 6 | $P(4\text{-}C_6H_4CF_3)_3$ | 140 | xylene | 79 |
| 7 | $P(4\text{-}C_6H_4CF_3)_3$ | 140 | mesitylene | 85 |

[a] Isolated yield relative to benzamide of >95% pure material.

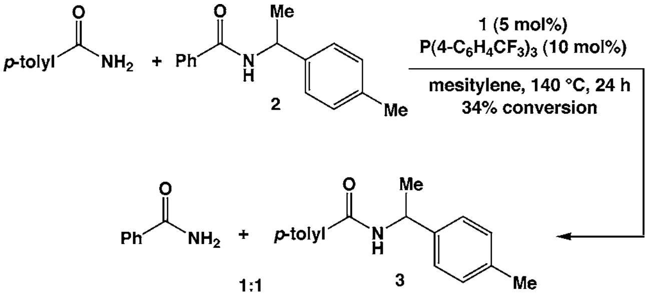
by a 1:2 mixture of $[PtCl_2(H_2C{=}CH_2)]_2$ (**1**) and $PPh_3$ at 120 °C for 24 h led to isolation of *N*-ethylbenzamide in 97% yield (eq 1). Although the platinum-catalyzed hydroamination of ethylene tolerated a range of amide derivatives, this procedure proved to be largely ineffective for the hydroamination of α-olefins.[14] We have continued our efforts in this area, and here we report the platinum-catalyzed Markovnikov hydroamination of vinyl arenes with carboxamides and related compounds.



eq 1

Reaction of benzamide and 4-methylstyrene (4 equiv) employing conditions optimized for the hydroamination of ethylene with carboxamides[12] led to isolation of *N*-(1-*p*-tolylethyl)benzamide (**2**) in only 24% yield (Table 1, entry 1). We noted with interest that **1** was a significantly more effective catalyst for the hydroamination of 4-methylstyrene with benzamide than was a mixture of **1** and $PPh_3$ (Table 1, entry 2). This observation suggested that an electron-deficient phosphine might be more suitable as a supporting ligand for the Pt(II)-catalyzed hydroamination of vinyl arenes than was $PPh_3$. Indeed, further experimentation validated this hypothesis (Table 1, entries 3−7). In an optimized procedure, reaction of a concentrated mesitylene solution of benzamide (2 M) and 4-methylstyrene (4 equiv) catalyzed by a mixture of **1** (2.5 mol %) and $P(4\text{-}C_6H_4CF_3)_3$ (5 mol %) at 140 °C for 24 h led to isolation of **2** in 85% yield relative to benzamide as a single regioisomer (Table 1, entry 7).[15,16]

**Scheme 1**



Electron-rich, electron-poor, and hindered vinyl arenes underwent platinum-catalyzed hydroamination with a range of aryl carboxamides, including *p*-methoxy-, *p*-bromo-, *p*-trifluoromethyl-, *p*-carbomethoxy-, *o*-methyl-, and *p*-OTBDMS-substituted benzamides, 2-naphthylcarboxamide, and benzo[1,3]dioxole-5-carboxamide to form the corresponding *N*-(1-arylethyl)carboxamides in moderate to good yield with excellent regioselectivity (Table 2, entries 1−14). In addition to arylamides, valeramide, 2-oxazolidone, and *p*-toluenesulfonamide also reacted with vinyl arenes under platinum catalysis to form the corresponding *N*-(1-arylethyl) amide derivatives in moderate to good yield with excellent regioselectivity (Table 2, entries 15−18). Despite the rather forcing conditions required to effect the catalytic intermolecular hydroamination of vinyl arenes, the protocol tolerated a number of polar functional groups, including aryl halides, carboxylic esters, acetals, and silyl ethers (Table 2, entries 4, 6, 10, and 13).

On the basis of heats of formation data,[17] we estimate an enthalpy of reaction for the hydroamination of a vinyl arene with a carboxamide of $\Delta H \approx -14$ kcal mol$^{-1}$.[18] In addition, the entropy of reaction for the hydroamination of ethylene

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(13) Hydroxyl groups: (a) Qian, H.; Han, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 9536. (b) Han, X.; Widenhoefer, R. A. *J. Org. Chem.* **2004**, *68*, 1738.

(14) In a single example, reaction of valeramide with propylene (100 psi) and a catalytic 2:1 mixture of $PPh_3$ and **1** at 120 °C for 80 h formed *N*-isopropylvaleramide in 73% isolated yield.[12]

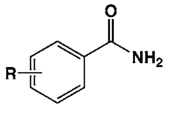
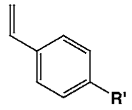
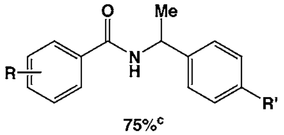
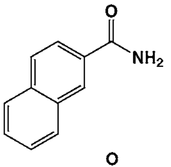
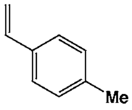
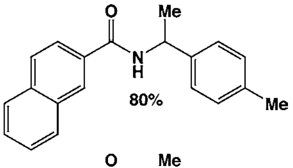
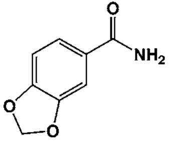
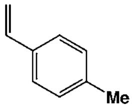
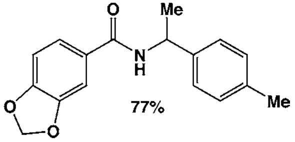
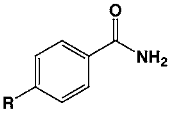
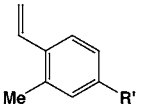
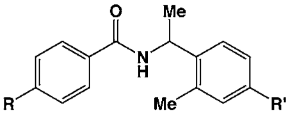
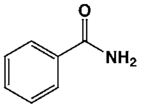
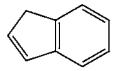
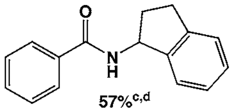
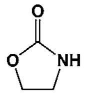
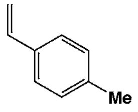
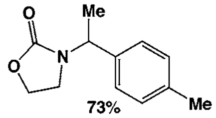
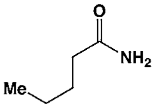
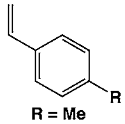
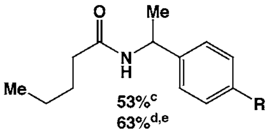
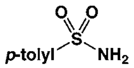
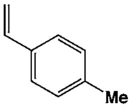
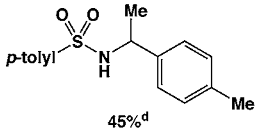
(15) In addition to **2**, reaction of benzamide (2 M) and 4-methylstyrene (4 equiv) catalyzed by **1** (2.5 mol %)/$P(4\text{-}C_6H_4CF_3)_3$ (5 mol %) at 140 °C for 24 h led to the isolation of (*E*)-1,3-bis(*p*-tolyl)-1-butene in ~15% yield based on 4-methylstyrene. Dimerization of the vinyl arene necessitated the use of an excess of vinyl arene. For example, reaction of benzamide (2 M) and 4-methylstyrene (1 equiv) catalyzed by **1** (2.5 mol %)/$P(4\text{-}C_6H_4CF_3)_3$ (5 mol %) at 140 °C for 24 h led to the isolation of **2** in only 43% yield.

(16) (a) Although strong acids such as HOTf catalyze the intramolecular hydroamination of olefins with carboxamides at elevated temperatures,[16b] the presence of a significant acid-catalyzed background reaction in the Pt-catalyzed hydroamination of vinyl arenes was ruled out, as reaction of benzamide, 4-methylstyrene, and a catalytic amount of HCl (5 mol %) in mesitylene at 140 °C for 24 h formed no significant amounts (<10%) of **2** as determined by GC analysis. (b) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 1471.

(17) Pedley, J. B.; Rylance, J. *Sussex N. P. L. Computer Analyzed Thermochemical Data: Organic and Organometallic Compounds*; University of Sussex: Brighton, UK, 1977.

(18) $\Delta H_f^0$ values for 1-butene, acetamide, and *n*-butylacetamide in the gas phase are −0.1, −56.9, and −72.9 kcal mol$^{-1}$, respectively. From these values, we calculate an enthalpy of reaction for the conversion of 1-butene and acetamide to *n*-butylacetamide of $\Delta H = -15.9$ kcal mol$^{-1}$. $\Delta H_f^0$ values for *n*-butane, styrene, and ethylbenzene in the gas phase are −30.1, 35.3, and 7.0 kcal mol$^{-1}$, respectively. These values combined with that for 1-butene indicate that the C═C bond of styrene is 1.7 kcal mol$^{-1}$ more stable than the C═C bond of 1-butene. From these values, we estimate an enthalpy of reaction for the hydroamination of styrene with acetamide of $\Delta H = -14.2$ kcal mol$^{-1}$.

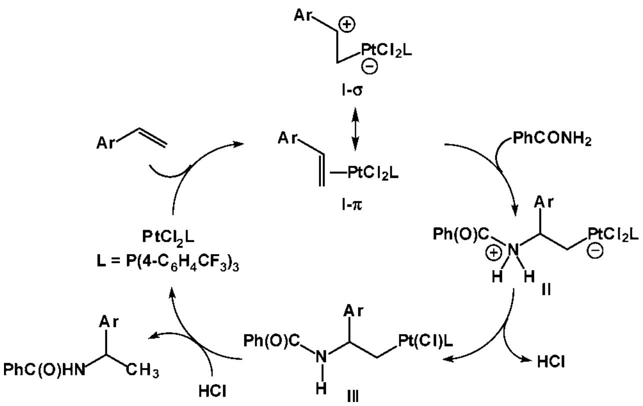
**Table 2.** Reaction of Amides (2 M) with Vinyl Arenes (4 Equiv) Catalyzed by a Mixture of $[PtCl_2(H_2C{=}CH_2)]_2$ (**1**) (2.5 Mol %) and $P(4\text{-}C_6H_4CF_3)_3$ (5 Mol %) in Mesitylene at 140 °C[a]

| entry | nucleophile | vinyl arene | product (yield)[b] |
|---|---|---|---|
|  |  |  |  |
| 1 | R = H | R' = H | 75%[c] |
| 2 | R = H | R' = Cl | 63%[c] |
| 3 | R = *p*-OMe | R' = Me | 75% |
| 4 | R = *p*-Br |  | 71% |
| 5 | R = *p*-$CF_3$ |  | 62% |
| 6 | R = *p*-$CO_2Me$ |  | 59% |
| 7 | R = *p*-$CH_3$ |  | 79% |
| 8 | R = *o*-$CH_3$ |  | 74% |
| 9 |  |  |  80% |
| 10 |  |  |  77% |
|  |  |  |  |
| 11 | R = H | R' = H | 68% |
| 12 | R = H | R' = Me | 71% |
| 13 | R = OTBDMS | R' = Me | 58% |
| 14 |  |  |  57%[c,d] |
| 15 |  |  |  73% |
|  |  |  |  |
| 16 |  | R = Me | 53%[c] |
| 17 |  | R = OMe | 63%[d,e] |
| 18 |  |  |  45%[d] |

[a] See Supporting Information for reaction times. [b] Isolated yield relative to benzamide of >95% pure material. [c] Catalyst loading: **1** (5 mol %) and $P(4\text{-}C_6H_4CF_3)_3$ (10 mol %). [d] Reaction temperature = 120 °C. [e] 4-Vinylanisole (1.1 equiv) was added slowly to the reaction mixture.

with ammonia was determined to be $\Delta S \approx -30$ e.u.[19] Using these values, we estimate 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,[18] which suggests that hydroamination is reversible under these conditions. Indeed, heating a 1:1 mixture of *p*-toluamide and **2** with a catalytic 1:2 mixture of **1** and $P(4\text{-}C_6H_4CF_3)_3$ at 140 °C for 24 h formed a ~2:2:1:1 mixture of *p*-toluamide, **2**, benzamide, and *N*-(1-*p*-tolylethyl)*p*-toluamide (**3**) (Scheme 1).

**Scheme 2**



The outer-sphere attack of indoles,[9a] alkoxides,[20] and amines[21] on platinum−olefin complexes has been established. On the basis of these precedents, we propose a mechanism for the platinum-catalyzed hydroamination of vinyl arenes involving outer-sphere attack of the amide on the platinum-complexed olefin of **I** to form zwitterionic complex **II** (Scheme 2). Thermodynamic,[22] NMR,[23] and X-ray crystallographic analyses[24] of Pd(II) and Pt(II) styrene complexes point to the zwitterionic character of the M−olefin interaction that places significant positive charge on the benzylic carbon atom. Significant contribution of this resonance structure (**I**-*σ*) to the Pt−olefin interaction of **I** would account for the high Markovnikov selectivity of the platinum-catalyzed hydroamination of vinyl arenes. Loss of HCl from **II** followed by protonolysis of the Pt−C bond of the resulting platinum *β*-aminoalkyl complex **III** would release the *N*-(1-arylethyl)-carboxamide with regeneration of the $PtCl_2$ catalyst.[25]

In summary, we have developed an effective protocol for the Markovnikov hydroamination of vinyl arenes with carboxamides and related derivatives to form *N*-(1-arylethyl) amide derivatives in good yield with high regioselectivity. Our efforts are currently directed toward expanding the scope

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(19) Steinborn, D.; Taube, R. *Z. Chem.* **1986**, *26*, 349.

(20) (a) Stille, J. K.; Morgan, R. A.; Whitehurst, D. D.; Doyle, J. R. *J. Am. Chem. Soc.* **1965**, *87*, 3282. (b) Whitla, W. A.; Powell, H. M.; Venanzi, L. M. *Chem. Commun.* **1966**, 310.

(21) Panunzi, A.; De Renzi, A.; Paiaro, G. *J. Am. Chem. Soc.* **1970**, *92*, 3488.

(22) Cooper, D. W.; Powell, J. *Inorg. Chem.* **1976**, *15*, 1959.

(23) (a) Kurosawa, H.; Majima, T.; Asada, N. *J. Am. Chem. Soc*. **1980**, *102*, 6996. (b) Kurosawa, H.; Urabe, A.; Emoto, M. *J. Chem. Soc., Dalton Trans.* **1986**, 891.

(24) (a) Miki, K.; Shiotani, O.; Kai, Y.; Kasai, N.; Kanatani, H.; Kurosawa, H. *Organometallics* **1983**, *2*, 585. (b) Van der Poel, H.; Van Koten, G. *Inorg. Chem.* **1981**, *20*, 2941.

(25) Protonolysis of Pt(II) alkyl complexes with HCl and other acids has been studied in detail. These studies have established a mechanism involving protonation at platinum followed by reductive elimination from the resulting platinum(IV) hydride complex. (a) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 5961. (b) Johansson, L.; Tilset, M. *J. Am. Chem. Soc.* **2001**, *123*, 739. (c) Prokopchuk, E. M.; Puddephatt, R. J. *Organometallics* **2003**, *22*, 787. (d) Crumpton-Bregel, D. M.; Goldberg, K. I. *J. Am. Chem. Soc.* **2003**, *125*, 9442. (e) Reinartz, S.; White, P. S.; Brookhart, M.; Templeton, J. L. *Organometallics* **2000**, *19*, 3854.

and elucidating the mechanisms of the platinum-catalyzed hydroamination of unactivated olefins with carboxamides.

**Acknowledgment.** Acknowledgment is made to the NSF (CHE-03-04994) for support of this research. R.W. thanks the Camille and Henry Dreyfus Foundation and GlaxoSmith-Kline for unrestricted financial assistance.

**Supporting Information Available:** Experimental procedures and spectroscopic data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050745F