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Direct, Catalytic Hydroaminoalkylation of Unactivated Olefins with *N*-Alkyl Arylamines

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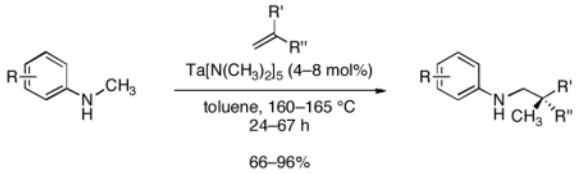
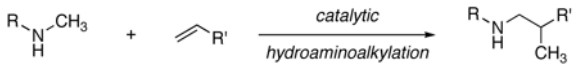
Abstract



A tantalum-catalyzed addition of *N*-alkylarylamine α-C–H bonds across olefins is reported. These reactions occur with mono- and 2,2-disubstituted olefins to form the branched insertion products in high yield and regioselectivity. The reactions encompass additions of the α-C–H bonds of cyclic and acyclic amines, as well as intramolecular additions. NMR studies indicate that the starting homoleptic, $Ta(NMe_2)_5$precatalyst converts to bis- and tris(*N*-methylanilide) complexes (amongst others) in solution. Deuterium-labeling studies suggest that reversible *ortho*-metalation of the arene substituent occurs under the reaction conditions. However, several experiments imply that this *ortho*-metalation does not lie on the reaction pathway. Instead, these complexes are proposed to eliminate amine to form *N*-aryl imine complexes, which insert olefins into the Ta–C bond and undergo protonolysis to regenerate the active catalyst and eliminate the addition product.

Recent efforts to develop the synthesis of amines from olefins have led to improved catalytic procedures for the addition of N–H bonds across olefins (hydroamination)[1] and for the tandem hydroformylation and reductive amination to form homologated amines (hydroaminomethylation)[2] We describe a complementary metal-catalyzed strategy for olefin amination: the addition of amine α-C–H bonds across olefins[3] to form branched alkylamines in a process that can be termed hydroaminoalkylation (eq 1). This reaction broadens the scope of α-functionalizations of amines that occur in the absence of typical coordinating directing groups[4, 5] to include reactions with olefins, and it displays an unusual selectivity for functionalization of saturated over aromatic C–H bonds through organometallic intermediates.



(1)

Over 20 years ago, Maspero[6] and Nugent[7] reported the α-alkylation of dimethylamine with simple olefins in the presence of homoleptic dimethylamido complexes of tantalum, niobium, and tungsten. Although this transformation was new at the time, yields did not exceed 38 %, even after one week of reaction time, and no improved conditions have since been reported. These additions were suggested[7] to occur by amine elimination to form an η^2-imine complex,[8] followed by olefin insertion into the resulting M–C bond, as shown in eq 2. Related

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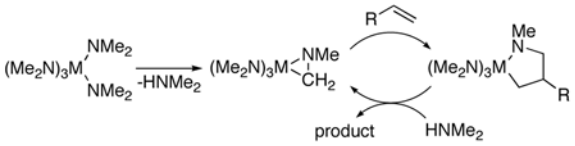
stoichiometric transformations of methylzirconocene amido complexes[9] and group V η^2-imine complexes[10] were subsequently developed. In parallel, Whitby and co-workers showed that the rate of formation of zirconocene-η^2-imine complexes was faster from *N*-alkylanilide complexes than from dialkylamido complexes.[11]



(2)

The last result suggested to us that the catalytic α-alkylation of amines might proceed more efficiently with *N*-arylalkylamines than with dialkylamines. Consistent with this hypothesis, the reaction of *N*-methylaniline with 1-octene formed the branched hydroaminoalkylation product in >95% yield within 24 h in the presence of 4 mol% $Ta(NMe_2)_5$[12a] with only a moderate excess of olefin. This reaction is shown as entry 1 in Table 1.

Reactions catalyzed by other d^0 homoleptic dialkylamido complexes, such as $Ta(NEt_2)_5$[12] (entry 2), $Nb(NMe_2)_5$[13] (entry 3), and $Zr(NMe_2)_4$[14] (entry 4), occurred to lower conversions. $Cp_2Zr(NMe_2)_2$[15] (entry 5) did not catalyze this transformation in substantial yields, although it is similar to the complexes that have been used for stoichiometric reactions of η^2-imine complexes with olefins.[9] Under otherwise identical conditions, *N*-methyl-trimethylacetamide, *N*-methyl-trifluoroacetamide, *N*-methyl-*p*-toluenesulfonamide, and *N*-methyl-methanesulfonamide did not form detectable levels of the analogous addition products, as determined by GC/MS and ^{1}H NMR spectroscopic analysis.

The scope of the olefin that reacts with *N*-methylaniline is summarized in Table 2. Mono- and 2,2-disubstituted olefins reacted in high yields (entries 1–6) using 4–8 mol% $Ta(NMe_2)_5$. Norbomene also added *N*-methylaniline in high yield (entry 7), but unstrained, 1,2-disubstituted olefins, such as *trans*-2-octene or cyclohexene, have not yet formed detectable levels of the expected alkylation products.

The selectivities of this process are notable. The branched alkylation products were formed as the sole detectable regioisomer, with the exception of the alkylaniline products shown in entry 2. Products arising from multiple alkylations were not observed. Many reactions of α-olefins are complicated by competitive isomerization processes. ^{1}H NMR analysis of these crude hydroaminoalkylation reaction mixtures revealed that only 10–20% of the unreacted olefin consisted of internal isomers. Finally, in contrast to most C–H bond functionalizations that occur through organometallic intermediates, the reactions occur preferentially at sp^3 C–H bonds over sp^2 C–H bonds.

The scope of the amine component is shown in Table 3. A variety of substituted alkylaniline derivatives added to 1-octene in high yield. For example, *N*-methyl-3,5-dimethylaniline, *N*-methyl-3,5-di-*t*-butylaniline, *N*-methyl-3,5-di-fluoroaniline, and *N*-methyl-4-fluoroaniline formed the branched addition products in high yields (entries 1, 2, 3, and 5, respectively). *N*-Methyl-4-methoxyaniline also reacted with 1-octene in high yield, and this aryl group can be cleaved from nitrogen by oxidation (entry 4).[16] The alkylation of 1,2,3,4-tetrahydroquinoline (entry 6) and *N*-(6-heptenyl)aniline (entry 7) illustrate the ability of this aminoalkylation process to form products that cannot be generated by aminomethylation with CO and H_2.

The higher yields from reactions of *N*-aryl alkylamines than from reactions of dialkylamines,[6, 7] along with the usual trend that activation of aryl C–H bonds occurs faster than activation of aliphatic C–H bonds, led us to investigate whether metalation of the aryl ring occurred during

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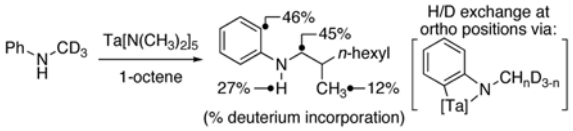
the catalytic process. Indeed, the product from reactions of *N*-(methyl-d_3)aniline contained 46% deuterium incorporation into the *ortho* position on the arene (eq 3). In addition, identical amounts of deuterium in the *ortho* position of the arene (15%) were contained in the reactant and product at 25% conversion (^{1}H NMR spectral analysis) Thus, the formation of *ortho*-metalated intermediates, as depicted in eq 3, appeals to occur faster than the overall catalytic process. However, the reaction of *N*-(methyl-d_3)-3,5-di-*tert*-butylaniline formed the expected alkylation product in 78% yield and with comparable rates to the reaction of *N*-(methyl-d_3) aniline, with only 16% deuterium incorporation into the *ortho* positions of the arene. This experiment implies that the amine α-alkylation occurs in a similar fashion when *ortho*-metalation is faster or slower than the overall process and that the *ortho*-metalation lies off of the reaction pathway. We suggest that the *N*-aryl substituents facilitate generation of an η^2-imine complex by serving as an electron-withdrawing group,[9a,11] without deactivating the catalyst by formation of a stable chelate.



(3)

To gain insight into the identity of the tantalum complexes in the catalytic system, we analyzed reactions of *N*-methyl-*p*-toludine by ^{1}H NMR spectroscopy. After heating this substrate with $Ta[N(CH_3)_2]_5$ and 1-octene in toluene at 160 °C for 3 h, the bis(anilide) and tris(anilide) complexes $[(p\text{-tol})(CH_3)N]_2Ta[N(CH_3)_2]_3$ (**1**) and $[(p\text{-tol})(CH_3)N]_3Ta[N(CH_3)_2]_2$ (**2**) (~ 1:1 ratio) accounted for >75% of the tantalum-amido species in solution (^{1}H NMR analysis).[17] Studies on the chemistry of these complexes relevant to this catalytic process are ongoing.

In summary, we have described an efficient C–H bond functionalization process that constitutes a hydroaminoalkylation of alkenes. The selectivity of this reaction appears to be controlled by the electronic properties of the amine, but this reaction does not require functionality on nitrogen, such as a pyridyl, iminyl, or carbamoyl groups, that directly coordinate to the metal.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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17. See Supporting Information for details.

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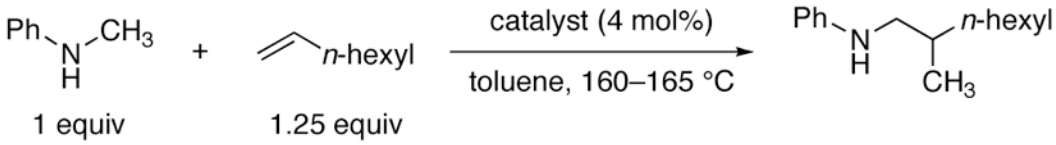
Table 1

Coupling of *N*-methylaniline and 1-octene by early metal dimethylamido complexes.



		% Yield[a]		
	Catalyst Precursor	**1.3 h**	**5.1 h**	**24 h**
1	$Ta[N(CH_3)_2]_5$	32	60	96
2	$Ta[N(CH_2CH_3)_2]_5$	23	41	66
3	$Nb[N(CH_3)_2]_5$	20	29	35
4	$Cp_2Zr[N(CH_3)_2]_2$	0.6	1.2	3.0
5	$Zr[N(CH_3)_2]_4$	0[b]	0[b]	0.1
6	none	0[b]	0[b]	0[b]

[a] Determined by GC using dodecane as an internal standard.

[b] None was observed under conditions where >0.05% could be detected.

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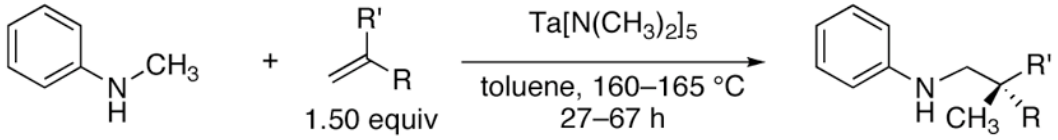
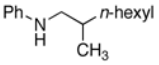
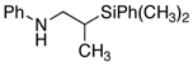
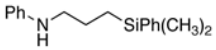
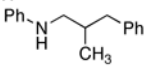
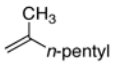
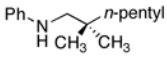
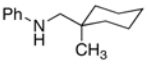
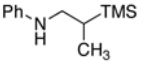
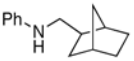
Table 2

Coupling of *N*-methylaniline with terminal olefins.



Entry	Olefin	Mol% Ta	Products(s)	Yield[a]
1		4		88%
				50%
2		4		28%
3		4		77%
4[b]		8		76%
5[b]		4		71%
6[b]		8		66%
7		4		96%

[a] Isolated yield after purification by flash-column chromatography.

[b] Reaction conducted neat.

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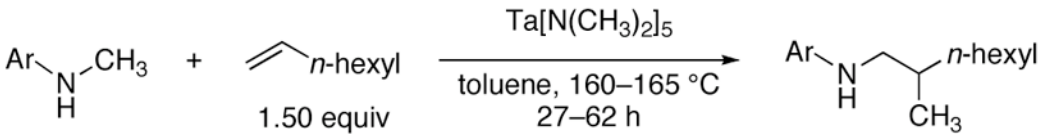
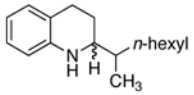
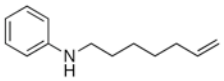
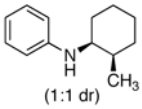
Table 3

Coupling of substituted anilines with 1-octene.



Entry	Arylamine	Product	Yield[a]
1	Ar = *m*-$(CH_3)_2$-C_6H_3		88<&
2	Ar = *m*-*t*-Bu_2-C_6H_3		93%
3	Ar = *m*-F_2-C_6H_3		84%
4	Ar = *p*-(CH_3O)-C_6H_4		90%
5	Ar = *p*-F-C_6H_4		78%
6		 (single diastereomer)	72%[b]
7		 (1:1 dr)	88%[c]

[a] Isolated yield after purification by flash-column chromatography.

[b] Reaction conducted in neat 1-octene (2.50 equiv) using 8 mol % $Ta(Nme_2)_5$; relative stereochemistry not assigned.

[c] 8 mol% $Ta(NMe_2)_5$.