Communication

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Zirconium Hydroaminoalkylation. An Alternative Disconnection for the Catalytic Synthesis of α-Arylated Primary Amines

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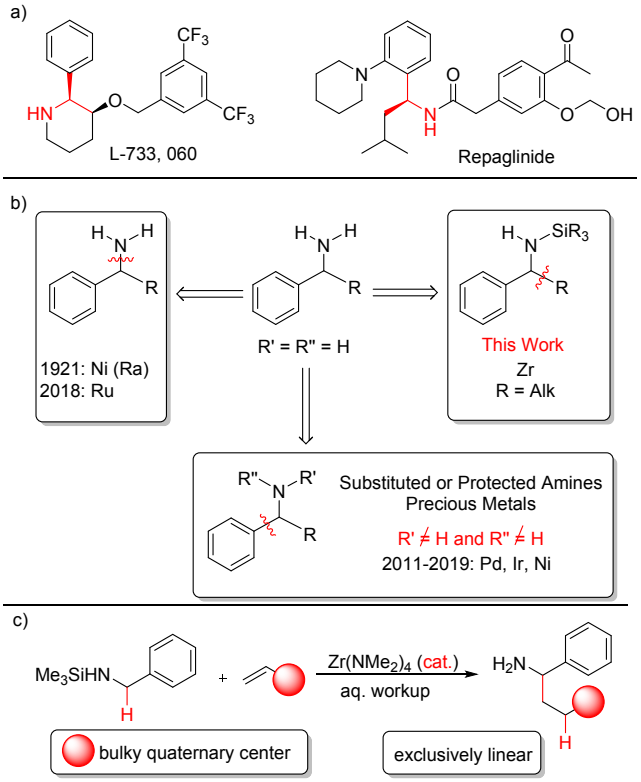
Supporting Information Placeholder

ABSTRACT: Primary amine products have been prepared using zirconium catalyzed hydroaminoalkylation of alkenes with *N*-silylated benzylamine substrates. Catalysis using commercially available $Zr(NMe_2)_4$, affords an alternative disconnection to access α-arylated primary amines upon aqueous work-up. Substrate dependent regio- and diastereoselectivity of the reaction is observed. Bulky substituents on the terminal alkene exclusively generate the linear regioisomer. This atom-economic catalytic strategy for the synthesis of building blocks that can undergo further synthetic elaboration is highlighted in the preparation of trifluoroethylated-α-arylated amines.

Primary α-arylated amines are important building blocks to prepare pharmaceuticals such as the antidepressant/anxiolytic L-733-060 and the antidiabetic repaglinide (Scheme 1a). There are three disconnections for the incorporation of an aryl group onto the α-carbon of an amine (Scheme 1b). Traditional stoichiometric transformations include reductive aminations with ammonia surrogates for C-N bond formation,[1] or nucleophilic addition of organometallic nucleophiles to protected imine intermediates to give α-arylated primary amines.[2] These routes generate stoichiometric amounts of waste while desirable catalytic variants offer reduced waste generation and often improved selectivity. Using C-N bond formation, the Mignonac reaction delivers the primary 1-phenylethylamine via reductive amination between acetophenone and ammonia, with a nickel catalyst, high pressure and heating.[3] More recently ruthenium catalyzed syntheses of primary amines were reported using carbonyl substrates.[4] Alternatively, the direct introduction of the aryl group via catalytic Csp^2-Csp^3 bond formation requires *N*-



Scheme 1. a. Examples of pharmaceuticals with α-arylated primary amines b. Disconnections and catalytic routes to prepare α-arylated primary amines c. Current work on zirconium catalyzed hydroaminoalkylation.

directing/protecting groups and subsequent reactions to afford primary α-arylated amine products.[5] An underexplored catalytic disconnection uses benzylamine substrates and catalytic Csp^3-Csp^3 bond formation α- to nitrogen. Here we show that catalytic hydroaminoalkylation of alkenes with *N*-

silylbenzylamine enables the isolation of primary α-arylated amines upon workup (Scheme 1c).

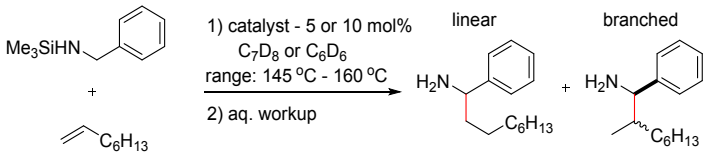
Hydroaminoalkylation is an atom-economic, emerging catalytic tool for the synthesis of Csp^3-Csp^3 bonds α- to nitrogen in both secondary and tertiary amine substrates.[6] Early transition metal,[7] late transition metal[8] and photoredox catalysis[9] feature mechanistically distinct hydroaminoalkylation reactions for the assembly of selectively substituted amines and *N*-heterocycles using simple alkenes as the alkylating agent. Control of regioselective hydroaminoalkylation remains a challenge with early transition metal catalysts that favor branched products[7f-h, 10] while late transition metal catalysts typically favor linear products.[8a, 8d, 8e, 11] Rovis and coworkers recently showed that primary amines protected as sulfonamides can be used for the hydroaminoalkylation of electron-deficient alkenes using visible-light photoredox catalysis.[9b] In early transition metal catalysis unprotected primary aminoalkene substrates can deliver aminated cycloalkanes by titanium or zirconium catalyzed *intramolecular* hydroaminoalkylation.[12] However, *intermolecular* hydroaminoalkylation of primary amines is unknown. Meanwhile, *N*-silylated amines have been used by Buchwald and co-workers for stoichiometric zirconium mediated C-C reductive coupling with alkynes to deliver unprotected primary allylamines upon workup.[13] Furthermore, we showed that *N*-silylated amines can be used in catalytic alkyne hydroamination (C-N bond formation) to give primary amine products after reduction and work-up.[14] We questioned if *N*-silylated amines could be used in catalytic hydroaminoalkylation to yield primary amine products suitable for further synthetic elaboration.

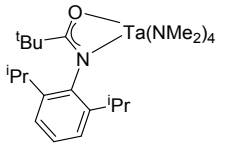
Here we show an alternative disconnection for the catalytic synthesis of α-arylated primary amines featuring the hydroaminoalkylation of activated and unactivated alkenes with *N*-silylated benzyl amines. Simple commercially available $Zr(NMe_2)_4$ was found to catalyze Csp^3-Csp^3 bond formation via C-H bond activation α-to nitrogen to give the desired products upon aqueous work-up (Scheme 1b). Furthermore, in the presence of sterically bulky vinyl substrates, the linear product is obtained exclusively (Scheme 1c). These primary amine products can be used as building blocks in further functionalization reactions relevant to medicinal chemistry, as demonstrated in the synthesis of *N*-trifluoroethylated α-arylated amine small molecules.

Results and Discussion

Initial tests focused on attempts to use *N*-silylated benzylamine as a substrate for hydroaminoalkylation with reported tantalum and titanium hydroaminoalkylation catalysts (Table 1, entries 1 - 5).[7f, 7h, 10b, 15] Known Ta catalysts were completely ineffective while reactivity with $Ti(NMe_2)_4$ gave a low yield of a mixture of regioisomers in a 1:1 ratio, with poor diastereoselectivity (2:1) for the branched products. The observed reactivity with Ti(IV), with only 4 ligands about the metal center in contrast to the 5 ligands of the similarly sized Ta (V) metal center, suggested that enhanced steric accessibility to the metal center is required for realizing reactivity with the sterically demanding silylated benzylamine substrates. Thus, to access a more sterically accessible metal center the larger covalent radius of Zr in $Zr(NMe_2)_4$ was tested (Table 1, entry 6). In this case an improved combined yield of 55% was observed with a 1:2 ratio of linear:branched products and a dr of 3:1. Thus, as well as offering higher yields, the Zr catalyst afforded products with modestly improved regioselectivity and diastereselectivity.

Table 1. Precatalyst screening for intermolecular HAA with *N*-silylbenzylamine.



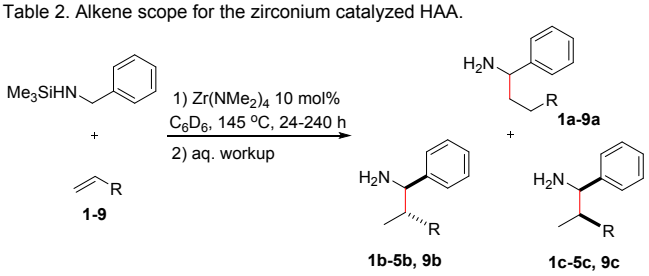
Entry	Precatalyst[a, b]	Time (h)	Yield[c]	Selectivity L:B	dr
1	$Ta(NMe_2)_5$	up to 96	-	-	-
2		up to 96	-	-	-
3	$Ta(CH_2SiMe_3)_3Cl_2$	up to 96	-	-	-
4	$[Ta(NMe_2)_3Cl_2]_2$	up to 96	-	-	-
5	$Ti(NMe_2)_4$	72	28	1:1	2:1
6	$Zr(NMe_2)_4$	72	55	2:1	3:1

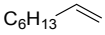
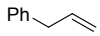
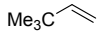
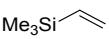
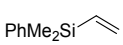
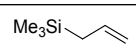
Reactions performed at a 0.5 mmol scale. Amine:alkene mmol ratio 1:1.5 for tantalum HAA; 1:1.8 for titanium and zirconium HAA. [a]Homoleptic complexes: 10% of precatalyst loading, solvent: C_6D_6 for Ti and C_7D_8 for Ta; Non-homoleptic complexes: 5% of precatalyst loading, solvent C_7D_8. [b]For tantalum HAA: up to 160 °C; for titanium and zirconium HAA: reactivity at 145 °C. [c] Isolated yield of mixture of regio- and diastereomers.

Next a series of alkenes (1-9) were evaluated for zirconium catalyzed hydroaminoalkylation with *N*-silylated benzylamine (Table 2). Results demonstrate the favored formation of the branched product when there is little steric bulk incorporated into the alkene (Entries 1-3). As the terminal alkene becomes increasingly sterically demanding, such as with vinylcyclohexane (Entry 4) the formation of the linear product is favored (linear:branched 3:1) and the even more sterically demanding 2-methylstyrene (Entry 5, Table 2) generated mostly linear product (17:1

linear:branched). The ratio of diastereomers formed for all products with alkyl substituents, regardless of steric bulk, was 3:1, while for 2-methylstyrene the ratio was 7:1, as determined by ^{1}H NMR spectroscopy (See SI). Further examination of the effect of steric bulk showed that incorporation of a sterically demanding quaternary center on the alkene affords exclusively the linear product (Entry 6). Notably, this is the first example of catalytic hydroaminoalkylation with such a sterically demanding unactivated substrate. This tolerance to steric bulk suggests that activated vinylsilanes could be used in these reactions, while offering functionality suitable for further synthetic elaboration. As shown in Entries 7 & 8, only linear products are observed as noted by an apparent triplet at 3.76 and 3.79 ppm in the benzylic region of the ^{1}H NMR spectra for products **7a** and **8a**, respectively (See SI). Vinyl silanes afford improved reactivity, in addition to complete regioselectivity. Notably, allyltrimethylsilane (Entry 9), the next homologue, affords the product with almost the opposite regioselectivity (1:7 linear:branched), once again illustrating profound substrate controlled regioselectivity. This simple catalyst cannot promote the hydroaminoalkylation of internal alkenes.

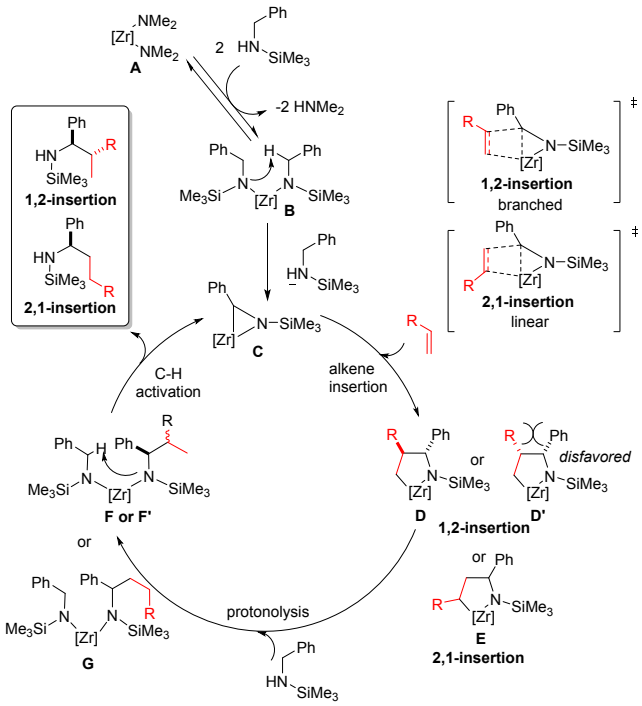
Table 2. Alkene scope for the zirconium catalyzed HAA.



Entry	Alkene (1-9)	Time (h)	Yield % (a+b+c)[a]	Selectivity [a:(b+c)][b]	dr b/c[b]
1		48	78	1:3	3:1
2		72	55	1:2	3:1
3		72	82	1:2	3:1
4		72	66	3:1	3:1
5		48	56	17:1	7:1
6		240	47	99:1	-
7		24	52	99:1	
8		24	58	99:1	-
9		240	68	1:7	3:1

Reactions performed at a 0.5 mmol scale. Amine:alkene mmol ratio 1:1.8. Catalyst loading: 10 mol%. [a]Isolated yields of mixtures of regio- and diastereoisomers. [b]Regio- and diastereoselectivity ratios calculated based on the relative integrations of the benzylic peaks of the ^{1}H NMR spectra of the isolated mixtures of regio- and diastereoisomers (see SI).

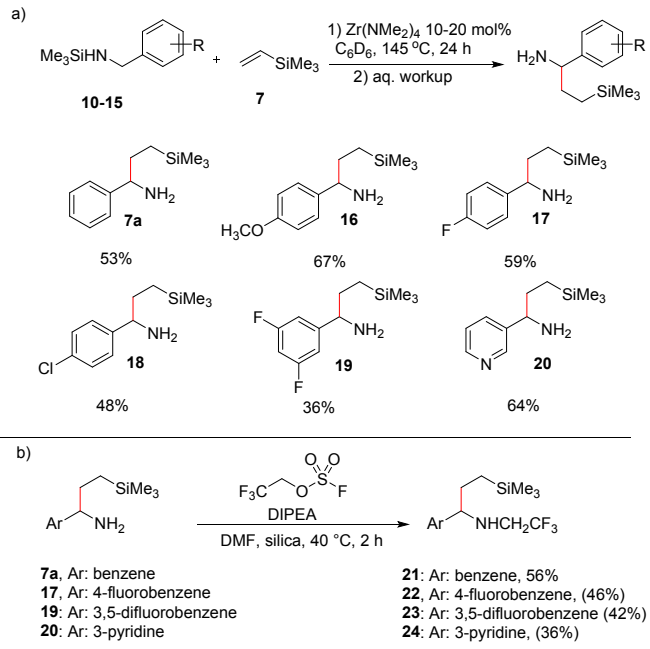
Analysis of the proposed mechanism for early transition metal catalyzed hydroaminoalkylation presented in Scheme 2,[6a, 7f, 16] provides a rationale for the change in regioselectivity and preferred diastereomer formation when using the sterically demanding silylbenzylamine substrate. Transamination of the amido groups of complex **A** with *N*-silylamine leads to complex **B,** which upon hydrogen abstraction leads to catalytically active zirconaaziridine **C**. Zirconaaziridine **C**, with its phenyl substituent, undergoes alkene insertion into the more reactive C-C bond and forms the zirconapyrrolidine intermediate **D** or **E**, where the steric bulk of the alkene affects the regioselectivity of the reaction. In the formation of intermediate **D** two diastereomers can result (**D** and **D'**), with the *trans*-orientation of the metallacyclic intermediates giving the major diastereomer.[17] This is consistent with computational investigations of early transition metal catalyzed hydroaminoalkylation[7b, 18] which propose that polarized, activated alkenes, such as vinyl silanes, offer enhanced reactivity and modified regioselectivity due to substrate and catalyst dependent electronic control. For example, a bulky Ti complex affords the linear product with dimethylphenylvinylsilane[7e] while Ta hydroaminoalkylation catalysts offer mixtures of regioisomers with vinylsilane substrates.[7g, 15]



Scheme 2. Proposed mechanism, including regioselective and diastereoselective reactivity, in the hydroaminoalkylation of alkenes with *N*-silylamines.

Finally, the five-membered intermediates **D, D'** or **E** undergo protonolysis with an incoming equivalent of amine to give rise to zirconium complex **F**, **F'** or **G** which in turn, upon hydrogen abstraction leads to reformation of zirconaaziridine **C** with concomitant liberation of the desired α-arylated amine products.

With substrate controlled regioselectivity in hand, we synthesized a series of *N*-silylated benzylamines from commercially available starting materials (see SI). This catalytic approach allows for the facile synthesis of variously substituted α-aryl primary amines using this alternative disconnection (Scheme 3a). With the *meta*- and *para*-substituted *N*-silylated benzylamines, either electron-withdrawing or electron-donating groups afford reactivity leading to primary amines in low to moderate yields (36-67%). We were pleased to note that heteroaromatic substrates (**20**) could also be accommodated.



Scheme 3. a. Amine scope. Reactions performed at a 0.5 mmol scale. Amine:vinylsilane mmol ratio 1:1.8. Catalyst loading: 10 mol% for amines 7a, 18-23; 20 mol% for amine 24. b. Trifluoroethylation of the linear primary amines. Isolated yields are reported with ^{19}F NMR yields in parentheses.

Ready access to a family of α-arylated primary amine building blocks offered the opportunity to pursue further substitution to make small molecules that may be suitable for application in medicinal chemistry. The pharmaceutical value of 2,2,2-trifluoroethylated amines lies in the modified amine basicity, which in turn defines the targeted delivery of potential pharmaceuticals.[19] Furthermore, the incorporation of fluorinated substituents is known to increase the lipophilicity and bioavailability of the resulting molecules.[20] Consequently, a recently developed strategy for the efficient installation of trifluoroethylated substituents onto primary amines[21] was exploited to further functionalize the unprotected products obtained from hydroaminoalkylation. Thus, amines **7a**, **17**, **19** and **20** were trifluoroethylated using sulfuryl fluoride and 2,2,2-trifluoroethanol to give new α-arylated-fluorinated secondary amine derivatives in yields ranging from 36-56% (Scheme 3b). This sequential transformation highlights the modular, catalytic approach for the facile assembly of unprotected small molecules ready to be used in further synthesis.

Conclusions

To summarize, we have developed the first example of intermolecular zirconium catalyzed hydroaminoalkylation for primary amines. The increased steric accessibility of this 4-coordinate early transition metal has allowed for the use of the sterically demanding *N*-silylbenzylamine substrates in hydroaminoalkylation to access primary α-arylated amines directly. This approach featuring readily modified benzyl amine substrates and simple alkenes offers a complementary catalytic Csp^3-Csp^3 disconnection strategy to prepare these small molecules that may be building blocks for the assembly of biologically active products. The use of zirconium, combined with steric substrate control, offers selective access to the linear regioisomer. Finally, this catalytic preparation of unprotected primary amines can be isolated, purified and subjected to further modification to obtain fluorinated secondary amine building blocks. Future work includes reaction sequence development to access amino acid derivatives, as well as catalyst development to improve catalytic activity and regio- and stereoselectivity of this synthetic approach.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:
Full experimental procedures and spectroscopic data

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Author Contributions

All authors contributed equally.

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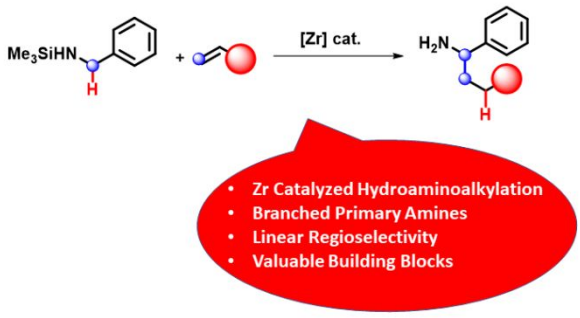
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• Zr Catalyzed Hydroaminoalkylation
• Branched Primary Amines
• Linear Regioselectivity
• Valuable Building Blocks