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Tetrabenzylhafnium as a New Organometallic Reagent for Imine Addition Resulting in α-Branched Amines

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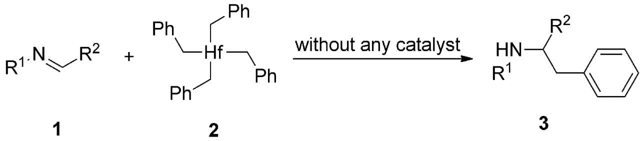
Tetrabenzylhafnium has been explored as a new organometallic reagent for the imine addition reaction. This reagent tolerates a wide scope of imines, affording α-branched amines in excellent yields without the use of any additive or catalyst. This new reagent shows higher efficiency than that observed for classic Grignard and organolithium reagents.

Introduction

The development of addition reactions between organometallic reagents and imines has become an interesting and challenging topic in modern organic chemistry,[1] because this approach has served as one of the most attractive routes to α-branched amines, which belong to an extremely important class of compounds used in synthetic methodologies and in bioorganic and medicinal chemistry, and such functionalities have been found in many natural products as well as pharmaceutically related compounds.[2,3] In the past decades, several main group metals and early transition metals have been developed as organometallic nucleophiles for addition reactions to imines, especially in their asymmetric forms. Pioneering work in this area included the study of organolithium,[4] Grignard,[5] and dialkylzinc[6] reagents. Following these early successes, more organometallic reagents, such as organostannanes,[7] allylsilanes,[8] aryltitaniums,[9] alkylcoppers,[10] and arylboroxines,[11] were explored for addition reactions to imines, but such reactions usually required additional catalysts.

Group 4 halides and their derivatives have been developed as precursors for use in chemical vapor deposition and atomic layer deposition of microelectronic thin films.[12] Furthermore, titanium and zirconium compounds have been widely used as efficient catalysts or reagents in a variety of organic reactions during the past few years.[13] In contrast, related applications of hafnium compounds in organic synthesis still remain in their preliminary stages. Until now, there were only limited examples reported for hafnium derivatives as catalysts used in organic methodologies[14] and olefin polymerization.[15] In 2009, Shibata and coworkers reported a highly α-selective addition reaction of prenyltributyltin to imines, which was believed to proceed through transmetalation between allyl-$SnBu_3$ and $HfCl_4$ in situ.[16] Meanwhile, many reports have shown that tetraalkylhafniums could be conveniently prepared from $HfCl_4$.[17] Tetraalkylhafnium reagents are sensitive to air and moisture. Furthermore, these organometallic compounds show the ability to coordinate with amines and carbonyl groups.[18] Inspired by these reports and our recent studies on hafnium, we conceived that a tetraalkylhafnium may be developed as a new type of organometallic nucleophile for the addition reaction to imines. Herein, we report that tetrabenzylhafnium was used as an efficient organometallic reagent for the addition to imines, affording α-branched amines under mild and convenient conditions (Scheme 1). It is noteworthy that hafnium is yet another metal that can be used as an organometallic reagent in nucleophilic addition reactions, in addition to previously reported lithium, magnesium, zinc, stannum, silicon, copper, and boron.[4–11]



Scheme 1. Tetrabenzylhafnium nucleophilic addition to imines.

Results and Discussion

At the beginning of the exploration, N-tosylimine (**1a**) and tetrabenzylhafnium (**2**) were chosen as substrates. The reaction was carried out with acetonitrile as solvent at 15 °C (Table 1).[16] Fortunately, the reaction proceeded smoothly, affording α-branched amine **3a** in good yield af-

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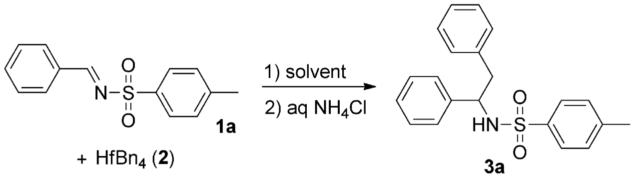
ter 2 h (81%; Table 1, Entry 1). Encouraged by the initial result, the optimization of the reaction conditions was then carried out to improve the reaction efficiency. Various solvents were screened (Table 1, Entries 2–7), and THF was found to be the best choice, resulting in 88% yield. Screening of the reaction time disclosed that this transformation proceeded quickly and was complete within 30 min (Table 1, Entry 9). Extending the reaction time resulted in a slight decrease in the yield. Further examination revealed that the temperature was not crucial for this reaction. Lowering the reaction temperature to 0 or to –20 °C showed no obvious effect on the yield (Table 1, Entries 10 & 11). Finally, the loading of tetrabenzylhafnium was examined, and it was found that the use of 1.2 equiv. of **2a** gave the highest yield (92%; Table 1, Entry 13). Further investigation found that a very low yield was obtained when 0.3 equiv. of tetrabenzylhafnium was used in the reaction (17%; Table 1, Entry 14), and this is probably because only one benzyl group could be transferred from the hafnium reagent during the addition process.

Table 1. Optimization of reaction conditions.[a]

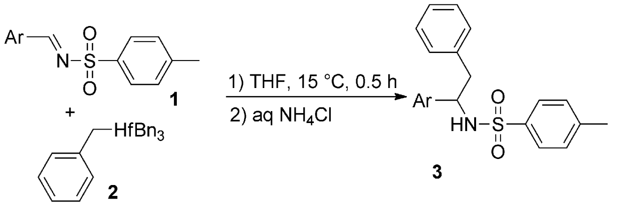


Entry	Solvent	Time [min]	T [°C]	HfBn$_4$ [equiv.]	Yield [%][b]
1	CH_3CN	120	15	1.5	81
2	toluene	120	15	1.5	20
3	CH_2Cl_2	120	15	1.5	54
4	$CHCl_3$	120	15	1.5	31
5	hexane	120	15	1.5	trace
6	Et_2O	120	15	1.5	74
7	THF	120	15	1.5	88
8	THF	15	15	1.5	81
9	THF	30	15	1.5	90
10	THF	30	–20	1.5	86
11	THF	30	0	1.5	89
12	THF	30	15	1.0	83
13	THF	30	15	1.2	92
14	THF	30	15	0.3	17

[a] Reaction conditions: imine (0.5 mmol), solvent (5 mL). [b] Isolated yield.

After determining the optimized reaction conditions, a variety of *N*-tosylimines was studied to investigate the scope of the new addition process (Table 2). Tetrabenzylhafnium could directly add to all the imines without any catalyst or additive, resulting in good to excellent yields of the products (84–98%). Variation of the substituents on the aromatic rings did not have a significant effect on the chemical yield. Both electron-rich (Table 2, Entries 4 & 9) and electron-deficient (Table 2, Entries 2, 3, 6, and 7) aryl-substituted imines worked well, and even substituents such as fluoride (Table 2, Entry 8) and methoxy (Table 2, Entries 5 & 10) were tolerated. Notably, 2-naphthylimine (**1k**) was also well tolerated in this reaction, and the corresponding product was obtained in high yield (88%; Table 2, Entry 11). Furthermore, these obtained α-branched *N*-tosyl-protected amines belong to an important class of biologically active compounds, and the reported synthetic methods for them were limited to the ring opening of aziridines until now.[19]

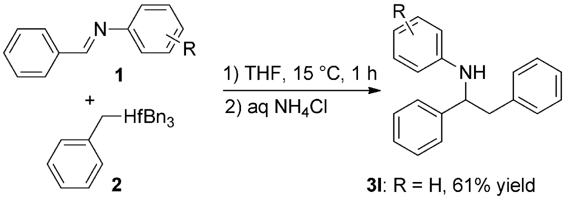
Table 2. Scope of imines for the addition with HfBn$_4$.[a]



Entry	Substrate	Ar	Product	Yield [%][b]
1	**1a**	Ph	**3a**	92
2	**1b**	2-ClC_6H_4	**3b**	91
3	**1c**	2-BrC_6H_4	**3c**	93
4	**1d**	2-$CH_3C_6H_4$	**3d**	93
5	**1e**	2-$OCH_3C_6H_4$	**3e**	89
6	**1f**	3-ClC_6H_4	**3f**	85
7	**1g**	3-BrC_6H_4	**3g**	86
8	**1h**	4-FC_6H_4	**3h**	92
9	**1i**	4-$CH_3C_6H_4$	**3i**	84
10	**1j**	4-$OCH_3C_6H_4$	**3j**	98
11	**1k**	2-naphthyl	**3k**	88

[a] Reaction conditions: imine (0.5 mmol), HfBn$_4$ (0.6 mmol), THF (5 mL), 15 °C. [b] Isolated yield.

Then, the optimized reaction conditions were applied to other less-active imines, which were generated from aniline (Scheme 2). To our delight, tetrabenzylhafnium could also add directly to these imines to afford the desired products, although obvious lower chemical yields were observed, especially for imines lacking a substituent.

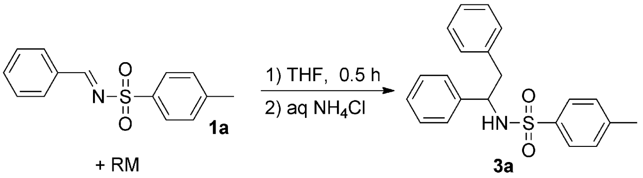


3l: R = H, 61% yield
3m: R = 4-MeO, 79% yield

Scheme 2. Tetrabenzylhafnium addition to imines **1l** and **1m**.

The reactivity of this new organometallic reagent was then examined by comparing it with well-known organometallic reagents, such as benzylmagnesium chloride and benzyllithium (Table 3). Tetrabenzylhafnium, benzylmagnesium chloride, and benzyllithium were used as nucleophiles in the addition reaction to add *N*-tosylimine (**1a**) under the same conditions at 15 °C. As shown in Table 3, tetrabenzylhafnium showed the highest efficiency. BnMgCl added to **1a**, although an obvious lower yield was observed (46%; Table 3, Entry 2) and no byproduct was detected. When using benzyllithium as the nucleophile, only a trace amount of the desired product was detected (Table 3, Entry 3) and a large amount of the imine substrate was recovered. Similar results were observed when the reaction temperature was decreased to –20 °C (Table 3, Entries 4–6). These above results disclosed that the preliminary trend for the addition reactivity is in the order of tetrabenzylhafnium > benzylmagnesium chloride > benzyllithium.

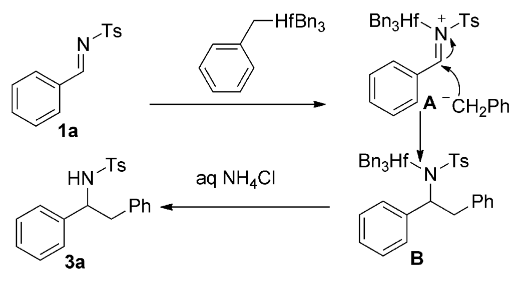
Table 3. Addition to imine **1a** with different organometallic reagents.[a]



Entry	RM	T [°C]	Yield [%][b]
1	$HfBn_4$	15	92
2	BnMgCl[c]	15	46
3	BnLi[d]	15	trace
4	$HfBn_4$	–20	86
5	BnMgCl[c]	–20	41
6	BnLi[d]	–20	n.r.

[a] Reaction conditions: imine (0.5 mmol), RM (0.6 mmol), solvent (5 mL). [b] Isolated yield. [c] 20 wt.-% in THF. [d] 1.2 M in hexane.

Based on previous reports of the addition of organometallic reagents to imines,[1] one proposed pathway to account for this new process is offered in Scheme 3. In the initial step, tetrabenzylhafnium coordinates with the lone pair of electrons on the nitrogen atom of the imine and activates imine **1a**, resulting in intermediate **A**. This coordination mode has also been found in other reported hafnium complexes.[18] Then, intermediate **A** undergoes nucleophilic addition by the benzylic anion, giving intermediate **B**. The reaction is finally quenched by aqueous NH_4Cl to form product **3a**. In this process, coordination with the strong Lewis acid hafnium compound is believed to significantly enhance the electrophilicity of the C=N bond, which makes the addition of the benzyl carbanion easier. This may contribute to the very smooth and quick transformation without any catalyst.



Scheme 3. Proposed mechanism for the addition of tetrabenzylhafnium.

Conclusions

In summary, tetrabenzylhafnium has been developed as a new organometallic reagent for the addition to imines, which can greatly expand the research on hafnium metal. The new system allowed the reaction to proceed smoothly under mild conditions and tolerates a wide scope of substrates, affording α-branched amines in excellent yields without the use of any additive or catalyst. This reagent also shows higher efficiency when compared with classic Grignard and organolithium reagents. Further research will focus on the investigation of the asymmetric reaction and the application of this organometallic reagent to other nucleophilic addition reactions.

Experimental Section

General Information: All imine addition reactions were performed in oven-dried vials under a N_2 atmosphere. THF was dried and distilled prior to use. $HfBn_4$[17] and all the imines[20] were prepared according to reported methods. Other chemicals were used as obtained from commercial sources without further purification. Flash chromatography was performed using silica gel 60 (200–300 mesh). Thin-layer chromatography was carried out on silica gel 60 F-254 TLC plates (20 cm × 20 cm). IR spectra were collected with a Bruker Vector 22 in KBr pellets. ^1H and ^{13}C NMR (TMS used as internal standard) spectra were recorded with a Bruker ARX 300 spectrometer. High-resolution mass spectra for all the new compounds were obtained by using a Micromass Q-Tof instrument (ESI).

Tetrabenzylhafnium (2): Powdered Mg (50 mmol), diethyl ether (5 mL), I_2 (one grain) were combined in a 100-mL round-bottomed flask equipped with a positive flow of nitrogen and a condenser. After initiation (the color of I_2 disappeared), the corresponding substituted benzyl chloride (46 mmol) dissolved in diethyl ether (50 mL) was added dropwise over 30 min with stirring. The reaction mixture was heated at reflux for 1 h and then cooled to –40 °C. $HfCl_4$ (13 mmol) was added to the mixture, which was then stirred for 3 h in the dark, covering the flask with aluminum foil. The solvent was removed under vacuum, and the residue was extracted with CH_2Cl_2. Again, CH_2Cl_2 was removed under vacuum to afford the yellow solid, which was recrystallized from hot heptane to give desired product **2**.

Procedure for the Addition of $HfBn_4$ to *N*-Tosylimines: To an oven-dried reaction vial flushed with N_2 was added $HfBn_4$ (0.6 mmol), anhydrous THF (5.0 mL), and the respective *N*-tosylimine (0.5 mmol). The reaction mixture was stirred at 15 °C for 0.5 h and quenched with saturated NH_4Cl (3.0 mL), followed by H_2O (5.0 mL). The organic layer was removed, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by TLC plate (hexane/EtOAc, 6:1).

Procedure for the Addition of $HfBn_4$ to *N*-Phenylimines: To an oven-dried reaction vial flushed with N_2 was added $HfBn_4$ (0.6 mmol), anhydrous THF (5.0 mL), and the respective *N*-phenylimine (0.5 mmol). The reaction mixture was stirred at 15 °C for 1 h and then quenched with saturated NH_4Cl (3.0 mL), followed by H_2O (5.0 mL). The organic layer was removed, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by TLC plate (hexane/EtOAc, 10:1).

Procedure for the Addition of Organometallic Reagents to Imine 1a: To an oven-dried reaction vial flushed with N_2 was added imine **1a** (0.5 mmol), anhydrous THF (5.0 mL), and the respective organometallic reagent (0.6 mmol). The reaction mixture was stirred at the expected temperature for 0.5 h and then quenched with saturated NH_4Cl (3.0 mL), followed by H_2O (5.0 mL). The organic layer was removed, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated to give the crude product, which was purified by TLC plate (hexane/EtOAc, 6:1).

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of all the products.

Acknowledgments

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