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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201909151
Angew. Chem. 10.1002/ange.201909151

Link to VoR: http://dx.doi.org/10.1002/anie.201909151
http://dx.doi.org/10.1002/ange.201909151

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COMMUNICATION

Ti-Mediated Synthesis of Spirocyclic *NH*-Azetidines from Oxime Ethers

Nicole Erin Behnke[a]+, Kaitlyn Lovato[a]+, Muhammed Yousufuddin[b], and László Kürti*[a]

Abstract: The Ti(IV)-mediated synthesis of spirocyclic *NH*-azetidines from oxime ethers with an alkyl Grignard reagent or terminal olefin ligand-exchange coupling partner is described. Through a proposed Kulinkovich-type mechanism, a titanacyclopropane intermediate forms that can act as a 1,2-dialkyl anion equivalent and inserts into the 1,2-dielectrophilc oxime ether to ultimately give rise to the desired *N*-heterocyclic four-membered ring. This transformation proceeds in moderate yield to furnish previously unreported and structurally diverse *NH*-azetidines in a single step.

The synthesis of substituted azetidines has become an emerging interest to synthetic chemists as these small nitrogen heterocycles display promising and significant biological activity and efficacy in active pharmaceutical ingredients.[1] For example, the 2-arylazetidine scaffold has been shown to display similar binding affinity for the nicotinic acetylcholine receptor (nAChR) compared to known nAChR agonists (e.g. nicotine and carbachol), which are promising therapeutic leads for conditions such as Parkinson's disease, Tourette's syndrome, attention deficit disorder etc.[2] The bioisosteric replacement of a larger nitrogen heterocycle (i.e. piperidine) with its four-membered counterpart was shown to improve the potency and stability of a serotonin receptor subtype 2C (5-HT2C) agonist (Figure 1).[3] It is also worth noting that the marketed pharmaceuticals Azelnidipine (CalBlock®) and Ximelagatran (Exanta®) both possess an azetidine moiety (Figure 1).[4] Additionally, Penaresidin A, a natural product isolated from a marine sponge, has an *NH*-azetidine moiety and has been observed to possess actomyosin ATPase-activation activity, further exemplifying the importance of this structural motif.[5] Given the utility of the azetidine ring and the previously unreported 1-azaspiro[3.5]nonane *NH*-azetidine structures (Scheme 1C), we set out to identify a new method that would provide synthetic access to these types of molecules.

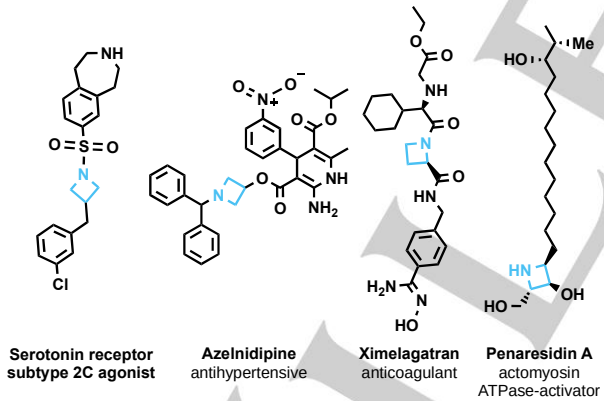
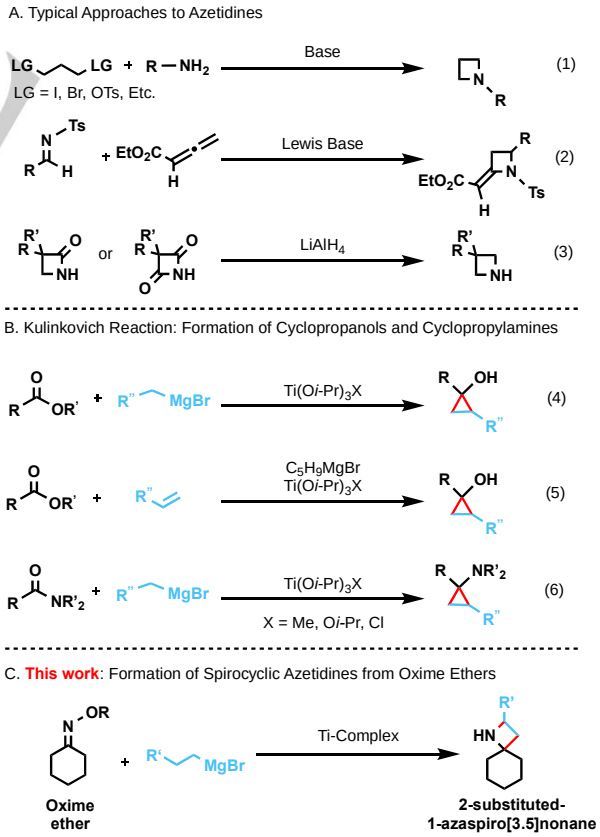


Figure 1. Biologically active compounds with azetidine rings.

Currently, many synthetic methods exist to access a variety of *N*-protected azetidine scaffolds.[6] For example, *NR*-azetidines can be synthesized from 1,3-halo compounds or 1,3-diol derivatives via double alkylation of a primary amine (Scheme 1, A1).[7] Substituted azetidines can also be synthesized via various [2+2] cycloadditions, including the reaction of aldimines with ethyl 2,3-butadienoate under Lewis basic conditions (Scheme 1, A2).[7-8] *NH*-azetidines have been successfully synthesized from pre-functionalized starting materials (i.e. 2-azetidinones and malonimides) via reduction using $LiAlH_4$ (Scheme 1, A3).[9] However, few ring substituents can survive these harsh conditions. Despite significant advances in this field, a simple and direct synthesis of spirocyclic *NH*-azetidines has remained



Scheme 1. Methods for the synthesis of azetidines.

[a] N.E. Behnke+, K. Lovato+, Prof. Dr. L. Kürti
Department of Chemistry
Rice University
6500 Main Street, Houston, TX, 77030 (USA)
E-mail: kurti.laszlo@rice.edu
[b] Dr. M. Yousufuddin
Life and Health Sciences Department
The University of North Texas at Dallas
7400 University Hills Boulevard, Dallas, TX, 75241 (USA)
[+] These authors contributed equally to this work.

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elusive. Given our group's interest in electrophilic amination and heterocycle synthesis, we initiated our study by investigating the possibility of converting oxime ethers into *NH*-azetidines in a single step.[10]

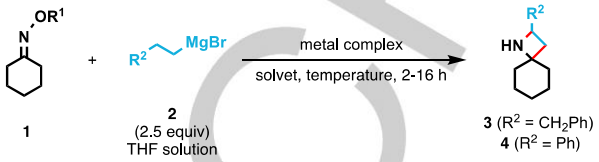
We became attracted to the idea that the mechanism of the Kulinkovich reaction could be employed to synthesize the desired 1-azaspiro[3.5]nonane heterocyclic scaffolds.[11] The standard Kulinkovich reaction utilizes esters and a Grignard reagent to synthesize cyclopropanols through a titanacyclopropane intermediate (Scheme 1, B4).[12] Several variations of this reaction exist, including ligand exchange with olefins and reactions of amides and nitriles with a Grignard coupling partner to form cyclopropanols and cyclopropyl amines (Scheme 1, B5-6)).[13] For this study, we decided to focus on the process that incorporates the Grignard reagent into the final product. We proposed that *O*-alkyl oximes, which possess a leaving group on the imine nitrogen and differ electronically from the usual starting materials used to synthesize cyclopropanols and cyclopropyl amines, would be ideal substrates for this Kulinkovich-type synthesis of *NH*-azetidines.

Using cyclohexane oxime ethers and primary alkyl Grignard reagents, we began the optimization process under similar conditions utilized in traditional Kulinkovich reactions (Table 1). To our delight, a preliminary proof-of-concept experiment (Table 1, entry 1) successfully formed spirocyclic *NH*-azetidine **3** in 14% isolated yield. Our initial screens focused on modifying the nature of the leaving group. With bulkier leaving groups (Table 1, entry 1 vs 2-4), only trace quantities or none of the desired product were observed. To investigate the requirement of a leaving group, the unsubstituted oxime was tested as a control and, as predicted, did not yield the corresponding azetidine in measurable quantities (Table 1, entry 5). Moving forward, the least hindered methyl group was used as the ideal oxime *O*-substituent. During the optimization studies, it was discovered that raising the temperature from 0 °C to room temperature improved the efficiency of the reaction (Table 1, entry 2 vs 6).

Next, the nature of the metal complex and its loading were evaluated. Investigating a variety of ligands on the Ti(IV) species did not significantly improve the outcome and even restricted the reaction pathway in several instances (Table 1, entries 7-9). With another Group(IV) metal complex, the oxime ether did not react (Table 1, entry 10). Instead, a stoichiometric amount of the inexpensive and easy-to-handle[14] Ti(O*i*-Pr)$_4$ was chosen and this produced 40% of azetidine **4** (Table 1, entry 11). All attempts to render this process catalytic were unsuccessful (Table 1, entry 12). Using a mixed ethereal system (Et_2O/THF) by adding Et_2O to the THF solution of the Grignard reagent resulted in improved yield (Table 1, entry 11 vs 13-14). Increasing the temperature to 40 °C did not improve the yield of the reaction (Table 1, entry 15). Without extensive literature on the isolation of *NH*-azetidines, a significant challenge arose in screening of workup and chromatography conditions for these four-membered polar and somewhat unstable 2º amines[15] (see Supporting Information for details). Overall, the optimization screens revealed that the formation of an *NH*-azetidine from an oxime ether in combination with 2.5 equivalents of the Grignard reagent and a stoichiometric amount of Ti(O*i*-Pr)$_4$ proceeds best over a period of 6 hours at ambient temperature (Table 1, entry 16).

Using the optimized reaction conditions, the scope of *NH*-azetidine formation from oxime ethers (**5**) and primary Grignard reagents with hydrogens in the beta-position (**6**) was examined (Scheme 2). The scale-up of azetidine **4** from 1.0 to 2.5 mmol proceeded well with a slight increase in the isolated yield (51% to 53%). To create product diversity, the length of the aliphatic chain and electronic properties of the phenyl ring of the Grignard reagent were modified to synthesize spirocyclic azetidines **8-11** in good yield. To the best of our knowledge, none of these *NH*-azetidines have been previously reported. Therefore, we confirmed the structure of HCl salt **8** using single-crystal X-ray crystallography. Additionally, since these *NH*-azetidines were observed to decompose over time, conversion to the more stable HCl salts was a viable solution for long term storage and stability.

Table 1. Optimization of *NH*-azetidine formation from oxime ethers and Grignard reagents.



Entry[a]	R^1	R^2	Metal (equiv)	Temp (°C)	Solvent	Yield
1	Me	CH_2Ph	Ti(O*i*-Pr)$_3$Cl (1)	0	THF	14%
2	*i*-Pr	CH_2Ph	Ti(O*i*-Pr)$_3$Cl (1)	0	THF	trace
3	*t*-Bu	CH_2Ph	Ti(O*i*-Pr)$_3$Cl (1)	0	THF	trace
4	Bn	CH_2Ph	Ti(O*i*-Pr)$_3$Cl (1)	0	THF	none
5	OH	CH_2Ph	Ti(O*i*-Pr)$_3$Cl (1)	0	THF	trace
6	*i*-Pr	CH_2Ph	Ti(O*i*-Pr)$_3$Cl (1)	rt	THF	13%
7	Me	Ph	$TiCl_4$ (1)	rt	THF	none
8	Me	Ph	Ti(OBu)$_4$ (1)	rt	THF	18%
9	Me	Ph	Ti(OMe)$_4$ (1)	rt	THF	trace
10	Me	Ph	Zr(OEt)$_4$ (1)	rt	THF	none
11	Me	Ph	Ti(O*i*-Pr)$_4$ (1)	rt	Et_2O	40%
12	Me	Ph	Ti(O*i*-Pr)$_4$ (0.01)	rt	Et_2O	none
13	Me	Ph	Ti(O*i*-Pr)$_4$ (1)	rt	DME	20%[b]
14	Me	Ph	Ti(O*i*-Pr)$_4$ (1)	rt	MTBE	32%[b]
15	Me	Ph	Ti(O*i*-Pr)$_4$ (1)	40	Et_2O	33%[b]
16	**Me**	**Ph**	**Ti(O*i*-Pr)$_4$ (1)**	**rt**	**Et_2O**	**51%[c]**

[a] The reactions were performed on a 0.5 mmol scale and 0.1 M concentration relative to the oxime ether and quenched with water unless otherwise stated. [b] NMR yield based on 0.1 mmol dibromomethane internal standard. [c] Reaction performed on a 1.0 mmol scale for 6 hours, quenched with 15% aqueous citric acid, and purified with a NH_3/MeOH solvent additive.

To further investigate the scope of the method, substitutions were made on the cyclohexane oxime in the beta- and gamma-positions (Scheme 2: **12**-**16**). Unfortunately, substitutions at the alpha-position were not well-tolerated presumably due to the steric hindrance surrounding the bulky 5-membered heterocyclic intermediate proposed in the mechanism (Scheme 3: **26**). Spirocyclic azetidine **12**, prepared from a beta-substituted cyclohexane oxime ether, was isolated in good yield as a 1:1 mixture of diastereomers. The yield of azetidine **13** was lower than comparable products and was hypothesized to be a result of steric hindrance depending on the flexibility of the methylene linker

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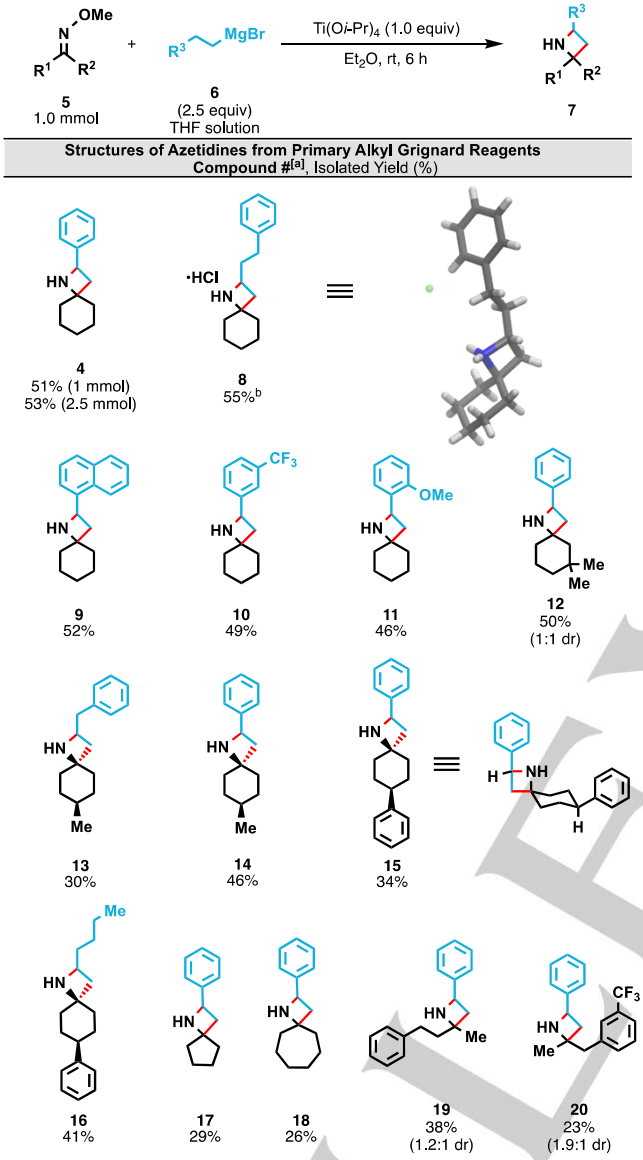
between the azetidine ring and the phenyl group. To test this prediction, a shorter-chain Grignard reagent was utilized and the yield increased to 46% as the conformational flexibility was removed (Scheme 2: **13** vs **14**). Increasing the bulkiness of the gamma-substituent on the oxime provided azetidine **15** in moderate yield. The transformation was also successful when

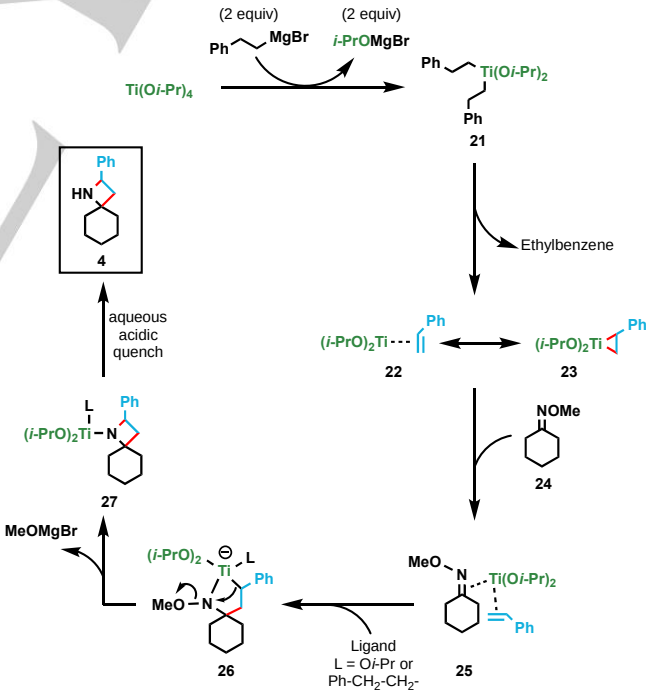


Scheme 2. Formation of *NH*-azetidines from Grignard reagents. [a] Ti(O*i*-Pr)$_4$ (1.0 mmol), Et$_2$O (0.2 M), and oxime (1.0 mmol) were combined in a dry flask under Ar before the dropwise addition of the alkyl Grignard reagent (2.5 mmol) over 5 minutes at room temperature. Upon consumption of the oxime by TLC (approximately 6 hours), the reaction was quenched with 15% aqueous citric acid (30 mL) and stirred overnight at room temperature until colorless. The aqueous layer was washed with hexanes (5 mL) and basified with 2 M NaOH until pH 12. The basic aqueous layer was extracted with EtOAc (2 × 50 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Column chromatography in 10% EtOAc:hexanes + 2% of 7 N NH_3 in MeOH produced the pure *NH*-azetidine. [b] Isolated as the free amine and then converted to the corresponding salt using 2 M HCl in ether for X-ray crystallography analysis.

using a completely aliphatic Grignard reagent (Scheme 2: **16**). Next, the ring size of the oxime ether coupling partner was varied and it was observed that any deviation from the six membered ring resulted in a slightly lower yield of the desired product (Scheme 2: **17**-**18**). Lastly, we were happy to see that non-spirocyclic azetidines (compounds **19**-**20)** could also be prepared in moderate yield.

Based on the results depicted in Scheme 2, the formation of azetidine diastereomers was dependent on the structure of the oxime starting materials. In the case of symmetrical oxime ethers with ring substitutions, single diastereomer products were observed (Scheme 2: **13**-**16**). For these examples, it is possible that the observed diastereomers could be favored due to the sterically encumbering 1,3-diaxial interactions presented by either the methyl or phenyl group being in the axial position (see Scheme 2: **15** for the three-dimensional structure of the favored conformation). Unsymmetrical oxime ethers, on the other hand, produced mixtures of azetidine diastereomers (Scheme 2: **12**, **19**-**20**).

The proposed mechanistic pathway for the synthesis of *NH*-azetidine **4** from oxime ether **24** and phenethyl Grignard reagent is described in Scheme 3. Based on a Kulinkovich-type reaction, the Ti(IV) complex first undergoes a double transmetalation with the excess Grignard reagent to form dialkylated species **21**. Through β-hydride elimination of ethylbenzene, titanacyclopropane intermediate **23**, which is considered a 1,2-aliphatic dianion equivalent, is formed.[16] Coordination of this Ti-complex with oxime ether **24,** (i.e. a 1,2-dielectrophile equivalent) occurs before insertion into the weaker terminal C-Ti bond. The 5-membered intermediate (**26**) breaks down through loss of a methoxide to form a four-membered heterocyclic species **27**. Finally, an aqueous acidic quench cleaves the N-Ti bond and the free *NH*-azetidine is released.



Scheme 3. Proposed Kulinkovich-type mechanism for *NH*-azetidine formation.

To probe the proposed mechanism, reactions were conducted using terminal olefins instead of Grignard reagents to form the desired azetidines (Scheme 4). If this mechanism is viable, ligand exchange should occur between the olefin and the titanacyclopropane intermediate.[17] Indeed, the oxime ethers were converted to the corresponding *NH*-azetidines with the

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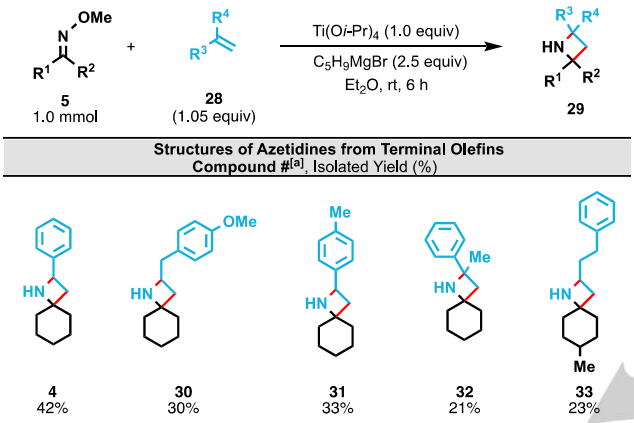
olefins incorporated into the product with yields up to 42% (Scheme 4: **4**, **30**-**33**). Interestingly, substitution on the 2-position of the terminal olefin was tolerated to provide azetidine **32** in moderate yield. These results signify that constructing further variations in structural diversity of spirocyclic *NH*-azetidines is possible via olefin exchange through the Kulinkovich-like mechanism.

In conclusion, two routes for the Ti-mediated synthesis of spirocyclic *NH*-azetidines from oxime ethers were evaluated. In the first pathway, oxime ethers were converted to *NH*-azetidines using primary Grignard reagents while the second pathway utilized olefin ligand-exchange partners. With these methods a diverse range of novel, previously unreported spirocyclic *NH*-azetidines were prepared in moderate yield through a proposed Kulinkovich-type mechanism.



Scheme 4. Formation of *NH*-azetidines from terminal olefins. [a] Terminal olefin (1.05 mmol), Et_2O (0.2 M), oxime (1.0 mmol), and Ti(O*i*-Pr)$_4$ (1.0 mmol) were combined in a dry flask under Ar before the dropwise addition of Cyclopentylmagnesium bromide (C_5H_9MgBr, 2.5 equiv) over 5 minutes at room temperature. Upon consumption of the oxime by TLC, the reaction was quenched with 15% aqueous citric acid (30 mL) and stirred overnight until colorless. Workup and purification conditions are identical to those described for azetidine formation from Grignard reagents in Scheme 1.

Acknowledgements

We thank Mr. Tobias Wilczek and Mr. Christopher Paasch (visiting students from the University of Cologne) for technical assistance with preliminary experiments. Additionally, Priv.-Doz. Dr. Martin Prechtl (University of Cologne) is recognized for obtaining DAAD support (Project ID 57386699) for the visiting students. The authors would also like to thank Mr. Brian Mercer (Biotage) for helpful discussions regarding purification. Financial Support from Rice University, the National Institutes of Health (R01 GM-114609-04), the National Science Foundation (CAREER:SusChEM CHE-1546097), the Robert A. Welch Foundation (grant C-1764), Amgen (2014 Young Investigators' Award for LK), Biotage (2015 Young Principal Investigator Award) and the National Science Foundation Graduate Research Fellowship (Grant No. 1842494, Award for LK) is greatly appreciated.

Keywords: Azetidine • Titanium alkoxides • Olefins • Aliphatic Grignard • Spirocycle

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[14] Solid Ti(O*i*-Pr)$_3$Cl was observed to readily oxidize in air before addition to the reaction. Liquid Ti(O*i*-Pr)$_4$ did not have this issue.

[15] The observed decomposition product was the primary amine resulting from ring-opening of the azetidine.

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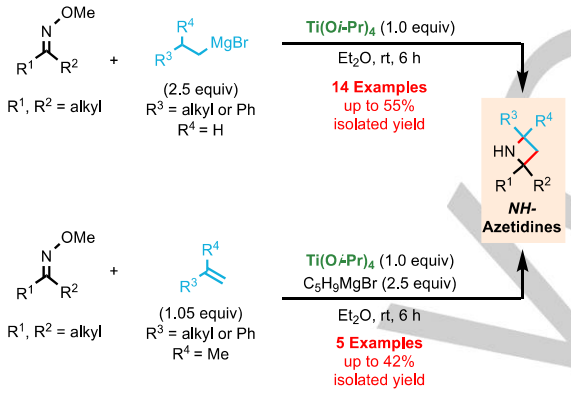

*Nicole Erin Behnke[+], Kaitlyn Lovato[+], Muhammed Yousufuddin, and László Kürti**

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