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Direct Primary Amination of Alkylmetals with *NH*-Oxaziridine

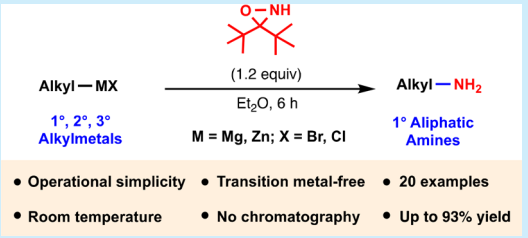
Nicole Erin Behnke,[†] Russell Kielawa,[†] Doo-Hyun Kwon,[‡] Daniel H. Ess,[‡] and László Kürti*[,†]

[†]Department of Chemistry, Rice University BioScience Research Collaborative, 6500 Main Street, Rm 380, Houston, Texas 77030, United States

[‡]Department of Chemistry and Biochemistry, Brigham Young University, Provo, Utah 84602, United States

Supporting Information

ABSTRACT: A method for the primary electrophilic amination of primary, secondary, and tertiary organometallic substrates from a bench-stable *NH*-oxaziridine reagent is described. This facile and highly chemoselective transformation occurs at ambient temperature and without transition metal catalysts or purification by column chromatography to provide alkylamine products in a single step. Density functional theory (DFT) calculations revealed that, despite the basicity of alkylmetals, the direct *NH*-transfer pathway is favored over proton and *O*-transfer.



Aliphatic amines comprise an important class of compounds that have applications in pharmaceuticals, textiles, agrochemicals, and surfactants.[1] Specifically, primary aliphatic amines are valuable targets for organic chemists as their functionality can be found throughout medicinally relevant compounds including those used in the treatment of diabetes and influenza (Figure 1).[2]

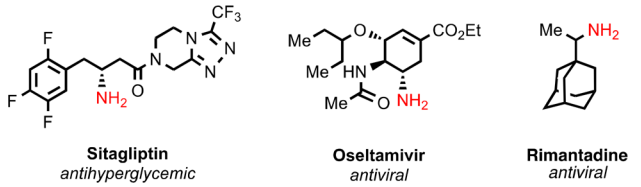


Figure 1. Representative examples of primary aliphatic amines in pharmaceuticals.

Generally, primary aliphatic amines are prepared through the Gabriel synthesis,[3] Staudinger reaction,[4] reduction of nitro groups[5] or nitriles,[6] or S_N2 reactions of alkyl halides. While these methods are well-studied,[7] our focus was to expand the scope of available synthetic routes for more difficult to access secondary and tertiary carbon systems and to investigate primary alkyl amine formation using umpolung, reversed polarity strategies. Compared to traditional approaches, protocols employing an electrophilic source of nitrogen for direct *N*-transfer to carbon-centered aliphatic nucleophiles have not been well established. Narasaka et al. demonstrated the two-step electrophilic amination of alkyl and aryl Grignard reagents with *O*-sulfonyloximes to form amine salts.[8] While synthetically valuable, the overall transformation requires harsh reaction conditions (i.e., strong acid, reflux temperatures, long reaction times) to remove the protecting group and liberate the amine salt. Alternatively, Vidal et al. showed the use of a protected oxaziridine for *N*-Boc-transfer to alkyl and aryl diorganozinc reagents.[9] However, this process is limited by substrate scope, generally low yields, and isolation of the protected instead of free amine.

Recently, work from the Kürti group established the first examples of nondeprotonative primary amination of arylmetals with *NH*-oxaziridines (Figure 2A,B).[10] These transformations

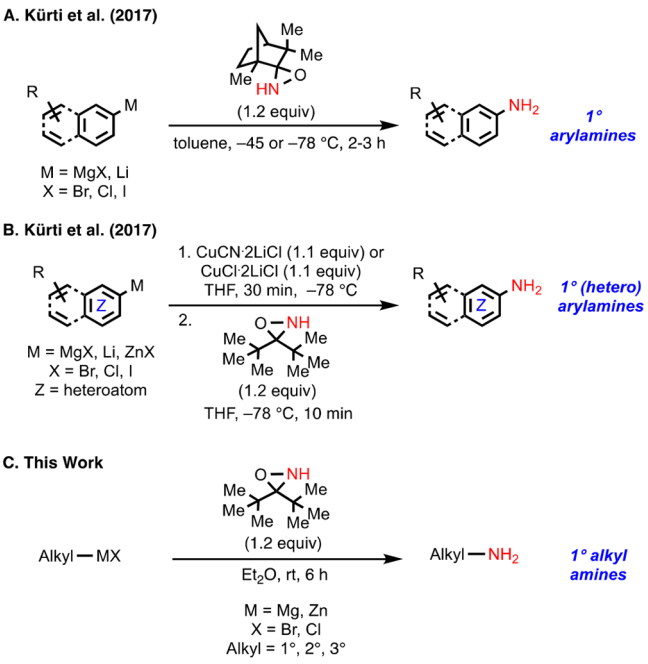


Figure 2. Exploring the reactivity of primary amination with *NH*-oxaziridines.

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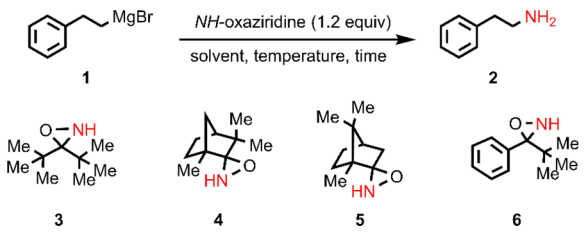
utilize electrophilic amination as a practical process for *N*-transfer and the direct, transition-metal free synthesis of primary anilines. While these methods are widely applicable and tolerate a range of functional groups, the scope was limited to arylmetal substrates and was initially unsuccessful with more basic alkylmetal substrates under the optimized reaction conditions. In order to expand upon previous findings and increase the diversity of using *NH*-oxaziridines for primary electrophilic amination, this work focuses on further exploration of the direct amination of alkylmetals (Figure 2C).

Additionally, the goal of this study was not only to expand the substrate scope for the synthesis of aliphatic amines on primary carbon atoms but also to directly access primary amines on more hindered secondary and tertiary carbon centers.

To synthesize these primary amines, we began by altering the reaction conditions from those reported for *NH*-transfer to arylmetals in order to find an ideal balance between nucleophilicity and basicity (Table 1).[10b] These preliminary

Table 1. Optimization of Reaction Conditions for Primary Amination of Alkylmetals with *NH*-Oxaziridine



entry[a]	oxaziridine	solvent	catalyst (10 mol %)	temp (°C)	time (h)	yield
1	3	THF	none	rt	1	64%
2	3	THF	none	rt	2	78%
3	3	THF	none	rt	4	82%
4	4	THF	none	rt	4	<50%[b]
5	5	THF	none	rt	4	<30%[b]
6	6	THF	none	rt	4	44%
7	3	THF	$Co(acac)_2$	rt	6	none
8	3	THF	$Fe(acac)_3$	rt	6	trace
9	3	THF	$Cu(acac)_2$	rt	6	<40%[b]
10	**3**	**Et_2O**	**none**	**rt**	**6**	**83%**
11	3	Et_2O	none	0	6	trace
12	3	Et_2O	none	−78	6	trace

[a]Reactions were conducted on a 1.0 mmol scale. Grignard (1.0 equiv) was added dropwise to a solution of *NH*-oxaziridine (1.2 equiv) in solvent (5.0 mL) at indicated temperature and stirred for 1−6 h. Acid/base workup was conducted for isolation of the free amine. [b]Workup conditions did not yield pure products (i.e., 50−60% purity only).

experiments, which modified the reaction temperature and time, produced primary aliphatic amine **2** in good yield and demonstrated a viable pathway for *N*-transfer from *NH*-oxaziridines to alkylmetals (Table 1, entry 1). Additionally, through initial experiments, it was discovered that purification by silica gel or basic alumina chromatography strongly binds the product and was unnecessary for isolation of the desired amine. Instead, a simple acid/base workup procedure that initially quenches the reaction with 2 M aqueous HCl and subsequently basifies with 2 M NaOH resulted in good isolated yield of the free amine.

Further optimization of the reaction conditions for *NH*-transfer is shown in Table 1. First, the impact of the reaction time was studied, and the yield of amine **2** increased as the time was extended from 1 to 4 h (Table 1, entries 1−3). Next, all readily available bench-stable *NH*-oxaziridines (**4**−**6**),which are known to act as exclusive *N*-transfer agents, were evaluated and compared to the results obtained with oxaziridine **3** (Table 1, entry 3 vs 4−6). Although the desired primary amine **2** was obtained with oxaziridines **4** and **5**, we experienced an increased difficulty in isolating it due to impurities from the camphor and fenchone byproducts. The addition of Co(II), Fe(II), or Cu(II) catalysts examined whether a partially transmetalated system would increase the yield of aminated product, which were chosen based on findings from Knochel et al. in the Co(II)-catalyzed electrophilic amination of arylzinc pivalates (Table 1, entries 7−9).[11] While Co(II) inhibited the transformation, primary amine **2** was formed with the Fe(III) and Cu(II) catalysts, albeit in yields lower than in the absence of transition metals. Next, the use of Et_2O instead of THF as solvent was investigated (Table 1, entry 3 vs 10). Although the yields were comparable (82% vs 83%), we found that running the reaction in the more nonpolar solvent, Et_2O, produced amine **2** with slightly higher purity. Finally, temperature screens showed that low temperatures (0 and −78 °C) hindered the amination pathway, and only trace amounts of the product were observed (Table 1, entries 9−11). Overall, the optimization studies revealed that the *NH*-transfer reaction proceeds with maximum efficiency at ambient temperature and does not require transition metal catalysis or purification by column chromatography.

With the optimized reaction conditions, the scope of *NH*-transfer from oxaziridine **3** to the primary carbon atoms of organometallic reagents was explored (Scheme 1). The transformation produced good to excellent yields for the corresponding primary aliphatic amines. While most substrates were isolated as free amines, several examples were obtained as the corresponding HCl salts (**16**, **18**, **21**) to ease the isolation process. Benzylic amines were produced in high yields (up to 93%) with electron-donating substituents at the *ortho*-, *meta*-, and *para*-positions (Scheme 1, **9**−**12**). The Grignard reagents for substrates **9**−**11** were prepared in diethyl ether instead of THF; it was experimentally determined that adding the Grignard reagent at −78 °C and allowing the reaction to subsequently warm to room temperature drastically increased the yield and purity of the isolated amine for these substrates.

Increasing the chain length continued to produce the primary amines in good yield (Scheme 1, **13**−**16**). Substitutions at the *ortho*- and *meta*-positions were well tolerated for these substrates along with both electron-donating and electron-withdrawing functional groups (Scheme 1, **14** vs **15**). Adding substituents to the carbon atom adjacent to the site of *NH*-transfer furnished the corresponding amine in moderate yield (Scheme 1, **16**). Further extension of the carbon chain to three atoms gave the corresponding primary amines in good yield (Scheme 1, **17** and **18**). Interestingly, inserting an ether linkage between the phenyl ring and aliphatic chain had little effect on the transformation, and the product was isolated in 67% yield (Scheme 1, **19**).

As a general trend, increasing the length of the chain from two to four carbon atoms led to a slight decrease in yield (83% vs 73% vs 71%) of the corresponding amine, but overall, the amination efficiency was unaffected (Scheme 1, **2** vs **17** vs **20**).

Amination of a completely aliphatic Grignard reagent was also successful (Scheme 1, **21**). It was discovered that the amination pathway proceeds with good yield for organozinc substrates in addition to Grignard reagents (Scheme 1, **22**). The presence of

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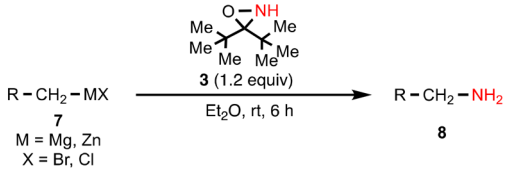
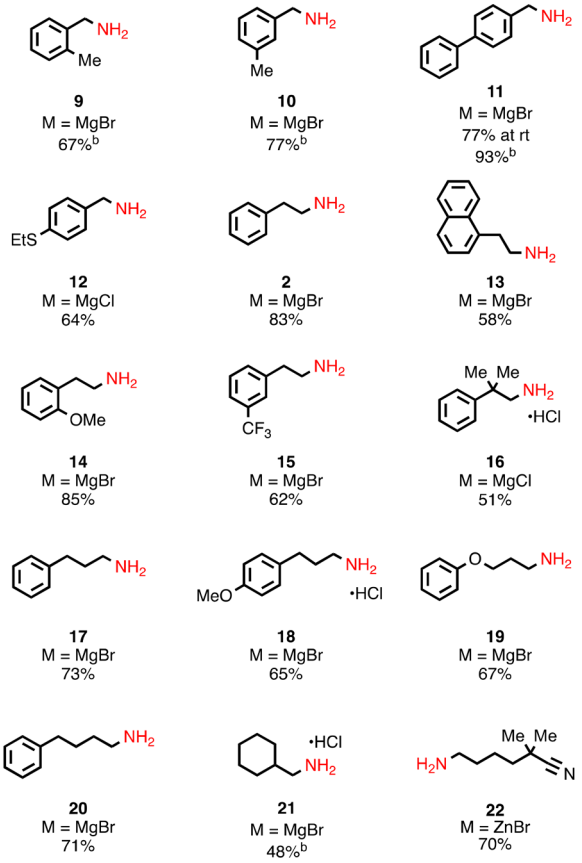
Scheme 1. Formation of Primary Amines from Primary Organometallic Reagents[a]



Structures of Primary Amines from Primary Organometallic Reagents
Compound #[a], Metal, Isolated Yield (%)

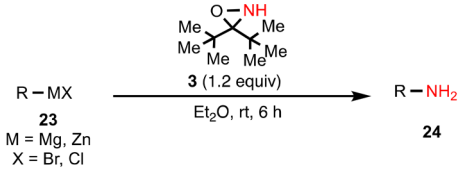


[a][Reaction conditions: oxaziridine (1.2 mmol) and Et_2O (5.0 mL) were combined in a dry flask under Ar before the dropwise addition of alkyl organometal (1.0 mmol) at rt. [b]Grignard addition conducted at −78 °C before the reaction warmed to rt.

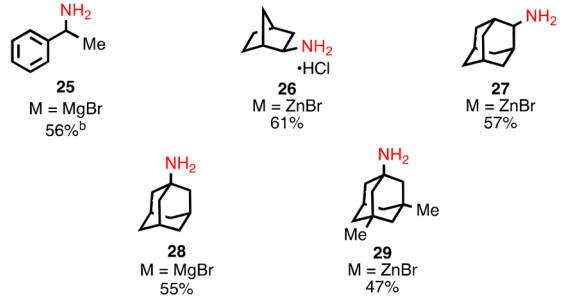
an electrophilic nitrile functionality was well tolerated under these conditions.

The substrate scope was further expanded to include *NH*-transfer to alkylmetal substrates on more difficult to access secondary and tertiary carbon atoms (Scheme 2). Amination of the benzylic position of a secondary Grignard reagent produced the corresponding amine in good yield (Scheme 2, **25**). Additionally, the primary amination method was also successful for secondary alkyl organozinc and Grignard reagents derived from norborane and adamantane, respectively (Scheme 2, **26** and **27**). Compound **26** was isolated as the *exo*-isomer, which indicates retention of configuration from the commercially available *exo*-2-norbornylzinc bromide (see SI, compound **26′**). Finally, primary amination of sterically hindered tertiary organometals proceeded in moderate isolated yield up to 55% for both Grignard and organozinc substrates (Scheme 2, **28** and **29**).

Scheme 2. Formation of Primary Amines from Secondary and Tertiary Organometallic Reagents[a]



Structures of Primary Amines from 2° and 3° Alkylmetal Reagents
Compound #[a], Metal, Isolated Yield (%)



[a]Reaction conditions: oxaziridine (1.2 mmol) and Et_2O (5.0 mL) were combined in a dry flask under Ar before the dropwise addition of alkyl organometal (1.0 mmol) at rt. [b]Grignard addition conducted at −78 °C before the reaction warmed to rt.

Similar to the reactions of aryl Grignard reagents with the fenchone-derived *NH*-oxaziridine,[10b] the addition reactions reported in Schemes 1 and 2 with alkyl organomagnesium and organozinc reagents show significant selectivity for *N*-attack amination versus protonolysis or *O*-attack hydroxylation. Therefore, we used density functional theory (DFT) calculations to examine the transition states to determine if this is a result of kinetic selectivity. Calculations were carried out in Gaussian09[12] using M06 and M06-L for energies, geometries, and thermochemical analysis.[13]

We used a dinuclear phenethyl model $[(PhCH_2CH_2)MgBr]_2$ and a mononuclear secondary adamantyl $(C_{10}H_{16})ZnBr$ model[14] in a continuum SMD[15] model for diethyl ether solvent. Gibbs energies and enthalpies reported are relative to these models and oxaziridine **3**. Scheme 3 confirms that the origin of amination preference in these reactions is kinetic, despite the high basicity of alkyl Grignard reagents. With M06-2X/def2-TZVP, the phenethyl *N*-attack transition state (**TS1**) is lower in energy than proton transfer (**TS2**), although on the enthalpy surface this is only a 1.1 kcal/mol difference. The *O*-attack transition state (**TS3**) is 7.9 kcal/mol higher in energy. We also calculated this kinetic selectivity with ωB97X-D/def2-TZVP, which has a larger 3.6 kcal/mol $\Delta\Delta H^{\ddagger}$ value between **TS1** and **TS2**.

Similar to the organomagnesium reagents, Scheme 4 depicts the three transition states that showcase kinetic *N*-attack selectivity. **TS4** shows Zn coordination to the N atom of **3** that provides transfer of the adamantyl group from Zn to nitrogen with simultaneous N−O bond cleavage. The $\Delta H^{\ddagger}$ for this process is 12.2 kcal/mol, relative to separated reactants, and leads to the ketone and $(C_{10}H_{16})NHZnBr$ intermediate. Proton transfer and *O*-attack are significantly higher in energy. Proton transfer by **TS5** has $\Delta H^{\ddagger}$ = 28.6 kcal/mol and *O*-attack by **TS6** has $\Delta H^{\ddagger}$ = 24.7 kcal/mol. We also sampled the ωB97X-D, M06-L, and M06 functionals. All of these functionals suggested that the kinetic selectivity for *N*-attack versus proton transfer is larger than 4 kcal/mol.

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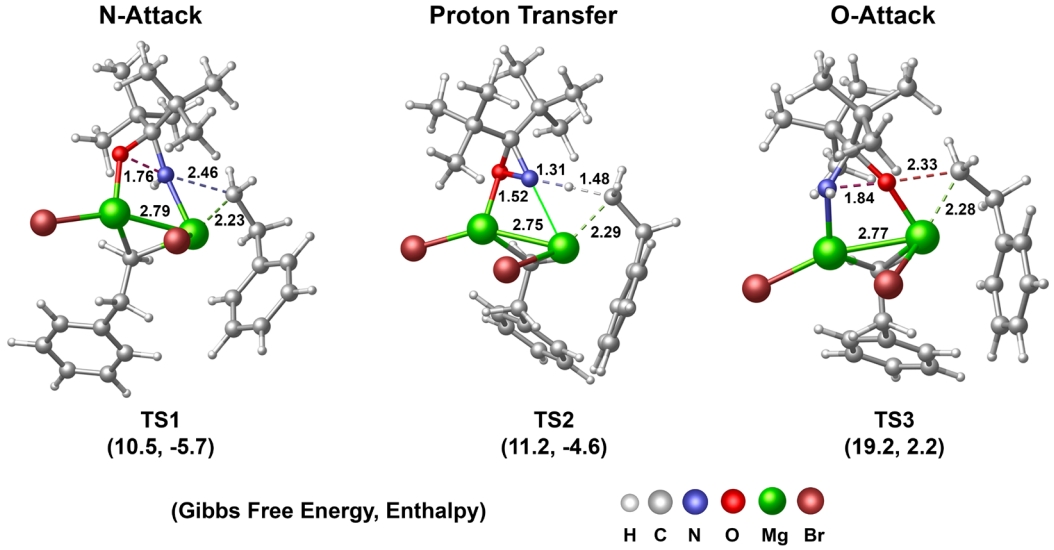
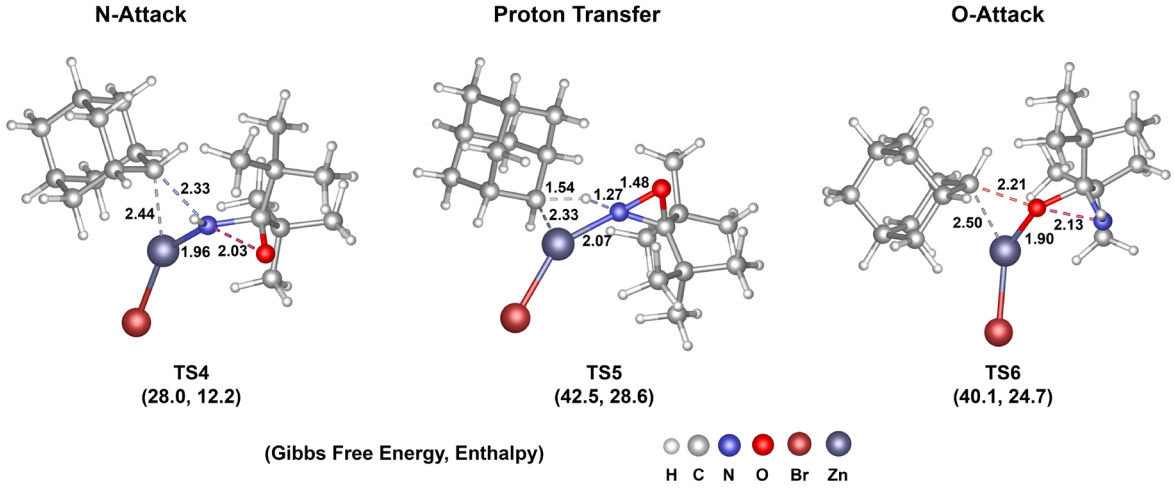
Scheme 3. M06-2X/def2-TZVP//M06-2X/6-31G[LANL2DZ for Br] DFT-Calculated Transition-State Structures for Phenethyl Grignard *N*-Attack, Proton Transfer, and *O*-Attack of Oxaziridine 3 (kcal/mol)**



Scheme 4. M06-2X/def2-TZVP//M06-L/6-31G[LANL2DZ for Zn and Br] DFT-Calculated Transition-State Structures for Zn-Adamantyl *N*-Attack, Proton Transfer, and *O*-Attack of Oxaziridine 3 (kcal/mol)**



In conclusion, we have developed an operationally simple and mild protocol for the primary electrophilic amination of alkylmetals, a transformation that has been missing from the toolbox of synthetic chemists. This approach utilizes a bench-stable *NH*-oxaziridine as the nitrogen source and is capable of the efficient electrophilic amination of primary, secondary, and even tertiary alkylmagnesium and alkylzinc halides. DFT calculations concluded that the *N*-transfer pathway is more favorable compared to the proton- and *O*-transfer pathways for both alkylmetal species.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03734.

Experimental details, compound characterization, and NMR spectra (PDF)

Three-dimensional structures (XYZ)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kurti.laszlo@rice.edu.

ORCID

Daniel H. Ess: 0000-0001-5689-9762
László Kürti: 0000-0002-3412-5894

Notes

The authors declare no competing financial interest.

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