Title: Rapid heteroatom-transfer to arylmetals utilizing multifunctional reagent scaffolds

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Summary:

Arylmetals are highly valuable C–nucleophiles, readily and inexpensively prepared from aryl halides or arenes and widely used on both laboratory and industrial scales to react directly with a wide range of electrophiles. While C–C bond formation has been a staple of organic synthesis, the direct transfer of primary amino (–NH_2) and hydroxyl (–OH) groups to arylmetals in a scalable and environmentally friendly fashion remains a formidable synthetic challenge due to the absence of suitable heteroatom-transfer reagents. Here, we demonstrate the use of bench-stable N–H and N–alkyl oxaziridines derived from readily available terpenoid scaffolds as efficient multifunctional reagents for the direct primary amination and hydroxylation of structurally diverse aryl- and heteroarylmetals. This practical and scalable method provides one-step synthetic access to primary anilines and phenols at low temperature and avoids the use of transition metal catalysts/ligands/additives, nitrogen protecting groups, excess reagents and harsh workup conditions.

Text:

Nitrogen- and oxygen-substituted aromatic rings (i.e., anilines and phenols) appear as substructures in a large number of industrially and commercially significant organic compounds such as active pharmaceutical ingredients, agrochemicals and functional materials.[1,2] For example, primary anilines (i.e., Ar–NH_2) and phenols (i.e., Ar–OH) are used as intermediates or building blocks for the preparation of drug candidates, azo dyes as well as polyanilines.[1,2] Today anilines are mostly prepared via one of the following methods: (a) reduction of aromatic nitro compounds[3]; (b) transition metal-catalyzed (Pd, Ni or Cu) cross-coupling of haloarenes and arylboronic acids with ammonia or substituted primary and secondary amines[4-7]; (c) transition metal-catalyzed (Pd, Ni or Cu) electrophilic amination of various organometallics[8-11] (e.g., Li, Zn and B); (d) nucleophilic aromatic substitution (S_NAr) and nucleophilic substitution of hydrogen in electron-deficient systems[12-15] as well as the (e) direct C–H amination[16] of aromatic rings. Phenols are often prepared via the following methods: (a) S_NAr in heteroaromatic

systems[1,14,15,17]; (b) oxidation of arylboronic acids and derivatives[18] and (c) metal-catalyzed direct hydroxylation of aromatic rings.[19,20]

Nearly all the methods that are catalyzed or mediated by transition metals and their complexes require forcing conditions (high temperature, high pressure, strong oxidants, etc.), which results in limited functional group tolerance. From a practical and environmental point of view, transition metal-free processes are much preferred, especially in the pharmaceutical industry, where the removal of undesired metal contamination can be expensive.[21] Therefore, we became intrigued by the possibility of the application of readily available and inexpensive aryl-Grignard[22,23] and aryllithium[24] reagents (i.e., Ar–Mg–X and Ar–Li) that might be directly primary aminated or hydroxylated utilizing bench-stable aminating and hydroxylating reagents. A survey of the literature revealed that direct primary amination of arylmetal reagents (i.e., ArMgX, ArLi) is exceedingly problematic as most hydroxylamine-derived aminating agents (H_2N–OR, where OR = leaving group) undergo rapid proton transfer, thus consume a total of three equivalents of the precious arylmetal substrate and tend to give poor yield of the desired primary arylamine upon workup (Fig. 1a).[25-27] It was also surprising to find that currently there are no general methods/reagents available for the direct hydroxylation of structurally diverse arylmetal reagents that would allow the efficient synthesis of phenols under operationally simple and mild reaction conditions.

Over the past two decades, several approaches have been developed for the two-step synthesis of primary arylamines from the corresponding arylmagnesium or aryllithium reagents. In the first approach (Fig. 1a), an electrophilic nitrogen source is reacted with an arylmetal and, after C–N bond formation, the activating group is removed typically under harsh conditions (i.e., strongly acidic hydrolysis at elevated temperatures).[28-31] Additionally, the free primary amine has to be liberated from its salt using basic conditions. Clearly, this type of approach prohibits the use of highly functionalized arylmetal reagents or those that have acid- or base-sensitive functionalities. In the second approach (Fig. 1b), an *O*-alkylhydroxylamine (e.g., methoxyamine) is first treated with MeLi and the resulting lithium amide has to be used in large excess for the efficient amination of the arylmetal reagent.[25-27] Although the arylamine can be obtained in the free-base form right after the aqueous workup, the need to use two separate organometallic reagents (one of them in excess) and the modest overall efficiency/yield are the two obvious drawbacks of this method. Recently, our group and the Morken group pioneered the development of a transformation in which arylboronic acids or borate esters may be converted to the primary arylamines in the absence of transition metal catalysts, however elevated temperatures are often required (Fig. 1c).[32,33] The direct hydroxylation of arylmagnesium or aryllithium reagents has not been extensively exploited beyond what was shown by F.A. Davis.[34,35] One method by the Jamison group stands out (Fig. 1d) as being quite general, however, it uses oxygen (O_2) in air at high pressure (250 psi) and requires a specialized flow reactor system.[36]

Given the apparent gaps in existing synthetic methodology, we decided to develop a mild and direct primary amination as well as hydroxylation of structurally diverse and abundant arylmetal reagents (i.e., arylmagnesium halides and aryllithiums) in which the unprotected primary aniline and phenolic products are readily isolated in their non-ionized (i.e., free-base) form. To achieve this goal, suitable bench-stable/highly chemoselective reagents are required that will allow the primary amination and hydroxylation to proceed rapidly at or below ambient temperature and without the need to use excess reagents (i.e., ideally a near 1:1 molar ratio of arylmetal and the

aminating or hydroxylating reagent). The new method would enable the introduction of valuable unprotected primary amino ($-NH_2$) as well as hydroxyl groups (–OH) into a large variety of functionalized aromatic rings even at a later stage of a complex synthetic sequence.

When arylmetals react with non-hindered primary and secondary amines, the N–H group undergoes fast proton transfer, quenching the arylmetals (Fig. 1e). This is a major drawback of amination approach **e** (Fig. 1e). Highly sterically hindered secondary amines have reduced kinetic acidity, thus resist N–H deprotonation even in the presence of excess alkyllithium reagents at elevated temperatures, as shown by Corey (Fig. 1f; **13**→**14**).[37] We surmised that a sterically hindered electrophilic nitrogen source may also resist deprotonation due to the reduced kinetic acidity of the N–H bond and thus avoiding the unproductive protonation of the arylmetal reagent.

When looking for alternative reagents to replace *O*-alkylhydroxylamines as aminating agents, we considered sterically hindered N–H oxaziridines (Fig. 1g).[38-41] Compared to the widely used and studied N–sulfonyloxaziridines (e.g., Davis' oxaziridines), N–H oxaziridines have only been rarely exploited in synthesis due to their perceived low stability/high reactivity. However, a handful of bench-stable N–H oxaziridines have been reported and used for the amination of alcohols and enolates, albeit in fairly limited ways.[39,40,42,43] N–H Oxaziridines (Fig. 1, **16** and **18**) are readily prepared from inexpensive terpenoids (camphor and fenchone) on multi-decagram scale. Preliminary differential scanning calorimetry (DSC) profile demonstrated an onset for decomposition around 100 ˚C. In an explosive screening, compound **18** gave a maximum pressure rise rate of 480.06 bar/min, therefore it does not pose an explosion hazard with respect to transport classification. However, further safety assessments are currently under way to evaluate the safety profile for these oxaziridine ragents (see DSC data on page 102 of the Supplementary Information). Moreover, density-functional calculations suggest that the fenchone-derived N–H oxaziridine has a low kinetic acidity for reactivity with arylmetals (see later results).

Our hypothesis was that N–H oxaziridines such as **16** and **18** might undergo amination with arylmetal reagents faster than the deprotonation of their N–H functionality. Indeed, we found that camphor-derived N–H oxaziridine **16** was an efficient N–H-transfer agent and reacted smoothly with 2-naphthylmagnesium bromide (**15**) to afford the corresponding 2-naphthylamine (**17**) directly in its unprotected free-base form (Fig. 1h). Remarkably, the use of either a large excess of aminating reagent (**16**) or arylmetal substrate (**15**) was not required in order to obtain a synthetically useful isolated yield (50%; 1 mmol scale) in this direct primary amination reaction. The main side product was the protonated aryl-Grignard reagent (i.e., naphthalene, 25% isolated yield), suggesting a competing deprotonation of the N–H group. We presumed that this undesired deprotonation pathway could potentially be suppressed by increasing the steric bulk and thus decreasing the kinetic acidity of the N–H oxaziridine. In fact, reaction of the more sterically hindered fenchone-derived N–H oxaziridine (**18**) with 2-naphthylmagnesium bromide (**15**) furnished 2-naphthylamine (**17**) in a significantly improved isolated yield (>80%; Fig. 1i). Apparently the kinetic acidity was indeed lower in the case of **18** compared to **16**. Remarkably, both **16** and **18** acted as exclusive N-transfer agents – the trace amounts (<1%) of phenols that we detected were presumably the products of air oxidation.

Naturally, it was intriguing to contemplate if direct N–alkyl-transfer was also a possibility by utilizing the N–alkyl versions of oxaziridines **16** and **18**. To our great surprise, N–Me

oxaziridine **19a** (the N–Me analogue of **16**) did not react at all with 2-naphthylmagnesium bromide (**15**) at −78 ˚C, however at ambient temperature it acted as an effective and exclusive *O*-transfer reagent and converted **15** to the corresponding phenol **20** in good isolated yield (Fig. 1j). A control experiment in the absence of **19a** but still under argon atmosphere, led to the formation of only trace amounts of **20**, indicating that the origin of oxygen atom in phenol **20** is the oxaziridine (i.e., **19a**) and not the adventitious oxygen (O_2) from air. It is clear from these results that this reagent scaffold is multifunctional, since it can be easily modified to transfer either hetereoatom.

Encouraged by these promising preliminary results, we conducted systematic optimization studies (see Supplementary Tables 1 & 2) which concluded that the highest isolated yields are obtained at −78 ˚C in toluene/THF mixture when using a 1:1.2 ratio of arylmetal and aminating agent. With the optimum reaction conditions in hand, the stage was set to explore the scope and limitations of this method by subjecting dozens of substituted arylmetal reagents to primary amination (Tables 1 & 2). The initially tested aryl Grignard reagents represent an extensive sampling of both fused- and monocyclic aromatic rings as well as electron-rich and electron-deficient examples (Table 1). Fused aromatic rings (entries 1-5, Table 1) and biaryl systems (entries 11-16) underwent smooth primary amination with good to excellent isolated yields except for one instance (entry 4) in which an electronegative fluorine atom was in the *para* position of the carbon-magnesium (C–Mg) bond. Ring-halogenated substrates (entries 30-43, Table 1) furnished the corresponding primary anilines in moderate to good yields and clearly illustrate the true complementary nature of this method to transition metal-catalyzed aminations given that halogen atoms are well-tolerated.

When one or more alkyl substituents are located adjacent to the aryl-metal bond (i.e., *ortho* positions), primary aminations proceed only in fair to moderate yields (entries 7, 9, 28 & 37, Table 1), however, substrates with *o*-methoxy substituents (entries 18 & 20, Table 1) furnished the primary arylamines in good isolated yields. It is likely that when both the substrate and the aminating agent are sterically bulky, the rate and efficiency of primary amination are reduced – in these cases the elevation of reaction temperature (–45 ˚C instead of −78 ˚C) was necessary to observe synthetically useful reaction times and isolated yields (see specifically entry 37, Table 1). It is worth pointing out that substrates having tertiary amine moieties ($-NR_2$), that are usually quite sensitive to oxidation, furnished the corresponding primary arylamines in good to excellent yields (entries 44-46, Table 1). These cases highlight the remarkable chemoselectivity of aminating agent **18**.

In order to further illustrate the unprecedented mildness of our direct primary amination method, we selected aromatic and heteroaromatic substrates that have redox- or hydrolytically-sensitive moieties (Table 2) such as a primary alkyl halide (entry 52), isolated and conjugated olefins (entries 47, 48 & 53), a 1,3-diene (entry 49), alkynes (entries 50-51), ethers and thioethers (entries 54-60), acetals and ketals (entries 61-63), one or more halogen/pseudo-halogen atoms (entries 64-72) and heterocycles (entries 73-76, 78 & 79). In a few of cases (entries 58, 64, 70, 74, 75 & 79) the isolated yields were poor (e.g., <30%) that can be attributed to a combination of steric and electronic factors or to the volatility of the product (entry 58). Even bis-metallated arenes can undergo efficient double amination (entry 77). Most of these functionalities are well-tolerated under the reaction conditions – especially noteworthy is the high isolated yields of anilines featuring either highly acid-sensitive acetal or ketal functionalities (entries 61-63),

oxidatively highly sensitive thioether moieties (entries 59-60) and bromine atoms that usually lead to side reactions under transition metal-catalysis. This methodology can also be used for the late-stage functionalization of structurally complex and pharmaceutically relevant intermediates (e.g., estradiol derivatives **29h** & **29i**, terpenoid derivative **29j** and a carbohydrate derivative **29k**).

Given the poor primary amination performance of N–H oxaziridine **18** with sterically hindered substrates, we decided to examine the impact of reducing the steric bulk around the oxaziridine moiety (Table 3). Therefore we prepared two additional N–H oxaziridines (**30** & **31**) that were, in our judgement, sterically less hindered than N–H oxaziridines **16** & **18** and were expected to improve the isolated yields of primary arylamines for a handful of challenging substrates (Table 3). We indeed found that as the steric bulk of the N–H oxaziridines was reduced, their primary amination performance improved markedly with sterically hindered arylmetals. In contrast, the primary amination of sterically unencumbered arylmetals (e.g., **15**→**23a**) became less efficient with the decreasing steric bulk of the N–H oxaziridines, presumably due to easier N–H deprotonation. It appears that N–H oxaziridine **18** can efficiently transfer the primary amino group (–NH_2) to most arylmetals. The results in Table 3 indicate that one can readily find a suitable N–H oxaziridine aminating agent for both sterically demanding and less nucleophilic arylmetals.

For the direct hydroxylation of arylmetals, several N–alkyl oxaziridines have been prepared and evaluated (see pages 7 & 8 of the Supplementary Information). N–Benzyl oxaziridine **19b** was selected as the optimal reagent given its ease of synthesis, bench stability and chemoselectivity. The examples in Table 4 amply illustrate the unprecedented functional group tolerance of this reagent as both oxidatively (entries 9, 17, 19, 20, 21 & 24) and hydrolytically (entries 22 & 23) sensitive functionalities remained untouched during the hydroxylation process. It is worth pointing out that phenols themselves are usually highly oxidatively sensitive even without additional electron-donating groups on their aromatic rings[1] – the fact that most of the phenol products were isolated in good yield attests to the unprecedented mildness of this method.

Our hypothesis of low kinetic acidity is based on M06-2X/def2-TZVP density-functional calculations in THF continuum solvent for reaction of **18** with $(PhMgBr)_2$ (modeled as dinuclear bridging and Schlenk-type structures, see page 65 of the Supplementary Information for details).[44] Consistent with this hypothesis is that the calculated pK_a for **18**, assuming MgBr coordination of the anion in THF solution, is ~34 – proton transfer between $(PhMgBr)_2$ and **18** is thermodynamically favorable (ΔG = −13.4 kcal/mol), therefore the selective amination versus proton transfer must be governed by kinetic pathways.[37]

Several kinetic pathways were readily ruled out. For example, outersphere one-electron transfer from $(PhMgBr)_2$ to **18** generates $[(PhMgBr)_2]^{\bullet+}$ and $\mathbf{18}^{\bullet-}$ with an energy penalty of >80 kcal/mol.[45] This large electron transfer energy is consistent with Woerpel's observations that Grignard reagents do not react with electrophiles (e.g. aldehydes) through one-electron transfer.[46] The ~30 kcal/mol strain energy of the oxaziridine ring and the relatively weak N–O bond could suggest homolytic N–O bond cleavage. However, constrained elongation of the N–O bond to the

corresponding 1,3-diradical suggests the bond energy is ~40 kcal/mol and this is significantly larger than alternative pathways. Isomerization products (e.g. amide) were not detected experimentally.[47]

The most viable amination pathway identified involves formation of a $(PhMgBr)_2$-**18** complex followed by nucleophilic phenyl group transfer to the nitrogen atom by **TS1** (Fig. 2a). This transition state features PhMg coordination to the N–H group, delivery of the phenyl anion to the N–O σ* orbital resulting in bond cleavage, and stabilization of the developing oxygen anion by the second Mg.[48] The $\Delta G^{\ddagger}$ for **TS1** is 19.7 kcal/mol relative a $(PhMgBr)_2$-**18** complex. Importantly, the $\Delta G^{\ddagger}$ for proton transfer between $(PhMgBr)_2$ and **18** by **TS2** (Fig. 2a) is 23.5 kcal/mol, which is 3.8 kcal/mol larger than **TS1**. Using another accurate functional (ωB97X-D/def2-TZVP) the $\Delta\Delta G^{\ddagger}$ between **TS1** and **TS2** is 5.5 kcal/mol.[49] This indicates that amination kinetically outcompetes proton transfer, but competitive $\Delta G^{\ddagger}$ values for **TS1** and **TS2** is consistent with a minor amount of arene product (~10-20%) found. The deuterium trapping experiments (Fig. 2c) support the hypothesis that in addition to the predominant N-transfer, deprotonation of the aminating agent also occurs to a minor extent at low temperatures. In other words, the active Grignard reagent **21b** is quickly consumed at the reaction temperature, hence no deuterated product (**35**) was observed. The density-functional calculations also show that for NH-oxaziridine **18** amination is also significantly favored over hydroxylation via **TS3** (Fig. 2a) with $\Delta G^{\ddagger} > 30$ kcal/mol. Transition-state calculations for phenyl group transfer between $(PhMgBr)_2$ and **19b** show that the N versus O selectivity is reversed and hydroxylation has an ~2 kcal/mol lower $\Delta G^{\ddagger}$ value (see pages 65-84 of the Supplementary Information for transition-state structures).

Conclusion:

We have demonstrated that bench-stable N–H and N–alkyl oxaziridines derived from inexpensive terpenoid scaffolds can serve as effective primary aminating and hydroxylating reagents to give rise directly to primary arylamines and phenols from readily available arylmetals in the absence of transition metal catalysts and under exceedingly mild conditions. This one step/one-pot method is expected to become widely used in both academic and industrial laboratories as it will provide practical and scalable synthetic access to a vast array of structurally diverse unprotected aromatic amines and hydroxyarenes to be used as building blocks or as value-added compounds. While this approach is a step in the right direction towards "greener" chemistry, the preparation of the oxaziridine reagents need further improvements in order to achieve a higher level of sustainability. Therefore more efficient synthetic routes to these reagents are currently being developed.

Supplementary Information Is Available.

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Author Contribution:

H.G and L.K. conceived this work; H.G., Z.Z. and L.K. designed the organic chemistry experiments; H.G., Z.Z. and N.E.B. conducted the organic chemistry experiments and analyzed the data; D-H. K., D.H.E. and L.K. designed the computational studies; D-H. K., J.C., S.J., and D.H.E. conducted the calculations and analyzed the data; D.H.E. and L.K. wrote the manuscript.

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Figure 1. Current approaches to primary arylamine and phenol synthesis from arylmetals in the absence of transition metal catalysts, impact of steric hindrance on kinetic acidity and the discovery of multifunctional oxaziridine reagents for heteroatom-transfer reactions. a-c, Known two-step procedures for the synthesis of primary arylamines (**4**) from the corresponding arylmetals (**2** & **2c**) using electrophilic aminating agents (**1**, **5** & **7**). **d,** Conversion of arylmagnesium halides (**2a**) to phenols (**12**) using molecular oxygen in a flow system. **e,** Non-hindered amines undergo rapid proton exchange with arylmetals. **f,** Sterically bulky secondary amines such as **13** does not undergo proton exchange with arylmetals. **g,** Our hypothesis: a sterically hindered electrophilic N-source such as an NH-oxaziridine will undergo NH-transfer rather than proton exchange when reacted with arylmetals. **h & i,** Camphor- and fenchone-derived N–H oxaziridines (**16** & **18**) react with 2-naphthylmagnesium bromide (**15**) directly at low temperature and under protective Argon atmosphere to afford 2-naphthylamine (**17**) upon simple aqueous workup. **j & k,** Camphor-derived N–Me and N–Benzyl oxaziridine (**19a** & **19b**) react with **15** directly to give 2-naphthol (**20**) upon workup.

Figure 2. Three-dimensional (3D) representation of competitive amination and proton-transfer transition states, proposed mechanism of N–transfer and deuterium-trapping experiments. a, Free energy barriers, enthalpy barriers in kcal/mol. (Top row numbers correspond to M06-2X while the bottom row to wB97X-D.) **b,** Proposed mechanism of the direct primary amination of aryl-metals using bench-stable NH-oxaziridines: **I.** The strained 3-membered oxaziridine ring is easy to open and **21a** attacks the N–O σ^* orbital. **II.** break-down of the aminal intermediate to afford the magnesium amide of the arylamine product. **c,** Deuterium-trapping experiments using delayed addition (2 h) at -78 ˚C in THF/toluene then quench with NH_4Cl (aq). Notes: 1. The aryl-Grignard reagent **21b** was titrated before use; 2. Approximately 0.2 mmols of **36** is present in the aryl-Grignard reagent due to inadvertent/unavoidable protonation during its preparation; 3. Addition of the D_2O after only 5 seconds, gave almost identical results.

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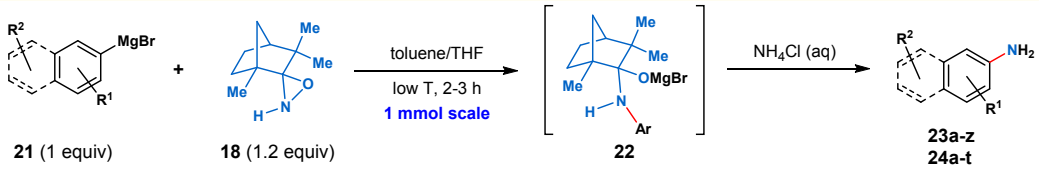
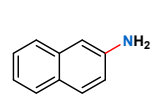
Table 1 | Direct primary amination of arylmagnesium halide substrates. Scope of substrates with N–H oxaziridine 18.



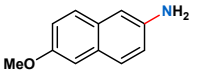
21 (1 equiv) **18** (1.2 equiv) **22** **23a-z** **24a-t**

Structure of Primary Arylamine Products

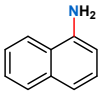
(Entry): **Compound #;** T (°C), t (h), Isolated Yield (%)



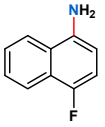
(1) **23a**
–78 °C, 2 h, 89%
80% (17.4 mmol)



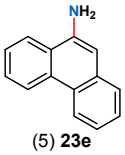
(2) **23b**
–78 °C, 2 h, 78%



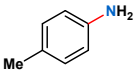
(3) **23c**
–45 °C, 2 h, 63%



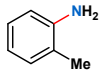
(4) **23d**
–45 °C, 2 h, 31%



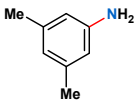
(5) **23e**
–45 °C, 3 h, 52%



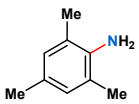
(6) **23f**
–78 °C, 2 h, 61%



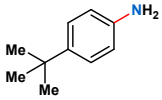
(7) **23g**
–45 °C, 2 h, 47%



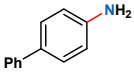
(8) **23h**
–78 °C, 2 h, 74%



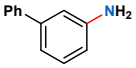
(9) **23i**
–45 °C, 3 h, 26%



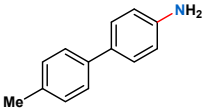
(10) **23j**
–78 °C, 2 h, 70%



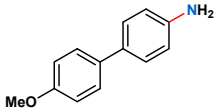
(11) **23k**
–78 °C, 2 h, 92%



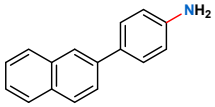
(12) **23l**
–78 °C, 2 h, 82%



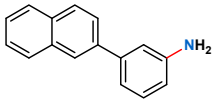
(13) **23m**
–78 °C, 2 h, 85%



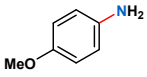
(14) **23n**
–78 °C, 2 h, 83%



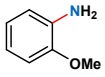
(15) **23o**
–78 °C, 2 h, 62%



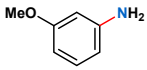
(16) **23p**
–78 °C, 2 h, 79%



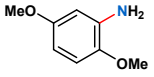
(17) **23q**
–78 °C, 2 h, 63%



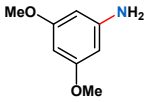
(18) **23r**
–45 °C, 2 h, 61%



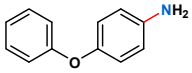
(19) **23s**
–78 °C, 2 h, 67%



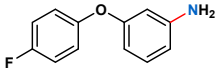
(20) **23t**
–45 °C, 2 h, 58%



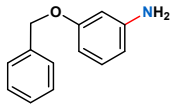
(21) **23u**
-78 °C, 2 h, 78%



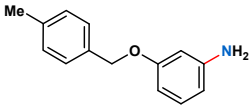
(22) **23v**
–78 °C, 2 h, 81%



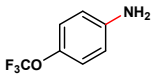
(23) **23w**
–78 °C, 2 h, 70%



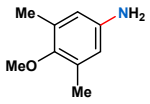
(24) **23x**
–78 °C, 2 h, 86%



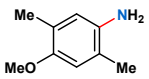
(25) **23y**
–78 °C, 2 h, 65%



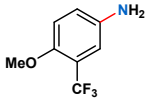
(26) **23z**
–20 °C, 2 h, 62%



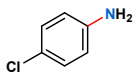
(27) **24a**
–78 °C, 2 h, 77%



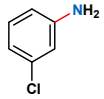
(28) **24b**
–45 °C, 2 h, 46%



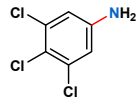
(29) **24c**
–78 °C, 2 h, 65%



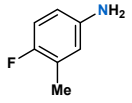
(30) **24d**
–78 °C, 3 h, 43%



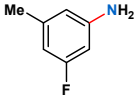
(31) **24e**
–78 °C, 2 h, 63%



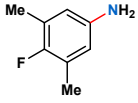
(32) **24f**
–45 °C, 2 h, 47%



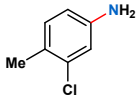
(33) **24g**
–78 °C, 2 h, 48%



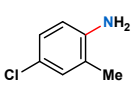
(34) **24h**
–45 °C, 2 h, 62%



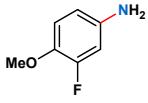
(35) **24i**
–45 °C, 2 h, 69%



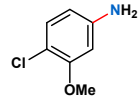
(36) **24j**
–45 °C, 2 h, 67%



(37) **24k**
–78 °C, 3 h, 16%
–45 °C, 2 h, 46%



(38) **24l**
–78 °C, 2 h, 68%



(39) **24m**
–78 °C, 3 h, 62%

(40) **24n**
–45 °C, 2 h, 61%

(41) **24o**
–45 °C, 2 h, 61%

(42) **24p**
–45 °C, 2 h, 77%

(43) **24q**
–45 °C, 2 h, 60%

(44) **24r**
–78 °C, 2 h, 79%

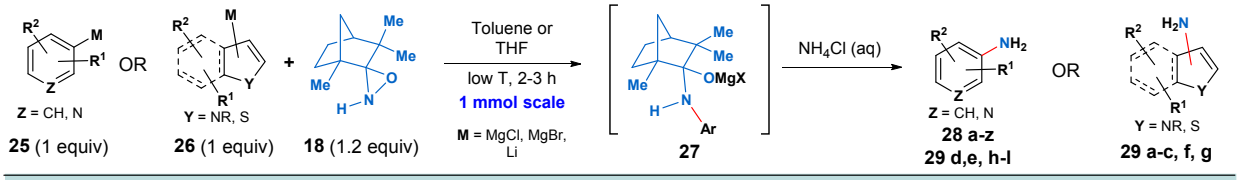
(45) **24s**
–78 °C, 2 h, 57%

(46) **24t**
–78 °C, 2 h, 83%

All aromatic Grignard reagents (**21**) have been prepared from the corresponding aryl halides using turnings of freshly activated Mg metal and THF as the solvent. The concentration of the arylmetal solution was targeted to be around 0.5 M but was carefully determined by titration immediately before use. The amination reactions were conducted on a 1 mmol scale at the indicated temperature and considered complete upon the full consumption of the aminating agent (**18**) by TLC analysis; a number of experiments showed that **18** undergoes decomposition in the presence of strong metal bases.

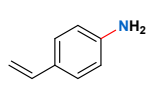
427
428

Table 2| Direct primary amination of aromatic and heteroaromatic arylmetal substrates using N–H oxaziridine 18.

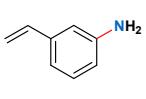


Structure of Primary Arylamine Products

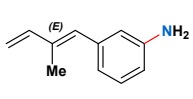
(Entry): **Compound #;** T (°C), t (h), Isolated Yield (%)



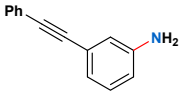
(47) **28a**
–78 °C, 2 h, 75%[a]



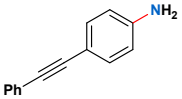
(48) **28b**
–78 °C, 2 h, 72%[a]



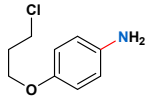
(49) **28c**
–45 °C, 2 h, 75%[a]



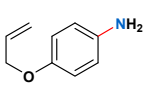
(50) **28d**
–78 °C, 2 h, 60%[a]



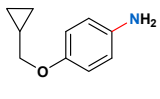
(51) **28e**
–78 °C, 2 h, 74%[a]



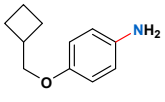
(52) **28f**
–78 °C, 2 h, 51%[a]



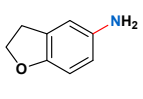
(53) **28g**
–78 °C, 2 h, 50%[a]



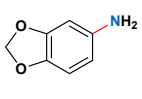
(54) **28h**
–78 °C, 2 h, 51%[a]



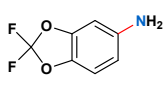
(55) **28i**
–78 °C, 2 h, 58%[a]



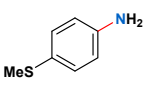
(56) **28j**
–78 °C, 2 h, 45%[a]



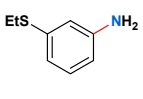
(57) **28k**
–78 °C, 2 h, 66%[a]



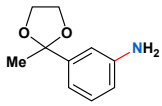
(58) **28l**
–78 °C, 2 h, 27%[a]



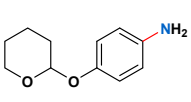
(59) **28m**
–78 °C, 2 h, 54%[a]



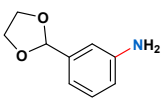
(60) **28n**
–78 °C, 2 h, 61%[a]



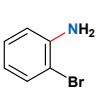
(61) **28o**
–78 °C, 2 h, 80%[a]



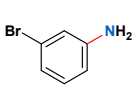
(62) **28p**
–78 °C, 2 h, 67%[a]



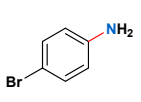
(63) **28q**
–78 °C, 2 h, 79%[a]



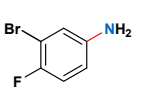
(64) **28r**
–20 °C, 2 h, 29%[b]



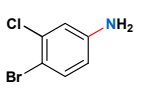
(65) **28s**
–45 °C, 2 h, 76%[b]



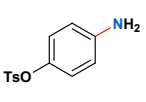
(66) **28t**
–45 °C, 2 h, 77%[b]



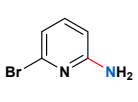
(67) **28u**
–45 °C, 2 h, 63%[b]



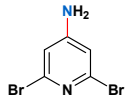
(68) **28v**
–45 °C, 2 h, 77%[b]



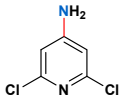
(69) **28w**
–30 °C, 2 h, 48%[a]



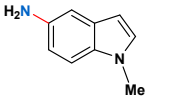
(70) **28x**
–78 °C, 2 h, 32%[d]†



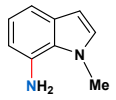
(71) **28y**
–25 °C, 2 h, 58%[c]



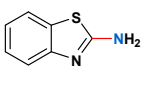
(72) **28z**
–25 °C, 2 h, 64%[c]



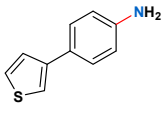
(73) **29a**
–45 °C, 2 h, 55%[b]



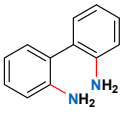
(74) **29b**
–45 °C, 2 h, 22%[b]



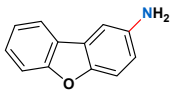
(75) **29c**
–30 °C, 2 h, 26%[c]



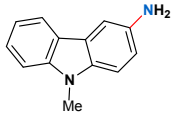
(76) **29d**
–78 °C, 2 h, 42%[a]



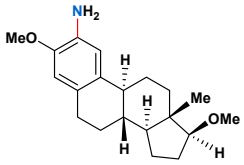
(77) **29e**
–78 °C, 3 h, 56%[a]



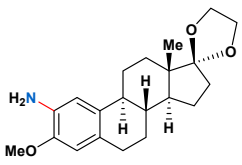
(78) **29f**
–45 °C, 2 h, 36%[e]



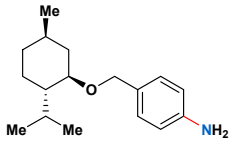
(79) **29g**
–78 °C, 2 h, 18%[d]



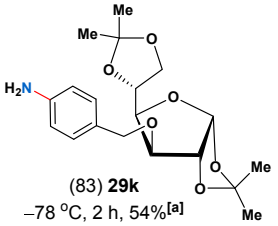
(80) **29h**
–45 °C, 2 h, 25%[e]†



(81) **29i**
–45 °C, 2 h, 32%[e]†



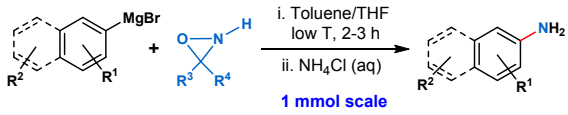
(82) **29j**
–78 °C, 2 h, 73%[a]



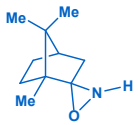
(83) **29k**
–78 °C, 2 h, 54%[a]

The aromatic and heteroaromatic metal reagents (**25** & **26**) have been prepared using one of the following methods: **[a]** from aryl halides using activated Mg metal; **[b]** from aryl halides using *i*-PrMgCl·LiCl complex (Knochel's procedure); **[c]** direct C–H deprotonation with TMPMgCl·LiCl; **[d]** performed with the aryllithium reagent via Li/hal exchange and **[e]** Li/Br exchange followed by transmetallation with $MgBr_2$. † = The primary amination was performed with N–H oxaziridine **30**.

Table 3| Direct primary amination of arylmagnesium halides with structurally and sterically different N–H oxaziridines.

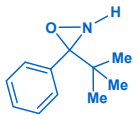


15, 21 (1 equiv) + **Oxaziridine** (1.2 equiv) → **23a, 23i, 24b & 24k**

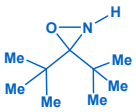


16

18



30



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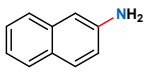
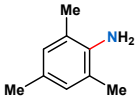
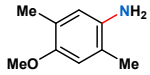
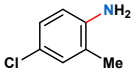
Structure of Primary Arylamine Products (Entry): **Oxaziridine Reagent #;** T (°C), t (h), Isolated Yield (%)			
 **23a**	 **23i**	 **24b**	 **24k**
(1) **16,** –78 °C, 2 h; **50%**	(1) **16,** –45 °C, 3 h; **26%**	(1) **16,** –45 °C, 3 h; **26%**	(1) **16,** –45 °C, 3 h; **57%**
(2) **18,** –78 °C, 2 h; **89%**	(2) **18,** –45 °C, 3 h; **0%**	(2) **18,** –45 °C, 3 h; **46%**	(2) **18,** –45 °C, 3 h; **46%**
(3) **30,** –78 °C, 2 h; **83%**	(3) **30,** –45 °C, 2 h; **31%**	(3) **30,** –45 °C, 2 h; **52%**	(3) **30,** –45 °C, 2 h; **65%**
(4) **31,** –78 °C, 2 h; **46%**	(4) **31,** –45 °C, 2 h; **0%**	(4) **31,** –45 °C, 2 h; **65%**	(4) **31,** –45 °C, 2 h; **9%**

Studies aimed at improving the efficiency of primary amination for sterically hindered (i.e., *ortho*-substituted) arylmetals. Four bench stable NH-oxaziridines (**16**, **18**, **30** & **31**) were evaluated as aminating agents under the indicated reaction conditions.

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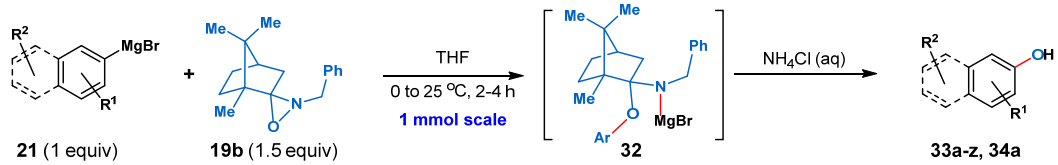
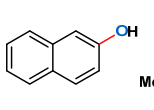
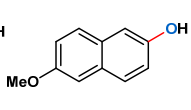
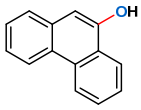
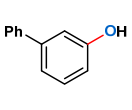
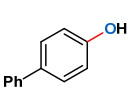
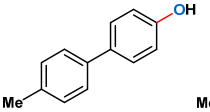
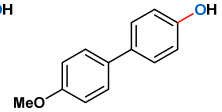
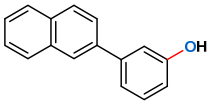
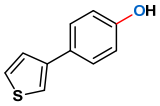
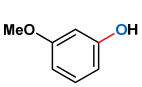
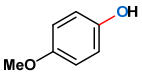
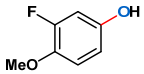
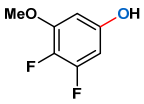
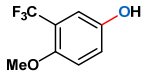
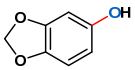
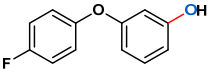
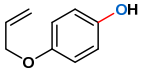
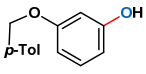
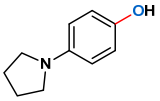
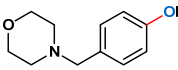
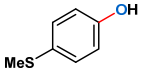
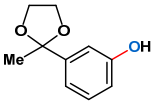
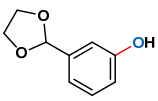
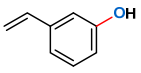
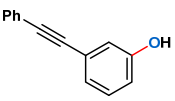
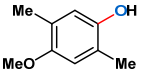
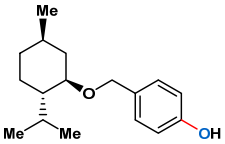
Table 4| Direct hydroxylation of arylmagnesium halide substrates with N–benzyl oxaziridine 19b.



21 (1 equiv) + **19b** (1.5 equiv) → **32** → **33a-z, 34a**

Structure of Hydroxyarene (Phenol) Products (Entry): **Compound #;** T (°C), t (h), Isolated Yield (%)						
 (1) **33a** r.t., 2 h, 86%	 (2) **33b** r.t., 4 h, 75%	 (3) **33c** r.t., 4 h, 57%	 (4) **33d** r.t., 2 h, 78%	 (5) **33e** r.t., 2 h, 79%	 (6) **33f** r.t., 2 h, 61%	 (7) **33g** r.t., 2 h,66%
 (8) **33h** r.t., 2 h, 64%	 (9) **33i** r.t., 2 h, 31%	 (10) **33j** r.t., 3 h, 75%	 (11) **33k** r.t., 2 h, 65%	 (12) **33l** r.t., 2 h, 46%	 (13) **33m** r.t., 2 h, 35%	 (14) **33n** r.t., 2 h, 37%
 (15) **33o** r.t., 2 h, 63%	 (16) **33p** r.t., 2 h, 65%	 (17) **33q** r.t., 2 h, 63%	 (18) **33r** r.t., 2 h, 51%	 (19) **33s** r.t., 2 h, 54%	 (20) **33t** r.t., 2 h, 76%	 (21) **33u** r.t., 2 h, 63%
 (22) **33v** r.t., 2 h, 64%	 (23) **33w** r.t., 2 h, 73%	 (24) **33x** r.t., 2 h, 39%	 (25) **33y** r.t., 2 h, 39%	 (26) **33z** r.t., 2 h, 40%	 (27) **34a** r.t., 2 h, 79%	

N–Benzyl derivative of camphor-derived oxaziridine (**19b**) serves as an exclusive *O*-transfer agent when reacted with arylmetals. Reaction with aryl-Grignard reagents were conducted between 0-25 °C followed by mild workup with aqueous NH_4Cl solution.

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