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Site-selective amination and/or nitrilation *via* metal-free C(sp^2)–C(sp^3) cleavage of benzylic and allylic alcohols†

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Benzylic/allylic alcohols are converted *via* site-selective C(sp^2)–C(sp^3) cleavage to value-added nitrogenous motifs, *viz.*, anilines and/or nitriles as well as N-heterocycles, utilizing commercial hydroxylamine-*O*-sulfonic acid (HOSA) and Et_3N in an operationally simple, one-pot process. Notably, cyclic benzylic/allylic alcohols undergo bis-functionalization with attendant increases in architectural complexity and step-economy.

Introduction

In recognition of increasingly strict conservational and regulatory imperatives,[1] much attention is now focused upon innovative functionalization methodologies[2] that are applicable to more readily available and economic feedstocks,[3] while simultaneously emphasizing environmentally friendly, especially metal-free, reaction conditions.[4] To these ends, there has been encouraging progress recently in the application of site-selective C(sp^2)–C(sp^3) and C(sp^2)–C(sp^2) cleavage strategies,[5] despite the comparatively high bond dissociation energy of most unstrained C–C bonds and the formidable challenges posed by discriminating amongst otherwise chemically equivalent C–C bonds[6] (Fig. 1).

Canonical syntheses of anilines[7] and other nitrogen containing functional groups are often trammeled by multi-step sequences,[8] harsh reaction conditions,[9] limited scope,[10] and/or lack of regioselectivity. Given the continuing interest in nitrogenous compounds,[11] especially anilines[12] and nitriles, by the pharmaceutical, dye, agricultural, and specialty materials markets, several novel, site-selective procedures have been introduced, *intra alia*, decarboxylative aminations,[13] transition metal cross-couplings (*e.g.*, Buchwald–Hartwig,[14] Chan–Lam[15]), electrophilic amination reagents,[16] ligand-directed aminations,[17] and boronate rearrangement.[18] More recently, influential examples from the Jiao[19,20] and Hashmi[21] laboratories pioneered efficient, site-specific C–C cleavages of benzylic alcohols, alkylarenes and styrenes to anilines. Herein, we describe the operationally simple, one-pot, site-selective C(sp^2)–C(sp^3) cleavage of benzylic/allylic alcohols using commercial hydroxylamine-*O*-sulfonic acid (HOSA)[22] and Et_3N to prepare value-added nitrogenous motifs, *viz.*, anilines and/or nitriles in addition to N-heterocycles. Of particular note are applications to cyclic alcohols that result in either symmetrical or unsymmetrical bis-functionalization with their attendant increases in architectural complexity and step-economy.

Results and discussion

Prompted by the above C–C cleavage reports and our prior aryl and alkene amination studies,[17a,18,23] we foresaw (i) the untapped potential to develop novel bis-functionalization applications with attendant improvements in architectural complexity and step-economy, (ii) extension to an additional

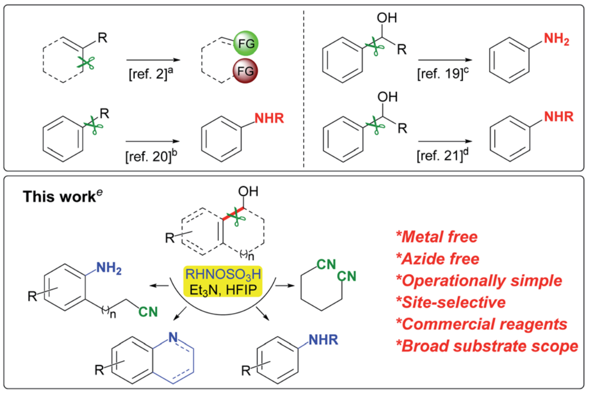

Fig. 1 Representative site-selective functionalizations *via* C(sp^2)–C(sp^3) and C(sp^2)–C(sp^2) cleavage. ^{a}Select examples of olefin α-cleavage. ^{b}Alkyl- and alkene-aryl cleavages. ^{c}C(sp^2)–C(sp^3) cleavages of acyclic benzyl alcohols to 1° anilines. ^{d}C(sp^2)–C(sp^3) cleavages of acyclic benzyl alcohols leading to 1° & 2° anilines. ^{e}This work: C(sp^2)–C(sp^3) cleavage of benzylic and allylic alcohols delivering anilines and/or nitriles or N-heterocycles. FG = functional group.

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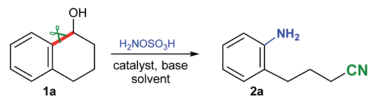
Table 1 Optimization table of cyclic benzyl alcohols *via* C–C cleavage[a]



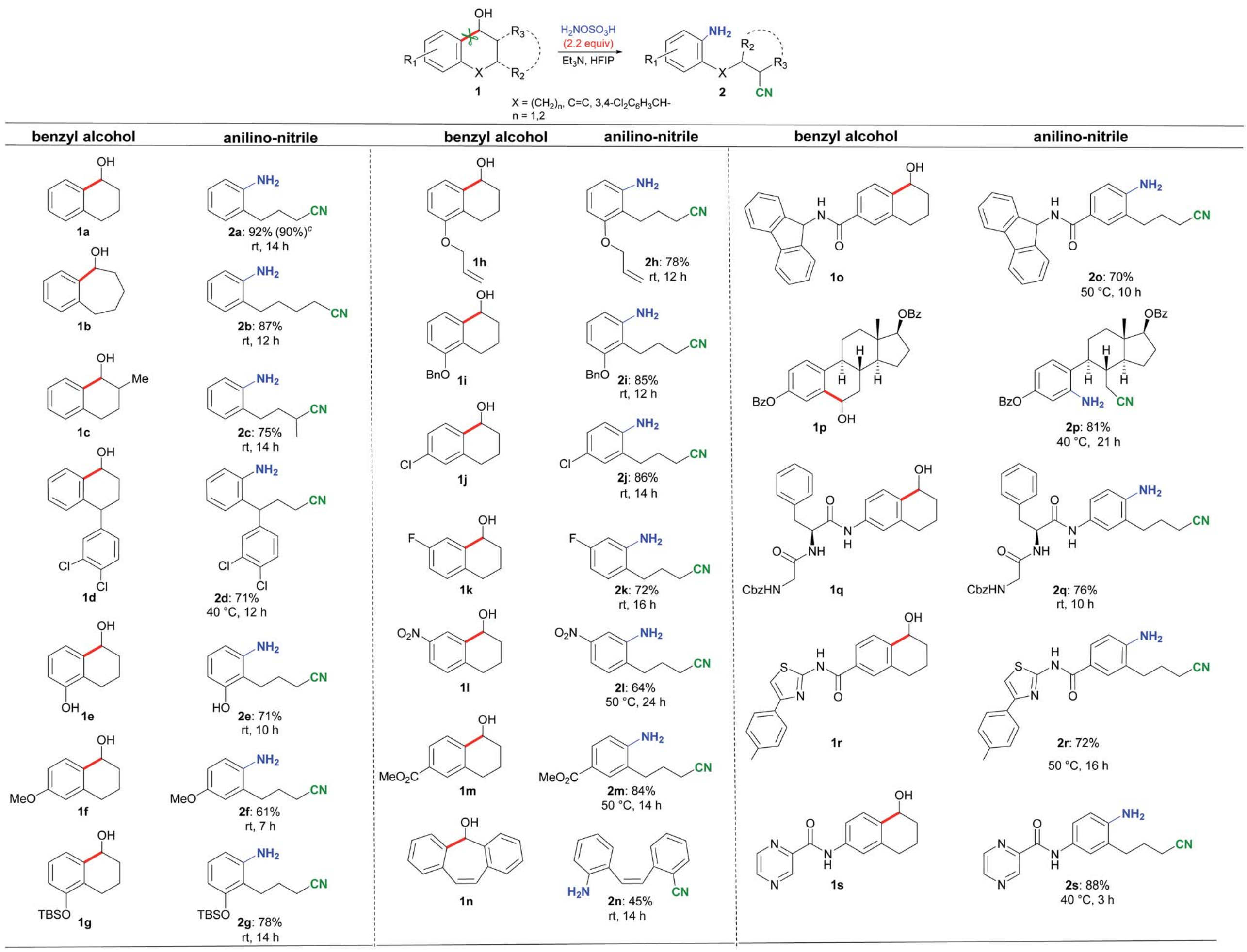
Entry	Photocatalyst (mol%) blue LED (470 nm)	Solvent	Base	Temp. (°C)	Time (h)	Yield (%)
1	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)PF_6$ (**2**)	HFIP	Et_3N	—	1	72
2	Eosin-Y	HFIP	Et_3N	—	1	70
3	—	HFIP	Et_3N	60	1	66
4	$[Ir\{dF(CF_3)ppy\}_2(dtbpy)]PF_6$ (**2**)	CH_2Cl_2	Et_3N	—	24	0
5	—	**HFIP**	**Et_3N**	**23**	**14**	**92**
6	—	HFIP	—	23	14	0
7	—	HFIP	Pyridine	23	14	79
8	—	HFIP	DMAP	23	14	85
9	—	TFE	Et_3N	60	24	42
10	—	THE	Et_3N	60	24	0
11	—	MeOH	Et_3N	60	24	<5
12	—	CH_2Cl_2	Et_3N	60	24	<5

[a] See ESI for additional details.

substrate class, *i.e.*, allylic alcohols, in addition to alkylarenes/styrenes, and (iii) utilization of a more acceptable aminating reagent. To these ends, a mixture of model substrate 1-tetrahydronaphthol (**1a**, α-tetralol) and aminating reagent hydroxylamine-*O*-sulfonic acid (HOSA) was screened with a variety of organic/inorganic bases in several common solvents (see ESI†) and discovered to give anilino-nitrile **2a**, whose differentiated nitrogen functionality was deemed to hold considerable synthetic potential. Following optimization of reagent ratios (see ESI†), the isolated yield of **2a** was raised to 92% using equimolar HOSA and Et_3N in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) at rt (Table 1); while CsOH as base was comparable to Et_3N, its deliquescence precluded routine use. These studies also revealed that a base for deprotonation of zwitterionic HOSA is crucial for reaction (entry 6). No or little reaction occurred in MeOH, CH_2Cl_2 or THF. For α-tetralol (**1a**, Table 1), the observed migratory aptitude (aryl ≫ alkyl) correlated with well established migratory aptitudes. Application of these conditions to seven-membered 2-methyl-α-tetralol (**1c**), and 4-(3,4-dichlorophenyl)-α-tetralol (**1d**) likewise gave good yields of the corresponding anilino-nitriles **2b–d**; of interest, **2d**'s benzhydryl hydrogen proved stable. Substituents on the aromatic ring also were well tolerated ranging from electron donating groups, *viz.*, free phenol (**1e**), methoxy (**1f**), silyl ether (**1g**), allyl ether (**1h**) and benzyl ether (**1i**) to halogens (**1j,k**) and even the more powerful electron withdrawing groups nitro (**1l**) and methoxycarbonyl (**1m**), although the latter two alcohols needed gentle warming to achieve acceptable reaction rates. As an indication of the mild reaction conditions, the labile *cis*-stilbene **2n** was obtained from dibenzosuberenol (**1n**) without isomerization to the thermodynamically more stable *trans*-isomer. Other sensitive and/or polyfunctional molecules that proved compatible with the bis-functionalization protocol are evident in 9*H*-fluoren-9-amide **2o**, seco-estradiol dibenzoate **2p**, *Cbz*-protected dipeptide **2q**, thiazole **2r**, and pyrazine **2s**, all of which were realized in good yields. The scope of the site-selective C–C cleavage was further explored using readily available acyclic benzyl alcohols leading to the corresponding anilines (Table 2). Access to aniline itself (**4a**) and *N*-methylaniline (**4a′**) from 1-phenylethanol **3a** proceeded smoothly (71% and 72% overall yield, respectively) using HOSA and *N*-methylhydroxylamine-*O*-sulphonic acid,[24] respectively. Additional substitution at the benzylic position capable of supporting a carbocation, *e.g.*, benzhydrol (**3a′**) and 2-phenylisopropanol (**3a″**), accelerated the reaction rate; the non-migrating phenyl of **3a′** was obtained as a 2 : 1 mixture of benzaldehyde and benzonitrile (54%). Also, moderate to strong electron donating aryl substituents were also more reactive as illustrated in **4b–f**, **4s** while simultaneously offering comparatively better yields vis-à-vis the hydrazoic acid based procedure;[19,20] even the easily oxidized *p*-phenylenediamines **4g,h** were well behaved. Additionally, examples containing 2-naphthyl **4i**, biphenyl **4j**, and quinoline **4k** as well as typical electron withdrawing substituents such as acetamide **4l**, bromide **4m**, and nitro **4n** delivered the corresponding anilines without incident. For validation within the context of polyfunctional bioactive scaffolds, benzyl alcohols derived from acebutolol, iloperidone, and adapalene were converted to anilines **4o–q**. To better understand the reaction course, **3r** was treated with 1 equivalent each of HOSA and Et_3N in HFIP as solvent resulting in **4r** (45%) and 4-phenylcyclohexanone (38%), most likely arising from hydrolysis of the intermediate imine. As might be expected, acid sensitive functionality such as acetonides and epoxides are not stable under the moderately acidic reaction conditions.

Extension of the bis-functionalization repertoire to cyclic allylic alcohol **5a** gave rise to adiponitrile (**6a**), an industrially

Table 2 Bis-functionalization of cyclic benzyl alcohols *via* C–C cleavage[a,b]



[a] Reactions conditions: benzyl alcohol (0.5 mmol), H_2NOSO_3H (2.2 equiv.), Et_3N (2.2 equiv.) at 0.15 M in hexafluoroisopropanol (HFIP) under argon. [b] Isolated yields. [c] 5 mmol scale. H_2NOSO_3H: hydroxylamine-*O*-sulfonic acid; HFIP: 1,1,1,3,3,3-hexafluoroisopropanol.

important commodity, whereas acyclic **5b** led to 2-phenylacetonitrile (**6b**) (Table 3). On the other hand, a 1 : 2 mixture of 3-phenylpropnitrile (**6c**) and 4-phenylbutyronitrile (**6c′**) was obtained from **5c**, although in good combined yield. Similarly, a 1 : 1.3 mixture of undecanenitrile (**6d**) and dodecanenitrile (**6d′**) was observed coming from **5d** reflecting the competing influences of charge distribution in the allylic carbocation *vs.* steric approach of HOSA. For trisubstituted allylic alcohol **5e**, nitrile **6e** was the minor product and Beckmann lactam **6e′**, resulting from initial addition of HOSA to the tertiary center, was favored. For some cyclic benzylic alcohols (Table 4), arene migration to the HOSA nitrogen (Fig. 2) directly resulted in a stable aromatic system, *e.g.*, phenanthridene (**7a**) from 9-hydroxyfluorene and dibenzoxazepine (**7b**) dibenzoxazepine (**7b**) from xanthydrol. In other systems, aromatization occurred following *in situ* oxidation of the intermediate imine, *e.g.*, quinoline (**7c**) from 1-indanol and substituted quinoline **7d**; the former *via* exposure to air during the course of the reaction and the latter induced by HOSA, itself a mild oxidant. Alternatively, the process can be paused after the first rearrangement step by restricting the amount of HOSA/Et_3N and the newly generated imine reduced *in situ*. For instance, the one-pot, sequential treatment of **1a** with just 1.2 equivalents each of HOSA and Et_3N, followed by sodium cyanoborohydride after **1a** was consumed, produced 1*H*-tetrahydrobenzazepine (**7e**) in 71% yield accompanied by **4a** (4%); 2-methyl-1*H*-tetrahydrobenzazepine (**7f**; 91%) was secured analogously from 1-methyl-1-tetrahydronaphthol (Table 5).

Control experiments (see ESI†) proved instructive in understanding the plausible mechanism. For example, **2f** in HFIP (0.15 M) at rt, but in the absence of HOSA and TEA, formed the corresponding HFIP ether **8** overnight, consistent with the formation of a carbocation intermediate. Treatment of **1a** with butylated hydroxytoluene (BHT) under our standard reaction condition resulted in no change in the yield of **2a** which doesn't support a long lived radical mechanism. On the other hand, the

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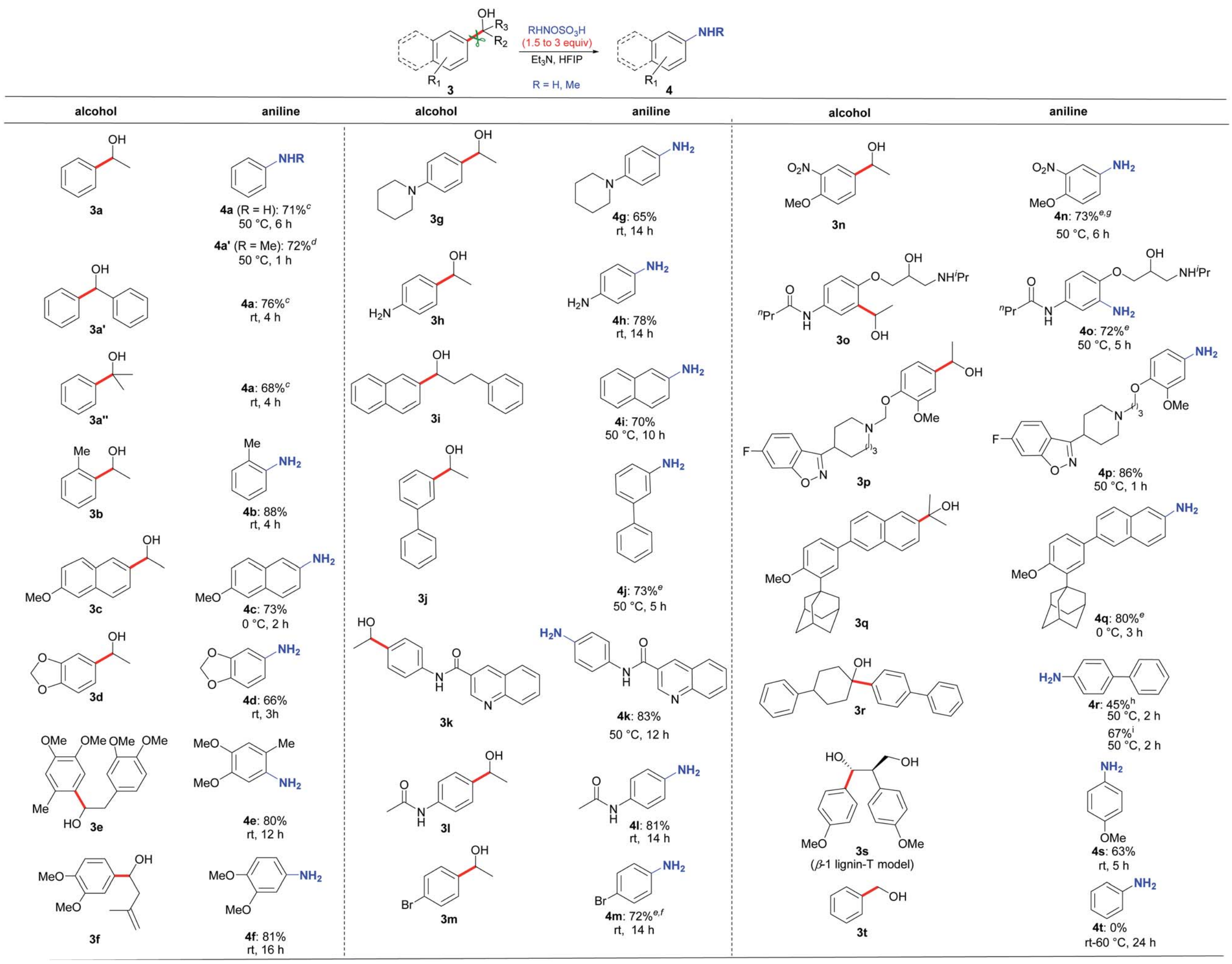
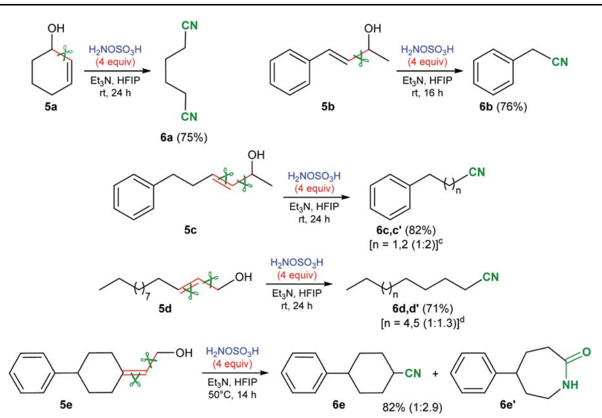
Table 3 Synthesis of anilines *via* C–C cleavage of acyclic benzyl alcohols[a,b]



[a] Reactions conditions: benzyl alcohol (0.5 mmol), H_2NOSO_3H (1.5 equiv.), Et_3N (1.5 equiv.) at 0.15 M in hexafluoroisopropanol (HFIP) under argon. [b] Isolated yields. [c] For convenience, isolated as the *N*-acetamide; overall yield for C–C cleavage and *N*-acylation. [d] $MeHNOSO_3H$ (3 equiv.) and Et_3N (1.5 equiv.). [e] 3 equiv. each of H_2NOSO_3H and Et_3N. [f] 1.5 equiv. each of H_2NOSO_3H and Et_3N gave **4m** (33%) and unreacted starting material (51%). [g] 1.5 equiv. each of H_2NOSO_3H and Et_3N gave **4n** (21%) and unreacted starting material (68%). [h] Using 1 equiv. each of H_2NOSO_3H and Et_3N, 4-phenylcyclohexanone was also isolated in 38% yield. [i] Using 1.5 equiv. each of H_2NOSO_3H and Et_3N, 4-phenylcyclohexanone was also isolated in 45% yield.

Table 4 Mono-/bis-nitriles *via* C–C cleavage of allylic alcohols[a,b]



[a] Reactions conditions: allylic alcohol (0.5 mmol), HOSA (4.0 equiv.), Et_3N (4.0 equiv.) at 0.15 M in hexafluoroisopropanol (HFIP) under argon. [b] Isolated yields. [c] Ratio determined *via* ^{1}H NMR. [d] Ratio determined *via* LC/HRMS.

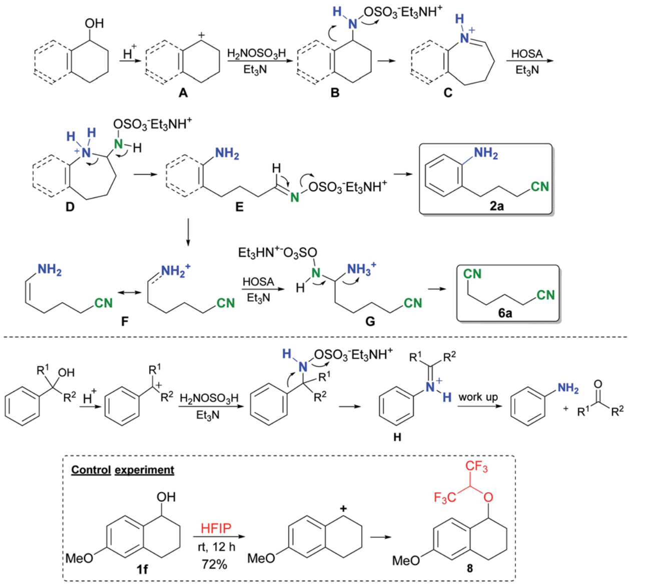


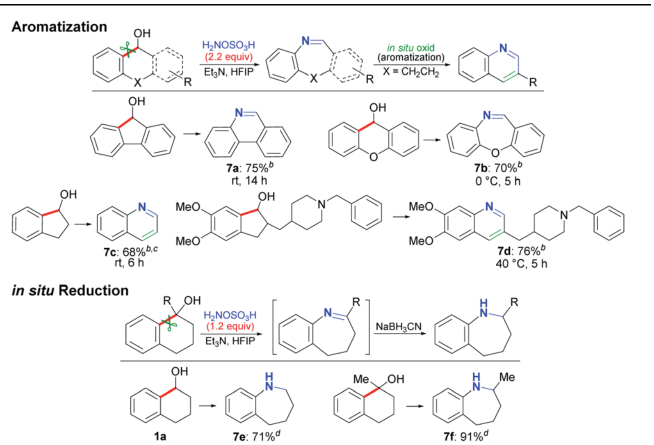
Fig. 2 Plausible bis-functionalization mechanism. Illustrated for (i) α-tetralol (**1** → **2a**) and 1-cyclohexenol (**5a** → **6a**) (ii) plausible mechanism for acyclic benzyl alcohols and (iii) control experiment consistent with carbocation intermediacy.

yield of **2a** was significantly decreased in the presence of 2 equiv. of TEMPO; however, control experiments suggested that the HOSA is decomposed by TEMPO under our reaction conditions (see ESI†).

Fig. 2 presents a generalized, mechanistic scenario by which benzylic and allylic alcohols undergo bis-functionalization either type of alcohol is readily converted to the corresponding hydroxylamine-*O*-sulfonate trimethylamine salt **B** *via* stabilized carbocation **A**. Subsequent rearrangement of **B** forms iminium **C** that in turn forms **D** upon addition of a second equivalent of triethylammonium HOSA. For benzyl alcohols, a quick succession of eliminations, firstly to aldoxime **E** by collapse of the aminal in **D**, and finally yields anilino-nitrile (illustrated by **2a**) *via* loss of sulfate and a proton. If an allylic alcohol is the substrate, **E** leads to imine-enamine **F** that eventually terminates at bis-nitrile (illustrated by **6a**) following an addition/elimination sequence similar to the one that led to **2a**.

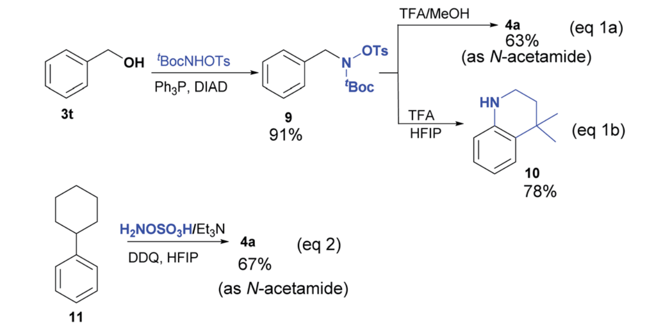
For acyclic benzyl alcohols, iminium intermediate **H** provided the corresponding anilines and aldehydes/ketones upon aqueous isolation.

Table 5 N-Heterocycles from cyclic benzyl alcohols *via* C–C cleavage[a,b]



[a] Reactions conditions: isolated yields. [b] Benzyl alcohol (0.5 mmol), HOSA (2.2 equiv.), Et_3N (2.2 equiv.) at 0.15 M in HFIP under argon. [c] Conducted open to atmosphere. [d] Used (i) HOSA (1.2 equiv.) and Et_3N (1.2 equiv.), 0 °C; (ii) $NaBH_3CN$ (2 equiv.), rt.

Table 6 Synthesis of anilines *via* C–C cleavage of alkylarenes and primary benzyl alcohols



Conclusions

The foregoing one-pot methodology exploits the site-selectivity of C(sp^2)–C(sp^3) cleavage of benzylic and allylic alcohols for non-hazardous, metal-free access to anilines and/or nitriles or, most notably for cyclic systems, to anilino-nitriles and bis-nitriles, respectively, with highly advantageous step and atom efficacy. In preliminary studies, we also sought to extend our methodology to substrates that are otherwise refractory and for this the reaction conditions were conflated with prior methodology.[19,25] Proof of principle was gained using the otherwise unreactive benzyl alcohol (**3t**) that was converted with commercial *N*-^{t}Boc-*O*-tosylhydroxylamine under Mitsunobu conditions to *O*-tosyloxime **9** that subsequently underwent rearrangement to aniline (**4a**) under the influence of trifluoroacetic acid in methanol (eqn (1a), isolated as the *N*-acetamide) (Table 6).

Unexpectedly, N-heterocycle (**10**) was observed (see ESI†) when **9** was stirred with excess TFA in HFIP as solvent (eqn (1b)), presumably involving three successive transformations (C–C cleavage, decarboxylation and rearrangement). α-Unfunctionalized alkylarenes, *e.g.*, **11**, are also inert to the standard reaction conditions, but could be coaxed to rearrange using a mixture of DDQ and HOSA/Et_3N (eqn (2)). Detailed studies will appear elsewhere.

Data availability

Data for this work, including optimization tables, general experimental procedures and characterization data for all new compounds are provided in the ESI.†

Author contributions

R. R. A. conceptualized the project, conducted the experiments, analyzed the data and wrote the original draft. J. R. F. provide project supervision and manuscript review.

Conflicts of interest

The authors declare no competing financial interests.

Acknowledgements

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