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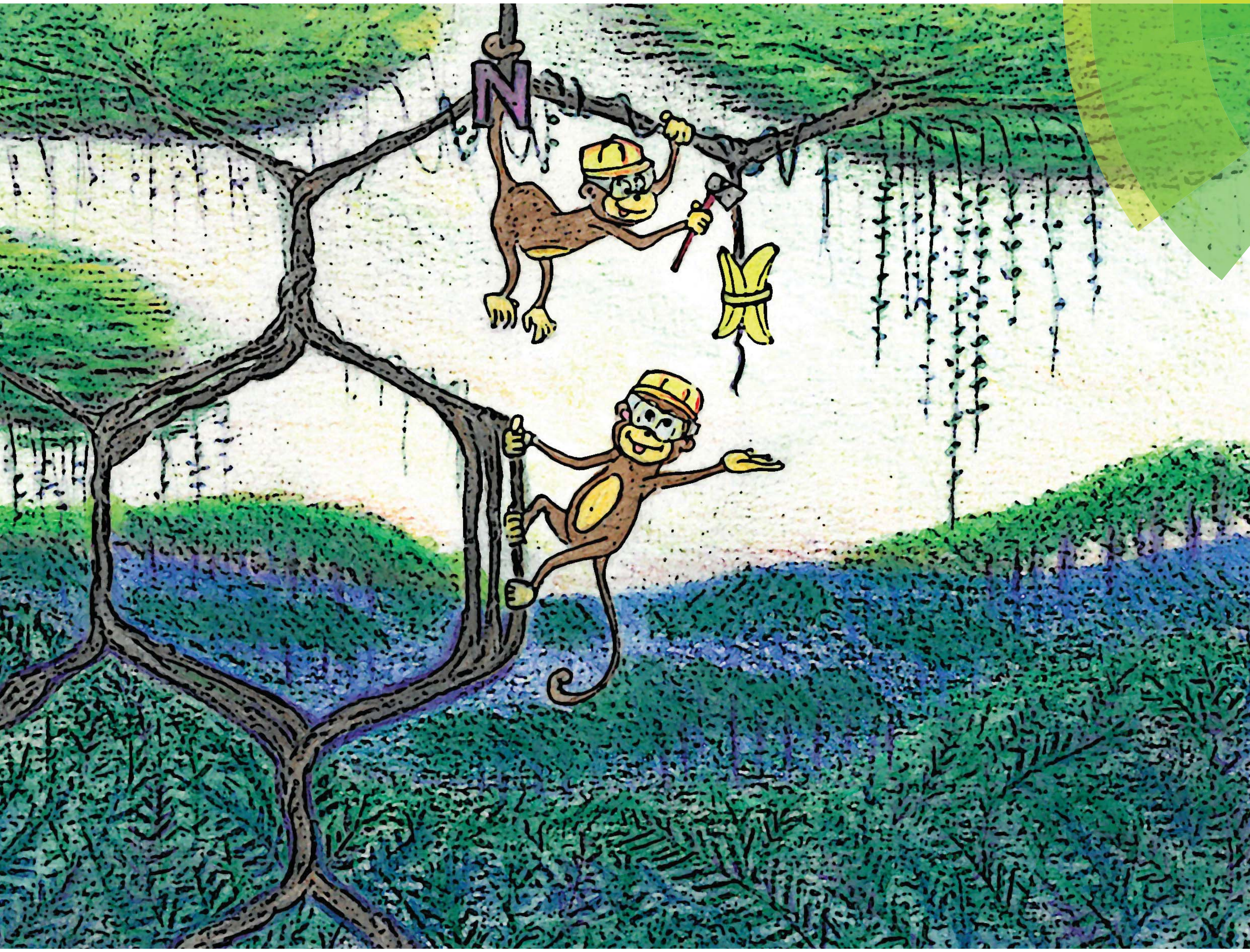

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Intramolecular hydride transfer onto arynes: redox-neutral and transition metal-free C(sp^3)–H functionalization of amines†

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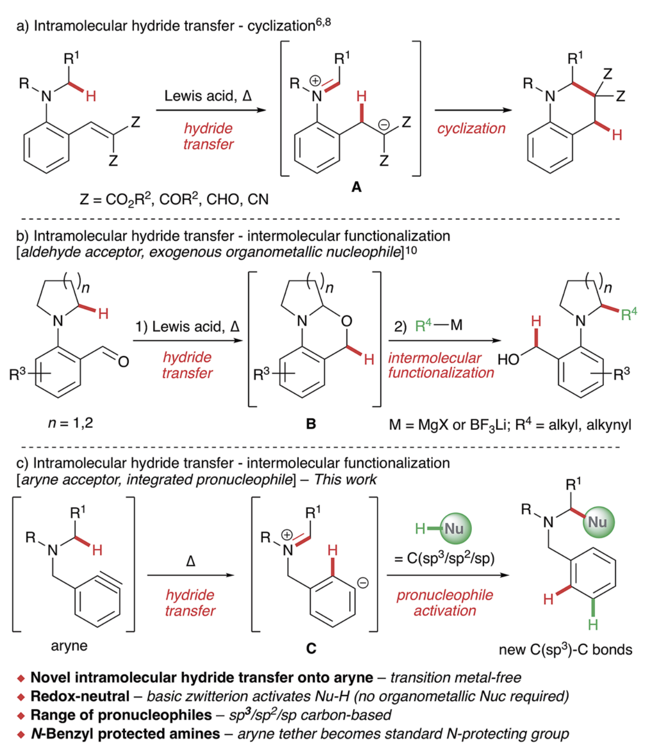
Transition metal-free intramolecular hydride transfer onto arynes is reported for the first time. This unique transformation is utilized in redox-neutral intermolecular α-functionalization reactions of different tertiary amines, generating C(sp^3)–C(sp^3/sp^2/sp) bonds in a single synthetic operation. Deuterium labeling studies support initial cleavage of the α-C–H bond *via* intramolecular 1,5-hydride transfer onto the aryne, which leads to activation of a range of integrated pronucleophiles and ultimately affords a new approach to cross-dehydrogenative coupling reactions which utilize aryne intermediates.

Introduction

The direct functionalization of C–H bonds offers a wealth of potential benefits to synthetic chemists,[1] with significant progress having been made in recent decades.[2] Activation of C(sp^3)–H bonds α- to heteroatoms is particularly appealing,[3] as evidenced by the burgeoning area of cross-dehydrogenative coupling (CDC) reactions,[4] whereby certain substrates, especially amines, are functionalized using a sacrificial external oxidant and generally in the presence of a transition metal catalyst.[5] α-Functionalization of amines has also received considerable recent interest through the development of redox-neutral processes[6] that exploit the propensity of tertiary amines to undergo 1,5-hydride transfer onto a tethered acceptor,[7] most commonly electron-deficient alkenes (Scheme 1a).[8,9] Here, Lewis acid-catalyzed intramolecular hydride transfer results in a zwitterionic intermediate **A** that cyclizes to generate a new C–C bond. Maulide and co-workers elegantly extended this strategy to develop a redox-triggered approach to the C–H functionalization of cyclic amines (Scheme 1b).[10] 1,5-Hydride transfer onto an aldehyde acceptor – employed as a sacrificial oxidant – resulted in aminal **B**, which underwent nucleophilic attack upon addition of organometallic reagents.

Given our interest in aryne chemistry,[11] we envisioned a related approach to a general α-functionalization of amines that employs arynes as internal hydride acceptors for the first time (Scheme 1c). This new transformation would reveal the unique zwitterionic intermediate **C**, prevented from undergoing intramolecular cyclization due to geometrical constraints. Significantly, zwitterion **C** contains a highly basic aryl anion that should be capable of activating a pronucleophile (Nu-H) within the reaction mixture,[12] obviating the use of exogenous organometallic reagents in a second operation and rendering the overall process redox-neutral. Finally, the aryne tether would



Scheme 1 C(sp^3)–H bond activation *via* intramolecular hydride transfer.

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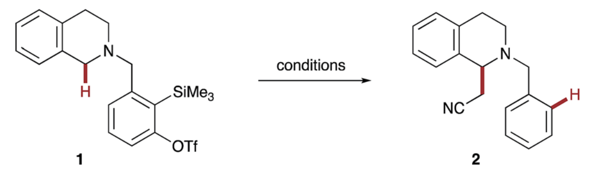
also operate as a latent *N*-benzyl protecting group; easily cleaved when desired.

Arynes are versatile reactive intermediates that have experienced a recent resurgence in interest[13] due to the development of precursors that act under mild conditions, such as 2-(trimethylsilyl)aryl triflates[14] and the hexadehydro-Diels–Alder reaction of polyalkynes.[15] Despite undergoing myriad additions with an extensive range of nucleophiles,[13] the reaction of arynes with C(sp^3)–H bonds *via* ionic hydride transfer has yet to be realized.[16–18] Herein we report this new transformation, which has enabled intermolecular α-functionalization of a range of tertiary amines with different carbon-based pronucleophiles, some of which are uncommon in CDC processes due to comparatively high pK_a values. Deuterium labeling studies are described which support initial 1,5-hydride transfer onto the aryne, followed by activation of the integrated pronucleophile. Overall this furnishes new C(sp^3)–C(sp^3/sp^2/sp) bonds in a single and operationally simple procedure *via* aryne-mediated CDC reactions.

Results and discussion

1,2,3,4-Tetrahydroisoquinoline (THIQ) was selected as the donor portion with which to initially evaluate our 1,5-hydride transfer hypothesis due to its biological activity and general synthetic utility.[19,20] A suitable aryne acceptor was then tethered onto the amine donor using the 2-trimethylsilyl-3-trifluoromethanesulfonyl benzaldehyde precursor reported by Smith III and Kim.[21] Acetonitrile was chosen as the initial pronucleophile as it is a common solvent for *o*-silylaryl triflate reactions and has been reported to undergo deprotonation by aryne-derived aryl anions.[12] Selected optimization experiments, using THIQ scaffold **1** as a test system, are presented in Table 1. Evaluation of common *o*-silylaryl triflate activators (entries 1–7) identified KF/18-crown-6 and tetrabutylammonium triphenyldifluorosilicate (TBAT) as the most promising reagents. The introduction of toluene as a co-solvent (toluene : acetonitrile, 3 : 1 by volume) enabled higher reaction temperatures which led to an increased yield with TBAT (entry 8). Both increasing and decreasing the reaction concentration resulted in lower yields (entries 9 & 10); most significantly at higher concentration due to competitive intermolecular amine arylation. At this stage we found that the α-cyanomethylated THIQ **2** could not be isolated cleanly during the reactions with TBAT, as the aryl silane by-product was a persistent contaminant, so we turned our attention to KF/18-crown-6 as the activator. A slight erosion in yield was observed for KF/18-crown-6 in the toluene–acetonitrile mixture (entry 11), presumably due to poorer solubility of fluoride. However, we were pleased to find that a solvent switch to 1,2-dimethoxyethane (DME) and acetonitrile (3 : 1 by volume) led to the complete consumption of aryne precursor **1** and the formation of the desired α-cyanomethylated THIQ **2a** in 77% isolated yield (entry 12). The DME : acetonitrile ratio could be lowered to 19 : 1 by volume with a small drop-off in the yield of **2** (59%, entry 13). Encouragingly, further reduction of the pronucleophile loading to 150 : 1 (approx. 10 equivalents of acetonitrile, see entry 14) afforded **2** in a respectable 35% yield,

Table 1 Selected optimization studies for the preparation of α-cyanomethyl-THIQ **2**[a]

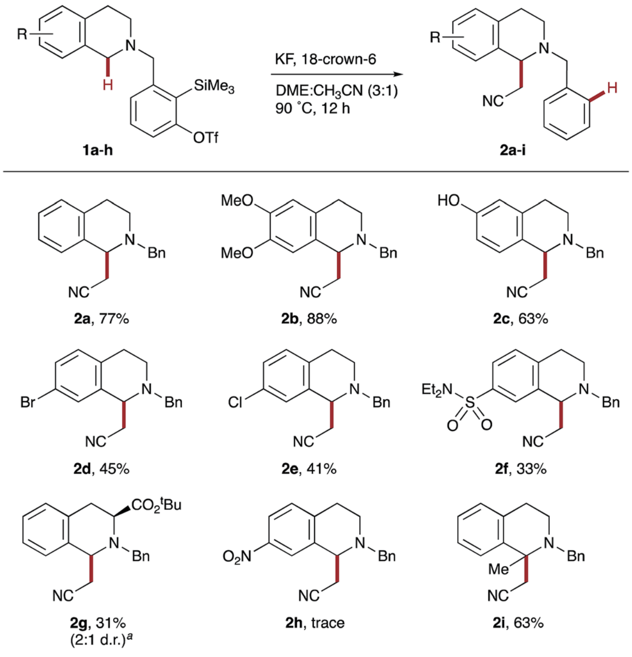


Entry	Activator	Additive	Solvent	T (°C)	Yield[b] (%)
1	CsF	—	CH_3CN	70	43
2	CsF	18-c-6	CH_3CN	70	60
3	KF	18-c-6	CH_3CN	70	70
4	Cs_2CO_3	18-c-6	CH_3CN	70	36
5	TBAF[c]	—	CH_3CN	70	29
6	TBAF·3H_2O	—	CH_3CN	70	23
7	TBAT	—	CH_3CN	70	66
8	TBAT	—	3 : 1 PhMe/CH_3CN	90	75
9	TBAT	—	3 : 1 PhMe/CH_3CN[d]	90	72
10	TBAT	—	3 : 1 PhMe/CH_3CN[e]	90	35
11	KF	18-c-6	3 : 1 PhMe/CH_3CN	90	64
12	KF	18-c-6	3 : 1 DME/CH_3CN	90	89 (77)
13	KF	18-c-6	19 : 1 DME/CH_3CN	90	59
14	KF	18-c-6	150 : 1 DME/CH_3CN	90	35

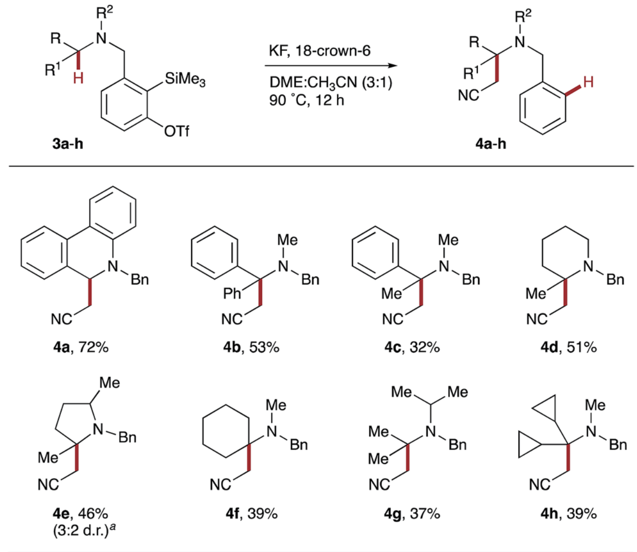
[a] Reaction conditions: activator (2.0 equiv.), additive (2.0 equiv.), solvent [0.01 M], 12 h. [b] ^{1}H NMR yield *vs.* dibromomethane internal standard, isolated yield in parentheses, all reactions proceeded to full conversion after 12 h. [c] 1.0 M in THF. [d] 0.005 M. [e] 0.05 M. TBAT = tetrabutylammonium triphenyldifluorosilicate.

which hinted at the potential to expand this method to more valuable pronucleophiles in the future. However, as the 3 : 1 volumetric ratio of DME : acetonitrile afforded the best yields and represented a good improvement in pronucleophile loading compared to the majority of CDC processes,[4] especially those involving this less common pronucleophile,[22] these conditions were selected for the study.

A range of substituted THIQs **1b–i** were found to be amenable to the optimized reaction conditions, affording the corresponding C1-cyanomethylated THIQs **2b–i** (Scheme 2). Electron-donating substituents such as methoxy (**1b**) and hydroxy (**1c**) were excellent substrates, giving high yields of **2b** and **2c**. It is particularly interesting to note that 6-hydroxy THIQ precursor **2c** was tolerated, as it demonstrated that the unprotected phenol did not cause significant quenching of the anion in zwitterionic intermediate **C** (see Scheme 1c). Halogens (Br, **1d** and Cl, **1e**) and moderately electron-withdrawing groups (SO_2NEt_2, **1f** and CO_2t-Bu, **1g**) were also viable substrates, affording the corresponding products **2d–g** in moderate yields; consistent with less hydridic C–H bonds and decreased carbocation stabilization in comparison to **1a–c**. The incorporation of a strongly electron-withdrawing nitro group into the THIQ scaffold (**1h**) was found to almost completely inhibit hydride transfer, with only traces of **2h** observed. Finally, 1-methyl THIQ **1i** proved an effective substrate, generating the quaternary cyanomethylated THIQ **2i** in a good yield. It is noteworthy that THIQs occupy a privileged position as benchmark substrates in



Scheme 2 Intramolecular hydride transfer onto aryne with THIQ derivatives. Reaction conditions: amine **1** (1.0 equiv.), KF (2.0 equiv.), 18-crown-6 (2.0 equiv.), DME : CH_3CN (3 : 1 by volume, 0.01 M), 90 °C, 12 h. Yields of isolated products throughout. [a]Ratio determined by ^1H NMR spectroscopy.



Scheme 3 Hydride transfer from linear and cyclic amine derivatives. Reaction conditions are as shown in Scheme 2. Yields of isolated products throughout. [a]Ratio determined by ^1H NMR spectroscopy.

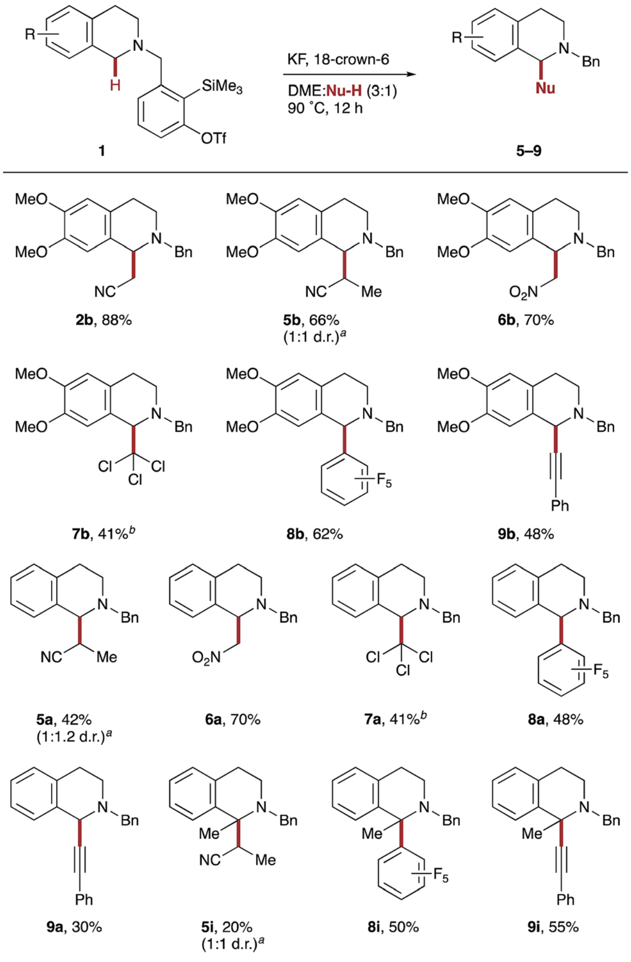
CDC reactions, affording α-functionalized products that typically contain an *N*-aryl group.[4] In comparison, the THIQs **2** produced here possess a synthetically practical *N*-benzyl protecting group.[23]

Having established the feasibility of intramolecular hydride transfer onto arynes with a range of THIQ derivatives, we continued our investigations by varying the structure of the tertiary amine donor. Starting with dihydrophenanthridine derivative **3a**, exposure to the established reaction conditions smoothly afforded **4a** in 72% yield (Scheme 3). α-Phenylbenzylamine precursor **3b** and α-methylbenzylamine **3c** generated the quaternary products **4b** and **4c** in 53% and 32% yields respectively. Interestingly, no benzobarrelene products from a potentially competitive intramolecular Diels–Alder pathway were identified.[24] Instead, the increase in conformational flexibility of the tether is proposed to account for the difference in reactivity between **3a** and **3b**/**c**.

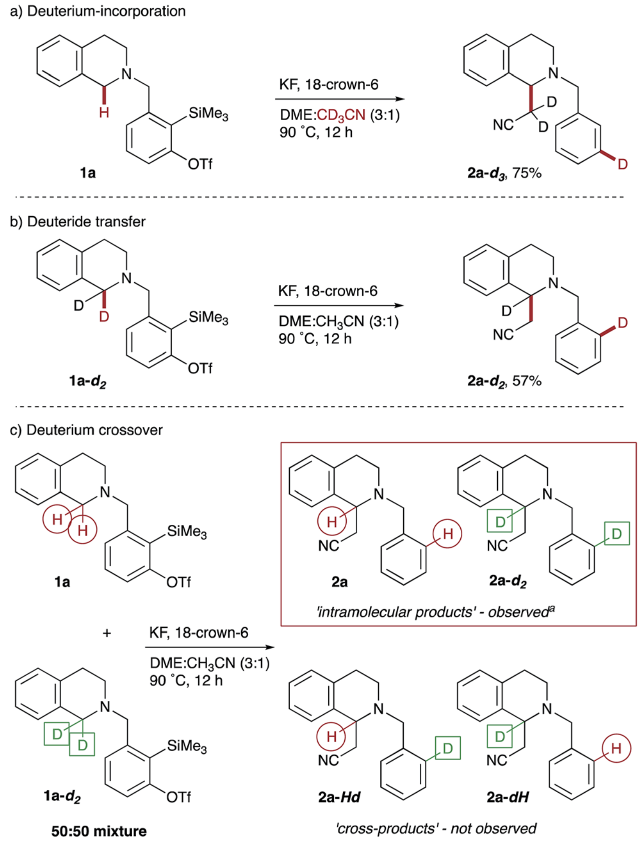
Pleasingly, hydride transfer was not restricted to benzylic C–H bonds and proved equally effective with precursors **3d–h** that each contained tertiary alkyl C–H bonds. Heterocyclic derivatives 2-methyl-piperidine **3d** and 2,5-dimethyl-pyrrolidine **3e** gave the corresponding α-quaternary heterocycles **4d** and **4e** in moderate yields. Similarly, the less conformationally-rigid amines **3f–h** also promoted hydride transfer onto arynes, yielding spirocyclic and acyclic C–H functionalized amines, **4f** and **4g**/**h**, respectively.

Having applied the principle of aryne-mediated hydride transfer and subsequent co-solvent activation to the α-cyanomethylation of tertiary amines, we looked at introducing alternative pronucleophiles in this process. Pleasingly, when dimethoxy-THIQ derivative **1b** was exposed to the standard reaction conditions, a range of different carbon-based coupling partners were found to be viable co-solvents (Scheme 4). For example, propionitrile, less acidic than acetonitrile ($pK_a = 32.5$ in DMSO *cf.* 31.3 for MeCN),[25] yielded β-substituted cyanoamine **5b** as a 1 : 1 mixture of diastereoisomers in 66% yield. Nitromethane, a more commonly used solvent in CDC reactions[4c] due to significantly higher acidity ($pK_a = 17.2$ in DMSO),[25] produced nitromethylated THIQ **6b** in a similarly good 70% yield. Interestingly, a more 'inert' solvent such as chloroform also operated as a coupling partner, producing trichloromethylated THIQ **7b** in 41% yield. It is noteworthy that better yields were obtained here at a lower 9 : 1 DME : Nu-H ratio and no products from dichlorocarbene intermediates were detected. The use of pentafluorobenzene enabled access to new C(sp^3)–C(sp^2) bond formation (**8b**) in good yield, illustrating the potential for α-amino C(sp^3)–H arylation with electron-deficient arenes in the absence of a transition metal catalyst. Lastly, C(sp^3)–C(sp) coupling could be achieved with phenylacetylene, affording **9b** in 48% yield; the addition of copper did not improve the outcome.[26] THIQ derivatives **1a** and **1i** also proved amenable to these aryne-mediated CDC reactions, affording the corresponding α-functionalized THIQs in moderate to good yields.[27]

Finally, we sought to probe our mechanistic hypothesis. Support for an ionic hydride transfer process came from the retention of the cyclopropane rings in amine **4h** (see Scheme 3), as it was reasoned that formation of a radical adjacent to nitrogen would result in rapid and irreversible cyclopropane ring-opening. Furthermore, conducting the cyanomethylation of **1a** in the presence of a radical scavenger, TEMPO (2.0 equiv.), did not prohibit the reaction. Next we performed a series of deuterium labeling studies, starting with the reaction of THIQ



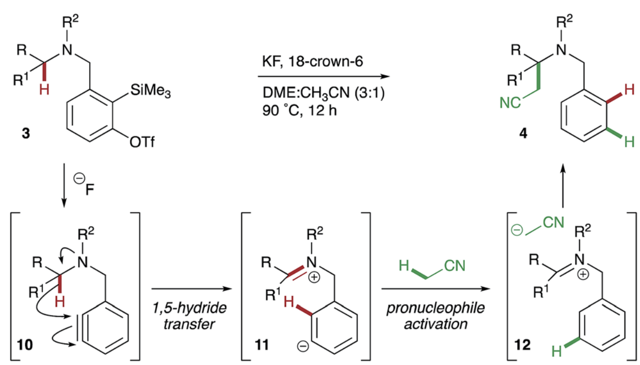
Scheme 4 Alternative pronucleophiles. Reaction conditions are as shown in Scheme 2. Yields of isolated products throughout. [a]Ratio determined by ^{1}H NMR spectroscopy. [b]DME : Nu-H (9 : 1 by volume, 0.01 M).



Scheme 5 Mechanistic experiments. Reaction conditions are as shown in Scheme 2. [a]Products **2a** and **2a-d_2** isolated as an inseparable mixture of isotopologues (5 : 3.5, as determined by ^{1}H NMR spectroscopy) in a combined 70% yield.

precursor **1a** in acetonitrile-d_3 as co-solvent, which resulted in deuterium incorporation solely at the *meta* position of the benzene ring in THIQ **2a-*d*$_3$** (Scheme 5a). Next, exposure of bisdeuterated precursor 1,1-d_2-THIQ **1a-*d*$_2$** to the reaction conditions afforded the corresponding product of 1,5-deuteride transfer, **2a-*d*$_2$**, with deuterium located at the *ortho* position of the benzene ring (Scheme 5b).[28] Finally, a competition reaction between an equimolar amount of THIQ precursor **1a** and the bisdeuterated isotopologue **1a-*d*$_2$** supported the intramolecular nature of the hydride transfer, as the monodeuterated crossover products **2a-*Hd*** and **2a-*dH*** were not observed (Scheme 5c).

Considering the experimental evidence, the following mechanism is proposed (Scheme 6). Treatment of *o*-silylaryl triflate precursor **3** with fluoride reveals an aryne **10** that subsequently undergoes reduction *via* the intramolecular 1,5-hydride transfer of a C–H bond α- to nitrogen. The reactive zwitterionic intermediate **11** deprotonates the acetonitrile pronucleophile, which then adds to iminium ion **12** in a Mannich-type reaction to yield α-cyanomethylated amine **4**.



Scheme 6 Proposed mechanism.

Conclusions

In summary, we have described an intramolecular hydride transfer that uses arynes as acceptor moieties for the first time and exploited this in the development of aryne-mediated CDC reactions of heterocyclic and aliphatic tertiary amines. This is a transition metal-free and redox-neutral process that generates a new C(sp^3)–C(sp^3/sp^2/sp) bond α- to nitrogen in a single synthetic operation. The approach is distinct from existing transition metal-free methods for C–H functionalization *via* hydride transfer as a Lewis acid is not required to activate the acceptor and intermediate zwitterion cyclization is geometrically inhibited. Furthermore, the highly basic aryl anion directly activates a number of diverse pronucleophiles – some of which are not often encountered in CDC processes due to high pK_a values – which enables integration of an intermolecular coupling partner in the same reaction vessel. The reduced aryne tether also operates as a practical *N*-benzyl protecting group for the corresponding α-functionalized secondary amines. Finally, reactions conducted during the initial optimization studies revealed that lower pronucleophile loadings can be employed in these processes, hinting at the potential to expand to more valuable coupling partners, although the associated erosion in reaction yield means that further optimization would be required. To this end, work is currently underway in our laboratory to establish a full structure–activity profile for hydride transfer onto arynes.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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27 Nitromethyl and trichloromethyl derivatives of **1i** could not be isolated, presumably due to dissociation being favoured by the increased stability of the C1-substituted iminium ion and the greater acidity of the corresponding co-solvents.

28 Slower rate of deuterium transfer relative to hydride transfer enables competing and deleterious intermolecular amine arylation, resulting in slightly lower yields of cyanomethylated product **2a**-d_2.