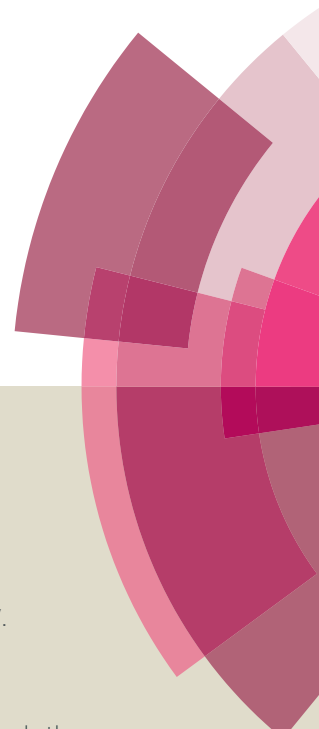
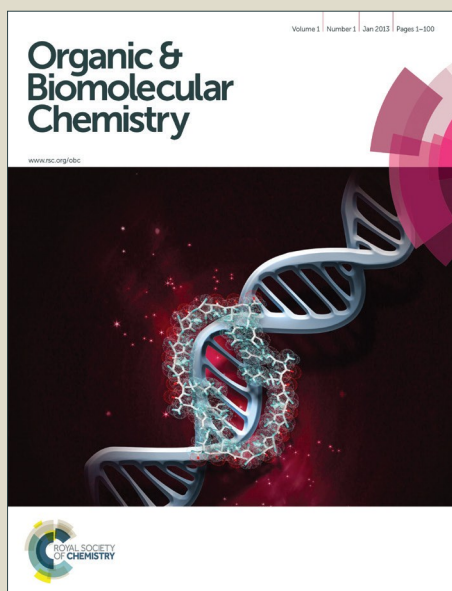


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ARTICLE

Synthesis of Trifluoromethylated Isoxazoles and Their Elaboration Through Inter- and Intra-molecular C-H Arylation

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We report conditions for the preparation of a range of trifluoromethylated isoxazole building blocks through the cycloaddition reaction of trifluoromethyl nitrile oxide. It was found that controlling the rate (and therefore concentration) of the formation of the trifluoromethyl nitrile oxide was critical for the preferential formation of the desired isoxazole products versus the furoxan dimer. Different conditions were optimised for both aryl- and alkyl- substituted alkynes. In addition, the reactivity at the isoxazole 4-position has been briefly explored for these building blocks. Conditions for intermolecular C-H arylation, lithiation and electrophile quench, and alkoxylation were all identified with brief substrate scoping that signifies useful tolerance to a range of functionalities. Finally, complementary processes for structural diversification through either intramolecular cyclisation or intermolecular cross-coupling were developed.

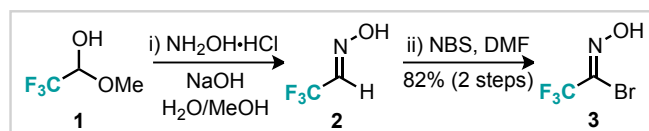
Introduction

The addition of fluorine to organic molecules does a great deal to alter chemical properties and behavior.¹ For example, in biologically active materials fluorine substituents can affect the charge distribution, electrostatic surface and solubility of chemical entities, often leading to positive outcomes.² Perhaps the most attractive property however is the ability to reduce the rate of metabolism compared to non-fluorous congeners, which ultimately leads to reduced dosing rates for both patients and crops.³ Furthermore, in the area of materials chemistry fluorous substituents can impart advantages such as reduced band gaps and higher quantum efficiencies in OLED devices.⁴

There are typically two strategic methods for introducing fluorous substituents. The late stage introduction, which has received much attention recently,⁵ is an important method, particularly for taking advantage of the radioactive properties of ¹⁸F labelled materials.⁶ Furthermore, with regards to trifluoromethylation, this doctrine serves as a convenient method to easily functionalise existing compound libraries, usually through a C-H, C-O, C-B, C-Sn or C-X bond transformation and more recently that of a C-N bond.⁷

Alternatively, a strategy involving the preparation of novel fluorinated building blocks which are then incorporated in a convergent manner (a fluorous synthon approach) is also of importance, particularly when it comes to scaling up the preparation of the compound of interest.⁸ Common to both strategic approaches is the fact that fluorine is not present in many naturally occurring organic compounds and so any reagents or building blocks must be derived from fluorine gas, or other mineral derived fluorines (such as HF, SF₄, SF₆ or HOF) thus requiring both highly skilled workers and specialised equipment and safety protocols.

Recently, we and others have been exploring cycloaddition methods to rapidly access a series of fluorinated intermediates, from simple fluorous synthon starting materials, that can further undergo a range of diverse modifications.⁹ Here we report a robust protocol for the preparation and cycloaddition of trifluoroacetone nitrile oxide with alkynes, followed by diversification *via* palladium-catalysed inter- and intra-molecular C-H activation reactions. We have also assessed the further derivatisation of these systems *via* anion and cycloaddition chemistry.



Scheme 1: Preparation of CF₃ nitrile oxide precursor

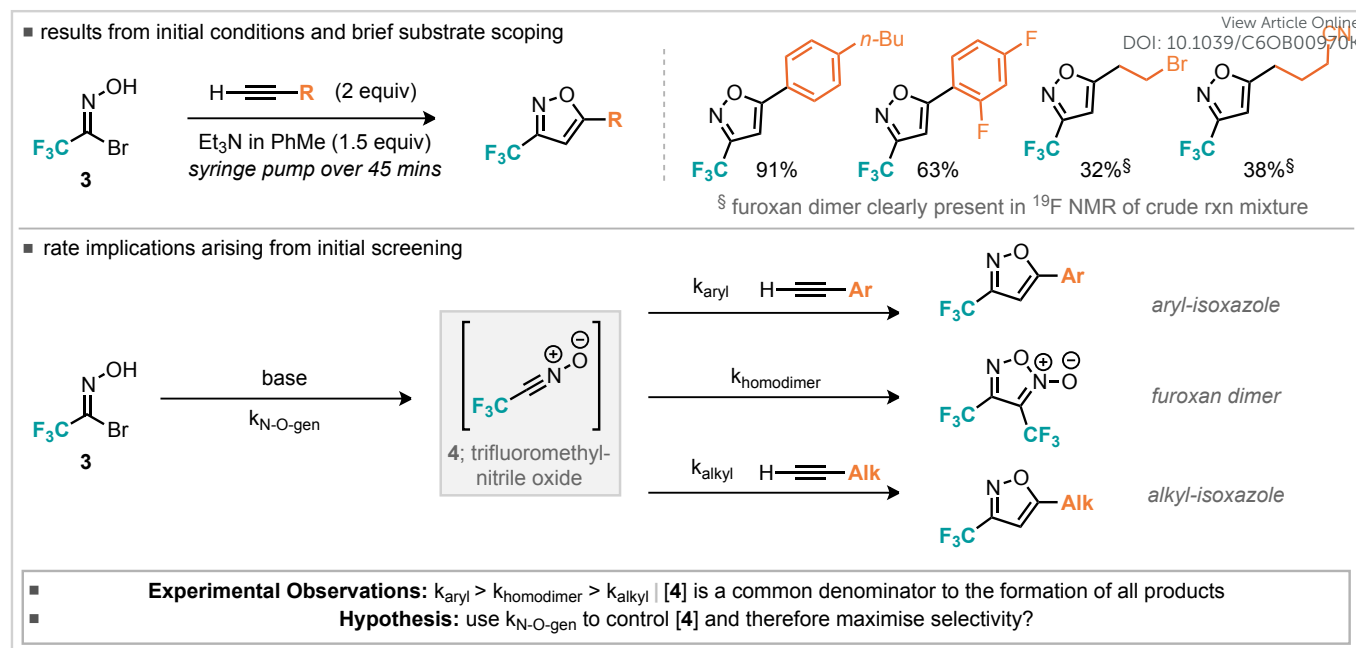
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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x



Scheme 2: Initial cycloaddition experiments and considerations

Results and Discussion

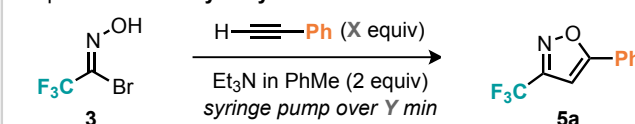
Our approach to the preparation of 3-trifluoromethyl isoxazoles hinged on a nitrile-oxide [3 + 2] cycloaddition reaction with alkyne substrates. Few examples of this approach are known. In order to synthesize the desired 5-substituted 3-trifluoromethylated isoxazoles via [3 + 2] cycloaddition reactions, a stable nitrile oxide precursor for trifluoroacetonitrile oxide was required. We decided to use hydroximoyl bromide **3**, prepared using a two-step procedure (Scheme 1) from the commercially available trifluoromethylated hemiacetal **1**.¹⁰ Owing to the volatility of both intermediate aldoxime **2** and hydroximoyl bromide **3**, these materials were extracted into an ethereal solution and then stored and used from this stock in subsequent steps.¹¹

With the desired trifluoromethyl nitrile oxide precursor in hand, we then focused on the [3 + 2] cycloaddition reaction with terminal alkynes. Early attempts with the cycloaddition reaction under similar conditions reported by Tanaka *et al.* with a small variety of alkynes revealed that the yield of isoxazole was rather dependent on the electronic properties of the alkyne (Table 1).¹² In general, more electron-deficient alkynes (in particular, alkyl alkynes) appeared to undergo slower cycloaddition with trifluoroacetonitrile oxide. Analysis of the ^{19}F NMR spectra of the crude reaction mixture for some alkyl alkynes (Scheme 2) indicated the presence of furoxan resulting from the unwanted dimerization reaction of trifluoroacetonitrile oxide.¹³

We considered the rates of the reactions explored in the context of these experimental observations. Empirically, the preliminary evidence suggests that the rate of nitrile oxide cycloaddition with aryl alkynes is greater or comparable to that of the dimerization of the CF_3 nitrile oxide, whereas the rate of cycloaddition between the nitrile oxide and alkyl alkynes

appears to be slower than the rate of furoxan formation. This suggested that control could be obtained by reducing the concentration of nitrile oxide relative to alkyne. Such control could potentially be achieved by invoking pseudo first-order conditions in nitrile oxide. This would be achieved by using a syringe pump to deliver either the base or the nitrile oxide precursor slowly to a flask containing all of the alkyne. With this in mind we therefore optimized procedures for aryl and alkyl alkynes separately, with particular attention to methods that limit formation of the furoxan. For the optimization studies of aryl alkyne cycloadditions, we used phenylacetylene as the substrate. Firstly, the number of equivalents of alkyne was assessed.

■ optimisation for aryl alkynes



Entry	alkyne equivs (X)	addition rate (Y)	base/solvent	yield ^a
1	1.0	45	$\text{Et}_3\text{N}/\text{PhMe}$	70%
2	2.0	45	$\text{Et}_3\text{N}/\text{PhMe}$	90%
3	3.8	45	$\text{Et}_3\text{N}/\text{PhMe}$	93%
4	2.0	45	$i\text{Pr}_2\text{NEt}/\text{PhMe}$	69%
5	2.0	45	Pyridine/ PhMe	9%
6	2.0	45	2,6-lutidine/ PhMe	5%
7	2.0	45	TBAF/THF	2%
8	2.0	45	$\text{Na}_2\text{CO}_3/\text{H}_2\text{O}$	82%
9	2.0	5	$\text{Et}_3\text{N}/\text{PhMe}$	81%
10	2.0	120	$\text{Et}_3\text{N}/\text{PhMe}$	96%

(a) Yield of isolated product

Table 1: Optimisation for aryl alkyne cycloaddition

■ optimisation for **alkyl alkynes**

Entry	addition rate (Y)	base/solvent	yield ^a
1	45 min	Et ₃ N/PhMe	38%
2	6 h	Et ₃ N/PhMe	58%
3	16 h	Na ₂ CO ₃ /H ₂ O	73%
4	24 h	Na ₂ CO ₃ /H ₂ O	74%

(a) Yield of isolated product

Table 2: Optimisation for alkyl alkyne cycloadditions

With 1.1 equiv of alkyne and dropwise addition *via* syringe pump of 2 equiv Et₃N/PhMe over 45 mins at r.t. (Table 1, entry 1), the corresponding isoxazole **5a** was isolated in 70% yield. Analysis of the crude reaction mixture by ¹⁹F NMR spectroscopy indicated the presence of furoxan. Increasing the alkyne equivalents to 2.0 and 3.8 gave yields of 90% and 93% respectively (Table 1, entries 2 and 3), indicating that an excess of alkyne relative to the nitrile oxide would be advantageous to suppressing furoxan formation. We decided to use 2.0 equiv of alkyne for subsequent reactions as it appeared that greater excesses of alkyne provided diminishing returns in terms of yield of desired isoxazole product. When a variety of bases were assessed only Et₃N, ⁱPr₂NEt and Na₂CO₃ provided good yields of isoxazole **5a** (Table 1, entries 3, 4 and 8), whereas weaker bases such as pyridine, 2,6-lutidine and TBAF produced negligible yields of **5a** (Table 1, entries 5-7). Finally, the rate of base addition was assessed; when the time taken for addition of Et₃N was decreased to 5 min, isoxazole **5a** was isolated in 81% yield (Table 1, entry 9). However, when the time taken was increased to 2 h, isoxazole **5a** was isolated in an improved yield of 96% (Table 1, entry 10).

■ substrate scope for **aryl alkynes**

	5a ; 96% [5.13 g]
	5b ; 73%
	5c ; 84%
	5d ; 99%
	5e ; 84%
	5f ; 60%

Scheme 3: Scope of the aryl alkyne cycloaddition

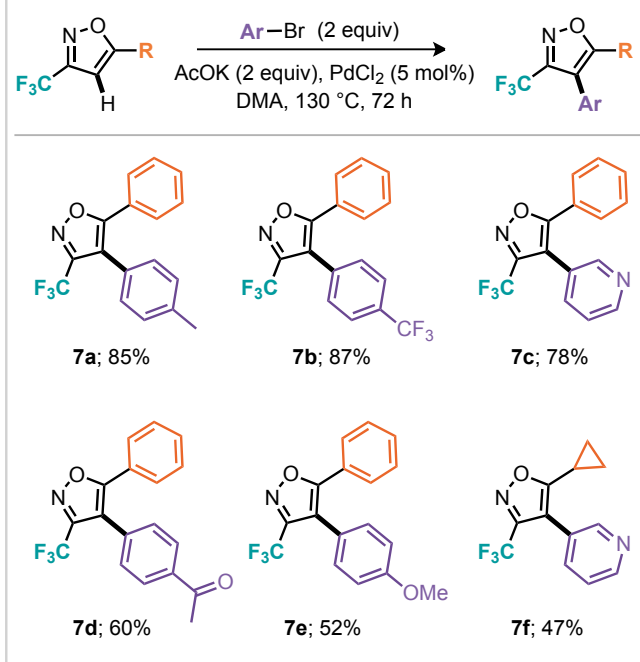
Evidently, using a slower rate of base addition to controllably unveil small amounts of nitrile oxide could further suppress the unwanted dimerisation reaction, since the relative concentration of the nitrile oxide compared to the alkyne was low. We then focused our attention on alkyl alkynes using 5-hexynenitrile as the substrate. Since it appeared that suppression of furoxan formation was required to obtain good yields of isoxazole, it was postulated that increasing the time taken for base addition would be a simple modification to the optimized procedure for aryl alkynes. Indeed, when the time taken for base addition was progressively increased to 16 h (Table 2, entries 1-3), higher yields of isoxazole **6a** were obtained; further increasing the time taken to 24 h (Table 2, entry 4) had little effect on yield.¹⁴ With optimized conditions for the cycloaddition reaction with aryl and alkyl alkynes established, we decided to explore the scope of the reaction.

■ substrate scope for **alkyl alkynes**

	6a ; 73%
	6b ; 54%
	6c ; 74%
	6d ; 77% [2.66 g]
	6e ; 75% [2.75 g]
	6f ; 64% [2.80 g]
	6g ; 62%
	6h ; 74%
	6i ; 65%
	6j ; 56%
	6k ; 63%

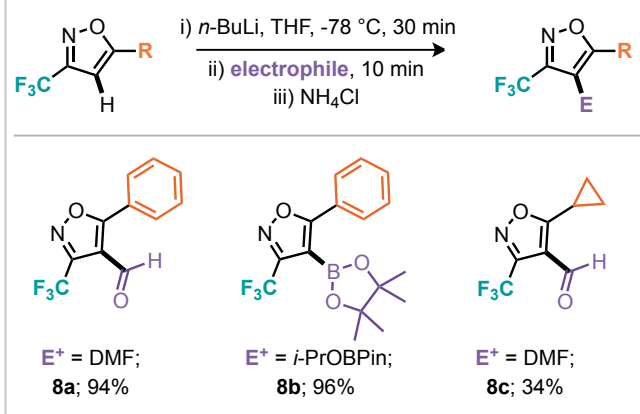
Scheme 4: Scope of the alkyl alkyne cycloaddition

■ Pd-catalysed C-H cross-coupling of 3,5-disubstituted isoxazoles



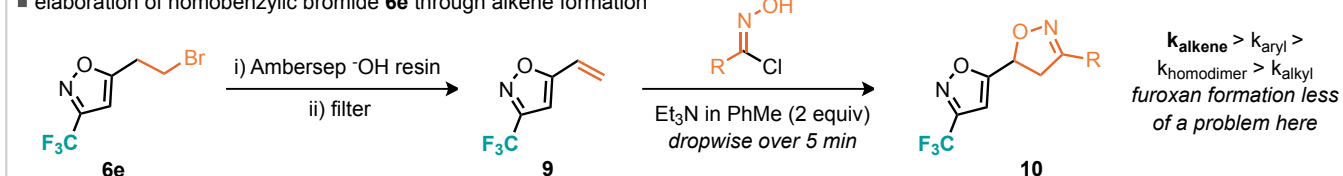
Scheme 5: Intermolecular C-H arylation

■ Lithiation and electrophile quench of 3,5-disubstituted isoxazoles

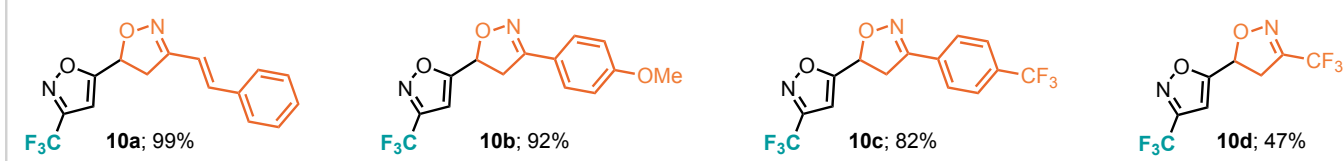


Scheme 6: Lithiation and electrophilic quench

■ elaboration of homobenzylic bromide **6e** through alkene formation

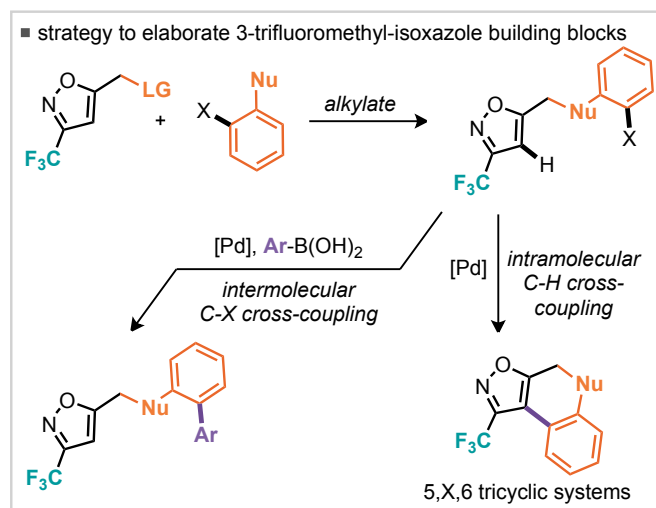


■ examples of isoxazole-isoxazoline scaffolds available by this approach



Scheme 7: elimination and nitrile oxide cyclisation

For the aryl alkyne examples explored, both electron-rich and electron-poor systems underwent cycloaddition, with the latter proceeding in lower yield, perhaps due to a mismatch in the electronics of the dipolarophile and 1,3-dipole. With regard to the alkyl alkynes a variety of functional groups were tolerated such as alkyl bromides, free alcohols, cyclopropanes, nitriles and ketones (Scheme 3). In addition, we explored some more exotic alkyl alkynes derived from nucleophilic aromatic substitution of heteroaromatic halides with propargyl alcohol. Of the three explored, all proceeded to the desired product in yields greater than 50% (Scheme 4, **6i**, **6j** and **6k**). For all of the explored substrates the cycloaddition reaction showed exclusive regioselectivity for the formation of 5-substituted isoxazoles, an observation congruent with the literature.¹⁵ Several examples were also conducted on larger scale and afforded greater than 2.5 grams of product in comparable or greater yields to the smaller scale reactions (**5a**, **6d**, **6e** and **6f**). Having demonstrated a broad substrate scope we next wished to explore the possibility of further manipulation of these 5-substituted 3-trifluoromethylisoxazoles by the introduction of functionality at the 4-position. Palladium-catalyzed C-H activation of isoxazoles has been demonstrated by Fall *et al.* on 3,5-dimethylisoxazole and 3-methyl-5-phenylisoxazole, but they note that electron-deficient isoxazoles were coupled much less efficiently.¹⁶ Indeed, the intermolecular cross-coupling of 4-bromotoluene and 5-phenyl-3-trifluoromethylisoxazole (**5a**) resulted in only 38% conversion to the desired 4-arylated isoxazole (**7a**), despite use of 5 mol% PdCl₂ and heating for 72 h. However, switching to 2 equiv aryl bromide allowed the desired product **7a** to be isolated in 85% yield. Alternative aryl bromide coupling partners for 5-phenyl-3-trifluoromethylisoxazole (**5a**), such as electron-rich, electron-deficient and heterocyclic bromides, were assessed (Scheme 5) and gave moderate to excellent yields. Further, 5-cyclopropyl-3-trifluoromethylisoxazole (**5g**) could also be coupled to 3-bromopyridine in 47% yield. Rather than undergoing cross-coupling of the C-H bond at the 4-position, lithiation at this position was also demonstrated using ⁿBuLi.



Scheme 8: Proposed strategy for rapid structural diversification through complementary cross-coupling

Again for the 5-phenyl-3-trifluoromethylisoxazole (**5a**) substrate, lithiation was straightforward (Scheme 6). Quenching of the thus formed organometallic species with DMF led to the corresponding aldehyde whereas a boron electrophile (*i*-PrOBPin) could be used to afford the boronic ester product **8b** in good yields. Notably, whilst the 5-cyclopropyl-3-trifluoromethylisoxazole (**5g**) also participated in this chemistry; the aldehyde product **8c** was isolated in reduced yield compared to the phenyl analogue.

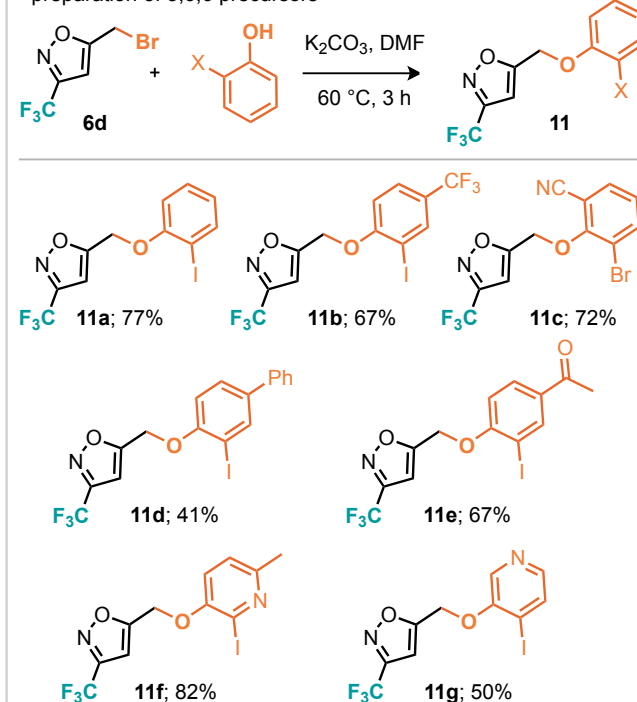
Other strategies to rapidly elaborate this ring system hinged around the versatile fluorinated, bromoalkyl building blocks **6d** and **6e**. Indeed, we found that homobenzylic bromide (**6e**) was an excellent surrogate for the 5-alkenyl-3-trifluoromethylisoxazole (**9**) through an elimination process. This alkene was most optimally accessed by stirring **6e** in the presence of the polymer-supported base, Ambersep® OH resin, followed by filtration of the resin and storage of the resultant volatile alkene (**9**) in an ethereal solution. The reactivity of this versatile alkene building block (**9**) was then explored in the context of nitrile oxide cycloaddition chemistry (Scheme 7). In this instance it is well documented that the rate of alkene cycloaddition is greater than that of the nitrile oxide homodimerisation process. Indeed, the nitrile oxide derived from cinnamaldehyde underwent smooth cycloaddition to give the isoxazole-isoxazoline bicyclic moiety (**10a**). Electron-rich and electron-poor benzaldehyde derivatives also proceeded without incident affording the 4-methoxy and 4-trifluoromethyl variants **10b** and **10c** in excellent yield. The cycloaddition reaction of electron-poor alkene building block **9** with the electron-poor trifluoromethyl nitrile oxide (**4**) did also afford the desired isoxazole-isoxazoline bicyclic product, but in reduced yield (47%) relative to the other examples explored, again likely due to a mis-match in electronics.

A strategy for derivatisation of the trifluoromethylated bromoalkyl building block **6d**, is described in scheme 8. The approach commences by using this material as an alkylating

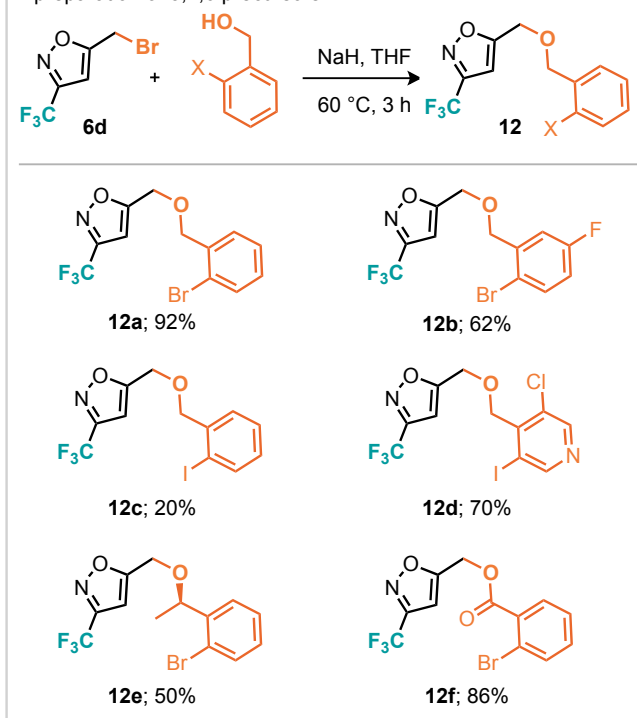
agent for an aromatic ring bearing a nucleophilic heteroatom and an adjacent halide function.

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■ preparation of 5,6,6 precursors



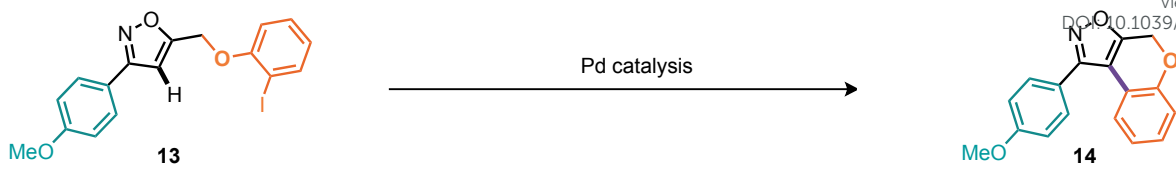
■ preparation of 5,7,6 precursors



Scheme 9: Conditions and scope for alkylation reaction

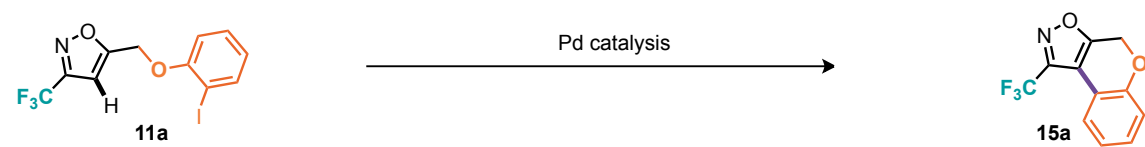
The halide on these resulting products could then potentially undergo two different cross-coupling reactions leading to rapid structural diversification.¹⁷

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	Entry	Base	Solvent	Ligand	Additive	Time (h)	Conversion	Isol. Yield
PdCl ₂ (5 mol%) Base (2.0 equiv) solvent, 130 °C	1	KOAc	DMA	-	-	72	98	12
	2		DMF	-	-	48	98	31
	3		Dioxane	-	-	48	- ^a	-
	K ₂ CO ₃	4	DMA	-	-	72	- ^a	-
		5	DMF	-	-	72	-	21
		6	Dioxane	-	-	72	- ^a	-
		7	DMA	-	-	72	- ^a	-
	Cs ₂ CO ₃	8	DMF	-	-	72	-	40
		9	Dioxane	-	-	72	- ^a	-
Pd(OAc) ₂ (5 mol%) Base (4.0 equiv) Ligand, Additive (2.0 equiv) solvent, 100 °C	10	K ₂ CO ₃	DMF	PCy ₃	TBAB	24	98	57
	11		DMF	dppf	TBAB	24	98	0
	12		DMA	P ^t Bu ₃ .HBF ₄	TBAB	24	98	42
	13		DMA	PCy ₃ .HBF ₄	TBAB	24	98	36
	14		DMA	Xantphos	-	24	98	52
Pd(OAc) ₂ (5 mol%) Base (4.0 equiv) Ligand, Additive (0.3 equiv) solvent, 65 °C	15	K ₂ CO ₃	DMA	P(Ph) ₃	TMBA	16	98	47
	16		DMA	P(Ph) ₃	PhCO ₂ H	16	98	38
	17		DMA	P(Ph) ₃	PivOH	16	98	51
	18		DMA	P(4-F-Ph)₃	PivOH	16	98	60
	19		DMA	P(4-Cl-Ph) ₃	PivOH	16	98	44

a) starting material recovered

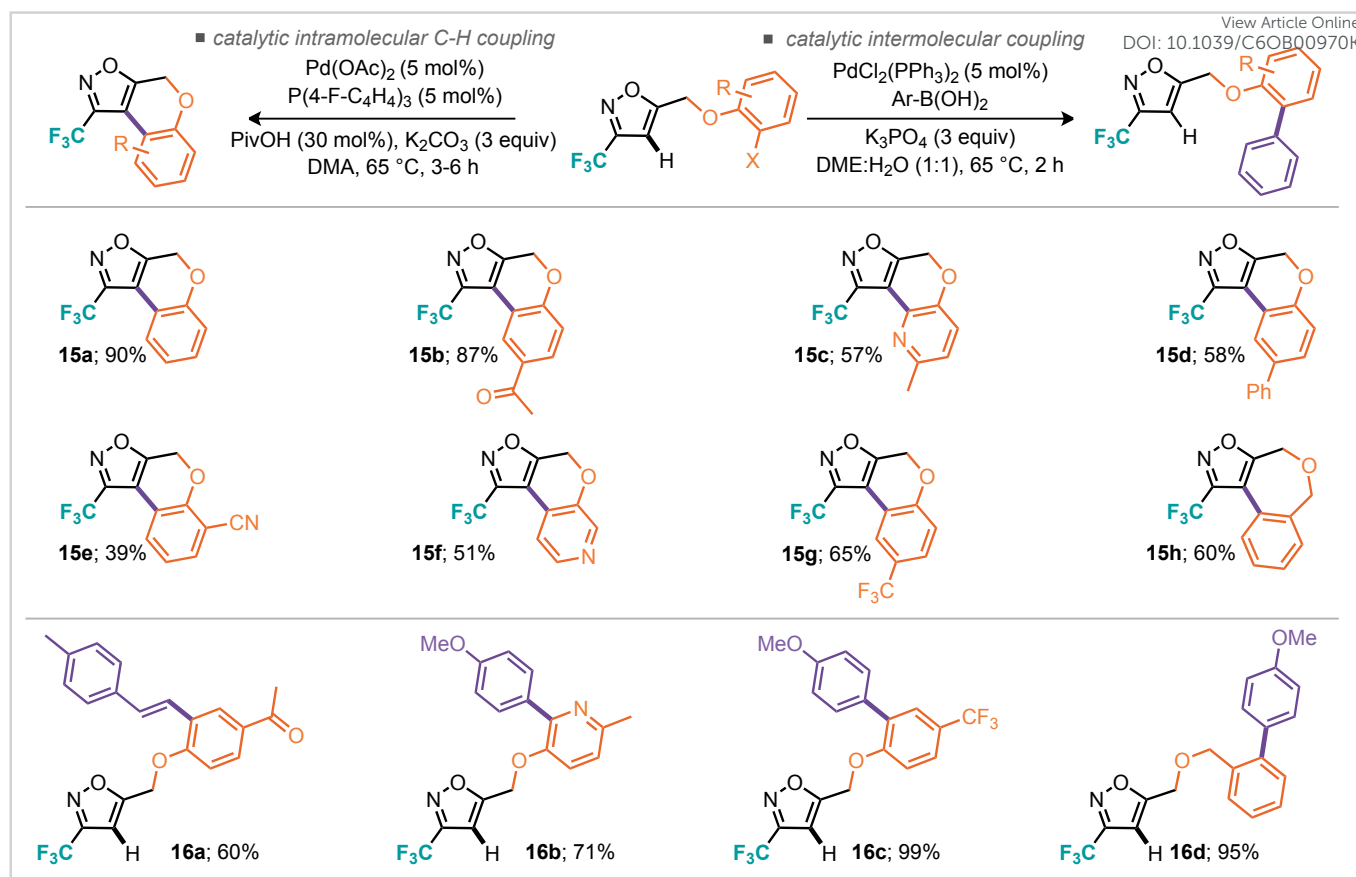


	Entry	Base	Solvent	Ligand	Additive	Time (h)	Conversion	Isol. Yield
Pd(OAc) ₂ (5 mol%) Base (4.0 equiv) Ligand, Additive (0.3 equiv) solvent, 65 °C	1	K ₂ CO ₃	DMA	P(Ph) ₃	PivOH	16	98	85
	2		DMA	P(4-F-Ph)₃	PivOH	16	98	90
	3		DMA	P(4-F-Ph) ₃	-	16	98	73

Table 3 & 4: Optimisation of the intramolecular C-H arylation reaction

One cross-coupling would be intermolecular and could likely be controlled by appropriate choice of base and inclusion of a coupling partner (boronic acid), whereas the other coupling would be an intramolecular C-H functionalizing ring formation leading to a novel series of trifluoromethylated tricyclic scaffolds. Indeed this approach also offers significant scope for varying linker size in the initial alkylation step and therefore the subsequent central ring size of the tricyclic system. Commencing with the alkylation of a variety of *ortho*-iodophenols with bromide **6d**, we found that optimal conditions consisted of gentle heating to 60 °C in DMF using potassium carbonate as base (scheme 9). Conditions for the alkylation of *ortho*-iodobenzyl alcohols were better conducted with sodium hydride in THF, which furnished several homologated products (scheme 9). Next we turned to the intramolecular C-H arylation reaction and looked to further

develop the cross-coupling conditions. Initially this was investigated on *para*-methoxyphenyl substrate **13**. Repeating our previously successful conditions for the intermolecular case on this substrate afforded 12% isolated yield of the intramolecular product (**14**) but 98% conversion of the starting material. The main byproduct was that derived from deiodination (Table 3, entry 1). Exploring DMF and 1,4-dioxane as solvent options, it was found that in DMF the reaction afforded an improved 31% yield of the cyclised product (Table 3, entry 2). Replacement of the KOAc base with K₂CO₃ and Cs₂CO₃ did not lead to dramatic changes in yield. Taking inspiration from the literature on intramolecular C-H arylation reactions of benzene systems via proton abstraction, we made a more significant change in our approach.¹⁸



Scheme 10: Conditions and scope for alkylation reaction

Table 3, entries 10-14 describe the results from the changed catalyst system, now including a ligand, additive and two further equivalents of base, whilst dropping the temperature by 30 °C and reaction time down to 1 day. Notably, in almost all cases the outcome was improved, with tricyclohexylphosphine ligand and tetrabutylammonium bromide as additive providing the superior result at 57% isolated yield. Indeed, we surveyed several other literature reports¹⁹ and found that the conditions reported by Fagnou *et al.* offered further improvements.^{19a} Under these conditions, which included reduced loading of additive and use of triarylphosphines, we made gains on both reaction time and temperature where the optimal conditions consisted of heating to 65 °C over 16 hours (Table 3, entry 18). Notably, P(4-F-Ph)₃ as ligand outperformed PPh₃, providing a 10% improvement in isolated yield (Table 3, cf entries 17 and 18). Applying these optimal conditions, as developed for the less reactive model substrate, to the 3-trifluoroisoxazole **11a** we were pleased to find that the tricyclic product (**15a**) could be isolated in 90% yield (Table 4, entry 2). Control reactions showed that P(4-F-Ph)₃ still provides notable benefit as does the presence of pivalic acid. With these optimal conditions, we then applied them to a range of the alkylated materials to successfully furnish a range of 5,6,6 tricyclic compounds including the pyridine derivatives **15c** and **15f** in moderate to excellent yields (Scheme 10). One example of a 5,7,6 tricycle

(**15h**) was also prepared in 60% yield using these C-H arylation conditions.

In order to demonstrate the diversity of this scaffold through cross-coupling we also found optimal conditions for the intermolecular Suzuki-Miyaura reaction. Inclusion of the requisite boronic acid and switching both the base and solvent system permitted smooth access to the linear products **16a-d** in good to excellent yield. Notably in the latter cross-coupling cases, no intramolecular cyclised product was detected signalling that the reactivity and structural diversity can truly be switched by a simple change in reaction conditions.

Conclusions

In summary, we report conditions for the preparation of a range of trifluoromethylated isoxazole building blocks through trifluoromethyl nitrile oxide cycloaddition. It was found that controlling the rate (and therefore concentration) of the formation of the trifluoromethyl nitrile oxide was critical for the preferential formation of the desired isoxazole products versus the furoxan dimer. Different conditions were optimised for both aryl- and alkyl- substituted alkynes. In addition, the reactivity at the isoxazole 4-position was then briefly explored for these building blocks. Conditions for intermolecular C-H arylation, lithiation and electrophile quench, and alkoxylation were all identified with brief substrate scoping that signifies useful tolerance to a range of functionalities. Finally we

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developed complementary processes for structural diversification through either intramolecular cyclisation or intermolecular cross-coupling, with a series of 5,6,6 and 5,6,7 tricyclic systems being formed.

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Notes and references

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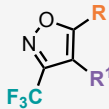
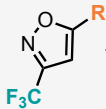
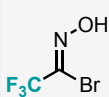
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