Reductive Alkylation of 2-Bromoazoles via Photoinduced Electron Transfer; a Versatile Strategy to C*sp*²–C*sp*³ Coupled Products.

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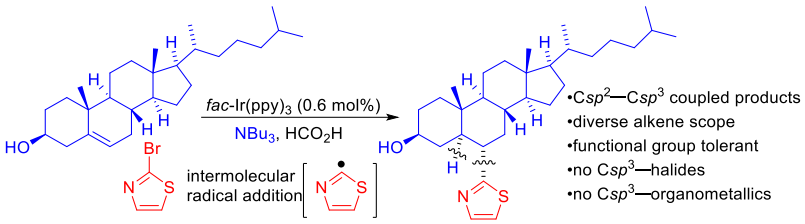
Supporting Information Placeholder



ABSTRACT: Access to C*sp*²–C*sp*³ coupled products is a challenging goal at the forefront of catalysis. The photocatalytic reductive-coupling of aryl bromides with unactivated alkenes is introduced as a convenient method that circumvents any need for synthesis of *sp*³-hybridized coupling partners. The reaction takes place via photoinduced electron transfer from a tertiary amine to an aryl bromide which fragments to provide an aryl radical and subsequently reacts with an alkene to form a C–C bond. Conveniently, the amine also serves as the final reductant. The method is operationally simple, functional group tolerant, and takes place with selectivities that will allow it to be used in the context of complex molecule synthesis.

Azoles are a privileged scaffold that have been investigated as therapeutics for numerous diseases[1] and 2-alkyl azoles have proven to be remarkable ROCK II inhibitors[2] and yet there are relatively few rapid syntheses. Consequently, there is a real need to develop simple methods that allow the rapid construction of complex 2-alkyl azoles in order to facilitate thorough SAR studies.

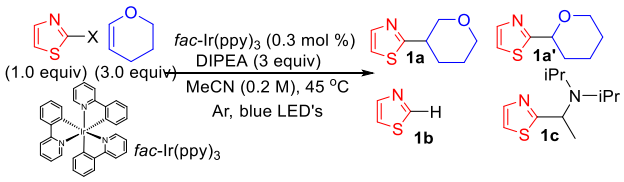
The classic method for making 2-alkyl azoles is via cyclodehydration[3] and is still the most prominently used, but it is limited to carboxylic acid derivatives (eqn 1, SI-15). Cross-coupling has the ability to expedite diversification and recent efforts have provided several strategies. The first is to couple 2-bromoazoles[4] and preformed C*sp*³–zincates (eqn 2). Alternatively, alkyl-halides[5] or hydrazones[6] have also been used along with a 2-H benzothiazoles (eqn 3).

Even more recently, oxidative methods have been used to generate a radical, either by C–H abstraction or radical decarboxylation (eqn 4) and have proven quite selective for addition of the alkyl radical to the 2-position of an azole.[7]

However, C*sp*³–halides, C*sp*³–organometallics or tosyl hydrazones represent a relatively small set of coupling partners that can be used as inputs for the cross-coupling. To maximize the utility of a method, a large number of coupling partners should be readily available. A strategy that has not been explored is the photocatalytic generation of a 2-azoylradical which could add across an alkene and be followed by reduction of the incipient alkyl radical, amounting to a formal C*sp*²–C*sp*³ cross-coupling (eqn 5).[8] Given the availability of alkenes, this transformation has the immediate potential to significantly alter the types of motif that can be synthetically accessed by rapid cross-coupling. Despite this strategic advantage, general methods that allow intermolecular reductive alkylation of aryl bromides have not been well developed.

Radical addition to alkenes is well known[9] and represents a promising strategy for the reductive alkylation of alkenes. Pioneering work in this area has even shown that aryl-bromides can be converted to the aryl radical and is[10] most often accomplished with the use of Bu_3SnH[11] or by SmI_2/HMPA.[12] Aside from toxicity issues associated with the organotin and HMPA, the major drawback is the limitation in scope which is due to fast over reduction of the desired aryl radical.[9b]

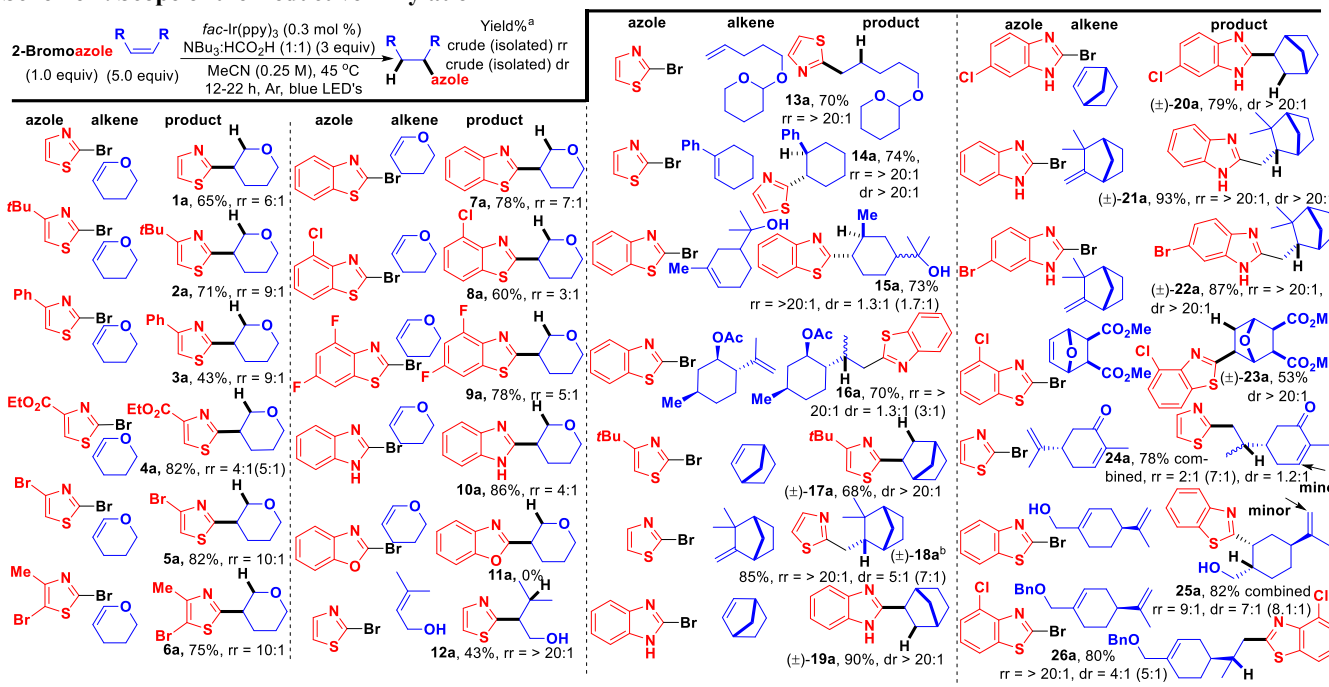
Table 1. Optimization of Reaction Conditions



entry	X	modifications	conv[a]	1a:1a':1b:1c[b]	time
1.	Cl		100%	0:0:31:69	23 h
2.	Br	none	100%	38:10:52:0	22 h
3.	Br	used $(i\text{Pr})_2N\text{Bu}$ instead of DIPEA	100%	52:13:35:0	2 d
4.	Br	used NBu_3 instead of DIPEA	24%	17:8:75:0	2 h
5.	Br	used NBu_3 instead of DIPEA	69%	30:8:62:0	23 h
6.	Br	used $(i\text{Pr})_2N\text{Bu}$ w/ HCO_2H (1:1)	100%	44:6:50:0	22 h
7.	Br	used NBu_3 w/ HCO_2H (1:1)	100%	51:8:41:0	22 h
8.	Br	entry 7, but 1.2 equiv alkene	100%	17:3:80:0	22 h
9.	Br	entry 7, but 2.0 equiv alkene	100%	26:6:67:0	22 h
10.	Br	entry 7, but 3.0 equiv alkene	100%	39:9:52:0	22 h
11.	Br	entry 7, but 5.0 equiv alkene	100%	57:13:32:0	22 h
12.	Br	entry 11, at 0.25 M	100%	65:10:25:0	22 h
13.	Br	same as entry 12, with 20% v:v H_2O	100%	60:10:30:0	22 h
14.	Br	entry 12, no $Ir(ppy)_3$	0%		22 h
15.	Br	entry 12, no light or amine	0%		22 h

a. Conversion determined by 1H NMR. b. product ratio determined by GCMS.

Scheme 1. Scope of the Reductive Alkylation



a. Yields correspond to isolated product. Regioisomeric ratio (rr) and diastereomeric ratio (dr) were determined by 1H NMR of the crude reaction mixture after workup and on the isolated material. b. Isolated as an inseparable mixture (7:1) of product and oxidatively coupled product.

Consequently, almost all synthetically useful examples of aryl radical addition to unactivated alkenes are intramolecular cyclizations that can outcompete fast reduction.[9, 11c]

We speculated that a visible light photocatalyst could facilitate a photoinduced electron transfer (PET) to the 2-bromobenzothiazole which would generate a 2-azoyl radical[13] chemo- and regioselectively that could engage unactivated alkenes to forge a new C–C bond.[14] Importantly, we hoped that the use of a photocatalyst and an amine might prove to be sufficiently slow at over reduction to allow the intermolecular C–C bond formation take place. Furthermore, if successful, this strategy might be extended to other reducible bromoarenes.

Previously, we showed that 2-chloroazoles[13c] could be used to functionalize the α-C–H of tertiary aliphatic amines. However, addition of electron-rich dihydropyran to 2-chlorothiazole (entry1, Table 1) yielded only reduced azole (**1b**) and carbinamine (**1c**) as the major products. However, use of the 2-bromoazole resulted in a complete change in reactivity (entry 2) in which the reductively coupled product was the major C–C-product and the carbinamine (**1c**) was not observed. Based on the work of Bunnett[15] and Rossi[16] who have shown that radical anions will fragment a bromide faster than the corresponding chloride, it is reasonable to think that the observed change in reactivity is due to the nature of the reactive intermediates involved. Specifically, we postulate that 2-chloroazoles undergo C–C formation via the radical anion while 2-bromoazoles undergo C–C formation via the radical. We next sought to increase the amount of C–C bond forming product to reduction product (i.e., **1a+1a'** vs. **1b**). Exchanging the ethyl of DIPEA for an isobutyl group (entry 3 vs. 2) resulted in a significant increase in the desired product albeit at the expense of reaction time. Furthermore, we observed that the product ratio was not constant throughout the course of the reaction (entry 4 vs. 5), with relative increases of **1a** as the reaction progressed. We suspected that this might be a result of acidic species generated under the reaction conditions that could be reducing the amount of free amine in solution and possibly accelerating the formation of the desired product via a proton coupled electron transfer.[17] Thus, we explored some acidic additives.[17a] Ultimately, we found a 1:1 mix of formic acid and tributylamine as the optimal additive.[13a]

We next explored the concentration of alkene. Consistent with a process in which there is a competition for reduction and alkylation of the azoyl radical, increased concentration of alkene led to more alkylated products (**1a** + **1a'** entries 8-11). Further concentrating the reaction also led to a slight improvement. In an attempt to check the operational flexibility of the reaction, we added water which resulted in only a slight decrease of the desired products. Finally, controls (entries 14 and 15) indicated that photocatalyst, light, and amine are necessary components of the reaction.[18] Using 0.3 mol% *fac*-tris-(2-phenylpyridine) ($Ir(ppy)_3$), a 1:1 mix of amine and formic acid (3 equiv), and 5 equivalents of alkenes, we began to explore the scope of the reaction.

Initially, we reacted a series of thiazoles with dihydropyran. We obtained a 65% yield in a 6:1 regioisomeric ratio (rr) for simple 2-bromothiazole (**1a**, Scheme 1). In most cases, substitution of the thiazole increased the selectivity (**1a** vs. **2a**-**7a**). Products **5a** and **6a** highlight an important feature of electron-addition induced fragmentation events which can be very selective and in these cases display perfect chemoselectivity for the 2-bromo over the 4-bromo and 5-bromo positions. The reaction works well for benzothiazole (**7a**). However, the inclusion of a 5-chloro or 5,7-difluoro slightly reduces the regioselectivity (**8a**, and **9a**). In contrast to thiazoles, we do not observe competitive reduction of 2-bromobenzimidazoles (**10a**) and consequently, yields are higher. Whereas, under these conditions 2-bromooxazole (**11a**) does not undergo reductive alkylation[19] and highlights the impact that the nature of the heterocycle has on the reaction.

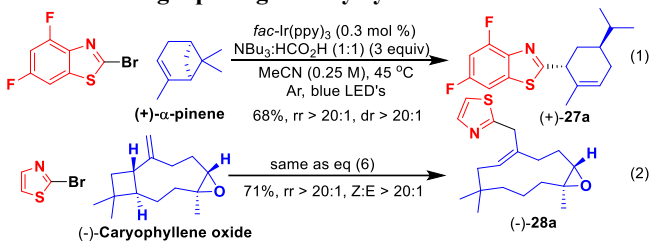
Next, we evaluated the nature of the alkene that could participate in the reductive alkylation. In general, we found the addition to be remarkably sensitive to the substitution pattern of the alkene. Specifically, the addition typically occurred at the less substituted carbon to provide the alkylated azoles in high regi-

oselectivity. The reaction works for mono-substituted- (**13a**), 1,1-disubstuted (**16a, 18a**, **21a**, **22a**, **24** and **26a**), 1,2-disubstituted (**5a-10a**, **17a**, **19a**, **20a**, **23a**), trisubstituted- (**12a**, **14a**, **15a**), and bridged-alkenes (**17a-23a**). A number of functional groups that likely would be sensitive to basic organometallics work well in this method, including free alcohols (**12a**, **15a**), acetates (**16a**), esters (**23a**), and enones (**24a**). Believing that we were forming an azoyl radical, we were pleased to see that weaker bonds, such as benzylic (**26a**), allylic (**25a**, **26a**) as well as acetal C–H's (**13a**) were well tolerated. Furthermore, we saw no addition to the phenyl rings (**14a**, **26a**), suggesting a preference for π-electrons of alkenes over those of arenes.

Additionally, in more complex molecules containing multiple alkenes we observed synthetically useful selectivities (**24a-26a**). Interestingly, comparison of perillyl alcohol derivatives (**25a**, **26a)** suggests that the presence of the free hydroxyl group can alter the inherent regioselectivity.

When these reaction conditions were applied to terpenoids containing a vinyl cyclobutane motif, we observed clean, reductive ring opening in good yields, high regioselectivity and diastereoselectivity. Addition of difluorobenzothiazole to α-pinene provided a 68% yield of an enantio- and diastereomerically pure trisubstituted cyclohexene (eqn 1, Scheme 2). The reaction of caryophyllene oxide afforded a single stereoisomeric product in good yield (eqn 2) with the epoxide functional group remaining unchanged. The selectivity of the ring opening event suggests that reductive azoylation of vinyl cyclobutanes may be a general and convenient method for the formal allylic substitution with concomitant ring enlargement.

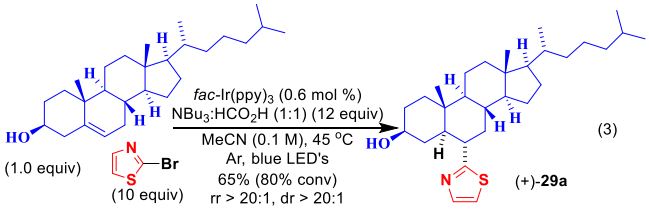
Scheme 2. Ring Opening of Vinylcyclobutanes



The ability to easily and directly expand the carbon framework of an alkene situated within a complex molecule presents an exciting possibility as a late stage functional group handle. Thus, we examined the thiazolation of unprotected cholesterol which gave a single stereoisomeric product (eqn 3, Scheme 3).

Next, we wanted to address a scenario in which the alkene was more precious than the azole. Thus, we were forced to look at the underlying problematic reduction that necessitated the use of an excess of 2-bromothiazole. The amine is the stoichiometric reductant[17a] and is essential to the reaction. We speculated[17a] that it could also be facilitating undesired reduction of the bromoazole.

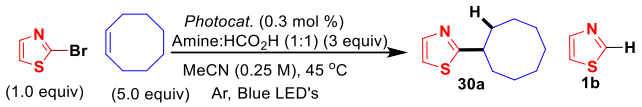
Scheme 3. Thiazolation of Cholesterol



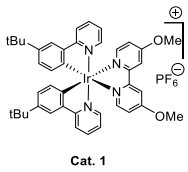
We hypothesized that lowering the concentration of free amine could decrease the undesired reduction pathway, since the reduction was likely directly dependent on the amine concentration.

We tested this hypothesis using 2-bromothiazole which is prone to reduction (Scheme 4). Iterative amine addition improved the product ratio (entry 2 vs. 1) and supported our hypothesis.

Scheme 4. Amine Dependent Reduction Pathway Study



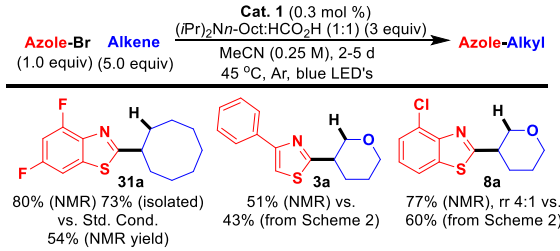
entry	cat.	amine	conv	**30a**:**1b**
1.	$Ir(ppy)_3$	Bu_3N	100%	25:75
2.	$Ir(ppy)_3$	Bu_3N (iterative incremental addition)	100%	52:48
3.	$Ir(ppy)_3$	$(iPr)_2Nn$-Oct	84%	36:64
4.	**Cat. 1**	Bu_3N	100%	22:78
5.	**Cat. 1**	$(iPr)_2Nn$-Oct	48%	44:56



We speculated that we could take advantage of the poor solubility of tertiary amines with long alkyl chains (in MeCN), to provide a convenient method for keeping a low concentration over time. Thus, we evaluated the solubility of several amine derivatives[17a] and chose $(iPr)_2Nn$-Oct which was approximately half as soluble as NBu_3. We were pleased to find that the use of the less soluble amine did lead to an improved ratio of the desired product (entry 3 vs. 1). We also recognized that decreasing the amine concentration might affect the rate of the photocatalytic reaction. Thus, we rescreened photocatalysts using the less soluble amine.[17a] We found that several more oxidizing photocatalysts resulted in increased alkylated product ratios, with **Cat. 1**[20] providing the fastest reaction among these catalysts.

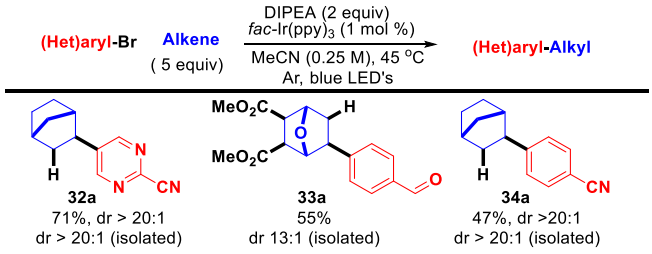
Using our modified conditions, we investigated more valuable 2-bromo-4,6-difluorobenzothiazole as well as several of the poorer yielding substrates from Scheme 1 (Scheme 5). In all cases we observed increases in yield. We expect that these conditions will be more ideal in cases where the azole is more precious and reaction time is not.[21]

Scheme 5. Reduction minimizing conditions



Finally, we suspected that this type of reactivity should be possible with other reducible bromoarenes. In our initial attempt, we subjected electron deficient bromopyrimidnes and benzenes to unoptimized conditions (Scheme 6). We found that all underwent reductive alkylation, allowing isolation of the alkylated pyrimidine (**32a**) and benzenes (**33a, 34a**). Importantly, these preliminary results suggest that photocatalytic reductive alkylation may be a general strategy for Csp^2–Csp^3 cross-coupling. Furthermore, it warrants development of substrate specific conditions which will likely be unique given the significant electronic differences between the aromatic motifs. In conclusion we have shown that photocatalysis has the ability to deliver Csp^2–Csp^3 cross-coupled products directly from 2-bromoazoles and unactivated alkenes.

Scheme 6. Reductive Alkylation as a General Strategy



The ability to utilize alkenes directly as a surrogate for the corresponding alkyl group is a powerful synthetic strategy. In

addition, the scope of the azole is general for thiazoles, benzothiazoles, and benzimidazoles and, in many cases, couples with excellent selectivity for the less substituted terminus of the alkene. The optional use of either alkene or azole as the limiting reagent is an attractive feature that should further enhance the utility. We have shown that this concept can be extended to other bromoarenes to generate both aryl and heteroaryl radicals in a controlled fashion, giving a sufficiently long-lived radical that it is capable of undergoing intermolecular C–C bond formation. Further exploration will expand the scope of the photocatalytic reductive coupling.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, additional optimization experiments, and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(18) In retrospect, 2-bromothiazole was an ideal substrate for optimization since we have empirically observed it has the greatest tendency to undergo reduction of all the azoles that we have studied.

(19) The major product identified by GCMS and ^{1}H NMR was the corresponding carbinamine, 1-(benzo[d]oxazol-2-yl)-N,N-dibutylbutan-1-amine.

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(21) Given the premium put on time in drug discovery efforts, along with the commercial availability of the photocatalyst, we expect these conditions only to be used in the event of a precious azole.