Regioselective Radical Amino-Functionalizations of Allyl Alcohols via Dual Catalytic Cross-Coupling

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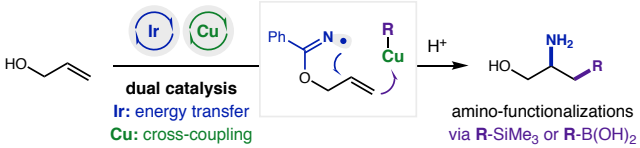
Supporting Information Placeholder

ABSTRACT: The regioselective amination and cross-coupling of a range of nucleophiles with allyl alcohols has been enabled by a dual catalytic strategy. This approach entails the combined action of an Ir photocatalyst that enables mild access to N-radicals via an energy transfer mechanism, as well as a Cu complex that intercepts the ensuing alkyl radical upon cyclization. Merger of this Cu-catalyzed cross-coupling enables a broad range of nucleophiles (e.g. CN, SCN, N_3, vinyl, allyl) to engage in radical amino-functionalizations of olefins. Notably, stereo, regio, and kinetic probes provide insights into the nature of this Cu-based radical interception.



Keywords: radicals, dual catalysis, photocatalysis, amination, imidate radicals

Given the ubiquity of β-amino alcohols in nature and medicine (Figure 1a), the rapid, selective conversion of simple, abundant alcohols to these biologically important motifs remains a key goal for organic synthesis.[1] We sought to enable such reactivity by harnessing open-shell intermediates, specifically N-centered radicals, for olefin difunctionalization.[2] Previously, Leonori and Studer have shown iminyl radicals enable conversion of γ,δ-unsaturated ketones to dihydropyrroles (Figure 1b).[3] Li, Xiao, Knowles, and Nevado have also developed methods to access heterocycles via amide or hydrazone radicals.[4] And we have converted alcohols to oxazolines by imidate radicals.[5,6] In all of these cases, an N-centered radical is generated by single-electron transfer (SET)[7] and an ensuing alkyl radical is terminated by *electrophilic* radical traps (e.g. NCS, NIS, acrylate). Inspired by G. Liu's pioneering contributions to generate and capture NFSI-derived radicals via Cu-based mechanisms,[8] we proposed a merger of these distinct approaches. In our alternate, dual catalytic strategy, we hypothesized Cu-mediated cross-coupling of silanes or boronic acids with C-radicals could be merged with an Ir-photocatalytic generation of N-radicals (Figure 1c). By utilizing *nucleophiles* as partners, we sought to significantly expand the range of accessible amino-functionalizations within N-radical cyclizations and thereby multiply the scope and utility of the resulting heterocyclic products.

In pursuit of such a dual catalytic strategy,[9] we proposed an energy transfer (EnT) mechanism[10] may be suitable to facilitate compatibility between the photocatalyst and key Cu intermediates. The fundamental challenge for dual photocatalysis is that excited Ir photocatalysts, which are both highly oxidizing and reducing, are prone to engaging with Cu via SET processes.[11] To avoid these deleterious pathways, we proposed triplet-sensitization (via EnT) may chemoselectively enable radical generation by direct activation of the organic substrate without adversely engaging catalytically relevant Cu intermediates in redox processes. While we have recently shown the compatibility of these dual catalytic cycles (EnT and cross-coupling) in the context of asymmetric C-H amination,[5f] this triplet-sensitization strategy has not yet been demonstrated for amino-functionalization – a process that could enable simultaneous generation of C-N and C-C bonds.[12]

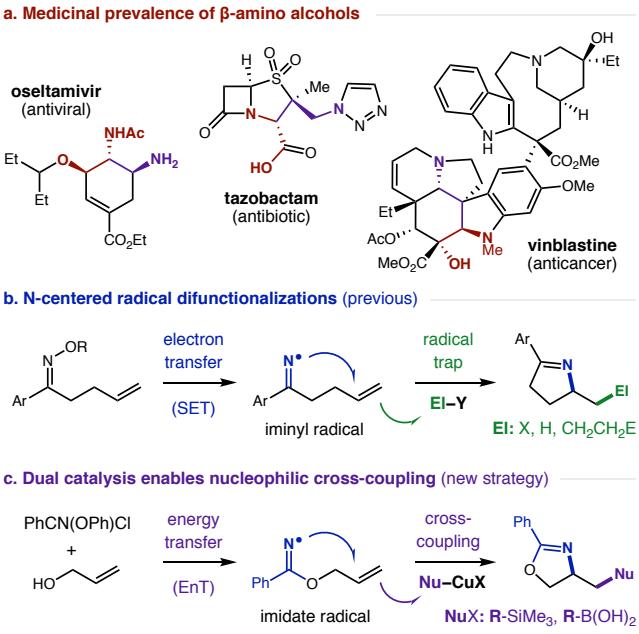
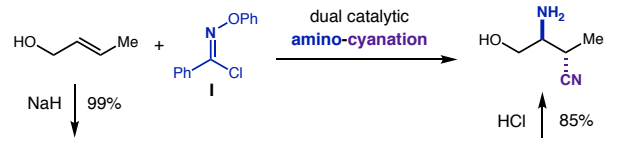
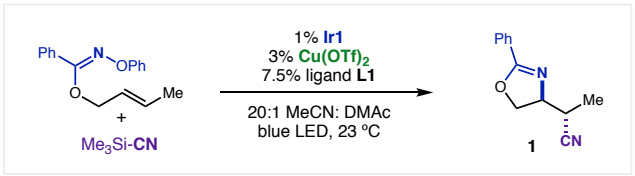


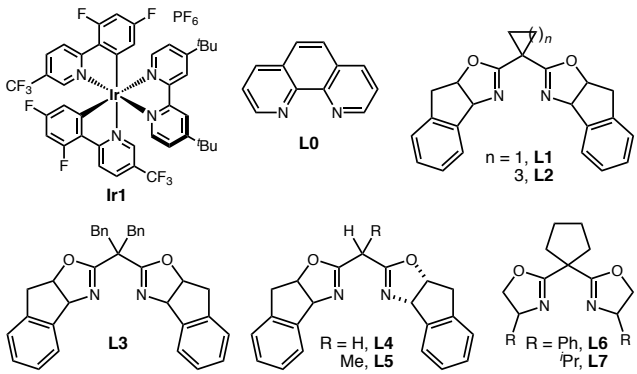
Figure 1. Merger of energy transfer and cross-coupling mechanisms to enable nucleophilic amino-functionalizations.

Table 1. Development of a radical amino-cyanation of alcohols.





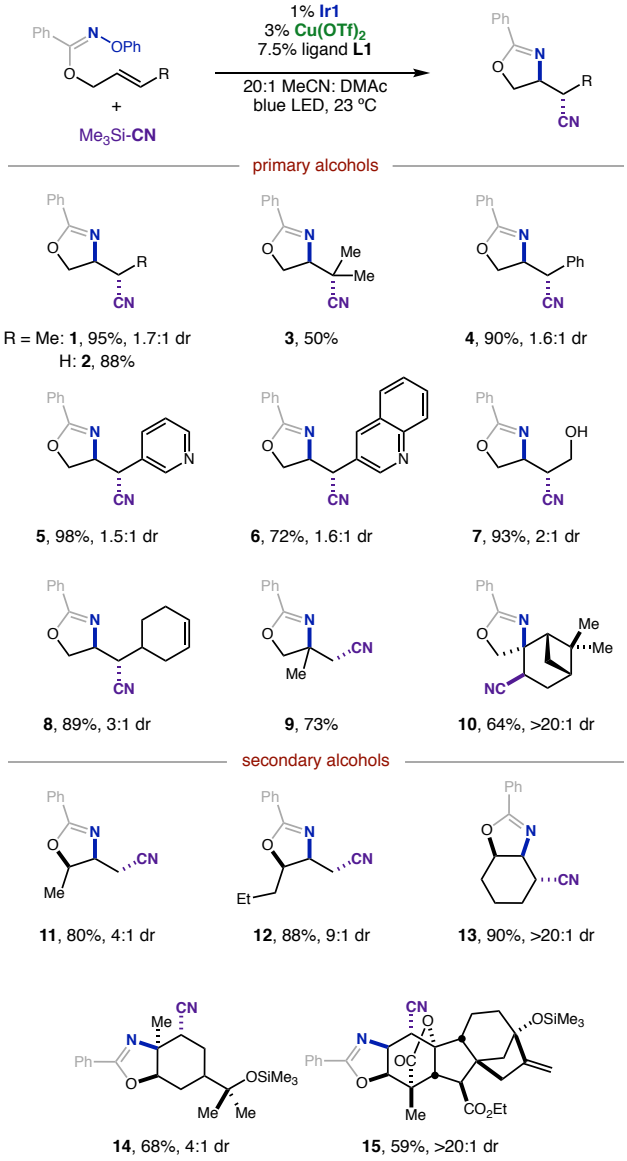
entry	variation from above	yield **1**
1	none	96%, 1.7:1 d.r.
2	$Ir(ppy)_3$ instead of **Ir1**	51%, 1.6:1 d.r.
3	$Ir(ppy)_2(dtbbpy)PF_6$ instead of **Ir1**	20% (70% SM)
4	$Ru(bpy)_3(PF_6)_2$ instead of **Ir1**	0% (>95% SM)
5	**L0** instead of **L1**	95%, 1.2:1 d.r.
6	**L2** instead of **L1**	98%, 1.6:1 d.r.
7	**L3-L8** instead of **L1**	≤ 1.2:1 d.r.
8	without **L1**	53%, 1.1:1 d.r.
9	without $Cu(OTf)_2$ and **L1**	0% (>95% SM)
10	without **Ir1**	0% (>95% SM)
11	without light	0% (>95% SM)
12	without DMAc	73%, 1.7:1 d.r.



Conditions: 0.1 mmol imidate, Me_3Si-CN (1.8 equiv), 1% Ir{dF(CF_3)ppy}$_2$(dtbbpy)PF_6 (**Ir1**), 3% $Cu(OTf)_2$, 7.5% **L1**, 20:1 MeCN:DMAc (0.05 M), blue LED (455 nm), 18 hrs, 23 °C. Yields and dr by ^{1}H NMR. DMAc: Dimethylacetamide.

To test our hypothesis, we prepared an oxime imidate of (*E*)-2-buten-1-ol (by combination with oxime acyl chloride **I** and NaH). We then subjected this allyl imidate to a nucleophile (1.8 equiv Me_3Si-CN) and pair of catalysts (1% Ir{dF(CF_3)ppy}$_2$(dtbbpy)PF_6 (**Ir1**), 3% $Cu(OTf)_2$, 7.5% **L1**). As shown in Table 1, visible light irradiation (455 nm, blue LED) in 20:1 MeCN:DMAc (0.05 M) for 18 hours at 23°C efficiently provides oxazoline **1** (entry 1, 96%, 1.7:1 dr), which is hydrolyzed to β-amino-γ-cyano alcohol by HCl. In support of our EnT proposal, the yield of this cyanoalkyl-oxazoline is diminished when photocatalysts with lower triplet energies are employed (entries 2-4). For example, when **Ir1** (62 kcal/mol) is replaced by either $Ir(ppy)_3$ (55 kcal/mol) or $Ir(ppy)_2(dtbbpy)PF_6$ (49 kcal/mol), EnT becomes less favored.[13] Instead, a less efficient SET mechanism likely occurs in these latter cases, as illustrated by lower conversion of starting material, especially for the less reducing catalyst (entry 3, -1.5 V; vs entry 2, -2.2 V), but likely not for **Ir1** (-1.4 V). This effect is most pronounced for $Ru(bpy)_3(PF_6)_2$, which affords no conversion – since both its triplet energy (46 kcal/mol) and reduction potential (-1.3 V)[13] are lower than oxime imidate (47 kcal/mol, -1.8 V),[5f,6] precluding either EnT or SET pathways. Lastly, a survey of bipyridyl (**L0**) and several bisoxazoline (**L1**-**L7**) ligands indicates the geometry of the **L1**-coordinated Cu complex has a significant impact on diastereoselectivity (entries 5-7), but not enantioselectivity (all ligands afford <40% ee, therefore racemic **L1** was used in this study). Lastly, control experiments without **L1**, $Cu(OTf)_2$, **Ir1**, light, or DMAc co-solvent demonstrate each of these components' roles in promoting reaction efficiency and selectivity (entries 8-12).

Table 2. Scope of radical amino-cyanation of imidates.

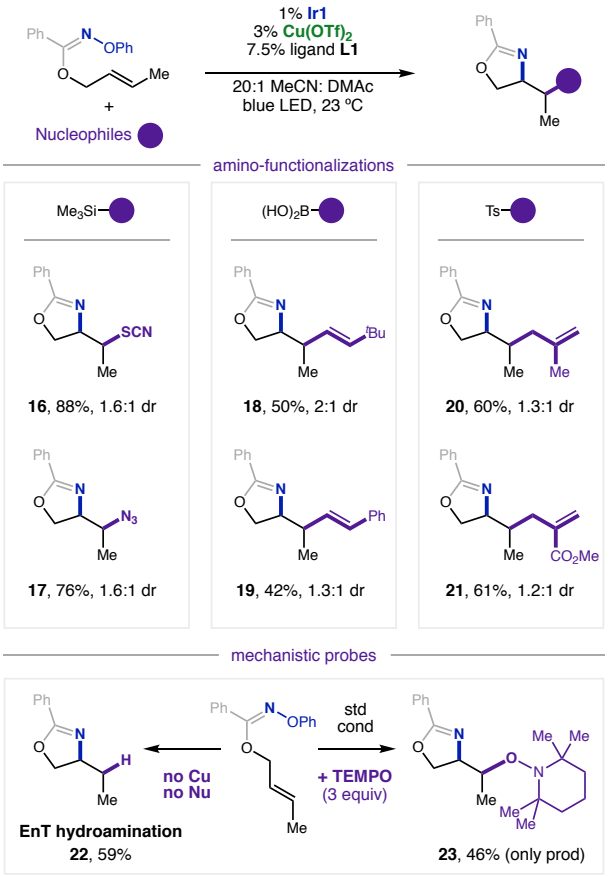


Conditions: 0.2 mmol imidate, Me_3Si-CN (1.8 eq), 1% **Ir1**, 3% $Cu(OTf)_2$, 7.5% **L1**, 20:1 MeCN:DMAc (0.05 M), blue LED (455 nm), 18 hrs, 23 °C. Isolated yields; dr by NMR.

With optimized reaction conditions in hand, we examined the synthetic generality of this radical amino-cyanation. As shown in Table 2, a wide range of allyl imidates derived from either primary or secondary alcohols are amenable to this dual catalytic transformation. Focusing particularly on probing variability of the γ-position where L_nCuCN must trap the C-radical, we were pleased to

find primary, secondary, tertiary, and benzylic substituents all promote this transformation (**1**-**4**) – with the sterically congested tertiary group predictably providing lowest efficiency in the series. Notably, heteroarenes such as pyridine and quinoline are well-tolerated (**5**-**6**) as well as free alcohols (**7**) and alkenes (**8**). Additionally, we found that the β-position may be fully substituted without deleterious effect (**9**-**10**). Finally, we investigated imidates of a range of secondary alcohols and were pleased to find these to be similar in efficiency and selectivity (**11**-**15**). Interestingly, pendant tertiary alcohols (**14**-**15**) were silylated *in situ* by Me_3Si-CN, but not primary ones (**7**). Notably, high diastereoselectivities (>20:1 dr, *anti*) were observed for cyclic and sterically demanding cases, including within natural product scaffolds (**10**, **12**, **13**, **15**). These data illustrate likely utility within other complex molecule derivatizations and medicinal chemistry applications.

Table 3. Nucleophilic, radical amino-functionalizations.



Conditions: See Table 2 for thiocyanation and azidation. See SI for full details of vinylation (2 eq $RB(OH)_2$), allylation (1.5 eq RTs), hydroamination (no nucleophile), and oxyamination (3 eq TEMPO). Isolated yields.

Having demonstrated broad synthetic utility for the N-radical precursor (i.e. alcohol component), we next probed the diversity of nucleophiles that could enable radical amino-functionalization. As shown in Table 3, six more classes of reactivity were shown to be possible. First, in addition to Me_3Si-CN, other silyl nucleophiles, such as Me_3Si-SCN and Me_3Si-N_3, efficiently yield amino-thiocyanation and amino-azidation, respectively (**16**-**17**). Next, vinyl boronic acids afford amino-vinylation with both alkyl and aryl substitution (**18**-**19**). Additionally, allyl *p*-tolylsulfones (allyl-Ts) yield amino-allylation with both electronically withdrawing and releasing substituents (**20**-**21**) – likely by addition-fragmentation, since the Cu catalyst is not needed for allylation, but it is essential for all other functionalizations. Finally, a pair of mechanistic probes yielded two additional classes of reactivity. When Cu catalyst and nucleophile were excluded, hydroamination was observed (**22**). This unexpected reactivity is noteworthy since previous photocatalytic methods require 1,4-cyclohexadiene[3a] or Hantzsch ester[6] as reductants via the SET manifold, whereas this EnT pathway simply employs MeCN as the H-atom source. Lastly, upon adding TEMPO (3 equiv) to the standard amino-cyanation conditions, oxy-amination was observed exclusively (**23**).

To better understand the mechanistic underpinnings of this broadly useful family of radical amino-functionalizations, a series of radical probes were designed and analyzed (Figure 2). First, alcohols with stereochemically pure (*Z*) and (*E*) olefins were each subjected to the reaction (Fig 2a). Notably, they both afford **4** with identical efficiency and stereoselectivity – suggesting N-radical generation and cyclization, as well as inversion of the resultant C-radical, occurs independently of the Cu. Moreover, the observed inversion of the alkyl radical serves as a radical clock ($<10^8$ s^{-1})[14] – indicating Cu interception either occurs slower or reversibly. Next, a regioselectivity competition was designed wherein an alcohol containing allyl and homoallyl units was subjected to the reaction (Fig 2b). In this case, the product of 5-*exo*-*trig* radical cyclization was observed exclusively (**24**) – in preference to either 6-*exo*-*trig* or 1,5-HAT reactivity – consistent with 300-fold rate differences found in N-radical cyclizations (up to 10^9 s^{-1}).[15] Lastly, a 5-hexenyl substituent was appended to the alcohol (Fig 2c). Upon subjecting to our amino-cyanation, only bicyclic adduct **25** was observed – indicating that Cu interception of the alkyl radical is either reversible or slower than 5-hexenyl cyclization (10^5 s^{-1}).[16] We have also determined the quantum yield of this reaction is less than unity (ϕ <1), indicating chain propagation is not operative. Finally, the oxime imidate is a strong Stern-Volmer quencher of the excited **Ir1** photocatalyst ($K_{SV} > 100$).[5f]

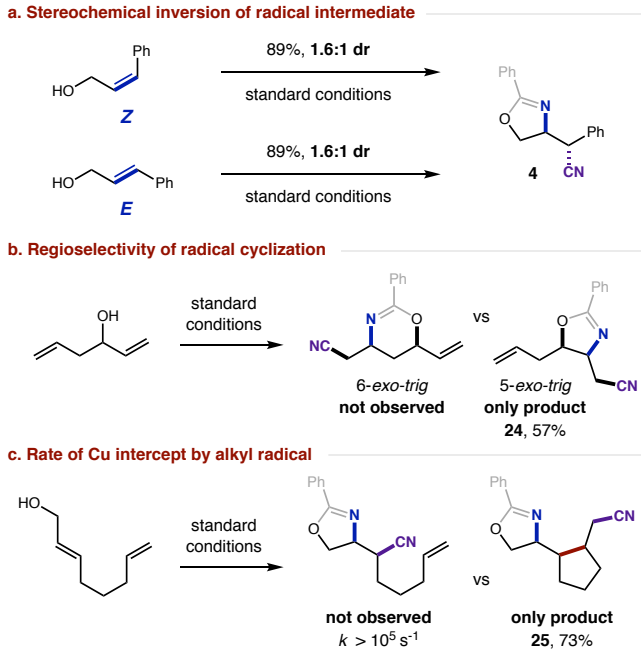


Figure 2. Radical clocks reveal mechanism entails (**a**) stereochemical inversion (**b**) regioselective cyclization, and (**c**) slow or reversible Cu intercept.

Combining the insights provided from these experiments, a dual catalytic mechanism is proposed in Figure 3. This radical cascade likely begins with transmetallation of the silyl (or boronate) nucleophile to Cu(I) (step *i*). Radical generation then occurs by Dexter energy transfer (EnT) from ***Ir(III)** after visible light-excitation of **Ir(III)**. Following triplet sensitization of oxime imidate **A** by ***Ir(III)** (step *ii*), the ground-state photocatalyst is regenerated along with excited organic species **A***. This triplet rapidly homolyzes to radical pair, **B** and •OPh, which is supported by a weakened N-O bond strength that we have computed to have a negative value (-18 kcal/mol).[5f] Since phenoxy radical (•OPh) is a potent oxidant, it may engage the LCu(I)Nu complex to form LCu(II)Nu(OPh) (step *iii*). The remaining N-centered imidate radical **B** then cyclizes to form epimerizable C-centered radical **C** (step *iv*). Next, the oxazoline substituted alkyl radical may be reversibly trapped by the Cu(II) complex to form organo-Cu(III) species **D** (step *v*).[17] Lastly, reductive elimination of the C-Nu bond (step *vi*) affords amino-functionalized product **E** along with LCu(I)X, which enables turnover of the second catalytic cycle. As further support of this mechanism, PhO-$SiMe_3$ was observed as the expected product of transmetallation when X=OPh, thereby lending support for the role of EnT-derived •OPh in the oxidation of Cu(I) (step *iii*).

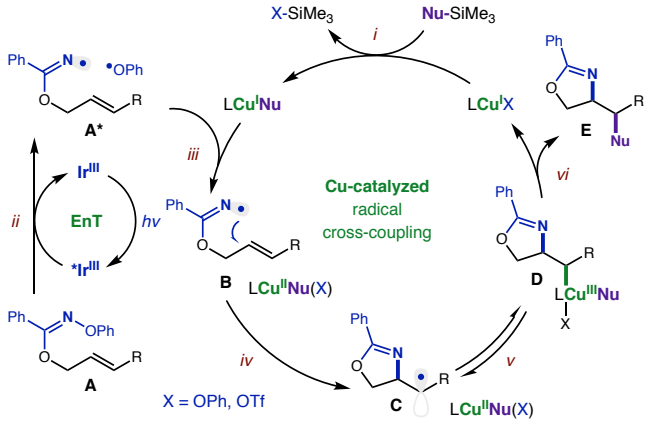


Figure 3. Proposed dual catalytic mechanism combines: (i) N-radical generation by Ir-photocatalyzed energy transfer (EnT) with (ii) Cu-catalyzed cross-coupling of nucleophiles.

In summary, we have developed a dual catalytic strategy for a broad range of amino-functionalizations that regioselectively incorporate amines and nucleophiles (e.g. CN, SCN, N_3, vinyl, allyl) onto allyl alcohols. This versatile transformation is enabled by the combined action of an Ir photocatalyst (via EnT activation) and Cu catalyst (via cross-coupling). This work represents a first application of this merged strategy for amino-functionalization, and the ensuing use of diverse nucleophiles that are now possible demonstrates the synthetic potential of this mechanism.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at:

Experimental procedures and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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