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Synergistic Catalysis

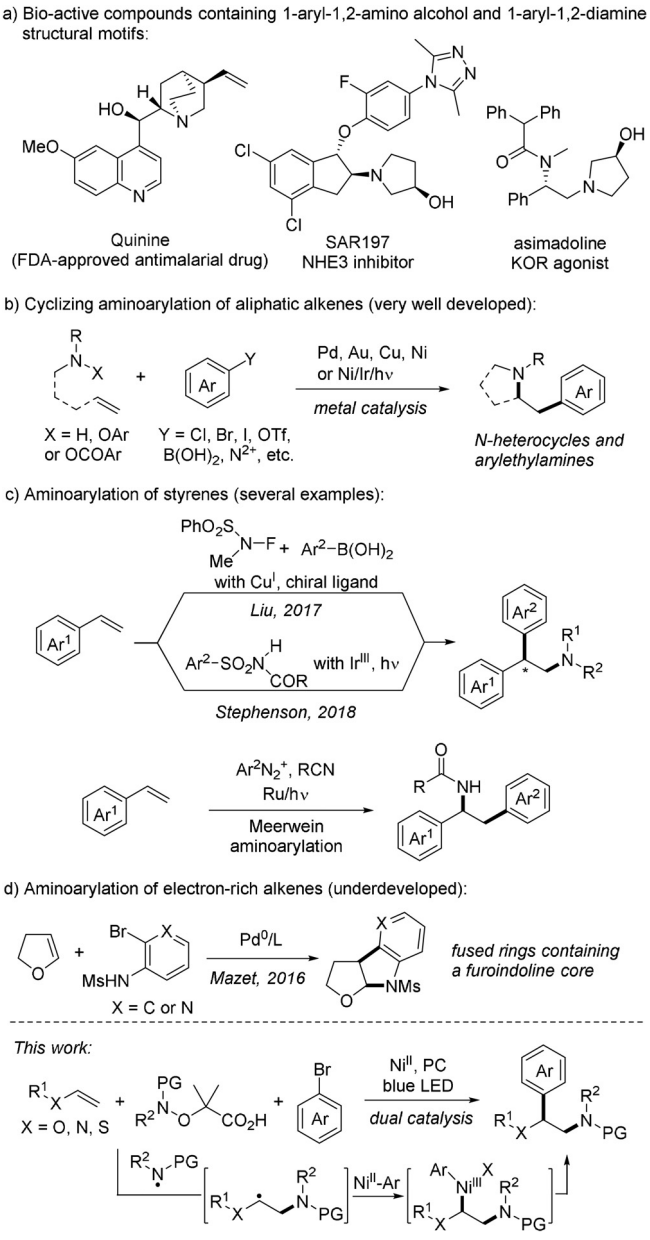
Three-Component Aminoarylation of Electron-Rich Alkenes by Merging Photoredox with Nickel Catalysis

*Heng Jiang, Xiaoye Yu, Constantin G. Daniliuc, and Armido Studer**

Abstract: *A three-component 1,2-aminoarylation of vinyl ethers, enamides, ene-carbamates and vinyl thioethers by synergistic photoredox and nickel catalysis is reported. 2,2,2-Trifluoroethoxy carbonyl protected α-amino-oxy acids are used as amidyl radical precursors. anti-Markovnikov addition of the amidyl radical to the alkene and Ni-mediated radical/transition metal cross over lead to the corresponding 1,2-aminoarylation product. The radical cascade, which can be conducted under practical and mild conditions, features high functional group tolerance and broad substrate scope. Stereoselective 1,2-aminoarylation is achieved using a L-(+)-lactic acid derived vinyl ether as the substrate, offering a novel route for the preparation of protected enantiopure α-arylated β-amino alcohols. In addition, 1,2-aminoacylation of vinyl ethers is achieved by using an acyl succinimide as the electrophile for the Ni-mediated radical coupling.*

Alkene 1,2-difunctionalization serves as a potent strategy to prepare diverse compounds from easily accessible feedstock chemicals.[1] Alkene 1,2-aminoarylation by sequential C-N and C-aryl bond formation is of great interest because the constructed 2-arylethylamine backbone is a common structural motif in alkaloids and pharmaceuticals (Scheme 1 a).[2] Transition-metal catalysed cyclizing 1,2-aminoarylation delivers N-heterocycles bearing a benzyl substituent at the 2-position of the ring (Scheme 1 b).[3] Such arylating cyclizations can also be achieved via intramolecular amidyl radical cyclization and metal-mediated aryl coupling.[4] Intermolecular amidyl radical addition to styrenes and Cu-catalysed enantioselective arylation was reported by Liu (Scheme 1 c).[5] 1,2-Aminoarylation of aryl alkenes was realized by Stephenson,[6] where C-N-bond formation was achieved by amidation of a styrene radical cation with a sulfonamide and β-arylation occurred via a radical Smiles rearrangement. Reversed regioselectivity for styrene aminoarylation can be obtained by Meerwein type aryl radical addition and subsequent Ritter amidation.[7]

However, known methods for intermolecular radical aminoarylation mainly work on aryl alkenes and reactions with electron-rich alkenes, such as vinyl ethers, enamides, and



Scheme 1. 1,2-Aminoarylation of alkenes.

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ene-carbamates leading to α-aryl-β-amino alcohols as well as α-aryl-β-aminoalkylamines have not been reported. This is surprising since such substructures are found widespread in pharmaceuticals (see above).[2] As a rare example, the Mazet group disclosed a Pd-catalysed aminoarylation of dihydrofurans (Scheme 1d).[8] However, intermolecular three-component variants are unknown.

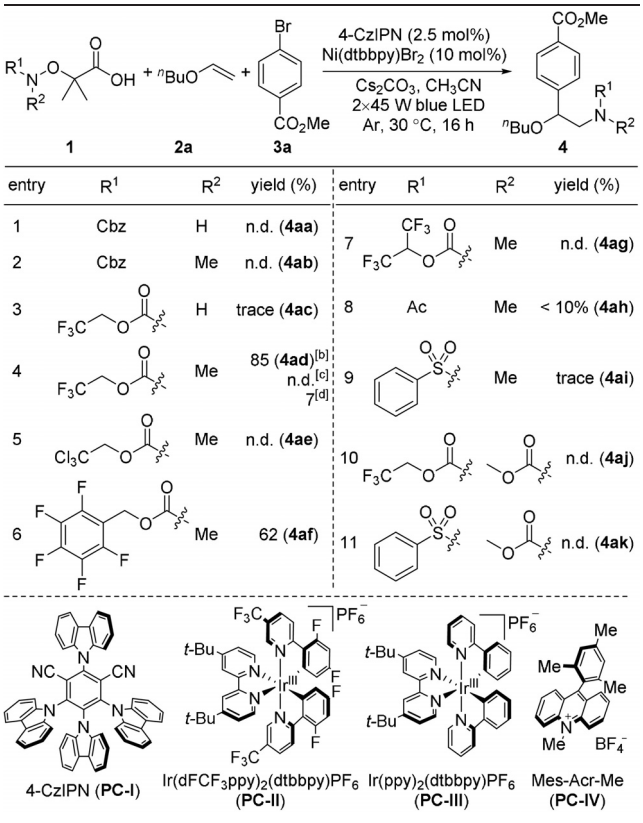
Inspired by Ni-catalysed radical alkene difunctionalizations to construct two geminal C-C bonds,[9] we envisioned that 1,2-aminoarylation of electron-rich alkenes could be realized by synergistic photoredox/Ni-catalysis (Scheme 1d).[10] α-Amido-oxy acids were supposed to be potent amidyl radical precursors, where N-radical generation can be achieved by SET oxidation using a photoredox catalyst.[11] After regioselective addition of the N-radical to the electron-rich alkene,[12] a Ni-mediated C-radical arylation should terminate the sequence. The Ni-oxidation state should be modulated by the photoredox catalyst.[13] Notably, potential side reactions including direct two component C-N coupling and C-O coupling of α-amido-oxy acids with aryl bromides leading to anilines or esters must be circumvented.[4a,14]

We commenced the study by using Cbz-protected N-radical precursors **1a** and **1b** in combination with butyl vinyl ether (**2a**) and methyl 4-bromobenzoate (**3a**) applying synergistic photoredox and nickel catalysis (Table 1). The desired **4aa** or **4ab** was not isolated with 4-CzIPN as the redox catalyst in combination with $Ni(dtbbpy)Br_2$ and Cs_2CO_3 in acetonitrile at room temperature under blue light irradiation (entries 1 and 2). Tuning N-radical reactivity by switching to the electron-deficient 2,2,2-trifluoroethyloxy carbonyl protecting group provided traces of **4ac**. 4-$CF_3CH_2OC(O)NHC_6H_4CO_2Me$ (27%) through direct C-N coupling was formed as major compound (entry 3).[4a] To our delight, the 1,2-aminoarylation compound **4ad** was the major product (85%) by using the N-radical precursor **1d**,[11b,14] and direct coupling to the corresponding anilide was almost entirely suppressed (entry 4). Noteworthy, the Ir-based catalyst **PC-II** gave a comparable yield, whereas with **PC-III** mainly the C-O coupling product was obtained (see SI).[15] Only 7% of **4ad** was obtained with **PC-IV**. Other protecting groups were also examined. (Perfluorophenyl)methyl carbamate **1f** gave **4af** in 62% yield (entry 6), whereas Troc-protected **1e** was not an efficient N-radical precursor (**4ae**, entry 5). Hexafluoroisopropoxy carbonyl, acetyl and phenyl sulfonyl moieties were found to be inefficient N-protecting groups for the aminoarylation reaction (**4ag**–**4ai**, entries 7–9). Replacing the N-methyl substituent by a methoxy carbonyl (Moc) group also led to suppression of the 1,2-aminoarylation (entry 10 and 11).

The N-radical precursor **1d** and acceptor **2a** were chosen to examine reaction scope with respect to the bromide component (Scheme 2). Various electron withdrawing groups including acyl, cyano, sulfonyl ester, formyl, trifluoromethyl and ester at the aryl bromide are tolerated, providing **4b**–**4k** in good to excellent yields (61–89%). A worse result was obtained for 1-bromo-4-chlorobenzene (**4l**, 33%) due to sluggish oxidative addition. Along these lines, aryl bromides bearing electron donating groups did not engage in the cascade due to failure of the oxidative addition with Ni^0. For 4-bromoanisole, an additional ligand screening was performed, but aminoarylation could not be achieved (see SI). However, aminoarylation products were obtained in moderate to good yields by using bromopyridines, providing an alternative pathway for alkene aminopyridination going beyond restrictions of three-component Minisci reactions (**4m**–**4t**, 55–88%).[16] In addition, halogenated pyrimidine, quinolone and benzothiazole heterocycles engaged in the reaction and **4u**–**4w** were isolated in moderate yields (47–53%).

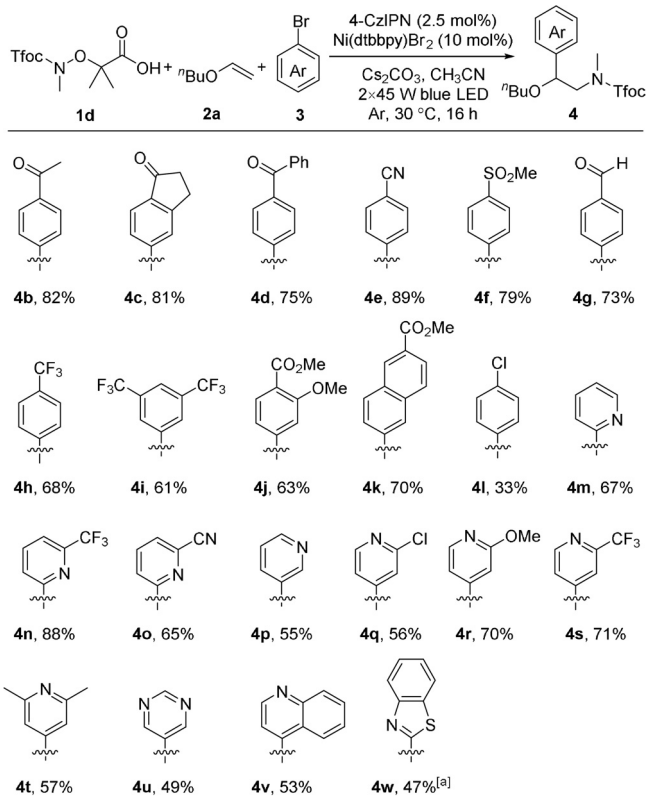
Next, the scope with respect to the alkene acceptor was examined using **3a** and **1d** as reaction partners (Scheme 3). Ethyl, cyclohexyl and *tert*-butyl vinyl ethers afforded very good results (**5a**–**5c**, 80–87%), whereas phenyl vinyl ether provided a slightly lower yield (**5d**, 65%). A free hydroxyl group was tolerated (see **5e**, 77%). Aminoarylation of 3,4-dihydropyran provided **5f** in 51% yield with complete *trans*-selectivity. However, 1,2-disubstituted linear vinyl ethers did not work, due to the slower initial N-radical addition to the alkene (see SI). Consequently, direct amidation of the aryl-Ni^{II}-species is faster. This finding further underlines the challenge of the introduced alkene aminoarylation. Ene-

Table 1: Aminoarylation of **2a** using different N-radical precursors **1** and **3a**.[a]

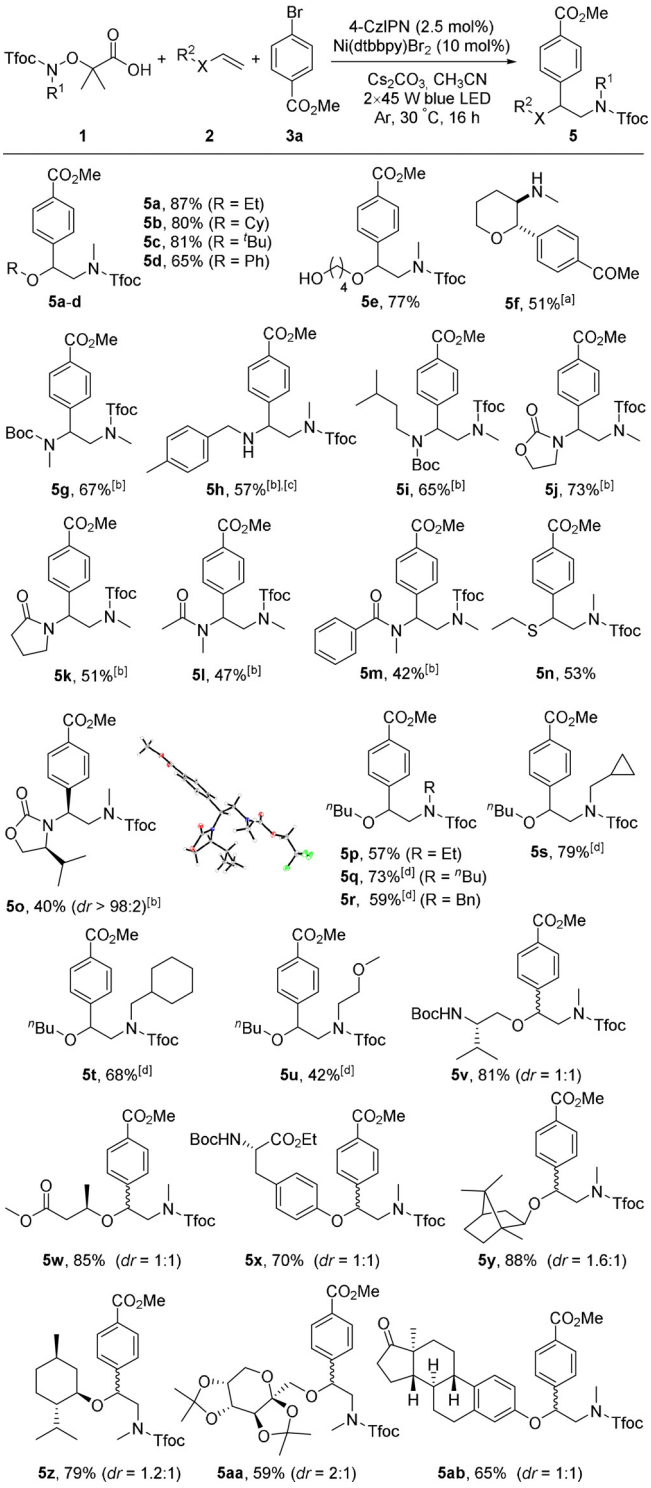


entry	R^1	R^2	yield (%)	entry	R^1	R^2	yield (%)
1	Cbz	H	n.d. (**4aa**)	7	$CF_3CH_2OC(O)$	Me	n.d. (**4ag**)
2	Cbz	Me	n.d. (**4ab**)	8	Ac	Me	< 10% (**4ah**)
3	$CF_3CH_2OC(O)$	H	trace (**4ac**)	9		Me	trace (**4ai**)
4	$CF_3CH_2OC(O)$	Me	85 (**4ad**)[b] n.d.[c] 7[d]	10	$CF_3CH_2OC(O)$		n.d. (**4aj**)
5	$Cl_3CCH_2OC(O)$	Me	n.d. (**4ae**)	11			n.d. (**4ak**)
6		Me	62 (**4af**)				

[a] Reaction conditions: A mixture of **1** (2 equiv), **2a** (4 equiv), **3a** (1 equiv), 4-CzIPN (2.5 mol%), $Ni(dtbbpy)Br_2$ (10 mol%), Cs_2CO_3 (2 equiv) in CH_3CN (0.1 M) was irradiated by two Kessil blue LEDs (45 W each) at 30 °C for 16 h. Isolated yields are provided. [b] Identical yields were obtained with **PC-I** and **PC-II**. [c] 2 mol% **PC-III** used. [d] 5 mol% **PC-IV** used.



Scheme 2. Variation of the aryl bromide. Reactions were performed under the optimized conditions unless otherwise noted and isolated yields are provided. Tfoc = 2,2,2-Trifluoroethoxy carbonyl. [a] Aryl chlorides were used instead of aryl bromides.

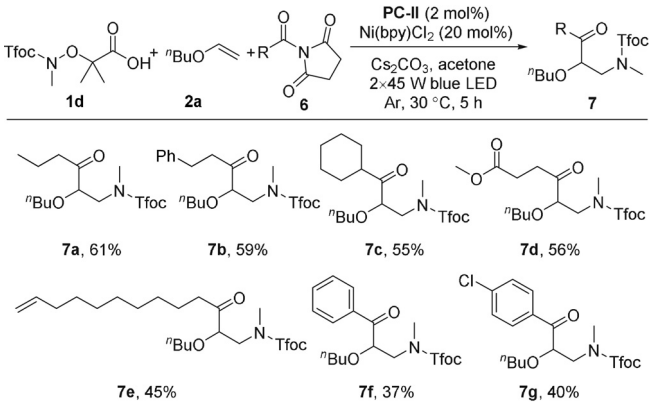


Scheme 3. Variation of the alkene **2**. Reactions were performed under the optimized conditions unless otherwise noted and isolated yields are provided. Tfoc = 2,2,2-Trifluoroethoxy carbonyl. [a] 4′-Bromoacetophenone was used and diastereoselectivity determined on **5f**, obtained after Tfoc removal. [b] **PC-II** (2 mol%) was used. [c] Overall yield of **5h** after Boc removal. [d] 6 equiv of **2a** used.

carbamates (see **5g**–**5j** and **5o**) and N-vinyl amides (**5k**–**5m**) served as N-radical acceptors to give protected α-aryl-β-aminoalkylamines. In this series, the less nucleophilic enamides afforded lower yields. Notably, excellent diastereoselectivity was obtained with the chiral N-vinyl oxazolidinone (see **5o**). The relative configuration was assigned by X-ray crystal structure analysis.[17] Vinyl thioethers that are generally not compatible with photoredox conditions also worked (**5n**, 53%). The N-methyl group of **1d** could be substituted by other alkyl groups such as ethyl (**5p**), *n*-butyl (**5q**), benzyl (**5r**), cyclopropylmethyl (**5s**), cyclohexylmethyl (**5t**) and 2-methoxyethyl (**5u**). Natural product derivatives, including L-valinol (**5v**), (*R*)-3-hydroxybutyric acid (**5w**), L-tyrosine (**5x**), (±)-isoborneol (**5y**), (−)-menthol (**5z**), D-glucose (**5aa**) and estrone (**5ab**) derived vinyl ethers afforded the aminoarylation products in good to satisfactory yields, albeit with low or no stereoselectivity.

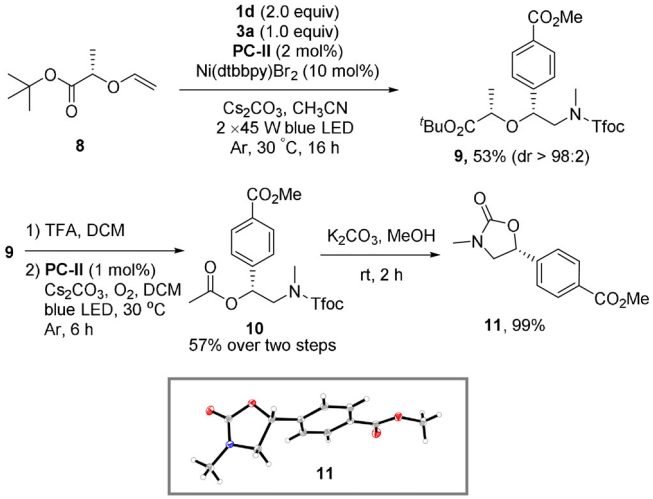
After extensive reaction screening we found that acyl succinimides **6** also engage as "electrophiles" in the three-component coupling (Scheme 4).[18] Thus, N-alkylcarbonyl succinimides **6a**–**6e** reacted with the N-radical precursor **1d** and vinyl ether **2a** in the presence of **PC-II** (2 mol%), $Ni(bpy)Cl_2$ (20 mol%) and Cs_2CO_3 in acetone to the aminoacylation products **7a**–**7e** (45–61%). Aroyl succinimides **6f** and **6g** showed slightly lower efficiencies, affording the protected β-amino ketones **7f** and **7g** in 37 and 40% yields.

Considering the enantioselective aminoarylation of butyl vinyl ether (**2a**), all attempts using chiral Ni-ligands failed. We therefore followed the chiral auxiliary approach and sought to



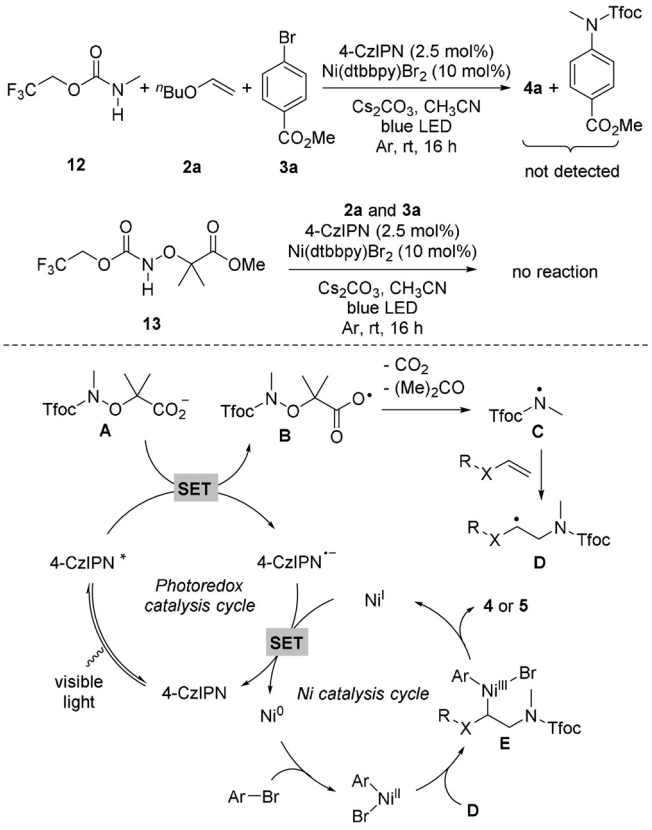
Scheme 4. Aminoacylation of alkene **2a**. Reaction conditions: A mixture of **1d** (2 equiv), **2a** (4 equiv), **6** (1 equiv), **PC-II** (2 mol%), $Ni(bpy)Cl_2$ (20 mol%), Cs_2CO_3 (2 equiv) in acetone (0.05 M) was irradiated by two Kessil blue LEDs (45 W each) at 30°C for 5 h. Isolated yields are provided.

prepare an optically pure protected amino alcohol through diastereoselective aminoarylation of readily accessed L-(+)-lactic acid derived vinyl ether **8**.[19] Acceptor **8** underwent aminoarylation to ester **9** with complete stereoselectivity (Scheme 5). The chiral auxiliary was removed in a two-step sequence by first cleaving the *tert*-butyl ester (TFA) and subsequent radical decarboxylative oxidation to give the optically pure protected β-amino alcohol **10**.[20] The absolute configuration was assigned by X-ray crystal structure analysis on **11**, obtained upon alcohol deprotection by transesterification and cyclization under basic conditions.[17]



Scheme 5. Preparation of an enantiomerically pure protected β-amino alcohol.

To elucidate the mechanism, control experiments were conducted. Aminoarylation did not occur in the absence of either photoredox or nickel catalyst. The N-radical could not be generated from the NH-amide, as demonstrated by replacing **1d** with **12**. Neither the aminoarylation product **4a** nor the aniline byproduct was formed (Scheme 6).



Scheme 6. Mechanistic studies and proposed catalysis cycle.

Replacing acid **1d** with the methyl ester **13** did not give any transformation, showing that amidyl radical generation does not occur via homolytic or reductive N-O bond cleavage. Based on these results and previous reports, the following mechanism is proposed. The catalysis cycle starts by photoexcitation of 4-CzIPN upon irradiation to generate the excited redox catalyst which oxidizes carboxylate **A**,[21] formed by deprotonation of **1**, to generate the carboxyl radical **B** and the reduced 4-CzIPN$^{\bullet-}$.[22] Sequential fragmentation of CO_2 and acetone generates the electrophilic N-radical **C**,[11] which then adds to alkene **2** to provide the radical **D**. 4-CzIPN$^{\bullet-}$ gets oxidized by Ni^I to close the photoredox cycle, thereby generating a Ni^0-species that undergoes an oxidative addition with the aryl bromide to provide a Ni^{II}-Ar intermediate. Trapping of the radical **D** with the Ni^{II}-Ar complex leads to the Ni^{III} species **E**. Reductive elimination gives **4** or **5** along with a Ni^I species, closing the nickel catalysis cycle.[13] Aminoacylation works in analogy by replacing the bromoarene with the acylated succinimide.

In summary, we reported a three-component aminoarylation of electron rich alkenes through synergistic photoredox/nickel catalysis. 2,2,2-Trifluoroethoxy carbonyl protected α-amino oxy acids are used as N-radical precursors and bromoarenes serve as the electrophilic coupling partners. Compared with traditional strategies such as addition of a Grignard reagent to glycine aldehyde derivatives,[23] this three component cascade features mild conditions and broad scope, providing a practical approach to the modular synthesis of α-aryl-β-amino alcohols and α-aryl-β-aminoalkyl-

amines. Optically pure α-aryl-β-amino alcohols can be prepared using cheap lactic acid as a chiral auxiliary. By using N-acylated succinimides as reaction partners, β-amino-ketones are accessible.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: amidyl radicals · aminoarylation · nickel catalysis · photoredox catalysis · synergistic catalysis

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