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Visible-light-mediated multicomponent reaction for secondary amine synthesis†

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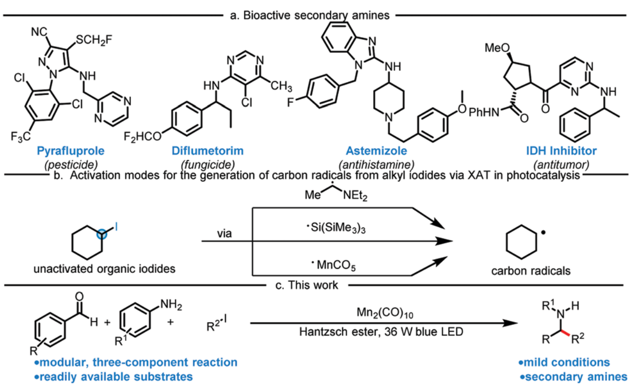
The widespread presence of secondary amines in agrochemicals, pharmaceuticals, natural products, and small-molecule biological probes has inspired efforts to streamline the synthesis of molecules with this functional group. Herein, we report an operationally simple, mild protocol for the synthesis of secondary amines by three-component alkylation reactions of imines (generated *in situ* by condensation of benzaldehydes and anilines) with unactivated alkyl iodides catalyzed by inexpensive and readily available $Mn_2(CO)_{10}$. This protocol, which is compatible with a wide array of sensitive functional groups and does not require a large excess of the alkylating reagent, is a versatile, flexible tool for the synthesis of secondary amines.

The physiological and chemical properties of molecules bearing secondary amines make them highly effective as pharmaceuticals and agrochemicals[1] (Scheme 1a). In addition, secondary amines are essential as building blocks for organic synthesis and as subunits of ligands for transition-metal catalysis.[2] The traditional strategy for synthesizing secondary amines relies on reductive amination of carbonyl compounds,[3,4] direct nucleophilic substitution reactions between primary amines and alkylation reagents such as alkyl halides or sulfonic esters,[5] organometallic addition reactions between carbonyl compounds and highly reactive Grignard or organolithium reagents.[6]

Another strategy involves multicomponent reactions, which involve condensation of three or more components to rapidly and efficiently deliver novel scaffolds with inherent molecular complexity. MCRs have the advantages of being atom- and step-economical, exhibiting shorter reaction times, and providing access to a highly diverse chemical space.[7] The Petasis reaction[8] is a three-component reaction that is unique in affording complex amines, but the majority of the previously reported applications of this reaction required aldehydes with adjacent heteroatoms to act as directing groups.[9] Owing to the disadvantages of the above-described strategies, the development of new methods for accessing secondary amines is an important challenge for chemical synthesis.

An alternative to this method would be the radical reaction, resulted in an influx of synthetically valuable approaches for the construction of amines whose synthesis would be challenging using two-electron reaction manifolds. Visible-light photoredox catalysis can promote single-electron transfer to produce radicals easily under mild conditions,[10] and there have been several reports of visible-light-mediated photoredox radical reactions that afford secondary amines;[11] but the reported examples require preformed imines, which limits the scope of these reactions relative to that of MCRs. Encouragingly, MCRs involving radicals have been developed for the synthesis of secondary amines[12] and are much simpler than previously reported methods. However, many of the radical precursors must be prefunctionalized, and the reactions require a precious metal catalyst (Ir or Ru). Replacement of these expensive catalysts with an inexpensive earth-abundant 3d transition



Scheme 1 Bioactive molecules with a secondary amine moiety and strate-gies for secondary amine synthesis.

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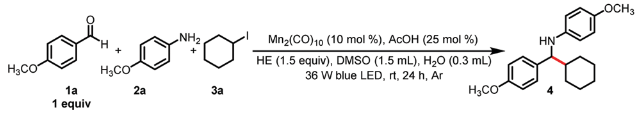
metal such as manganese would represent a significant advance.

Unactivated alkyl iodides are widely available organic compounds that are commonly used as building blocks in medicinal chemistry. However, they are impractical as feedstocks for redox chemistry because of their highly negative reduction potentials (*ca.* −1.67 V *vs.* SCE for ethyl iodide).[13] Methods based on tin or silicon reagents and trialkyl borane–O_2 systems have proven to be useful in obtaining carbon radicals from organic halides.[14] Activation modes for the generation of carbon radicals from alkyl iodides by halogen atom transfer in photocatalysis include silicon radicals (TTMSS) serve as a distinct class of halogen abstracting reagents,[15] nucleophilic *α*-aminoalkyl radicals abstract halogen atoms from alkyl iodides.[16] And because the weak Mn–Mn bond ($\sim$150 kJ mol^{-1}) of decacarbonyldimanganese, $Mn_2(CO)_{10}$, can be homolyzed by photoirradiation to form two manganese-centered pentacarbonyl radicals [$^{\bullet}Mn(CO)_5$],[17] which can easily generate an open-shell intermediate by homolytic cleavage of a C–I bond by means of halogen-atom transfer (Scheme 1b),[18,19] we reasoned that the use of $Mn_2(CO)_{10}$ as a catalyst would solve the problem posed by the highly negative reduction potential of alkyl iodides.[20] Indeed, we herein report that we have succeeded in developing a protocol for the synthesis of secondary amines by $Mn_2(CO)_{10}$-catalyzed three-component reactions of unactivated alkyl iodides, anilines, and benzaldehydes, which proceed *via* a unique mechanism (Scheme 1c).

Our initial experiments on the development of the proposed amine synthesis focused on the $Mn_2(CO)_{10}$-catalyzed reaction of 4-methoxybenzaldehyde (**1a**), 4-methoxyaniline (**2a**), and iodocyclohexane (**3a**) in DMSO/H_2O containing Hantzsch ester (HE) and AcOH under irradiation with a 36 W blue LED at room temperature (Table 1). We then varied the $Mn_2(CO)_{10}$ catalyst to Ir and Ru photocatalysts (entries 2 and 3). Unfortunately, the reaction failed to proceed under these photocatalysts. Lower yields were obtained when the reaction was conducted in other solvents (entries 4 and 5). Next, a variety of additives were tested in order to assess the potential for enhanced reactivity of imines, $LiSO_2CF_3$, $AlCl_3$, $LiBF_4$, and $ZnBr_2$ were inferior additives to AcOH (entries 6–9). HE can't be replaced by other simple reductants (entries 10–11). Control experiments established that essentially none of the desired product was generated in the absence of light or $Mn_2(CO)_{10}$ (entries 12 and 13), and omission of HE was detrimental to the yield (entry 14).

Table 1 Optimization of reaction conditions[a]



Entry	Deviation from standard conditions	Yield[b] (%)
1	None	75 (71[c])
2	$Ir(ppy)_3$	NR
3	$[Ru(bpy)_3]Cl_2{\cdot}6H_2O$	NR
4	THF instead of DMSO	15
5	DCM instead of DMSO	52
6	$LiSO_2CF_3$ instead of AcOH	62
7	$AlCl_3$ instead of AcOH	52
8	$LiBF_4$ instead of AcOH	37
9	$ZnBr_2$ instead of AcOH	50
10	TTMSS instead of HE	NR
11	NEt_3 instead of HE	NR
12	No light	NR
13	No $Mn_2(CO)_{10}$	NR
14	No HE	20

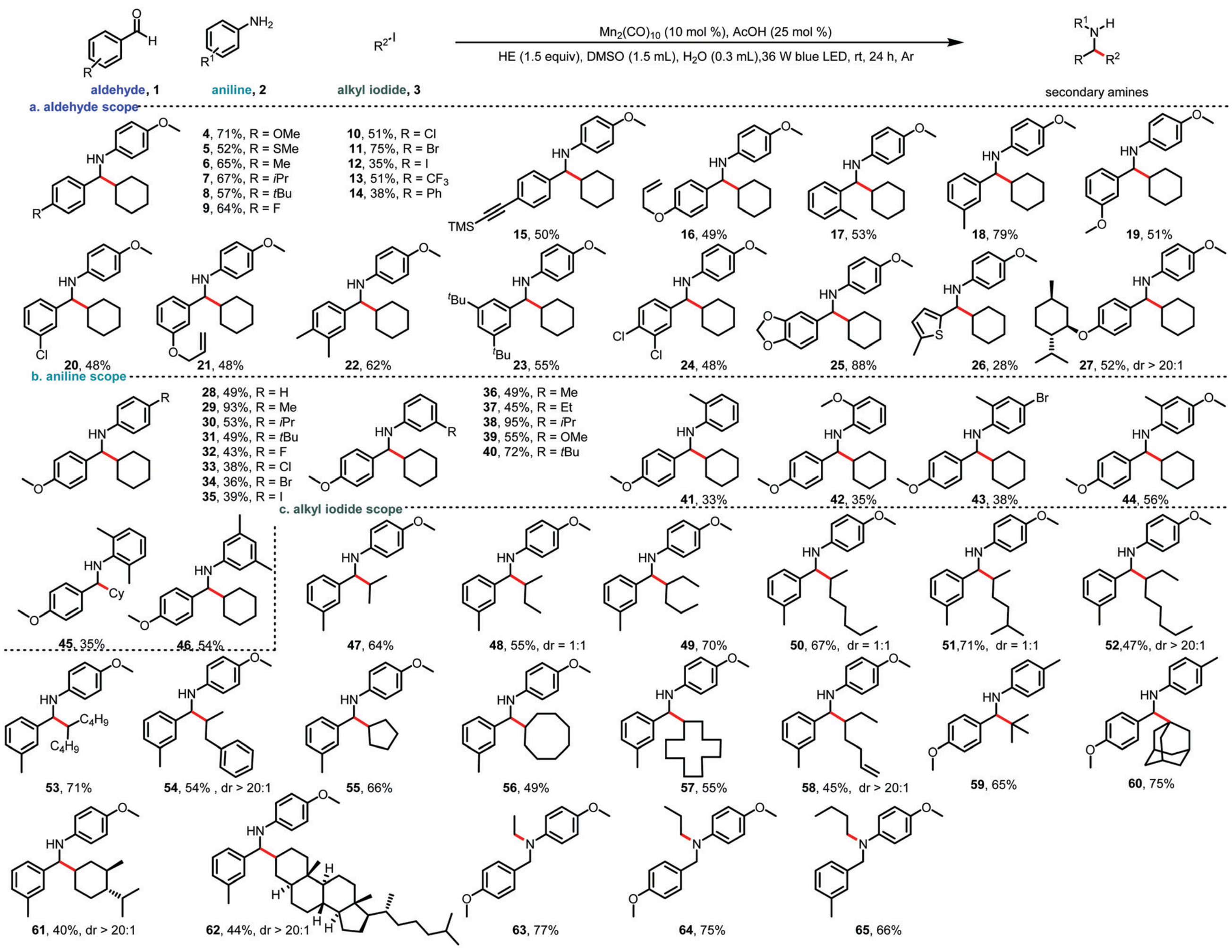
[a] Reaction conditions, unless otherwise noted: **1a** (0.3 mmol), **2a** (0.45 mmol), **3a** (0.45 mmol), photocatalyst (0.03 mmol), Hantzsch ester (HE, 0.45 mmol), additive (0.075 mmol), H_2O (0.3 mL), and solvent (1.5 mL) under Ar atmosphere. [b] Determined by ^1H NMR spectroscopy with dibromomethane as an internal standard. NR = no reaction. [c] Isolated yield.

Having determined suitable conditions for the three-component amination reaction, we explored its scope. We found that various aryl aldehydes **1** gave good yields of the amine products. The reaction tolerated electron-rich and electron-deficient aryl aldehydes, and aldehydes with a single *ortho*, *meta*, or *para* substituent were acceptable, as were poly-substituted aldehydes (Table 2a). In particular halogen-substituted benzaldehyde derivatives provided good yields of **9–12**, **20**, and **24**, which have a handle for further functionalization. We observed good functional group tolerance: ether, alkyl, and phenyl groups were all compatible with the reaction conditions, as were several relatively sensitive yet versatile functional groups – alkyne (**15**) and alkene (**16** and **21**). These results show the potential utility of this protocol for synthetic and medicinal chemistry applications. 2-Thiophenecarboxaldehyde was also a suitable substrate, although the yield of **26** was low. In addition, an aldehyde derived from menthol (**27**) showed uncompromised reactivity.

We were also gratified to observe broad tolerance with respect to the aniline component (Table 2b). Anilines with electron-donating and electron-withdrawing *para* substituents gave moderate to excellent yields of the desired products (**28–35**, 36–93% yield). Notably, no reduction of halogenated anilines was observed (**32–35**, **43**); the products retained the halogen atom, potentially allowing for subsequent orthogonal functionalization. Substituents at the *meta* position were also well tolerated (**36–40**, 45–95%), and the reaction was not sen-sitive to steric hindrance at the *ortho* position of the aniline (**41–45**, 33–56% yield).

Finally, we evaluated the scope of this Mn-catalyzed amination reaction with respect to the unactivated alkyl iodide (Table 2c). An array of unactivated secondary alkyl iodides, both acyclic (**47–54**, 47–71% yield) and cyclic (**55–57**, 49–66% yield) were suitable radical precursors. The reaction was also applicable to a secondary iodoalkane bearing a phenyl ring (**54**). The yield was not sensitive to steric effects, as indicated by the fact that sterically disfavored tertiary iodoalkanes gave good yields of the corresponding products (**59** and **60**). We also investigated the applicability of the protocol for biologically relevant substrates and found that the amination reactions of iodomenthol and 3-iodo dihydrocholesterol, which were prepared in one step from the corresponding alcohols, smoothly afforded target products **61** and **62**, respectively, in moderate yields. Notably, primary aliphatic iodoalkanes gave *N*-substituted tertiary amines (**63–65**) as the main products, which should be generated by nucleophilic substitution between

Table 2 Substrate scope of the amination protocol[a]



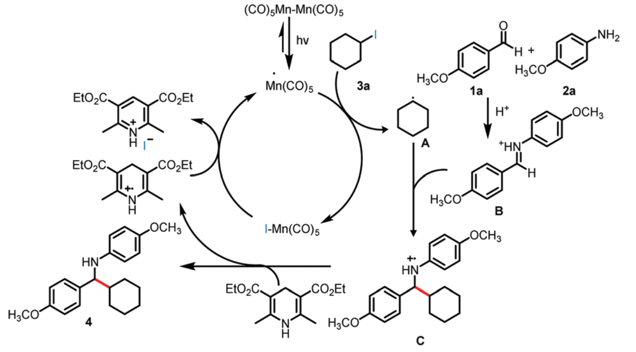
[a] Reactions were performed on a 0.3 mmol scale.

the secondary amines and primary alkyl iodides. In many cases the yields of the products are moderate because of the side-reactions such as reduction of imine to amine and nucleophilic substitution like this.

Next, to highlight the applications of this MCR, we scaled up a reaction of cyclohexyliodide, *p*-bromobenzaldehyde, and *p*-methoxyaniline under the standard conditions (except that the amount of catalyst was decreased to 5 mol %; Scheme 2). After reaction for 24 h, desired product **11** was obtained in 65% yield, which was slightly lower than the yield of the small-scale reaction. The bromine substituent of **11** allowed for subsequent orthogonal functionalization; specifically, **11** smoothly underwent Suzuki coupling with an arylboronic acid to afford **66** (54%) and Sonagashira coupling with phenylacetylene to provide **67** (58%) (Fig. S2, ESI†).

We next turned our attention to some mechanistic experiments (Fig. S3, ESI†). First, we used (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and benzyl acrylate as radical scavengers to determine whether the reaction involved a radical process. Both TEMPO (2.5 equiv) and benzyl acrylate completely inhibited the formation of **18**, and TEMPO adduct **68** was detected by mass spectrometry. In addition, radical trapping product benzyl 3-cyclohexylpropanoate (**69**) was isolated from the reaction in the presence of benzyl acrylate, further supporting the intermediacy of an alkyl radical. Moreover, light on/off experiments (see the ESI† for details) illustrated a total interruption of the reaction process in the absence of light and recuperation of reactivity on further illumination, this suggests that light is essential for this transition, and any chain propagation process should be short-lived.

On the basis of the above-described experiments and the literature, we propose that the amination reactions occur *via* the mechanism shown in Scheme 2. Upon irradiation with the blue LED, $Mn_2(CO)_{10}$ homolysis generates [$^{\bullet}Mn(CO)_5$], which abstracts iodine from iodocyclohexane (**3a**) to generate nucleophilic radical species **A** and $Mn(CO)_5I$. The iodine-abstraction step is irreversible, owing to the difference between the dissociation energies of the Mn–I bond of $Mn(CO)_5I$ (67 kcal mol^{-1})



Scheme 2 Proposed mechanism.

and the C(sp^3)–I bond of iodocyclohexane (60 kcal mol^{-1}).[20a] Radical **A** then adds to iminium ion **B** (generated *in situ* by a condensation reaction between **1a** and **2a** then protonated by AcOH) to form radical cation **C**. Subsequent reduction of **C** gives tertiary amine product **4** and makes a Hantzsch ester to the radical cation, HE^{+},[21] which reacts with $Mn(CO)_5I$ to regenerate the active catalyst [$^{\bullet}Mn(CO)_5$] and terminate the photocatalytic cycle.

In summary, we have developed a simple, scalable, and modular three-component method for the synthesis of secondary amines with catalysis by $Mn_2(CO)_{10}$, an inexpensive complex of an earth-abundant metal, under visible-light-mediated conditions. This method employs readily accessible or commercially available materials to deliver an array of structurally and functionally diverse products, which would otherwise be difficult to obtain in a single synthetic sequence under such mild conditions. The method avoids traditional and superstoichiometric radical initiators; the broad substrate scope, excellent functional group tolerance, and mild conditions suggest that it can be combined with other synthetic methods to rapidly generate structural diversity.

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Conflicts of interest

There are no conflicts to declare.

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