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# Formal Bromine Atom Transfer Radical Addition of Nonactivated Bromoalkanes Using Photoredox Gold Catalysis

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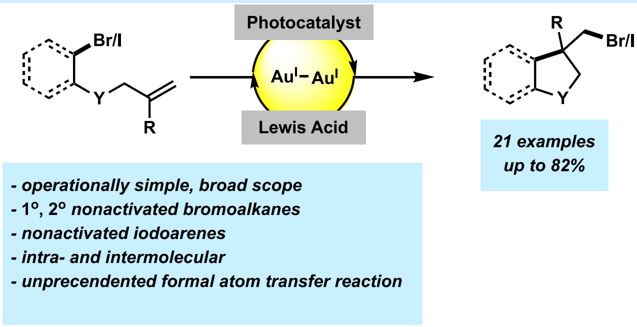
**ABSTRACT:** Organic transformations mediated by photoredox catalysis have been at the forefront of reaction discovery. Recently, it has been demonstrated that binuclear Au(I) bisphosphine complexes, such as $[Au_2(\mu\text{-dppm})_2]X_2$, are capable of mediating electron transfer to nonactivated bromoalkanes for the generation of a variety of alkyl radicals. The transfer reactions of bromine, derived from nonactivated bromoalkanes, are largely unknown. Therefore, we propose that unique metal-based mechanistic pathways are at play, as this binuclear gold catalyst has been known to produce Au(III) Lewis acid intermediates. The scope and proposed mechanistic overview for the formal bromine atom transfer reaction of nonactivated bromoalkanes mediated by photoredox Au(I) catalysis is presented. The methodology presented afforded good yields and a broad scope which include examples using bromoalkanes and iodoarenes.



Photoredox catalysis has been a growing field in synthetic organic chemistry. Photochemistry combined with radical chemistry can perform photoinduced single-electron transfers (PET or SET) and follow one-electron reaction pathways.[1] The harnessing of both fields of chemistry synergistically makes for a great match for accessing new chemical reactions. While some traditional radical reactions require strong oxidants and harsh conditions, photoredox chemistry allows for the formation of new C−C bonds under mild conditions.[2] Organic chemists now have new methods of functionalization using transition metal or organic dye photosensitizers, imitating what biomolecules can do in Nature, where photons can be transformed into chemical energy.[3] In 1945, Kharasch and co-workers reported the first atom transfer radical addition (ATRA) reaction, utilizing it in the difunctionalization of alkenes.[4] ATRA reactions became a great method to functionalize unsaturated C−C bonds. The addition of electrophilic radicals derived from $\alpha$-bromoesters to relatively nucleophilic alkenes became a great way to perform the conventional ATRA reaction.[5] To this end, these reactions require harsh conditions and the need for radical initiators (peroxides, or triethyl borane), and additives (organotin reagents) as the reaction follows a radical chain-type mechanism (Scheme 1A). Recently, intramolecular formal ATRA reactions have been accomplished using transition metals. The groups of Sanford and Lautens utilized Heck reaction intermediates to perform carbohalogenation reactions starting from iodoarenes and have expanded their methodology by using Pd- and Ni-based catalysts (Scheme 1B).[6] In most cases, metal-catalyzed carbohalogenation reactions require the use of disubstituted geminal olefins (R = Me and R′ = H) to avoid $\beta$-hydride elimination products. Alexanian and co-workers have reported palladium-catalyzed carbocyclization of bromoalkanes.[7] Although this method generates mainly Heck type products, the formation of primary and secondary (when R = H) bromocycloalkanes via a formal bromine atom transfer radical addition (BrATRA) has been observed in a few cases. Bromine transfer reactions from nonactivated bromocycloalkanes remain largely undeveloped. In this context, we report a photoredox BrATRA reaction using dimeric gold complexes (Scheme 1C).[8] This strategy would also be waste limiting as a redox neutral reaction pathway could be achieved by an oxidative quenching cycle, combined with gold Lewis acid catalysis.[9]

Recently, we reported the homocoupling of alkyl radicals generated from bromoalkanes through the reductive elimination of a putative Au(III) intermediate.[10] Furthermore, the unprecedented alkylative semipinacol rearrangement demonstrated further evidence for the formation of Au(III) intermediates and subsequent reductive elimination processes.[11,12] Looking to probe the Au(III) intermediates further, we set out to investigate the elementary reaction more closely.

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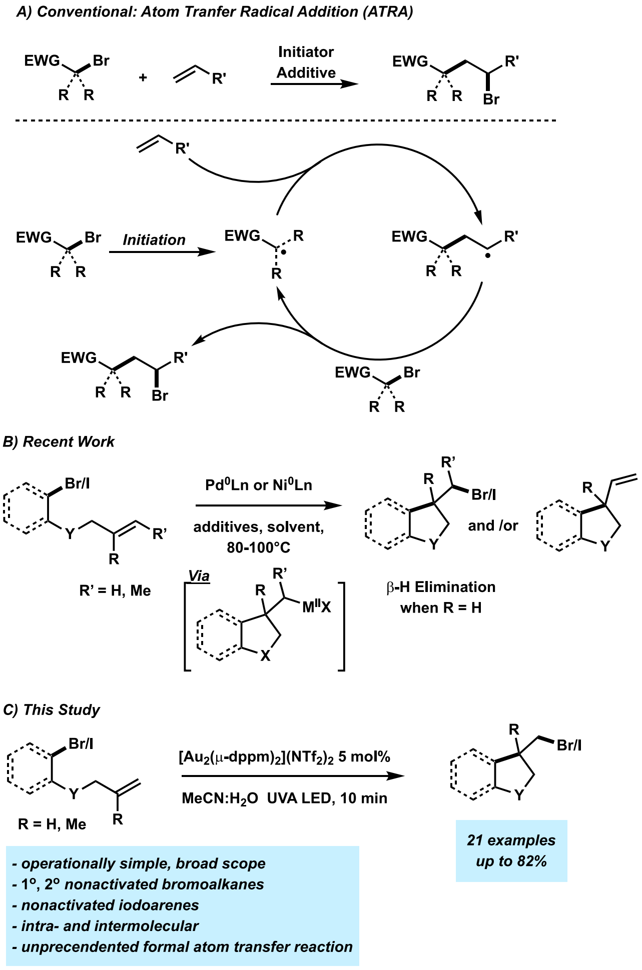
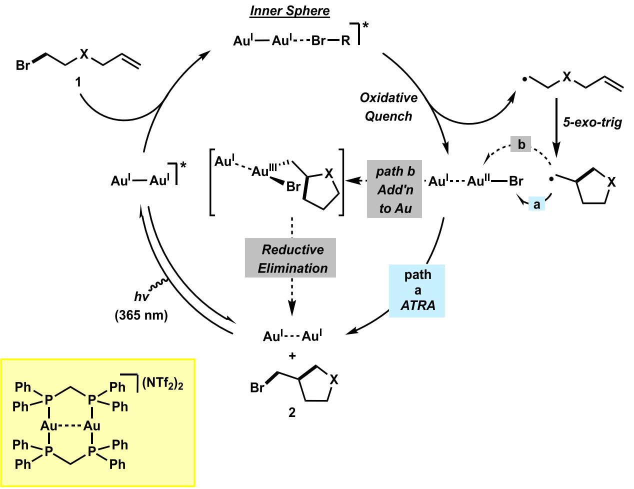
### Scheme 1. Previous and Present Work in Formal BrATRA Reactions



During this time, products deriving from the formal BrATRA were identified. Due to the unprecedented nature of the peculiar reaction, it demanded a closer look.

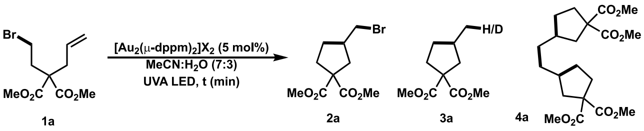
Mechanistically, we hypothesized that this transformation was mediated by the excitation of $Au_2(\mu\text{-dppm})_2(NTf_2)_2$ ($*[Au^I{-}Au^I]$) with UVA light followed by an oxidative quenching event with bromoalkene (**1**) through an inner sphere exciplex (bromoalkanes: $E_{1/2}^{red}$ = ∼−2.5 V vs SCE and $*[Au_2(\mu\text{-dppm})_2]Cl_2$: $E_{1/2}^{red}$ = −1.63 V vs SCE) as shown in Scheme 2.[13,15] The resulting free alkyl radical undergoes a 5-*exo-trig* cyclization to form a 5-membered ring exocyclic radical which can react further through path A or path B. Path A proposes an unprecedented atom transfer radical addition (BrATRA), where the alkyl radical abstracts a bromine atom from an Au−Br species, giving the new bromoalkene and regenerating the ground state of the gold catalyst. Path B proposes the addition of the radical to the $Au^{II}$ center to form an $[Au^I{-}Au^{III}{-}R]$ intermediate. This may also proceed via alkyl radical addition to the $Au^I$ center, giving $[R{-}Au^{II}{-}Au^{II}]$, followed by reorganization to the $[Au^I{-}Au^{III}{-}R]$ intermediate.[14] Reductive elimination of the alkyl group and the bromide can form **2** and regenerate the ground state of the catalyst. Alternatively, a chain reaction mechanism could be considered, but this is unlikely since this process requires the use of activated haloalkanes.[15]

### Scheme 2. Proposed Mechanism



Initial experiments showed that irradiation of bromoalkane **1** in the presence of $Au_2(\mu\text{-dppm})_2Cl_2$ (5 mol %) in MeCN/$H_2O$ (7:3) gave a mixture of products **2a** (56%), **3a** (10%), and **4** (14%) (Table 1, entry 1). It is important to note that we previously reported the specific formation of compounds **3a** and **4a** using the photoexcited $[Au_2(\mu\text{-dppm})_2]Cl_2$ under reductive quenching conditions.[9,13b,f] We found that the variation in counterions had an effect on the reaction performance; the reactions carried out with counterions such as OTf and $NTf_2$ provided better yields for the formation of **2a** than Cl, $SbF_6$, and $BF_4$ (entries 1−5). The best result was observed using $[Au_2(\mu\text{-dppm})_2][NTf_2]$ (5 mol %), where **2a** was obtained in 61% yield along with trace amounts of **3a** and **4a** (entry 5).

### Table 1. Optimization of Reaction Conditions



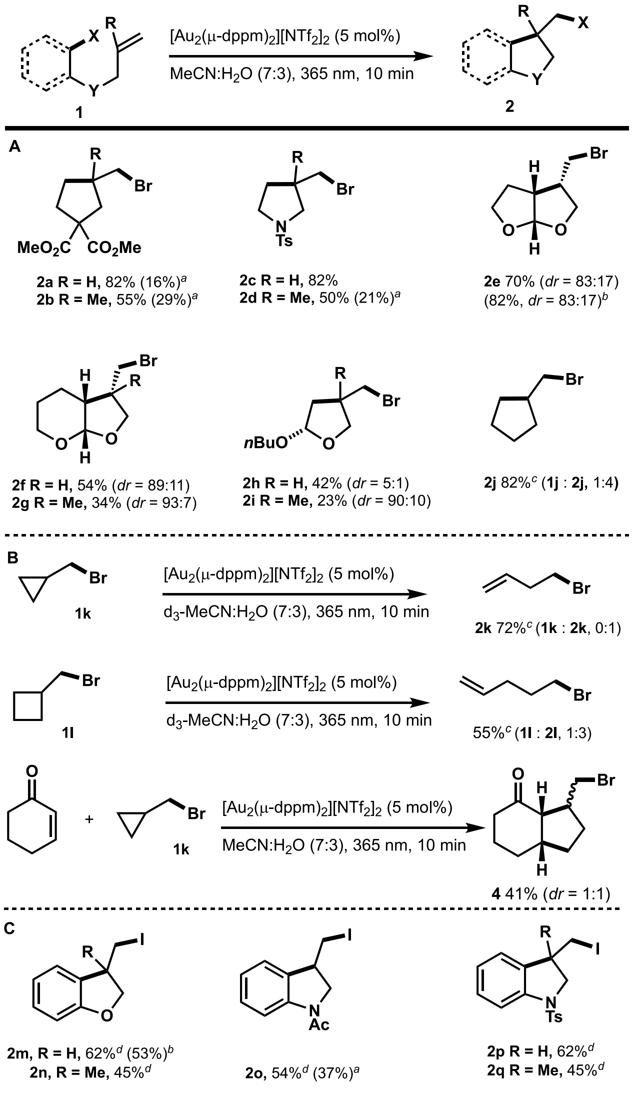
| entry | X | [M] | time (min) | **1a** (%) | yield (%)[a] **2a**/**3a**/**4a** |
|---|---|---|---|---|---|
| 1 | Cl | 0.067 | 180 | 0 | 56:10:14 |
| 2 | OTf | 0.067 | 180 | 0 | 53:2:0 |
| 3 | $SbF_6$ | 0.067 | 180 | 5 | 49:5:7 |
| 4 | $BF_4$ | 0.067 | 180 | 5 | 26:1:0 |
| 5 | $NTf_2$ | 0.067 | 180 | 4 | 61:4:5 |
| 6[b] | $NTf_2$ | 0.067 | 180 | 58 | 22:5:0 |
| 7[c] | $NTf_2$ | 0.067 | 10 | 0 | 80:3:8 |
| 8[d] | $NTf_2$ | 0.067 | 10 | 29 | 43:11:6 |
| 9[c] | $NTf_2$ | 0.033 | 10 | 0 | 82:3:8 |
| **10** | **$NTf_2$** | **0.033** | **10** | **0** | **82:16:0** |
| 11[e] | $NTf_2$ | 0.033 | 10 | 100 | 0:0:0 |
| 12[f] | $NTf_2$ | 0.033 | 10 | 100 | 0:0:0 |
| 13[g] | $NTf_2$ | 0.033 | 10 | 100 | 0:0:0 |

[a] $^1$H NMR yield using mesitylene as internal standard. [b] 2 mol % of the catalyst was used. [c] Deuterated solvents were used (MeCN-$d_3$/$D_2O$, 7:3). [d] Reaction run in MeCN-$d_3$. [e] In the absence of $Au_2(\mu\text{-dppm})_2(NTf_2)_2$. [f] In the absence of UVA LED light in the presence of photocatalyst. [g] Heating to 80 °C with photocatalyst in the absence of UVA LED irradiation.

Lowering the catalyst loading did not improve the yield of the reaction as only 42% conversion of **1a** was observed (entry 6). Monitoring the reaction with NMR in deuterated solvent revealed that the reaction was fully converted in 10 min providing **2a** in 80% yield with trace amounts of **3a** and **4a** (entry 7). The reaction run in only MeCN-$d_3$ led to poor conversion and yields (entry 8). Lowering the concentration to 0.033 M did not affect the yield of the reaction (entry 9). Using the same conditions but with nondeuterated solvents showed a similar yield of **2a** and a slight increase of **3a** (16%; likely due to hydrogen atom abstraction from the solvent), but no **4a** was observed (entry 10). Finally, control experiments showed that the photocatalyst and light were needed to perform the reaction (entries 11−13).

With optimized reaction conditions in hand, we explored the reaction scope using allyl-functionalized NTs− and malonate-tethered bromoalkanes as well as pyran- and furan-based compounds (Scheme 3). The investigation showed that all of the compound patterns listed above are compatible with our methodology. Having monosubstituted olefins and disubstituted terminal olefins was also compatible with our methodology (Scheme 3A). The cyclization of malonate-based substrates **1a** and **1b** gave the desired compounds **2a** and **2b** in 82% and 55% yields, respectively. In both cases, small amounts of the reduced side products **3a** (16%) and **3b** (29%) were observed. Moving onto the NTs-based substrates, the use of monosubstituted alkenes **1c** provided the desired product **2c** in 82% yield with trace amounts of its reduced counterpart (>5%), while disubstituted olefins **1d** gave bromocycloalkane **2d** in 50% yield along with **3c** (21%). These results suggest that paths A or B are affected by steric hindrance leading to the formation of competitive processes. Switching to allyl ethers **1e**−**i**, the corresponding 5- and 6-membered rings **2e**−**i** were obtained in moderate to good yields. Volatile bromoalkanes were also employed, and their results were recorded using NMR spectroscopy (**2j**−**2l**). Using starting material **1j** provided a mixture of **1j** and the desired product **2j** (82%, 1:4 **1j**/**2j**). Furthermore, the opening of **1k** and **1l** was also compatible with the methodology (Scheme 3B). Linear alkyl bromides **2k** and **2l** were formed in good yields (72% and 55% respectively). These results provide support for the formation of free alkyl radicals in solution. Unfortunately, meaningful data was not obtained when varying the concentrations of gold catalyst, bromoalkane, or solution to obtain absolute rates for the transformation using radical clocking methods. Given the formation of **2k** through a radical ring opening, we envisaged an intermolecular photoredox cascade reaction between **1k** and cyclohex-2-enone. Under standard conditions, the desired bicyclic compound **4** was obtained in 41% as a mixture of diastereomer (1:1).

**Scheme 3. Intra- and Intermolecular Formal Bromine Atom Transfer Radical Addition Reaction Scope**



[a] Yields in parentheses correspond to the reduced product X = H. [b] Isolated yield at 1 mmol scale. [c] NMR yield using mesitylene as internal standard. [d] 15 min reaction time.

Next, we tested iodoarenes to see if similar reactivity to the bromoalkanes could be achieved (Scheme 3C). It should be noted that iodoalkanes are known to undergo chain reaction mechanisms and as such, were excluded from this study. In past methodologies, the use of iodoarenes resulted in products from $\beta$-hydride elimination when not using a blocking group; therefore, we were curious if our methodology was mild enough to isolate the corresponding iodoalkanes. Starting with O-tethered iodoarenes, the desired product was obtained in good yields. Having a monosubstituted olefin **1m** and disubstituted olefin **1n** gave the desired products **2m** and **2n** in 62% and 45% yields, respectively. Nitrogen-based substrates using Ac- and Ts- protecting groups were also compatible with the methodology, giving the desired product in good yields. Compared to other methods pertaining to this transformation, the described protocol showed no need of a blocking group to obtain the primary alkyl iodide.

The scope of the formal bromine transfer radical reaction was extended to substituted alkenes (Scheme 4). Interestingly, under the usual reaction conditions, the cyclization of alkene **1r** led to the formation of the desired bicyclic bromide **2r** in 29% (dr = 1:1) along with the elimination products **2r′** and **2r′′** in 54% yield (5:1). Similarly, the conversion of trisubstituted **1s** gave the desired product **2s** in 41% yield (dr = 2:1) along with the Heck-like compound **2s′′** in 58% yield. However, the photoredox cyclization of nonterminal olefin such as **1t** led to the exclusive formation **2t** and **2t′** in 75% yield as a mixture (2:1). This could be attributed to a fast elimination of the tertiary bromine in the reaction medium.

In conclusion, we have developed a mild and operationally simple intramolecular bromine atom transfer radical addition

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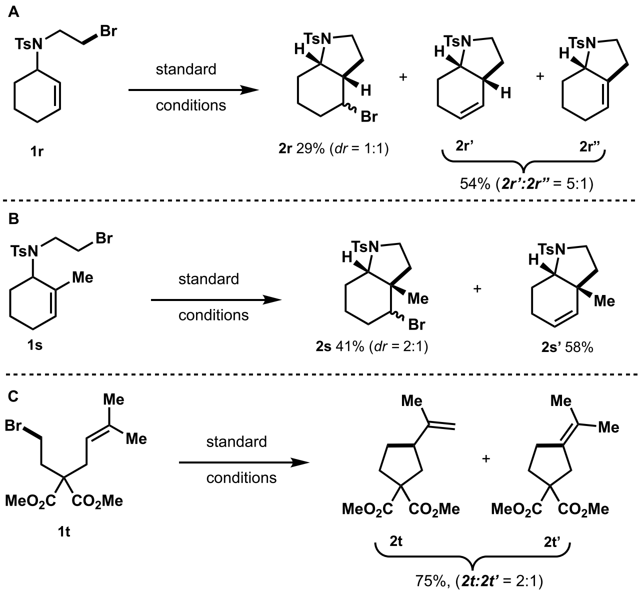
**Scheme 4. Bromine Atom Radical Transfer Using Substituted Alkenes**



(BrATRA) reaction taking advantage of the dual character of the $Au_2[\mu\text{-dppm}_2](NTf_2)_2$ as photoredox catalyst. The scope of this unprecedented formal BrATRA reaction includes the use of 1° and 2° bromoalkanes and iodoarenes. New forays into cross-coupling reactions, mechanistic investigation, and subsequent application to synthesis are underway and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03030.

General experimental procedures, detailed synthetic procedures, and analytical data for all compounds mentioned (PDF)

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### Notes

The authors declare no competing financial interest.

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