Advanced Synthesis & Catalysis

Accepted Article

Title: Gold Catalyzed Photoredox C1-Alkynylation of N-Alkyl-1,2,3,4-tetrahydroisoquinolines by 1-Bromoalkynes with Blue LED Light

Authors: Philip Chan, Yichao Zhao, and Jianwen Jin

To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201801289

Link to VoR: http://dx.doi.org/10.1002/adsc.201801289

10.1002/adsc.201801289

Very Important Publication

FULL PAPER

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Gold Catalyzed Photoredox C1-Alkynylation of *N*-Alkyl-1,2,3,4-tetrahydroisoquinolines by 1-Bromoalkynes with Blue LED Light

Yichao Zhao,[a] Jianwen Jin,[a] and Philip Wai Hong Chan[a,b]*

[a] School of Chemistry, Monash University, Clayton, Victoria 3800, Australia
Fax: (+61)–3–9905–4597; e–mail: phil.chan@monash.edu or p.w.h.chan@warwick.ac.uk
[b] Department of Chemistry, University of Warwick, Coventry CV4 7AL, United Kingdom

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

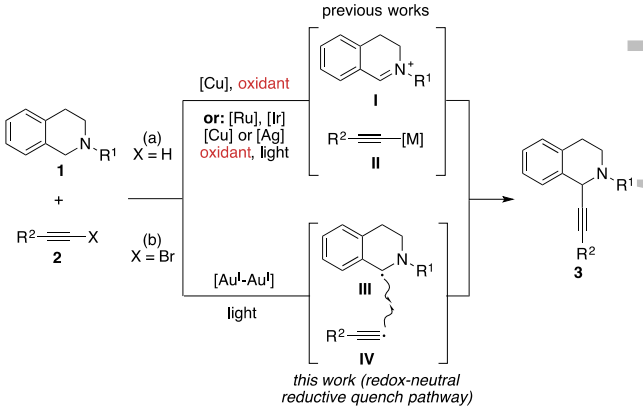
Abstract: A synthetic method that combines $[Au_2(\mu\text{-dppm})_2]Cl_2$ (dppm = bis(diphenylphosphanyl)methane) and blue LED (LED = light emitting diode) light (365 nm) to catalyze the regioselective C1-alkynylation of *N*-alkyl-1,2,3,4-tetrahydroisoquinolines (THIQs) with alkynyl bromides is described. The reaction mechanism was delineated to involve a reductive quench pathway to generate the two posited radical species of the nitrogen-containing heterocycle and organic halide. In contrast, radical formation *via* an oxidative quench pathway was suggested to be operative in analogous control experiments with a 1-iodoalkyne. The usefulness of this carbon-carbon bond forming strategy was also exemplified by its application to the formal synthesis of the opioid analgesic drug methopholine and synthesis of a protoberberine alkaloid derivative.

Keywords: alkynylation; gold; homogeneous catalysis; photoredox catalysis; synthetic methods

Introduction

THIQs are a key structural motif found in a wide variety of bioactive natural products and compounds of current agrochemical, materials and medicinal interest.[1–6] The nitrogen-containing heterocycle is also a versatile building block in organic synthesis and drug discovery programs. As a consequence, this has led to a myriad of elegant methods for the synthesis or functionalization of the *N*-heterocycle being developed. An illustrative example of this is the transition metal-catalyzed C1-alkynylation of THIQs with terminal alkynes in the presence of an oxidant at elevated temperatures or photoredox conditions (Scheme 1a).[3,6] Despite these advances, there remains a continued need to realize new and efficient catalytic methods for the synthesis and functionalization of the *N*-heterocycle from readily accessible substrates under mild and practical conditions.

A recent notable discovery in homogenous gold catalysis has been the photoredox cyclization of alkenyl- and alkynyl-containing alkyl and aryl bromides with $[Au_2(\mu\text{-dppm})_2]Cl_2$ in the role of the photosensitizer under blue LED light or sunlight conditions.[7–12] Following this pioneering work, the versatility of the readily available and bench-stable dimeric $Au_2(I,I)$ complex was further demonstrated in a number of studies examining the reactivity of a



Scheme 1. Transition Metal-Catalyzed C1-Alkynylation of THIQs by Alkyne Derivatives

range of organic halides with alkane, alkene and alkyne substrates.[10,13] The intra- or intermolecular coupling of the radical species generated in this manner were subsequently shown to produce a variety of synthetically valuable targets. To our knowledge, the analogous $Au_2(I,I)$-catalyzed photoredox reactions involving radical species **III** and **IV** generated from the respective *N*-heterocycle and alkynyl halide to effect $C(sp^3)$–C(sp) bond formation has so far remained unrealized.[11,14,15] In this regard, we were

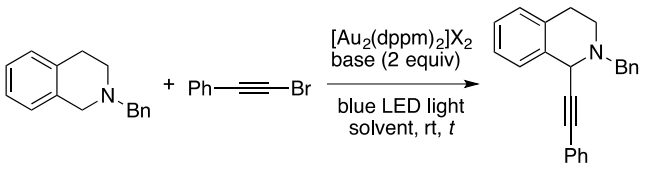
10.1002/adsc.201801289

drawn to the potential radical reaction chemistry of THIQs **1** with alkynyl bromides **2** (Scheme 1b). In doing so, we discovered that the two ensuing posited radical species were likely to be formed through a reductive quench pathway. Subsequent coupling of these two *in situ* formed radical species was then found to afford the C1-alkynylated THIQ ring system **3**. Herein, we report the details of this Au_2(I,I)-catalyzed photoredox chemistry that offers a convenient synthetic method for the regioselective C1-alkynylation of the *N*-heterocycle in moderate to excellent product yields. Achieved under blue LED light and redox neutral conditions at room temperature, the introduced acetylenic motif provides a useful handle for further functionalization at a position that is often occupied by a substituent in a wide spectrum of THIQ-containing bioactive compounds. This is demonstrated by its application to the formal synthesis of the opioid analgesic drug methopholine and synthesis of a derivative of the alkaloid protoberberine.[4,5] The proposed radical formation step is also shown to differ from that delineated in a previous study and this work exploring the dimeric Au(I)-mediated reactions of 1-iodoalkynes, which were found to occur *via* an oxidative quench pathway.[10j]

Results and Discussion

Our studies began by examining the dimeric gold(I)-catalyzed reaction of THIQ **1a** by (bromoethynyl)benzene **2a** with blue LED light at room temperature to establish the optimum reaction conditions (Table 1). Initial experiments revealed treating the *N*-heterocycle and 3 equiv of the alkynyl halide with 1 mol % of $[Au_2(\mu\text{-dppm})_2]Cl_2$ and Et_3N or $NaHCO_3$ (2 equiv) in acetonitrile for 16 h led to no reaction (entries 1 and 2). On the other hand, we were pleased to find that increasing the loading of the photosensitizer to 2.5 mol % with Na_2CO_3 or K_2CO_3 as the base afforded **3aa** in respective yields of 47 and 38% (entries 3 and 4). Slightly higher product yields of 57 and 62%, respectively, were obtained when the reaction was allowed to run for 22 h with Na_2CO_3 or NaOAc as the base (entries 5 and 6). However, repeating the reaction with Na_2CO_3 as the base and (+)-sodium L-ascorbate (VC-Na, 0.5 equiv) as an additive in acetonitrile, ethanol or DMF for 22 h were found to give no improvement in product yields with **3aa** being furnished in 41–51% yield (entries 7–9). Our studies subsequently showed that performing the reaction of **1a** with Na_2CO_3 in acetonitrile at a catalyst loading of 5 mol % and 0.25 equiv of the alkynyl halide for 42 h gave the best result, providing a product yield of 82% (entry 10). In a final set of control experiments under these latter conditions, a survey of the dimeric Au(I) complex containing NTf_2^-, OTf^-, BF_4^-, or SbF_6^- instead of Cl^- as the counteranion led to lower product yields of 42–77% (entries 11–14).

Table 1. Optimization of the Reaction Conditions.[a]



1a **2a** **3aa**

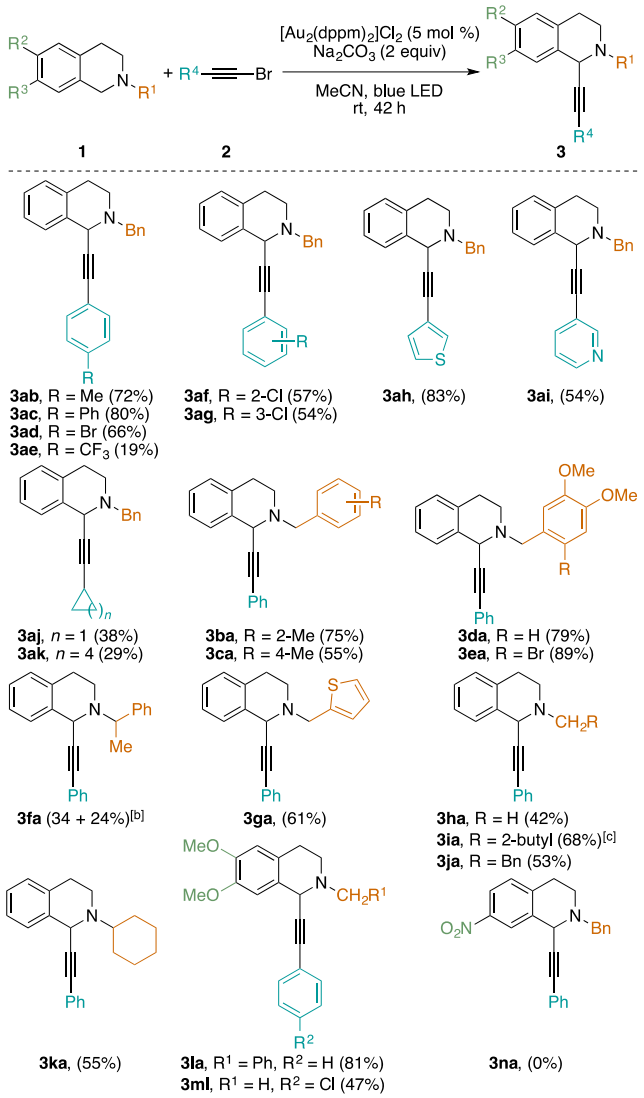
Entry	X^- (mol %)	Solvent	Base	*t* [h]	Yield [%][b]
1	Cl^- (1)	MeCN	Et_3N	16	0
2	Cl^- (1)	MeCN	$NaHCO_3$	16	0
3	Cl^- (2.5)	MeCN	Na_2CO_3	16	47
4	Cl^- (2.5)	MeCN	K_2CO_3	16	38
5	Cl^- (2.5)	MeCN	Na_2CO_3	22	57
6	Cl^- (2.5)	MeCN	NaOAc	22	62
7[d]	Cl^- (2.5)	MeCN	Na_2CO_3	22	41
8[d]	Cl^- (2.5)	EtOH	Na_2CO_3	22	46
9[d]	Cl^- (2.5)	DMF	Na_2CO_3	22	51
10[e]	Cl^- (5)	MeCN	Na_2CO_3	42	82[c]
11[e]	NTf_2^- (5)	MeCN	Na_2CO_3	44	65[c]
12[e]	OTf_2^- (5)	MeCN	Na_2CO_3	44	62[c]
13[e]	BF_4^- (5)	MeCN	Na_2CO_3	44	77[c]
14[e]	SbF_6^- (5)	MeCN	Na_2CO_3	44	42[c]

[a] All reactions were performed with 0.2 mmol of **1a**, 0.6 mmol of **2a**, given catalyst and base (2 equiv) in solvent (0.5 mL) at room temperature and time stated in the Table. [b] ^1H NMR product yield with CH_2Br_2 as the internal standard. [c] Isolated product yield. [d] (+)-Sodium L-ascorbate (0.5 equiv) was added as an additive. [e] Reaction was performed with 0.8 mmol of **1a** and 0.2 mmol of **2a**.

To define the generality of the present photoredox C1-alkynylation procedure, we next turned our attention to the C1-alkynylations of a series of THIQs and acetylenic bromides, and the results are summarized in Table 2. Overall, the dimeric Au(I)-catalyzed photoredox reaction conditions were found to be broad and provided a variety of C1-alkynylated THIQs **3ab**–**ma** in 19–83% yield from the corresponding *N*-heterocycles **1a**–**m** and alkynyl bromides **2a**–**l**. Reactions of **1a** with ethynyl bromides containing other aryl (**2b**–**g**), heteroaryl (**2h**,**i**) or cycloalkyl (**2j**,**k**) groups were found to proceed to give the corresponding C1-alkynylated THIQs **3ab**–**ak** in 19–83% yield. The C1-alkynylation of *N*-heterocycles with a pendant *N*-benzyl motif with substituents at various positions of the phenyl ring (**1b**–**f**) or at the benzylic carbon center (**1f**) by **2a** were also found to be well tolerated, providing the expected adducts **3ba**–**fa** in 55–89% yield. Likewise, THIQ substrates in which the *N*-benzyl group was replaced with other *N*-alkyl moieties, as in **1g**–**k**, were found to have little influence on the course of the reaction. In these

10.1002/adsc.201801289

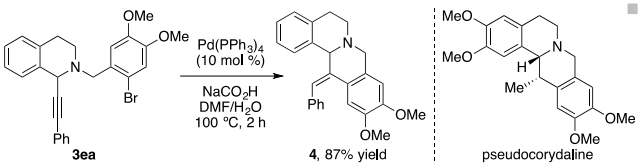
Table 2. C1-Alkynylation of THIQs **1a–n** with **2a–l** Catalyzed by $[Au_2(\mu\text{-dppm})_2]Cl_2$ Under Blue LED Light.[a]



[a] All reactions were performed at the 0.2 mmol scale with 5 mol % of $[Au_2(\mu\text{-dppm})_2]Cl_2$ and Na_2CO_3 (2 equiv) in acetonitrile (0.5 mL) at room temperature under blue LED light for 42 h. Values in parenthesis denoted isolated product yields. [b] Separable mixture of diastereomers in a ratio of 1.4:1. [c] Inseparable mixture of diastereomers in a ratio of 1:1.

experiments with **2a**, the corresponding C1-alkynylated THIQs **3ga–ka** were afforded in 42–68% yield. The reactions of THIQs containing an electron-donating (**1l**,**m**) or -withdrawing (**1n**) substituent on the benzofused ring of the substrate were the only instances that were found to give contrasting outcomes. Reactions of **1l** with **2a** and **1m** with **2l** gave the anticipated C1-alkynylated products **3la** and **3ml** in 81 and 47% yield, respectively. The assembly of **3ml** is also noteworthy as it is a reported intermediate in the synthesis of the opioid analgesic drug methopholine.[4] Its preparation by the present method thus represents a formal synthesis of the bioactive compound. However, the reaction of **1n** with **2a** was found to lead to the recovery of the starting materials. In the above experiments, on the other hand, no other products arising from the dehalogenation or alkynylation at the *N*-alkyl carbon center of the respective alkynyl halide and *N*-heterocycle were detected by ^{1}H NMR measurement of the crude reaction mixtures.

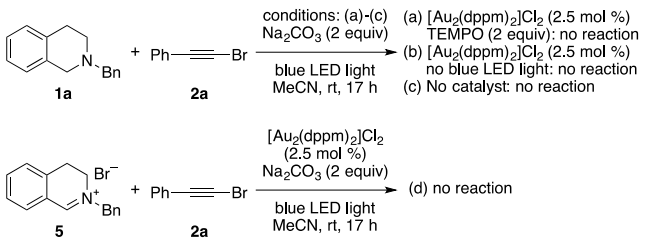
To further illustrate the synthetic utility of the present Au_2(I,I)-catalyzed photoredox route to C1-alkynylated THIQs, we applied the new method to the synthesis of a derivative of the protoberberine alkaloids.[5] As shown in Scheme 2, treating **3ea** to 10 % mol of $Pd(Ph_3P)_4$ in DMF and water (1:1 v/v) at 100 °C for 2 h was found to give the nitrogen-containing tetracyclic adduct **4** in 87% yield.



Scheme 2. Synthesis of the Protoberberine Derivative **4** from **3ea**

We next turned our attention to performing a series of control experiments with the aim of gaining an insight of the reaction mechanism (Scheme 3). The initial premise put forward in Scheme 1b reasoned that C(sp^3)–C(sp) bond formation between the *N*-heterocycle and alkynyl bromide might occur on generating the two respective radical species. Our results for reactions with an electron-withdrawing group on either substrate, as in **1n** and **2e**, giving either no reaction or a low product yield would argue in favor of the involvement of such radical intermediates. As shown in Scheme 3a, this argument was further corroborated by subjecting **1a** and **2a** to the Au_2(I,I)-catalyzed standard photoredox reaction conditions and 2 equiv of 2,2,6,6-tetramethylpiperdine 1-oxyl (TEMPO). On the basis of ^{1}H NMR measurements of the crude reaction mixture, no product formation could be observed and only the two substrates were found to be present. Added to this, the role of the dimeric Au(I) complex and blue LED light in facilitating the radical forming step could be shown by repeating the control experiment either in the absence of the light source or $[Au_2(\mu\text{-dppm})_2]Cl_2$ (Schemes 3b and c). In both instances, no reaction could be detected by either TLC analysis or ^{1}H NMR measurements. A pathway involving an iminium salt was next considered but discounted based on the findings of the following control experiment. Treatment of the iminium salt **5** with 3 equiv of **2a** under the Au_2(I,I)-catalyzed photoredox reaction conditions described in Scheme 3d was observed to result in only the two starting materials being detected based on ^{1}H NMR measurements.

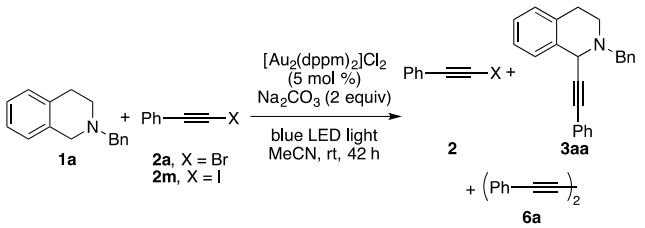
10.1002/adsc.201801289



Scheme 3. Control Experiments with **1a**, **2a** and **5**.

As the Au_2(I,I)-catalyzed photoredox reactions with blue LED light or sunlight have been proposed to proceed *via* either an oxidative or reductive quench pathway, a final set of control experiments described in Table 3 were also examined.[8–10] Under the standard photoredox reaction conditions with [Au_2(μ-dppm)$_2$]Cl_2, the reaction of equimolar amounts **1a** with **2a** or four equivalents of the latter were found to give **3aa** along with recovery of the alkynyl bromide in yields of 31–39% (entries 1 and 2). In contrast to our earlier findings disclosed in Table 1, entry 10 showing that **3aa** could be obtained in 82% when the molar ratio of **1a**:**2a** = 4:1, this led us to believe that the present reaction might occur by a reductive quench pathway. Previously, the alkynylation of acyclic amines by 1-iodoalkynes was likely to proceed by an oxidative quench pathway.[10j] This was further supported by results furnished on repeating these reactions once more but with (iodoethynyl)benzene **2m** in place of **2a** (entries 3–5). In these analogous control experiments, the use of equimolar amounts **1a** and **2m** or four equivalents of either the former or latter were found to afford **3aa** and **6a** in respective yields of 11–31 and 11–77%.

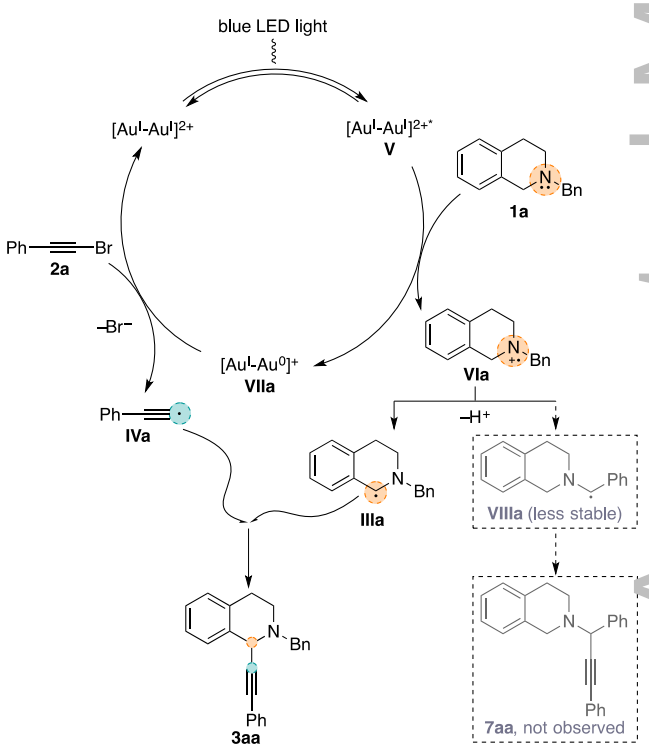
Table 3. Control Experiments with **1a**, **2a** and **2m**.[a]



Entry	**1a** + **2** (equiv)	Yield [%][b]			
		2a	**2m**	**3aa**	**6a**
1	**1a** (1) + **2a** (1)	31	-	32	-
2	**1a** (1) + **2a** (4)	39	-	39	-
3	**1a** (1) + **2m** (1)	-	-	11	16
4	**1a** (4) + **2m** (1)	-	-	31	11
5	**1a** (1) + **2m** (4)	-	-	20	77

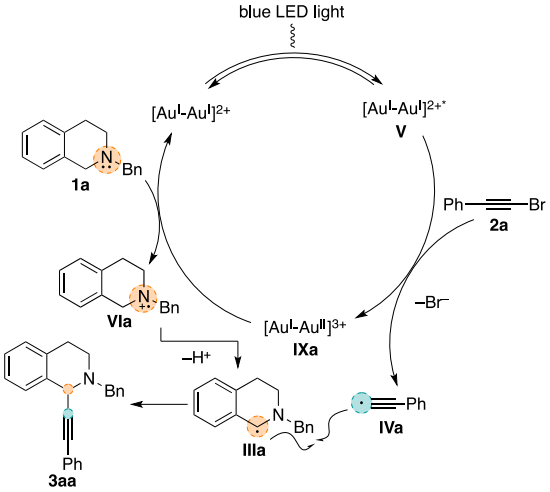
[a] All reactions were performed at the 0.2 mmol scale with **1a** and **2a** in the ratios stated in the Table, 5 mol % of [Au_2(μ-dppm)$_2$]Cl_2 and Na_2CO_3 (2 equiv) in acetonitrile (0.5 mL) at room temperature under blue LED light for 42 h. [b] Isolated product yields.

On the basis of the above results, a tentative mechanism for the present dimeric Au(I)-catalyzed photoredox C1-alkynylation of THIQs with alkynyl bromides under blue LED light is outlined in Scheme 4.[8–10,16] With the reaction of substrates **1a** and **2a** as a representative example, this could initially involve the exciplex species **V** of the dinuclear gold(I) complex being generated as it absorbs the blue LED light.[12] With the metal complex now in the photoexcited state, this might lead to a single-electron transfer (SET) from the *N*-heterocycle to the photosensitizer. As a result, this delivers the nitrogen-centered THIQ radical cation species **VIa** and [Au^I–Au^0]$^+$ complex **VIIa**. With the dimeric metal complex now a powerful reducing agent, a second SET event might subsequently occur between it and the alkynyl bromide. This would give the corresponding alkynyl radical species **IVa** as well as lead to the ground state Au_2(I,I) complex being regenerated. Deprotonation of **VIa** followed by radical C(sp^3)–C(sp) coupling of the ensuing carbon-centered THIQ radical species **IIIa** with **IVa** would then provide the C1-alkynylated product **3aa**. The origin of the observed product regioselectivity could be due to the preferential formation of **IIIa** over that of **VIIIa**, the most stable among other possible cyclic intermediates, which would lead to products of the type **7aa**.



Scheme 4. Proposed Mechanism for the Au_2(I,I)-Catalyzed C1-Alkynylation of THIQs with Alkynyl Bromides Under Blue LED Light Represented by **1a** and **2a** *via* a Reductive Quench Pathway.

At this juncture, it is worthy to note that our findings do not, however, definitively rule out the possibility of a reaction mechanism in which a background oxidative quench pathway is also operative (Scheme 5). There remains the likelihood that irradiation of the Au_2(I,I) complex by blue LED light might lead to the competitive transfer of an electron from the resulting photoexcited metal complex **V** to the alkynyl bromide. As a consequence, this triggers fragmentation of the latter to give the corresponding alkynyl radical species **IVa**. The [Au^{I}–Au^{II}]$^{3+}$ complex **IXa** also formed during this process may be reduced by **1a** through a SET event. This would regenerate the ground state Au_2(I,I) complex and produce the nitrogen-centered THIQ radical cation species **VIa**. Subsequent deprotonation of this newly formed species followed by radical C(sp^3)–C(sp) coupling of the ensuing carbon-centered THIQ radical species **IIIa** with **IVa** would then furnish the C1-alkynylated *N*-heterocyclic product.



Scheme 5. Proposed Background Oxidative Quench Pathway for the Au_2(I,I)-Catalyzed C1-Alkynylation of THIQs with Alkynyl Bromides Under Blue LED Light Represented by **1a** and **2a**.

Conclusions

In summary, we have developed an efficient synthetic method for the regioselective C1-alkynylation of THIQs that makes use of readily available alkynyl bromides under dimeric gold(I)-mediated redox neutral reaction conditions with blue LED light. The photoredox C(sp^3)–C(sp) bond formation reaction was shown to be applicable to a wide variety of substrates to provide access to a privileged scaffold containing a functional group handle for further chemical manipulation. This was exemplified by the formal synthesis of the opioid analgesic drug methopholine and synthesis of a protoberberine alkaloid derivative. Our studies also showed the marked differences in reactivity between an alkynyl bromide and iodide. In reactions with the organic bromide, the two posited radical species were suggested to be most likely formed *in situ* by a reductive quench pathway. This contrasts to their *in situ* generation in the analogous reactions with a 1-iodoalkyne, which was thought to result from an oxidative quench pathway.

Experimental Section

General Procedure for the Dimeric Gold(I)-Catalyzed Photoredox C1-Alkynylation of THIQs 1 by Alkynyl Bromides 2 with Blue LED Light

A 10 mL screw cap reaction tube was charged with THIQ **1** (0.8 mmol), 1-bromoalkyne **2** (0.2 mmol), Na_2CO_3 (42 mg, 0.4 mmol) and $Au_2(\mu\text{-dppm})_2Cl_2$ (8.5 mg, 0.01 mmol) followed by the addition of degassed MeCN (0.5 mL). The reaction was stirred at room temperature under irradiation of a blue LED light source contained in a glovebox. Upon completion, the solvent was removed under reduced pressure and the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: petroleum ether:Et_2O = 25:1) to afford the C1-alkynylated product.

2-Benzyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3aa)[4b] Pale yellow oil (53 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (tdd, *J* = 6.0, 3.2, 1.7 Hz, 4H), 7.29–7.23 (m, 2H), 7.23–7.16 (m, 5H), 7.11–7.01 (m, 3H), 4.71 (s, 1H), 3.91–3.80 (m, 2H), 3.05–2.89 (m, 2H), 2.78–2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.5, 134.1, 131.8, 129.3, 129.0, 128.3, 128.2, 128.0, 127.8, 127.2, 126.9, 125.8, 123.3, 87.6, 86.8, 59.6, 54.4, 45.8, 29.1.

2-Benzyl-1-(*p*-tolylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ab) Yellow oil (48 mg, 72% yield); IR (neat, cm^{-1}): 3061, 3027, 2918, 2824, 1654, 1603, 1508, 1452, 1028, 970, 816, 741, 699; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.52–7.48 (m, 2H), 7.40–7.34 (m, 4H), 7.33–7.27 (m, 2H), 7.21–7.10 (m, 5H), 4.81 (s, 1H), 4.01–3.90 (m, 2H), 3.16–2.99 (m, 2H), 2.88–2.78 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 138.5, 138.1, 135.7, 134.1, 131.7, 129.3, 129.0, 129.0, 128.3, 127.9, 127.2, 126.9, 125.8, 120.2, 86.9, 86.8, 59.6, 54.4, 45.8, 29.1, 21.5; HRMS (ESI) calcd. for $C_{25}H_{24}N$ (M^+ + H): 338.1908, found: 338.1905.

1-([1,1'-Biphenyl]-4-ylethynyl)-2-benzyl-1,2,3,4-tetrahydroisoquinoline (3ac) Pale yellow oil (64 mg, 80% yield); IR (neat, cm^{-1}): 3059, 3027, 2915, 2821, 1654, 1601, 1485, 1451, 1287, 1265, 1126, 1007, 839, 738, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64–7.44 (m, 11H), 7.42–7.29 (m, 5H), 7.24–7.15 (m, 4H), 4.86 (s, 1H), 4.05–3.93 (m, 2H), 3.19–3.01 (m, 2H), 2.95–2.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 140.4, 138.5, 135.5, 134.1, 132.3, 129.3, 129.1, 128.9, 128.4, 127.9, 127.6, 127.2, 127.1, 127.0, 127.0, 125.9, 122.2, 88.3, 86.7, 59.7, 54.5, 45.8, 29.1; HRMS (ESI) calcd. for $C_{30}H_{26}N$ (M^+ + H): 400.2065, found: 400.2053.

2-Benzyl-1-((4-bromophenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (3ad) Pale yellow oil (53 mg, 66% yield); IR (neat, cm^{-1}): 3061, 3026, 2915, 2821, 1701, 1654, 1584, 1484, 1452, 1259, 1069, 1010, 822, 735, 698; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.31 (m, 4H), 7.28–7.22 (m, 2H), 7.21–7.17 (m, 2H), 7.17–7.02 (m, 5H), 4.69 (s, 1H), 3.86–3.77 (m, 2H), 3.01–2.88 (m, 2H), 2.77–2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.2, 134.1, 133.3, 131.5, 129.2, 129.1, 128.4, 128.4, 127.8, 127.3, 127.1, 125.9, 122.3, 122.2, 88.9, 85.8, 59.7, 54.4, 45.8, 29.1; HRMS (ESI) calcd. for $C_{24}H_{21}BrN$ (M^+ + H): 402.0857/404.0837, found: 402.0847/404.0837.

2-Benzyl-1-((4-(trifluoromethyl)phenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (3ae) Yellow oil (15 mg, 19% yield); IR (neat, cm^{-1}): 3063, 3028, 2920, 2825, 1654, 1614, 1560, 1495, 1453, 1405, 1321, 1165, 1123, 1066, 1016, 841, 744, 730; ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 4H), 7.40–7.35 (m, 2H), 7.29–7.20 (m, 3H), 7.16–7.05 (m, 4H), 4.73 (s, 1H), 3.91–3.79 (m, 2H), 3.06–2.91 (m, 2H), 2.84–2.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 135.0, 134.1, 132.0, 129.7, 129.2 (d, J_{C-C} = 8.0 Hz), 128.4, 127.7, 127.3, 127.1, 127.0, 125.9, 125.2 (q, J_{C-F} = 3.8 Hz), 122.6, 90.3, 85.6, 77.2, 59.6, 54.3, 45.8, 29.0; HRMS (ESI) calcd. for $C_{25}H_{21}F_3N$ (M^+ + H): 392.1626, found: 392.1615.

2-Benzyl-1-((2-chlorophenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (3af) Pale yellow oil (49 mg, 57% yield); IR (neat, cm^{-1}): 3060, 3025, 2916, 2852, 1735, 1618, 1493, 1472, 1285, 1235, 1127, 1029, 737, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42–7.38 (m, 2H), 7.38–7.34 (m, 1H), 7.32–7.28 (m, 1H), 7.28–7.23 (m, 2H), 7.22–7.16 (m, 2H), 7.14–7.02 (m, 5H), 4.75 (s, 1H), 3.90 (s, 2H), 3.10–2.90 (m, 2H), 2.80–2.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.9, 135.2, 134.2, 133.5, 129.4, 129.2, 129.1, 129.0, 128.3, 127.8, 127.2, 127.0, 126.3, 125.8, 123.2, 93.2, 83.7, 59.6, 54.5, 45.9, 29.1; HRMS (ESI) calcd. for $C_{24}H_{21}ClN$ (M^+ + H): 358.1362, found: 358.1352.

2-Benzyl-1-((3-chlorophenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (3ag)[17] Yellow oil (38 mg, 54% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (ddt, *J* = 8.3, 6.1, 1.7 Hz, 3H), 7.29–7.20 (m, 3H), 7.20–7.02 (m, 7H), 4.70 (s, 1H), 3.88–3.78 (m, 2H), 3.01–2.89 (m, 2H), 2.80–2.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 135.2, 134.1, 134.1, 131.7, 129.9, 129.5, 129.2, 129.1, 128.4, 128.4, 127.8, 127.3, 127.1, 125.9, 125.0, 89.0, 85.6, 59.7, 54.3, 45.8, 29.1.

2-Benzyl-1-(thiophen-3-ylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ah) Pale yellow oil (55 mg, 83% yield); IR (neat, cm^{-1}): 3061, 3025, 2916, 2824, 1709, 1605, 1494, 1452, 1355, 1125, 989, 817, 781, 740, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.35 (m, 2H), 7.33 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.26 (ddt, *J* = 7.9, 6.4, 1.0 Hz, 2H), 7.22–7.14 (m, 3H), 7.11–7.01 (m, 4H), 4.69 (s, 1H), 3.89–3.78 (m, 2H), 3.03–2.89 (m, 2H), 2.77–2.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 135.5, 134.1, 130.2, 129.3, 129.0, 128.5, 128.3, 127.8, 127.2, 127.0, 125.9, 125.1, 122.2, 87.1, 81.8, 59.6, 54.5, 45.8, 29.1; HRMS (ESI) calcd. for $C_{22}H_{20}NS$ (M^+ + H): 330.1316, found: 330.1302.

2-Benzyl-1-(pyridin-3-ylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ai) Pale yellow oil (35 mg, 54% yield); IR (neat, cm^{-1}): 3026, 2915, 2823, 1726, 1605, 1493, 1474, 1452, 1406, 1286, 1186, 1125, 1093, 1023, 803, 737, 699; ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 2.2, 0.9 Hz, 1H), 8.42 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.62 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.40–7.35 (m, 2H), 7.29–7.23 (m, 2H), 7.23–7.04 (m, 7H), 4.73 (s, 1H), 3.89–3.78 (m, 2H), 3.02–2.90 (m, 2H), 2.83–2.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 148.5, 138.7, 138.2, 135.0, 134.2, 129.2, 129.1, 128.4, 127.7, 127.3, 127.1, 125.9, 122.9, 120.4, 91.2, 83.6, 59.7, 54.3, 45.8, 29.0; HRMS (ESI) calcd. for $C_{23}H_{21}N_2$ (M^+ + H): 325.1705, found: 325.1687.

2-Benzyl-1-(cyclopropylethynyl)-1,2,3,4-tetrahydroisoquinoline (3aj)[18] Pale yellow oil (22 mg, 38% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.30 (m, 2H), 7.30–7.14 (m, 3H), 7.13–6.99 (m, 4H), 4.43 (d, *J* = 1.5 Hz, 1H), 3.83–3.65 (m, 2H), 2.94–2.80 (m, 2H), 2.72–2.61 (m, 2H), 1.25–1.16 (m, 1H), 0.73–0.53 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 136.5, 134.2, 129.6, 129.2, 128.6, 128.0, 127.4, 127.0, 126.0, 90.6, 73.4, 59.7, 54.4, 45.9, 29.3, 8.8.

2-Benzyl-1-(cyclohexylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ak)[18] Pale yellow oil (19 mg, 29% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.34 (m, 2H), 7.28–7.22 (m, 2H), 7.22–7.16 (m, 1H), 7.16–7.11 (m, 1H), 7.07–6.97 (m, 3H), 4.47 (d, *J* = 1.8 Hz, 1H), 3.83 (d, *J* = 13.1 Hz, 1H), 3.73 (d, *J* = 13.1 Hz, 1H), 2.96–2.83 (m, 2H), 2.74–2.59 (m, 2H), 2.36 (ddd, *J* = 9.0, 4.5, 1.9 Hz, 1H), 1.74–1.60 (m, 4H), 1.41 (qd, *J* = 9.2, 4.6 Hz, 3H), 1.25 (ddd, *J* = 11.4, 7.1, 4.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 136.4, 133.9, 129.3, 128.8, 128.2, 127.7, 127.0, 126.6, 125.6, 91.3, 59.5, 54.0, 45.7, 33.1, 32.9, 29.2, 29.1, 26.0, 24.8.

2-(2-Methylbenzyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ba)[17] Pale yellow oil (51 mg, 75% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.32 (m, 3H), 7.21–7.14 (m, 4H), 7.12–7.04 (m, 5H), 7.04–7.00 (m, 1H), 4.68 (s, 1H), 3.89–3.75 (m, 2H), 3.05–2.86 (m, 2H), 2.76–2.63 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 136.4, 135.7, 134.3, 131.8, 130.4, 130.0, 129.0, 128.3, 128.1, 127.9, 127.2, 126.9, 125.8, 125.6, 123.4, 87.9, 86.8, 57.6, 54.5, 45.8, 29.3, 19.4.

2-(4-Methylbenzyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ca)[17] Yellow oil (37 mg, 55% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.50–7.46 (m, 2H), 7.41–7.37 (m, 2H), 7.35–7.27 (m, 4H), 7.21–7.13 (m, 5H), 4.82 (s, 1H), 3.98–3.88 (m, 2H), 3.15–3.00 (m, 2H), 2.90–2.77 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 135.6, 135.3, 134.1, 131.8, 129.3, 129.0, 128.2, 128.0, 127.8, 126.9, 125.8, 123.3, 87.6, 86.8, 59.4, 54.3, 45.8, 29.1, 21.2.

2-(3,4-Dimethoxybenzyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3da) Yellow oil (61 mg, 79% yield); IR (neat, cm^{-1}): ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.33 (m, 2H), 7.23–7.16 (m, 4H), 7.11–7.01 (m, 3H), 6.95 (d, *J* = 2.0 Hz, 1H), 6.90 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 4.71 (s, 1H), 3.85 (d, *J* = 6.0 Hz, 1H), 3.84–3.72 (m, 8H), 3.00–2.88 (m, 2H), 2.77–2.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.2, 135.5, 134.1, 131.8, 130.9, 129.0, 128.3, 128.1, 127.8, 127.0, 125.9, 123.3, 121.4, 112.3, 110.9, 87.6, 86.9, 59.4, 55.9, 55.9, 54.4, 45.6, 29.1; HRMS (ESI) calcd. for $C_{22}H_{20}NS$ (M^+ + H): 330.1316, found: 330.1302.

2-(2-Bromo-4,5-dimethoxybenzyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ea) Pale yellow oil (82 mg, 89% yield); IR (neat, cm^{-1}): 3001, 2931, 2834, 1598 1502, 1437, 1378, 1252, 1208, 1155, 1027, 959, 800, 736, 691. ^1H NMR (400 MHz, $CDCl_3$) δ 7.51–7.43 (m, 2H), 7.38–7.27 (m, 4H), 7.23–7.14 (m, 4H), 7.05 (s, 1H), 4.90 (s, 1H), 4.07–3.95 (m, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 3.22–2.92 (m, 2H), 2.87–2.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 148.5, 135.5, 134.1, 131.8, 129.8, 129.0, 128.2, 128.1, 127.8, 127.0, 125.9, 123.2, 115.5, 114.6, 113.2, 87.8, 86.7, 77.3, 58.5, 56.2, 56.1, 54.9, 45.5, 29.2; HRMS (ESI) calcd. for $C_{26}H_{25}BrNO_2$ (M^+ + H): 462.1068, found: 462.1054.

2-(1-Phenylethyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3fa) *diastereomer 1*: Pale yellow oil (23 mg, 34% yield); IR (neat, cm^{-1}): 3060, 3024, 2970, 2920, 2819, 1598, 1489, 1451, 1369, 1285, 1136, 1028, 939, 755, 736, 700; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.33 (m, 4H), 7.29–7.17 (m, 7H), 7.14–7.08 (m, 2H), 7.07–7.01 (m, 1H), 5.19 (s, 1H), 3.76 (q, *J* = 6.5 Hz, 1H), 2.89–2.70 (m, 2H), 2.70–2.61 (m, 1H), 2.57–2.49 (m, 1H), 1.44 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.1, 135.8, 134.6, 131.9, 129.1, 128.5, 128.2, 128.1, 128.0, 127.4, 126.9, 126.9, 125.9, 123.3, 87.4, 86.4, 62.0, 52.1, 43.8, 29.2, 21.8; HRMS (ESI) calcd. for $C_{25}H_{24}N$ (M^+ + H): 338.1908, found: 338.1905. *diastereomer 2*: Pale yellow oil (16 mg, 24% yield); IR (neat, cm^{-1}): 3061, 3026, 2921, 2825, 1560, 1490, 1370, 1263, 1027, 756, 738, 701; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49–7.42 (m, 4H), 7.38–7.28 (m, 5H), 7.18–7.08 (m, 5H), 4.60 (d, *J* = 1.1 Hz, 1H), 4.09 (q, *J* = 6.6 Hz, 1H), 3.24–3.02 (m, 3H), 2.94–2.85 (m, 1H), 1.51 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.1, 135.9, 134.2, 131.7, 128.8, 128.4, 128.2, 127.9, 127.9, 127.8, 127.7, 127.1, 126.8, 125.7, 123.4, 88.3, 86.8, 60.8, 53.5, 41.6, 29.5, 21.6; HRMS (ESI) calcd. for $C_{25}H_{24}N$ (M^+ + H): 338.1908, found: 338.1900.

1-(Phenylethynyl)-2-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (3ga) Pale yellow oil (40 mg, 61% yield); IR (neat, cm^{-1}): 3061, 3022, 2915, 2820, 1654, 1598, 1489, 1442, 1342, 1283, 1123, 1088, 1037, 755, 739, 690; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (ddt, *J* = 5.3, 2.6, 1.4 Hz, 2H), 7.24–7.19 (m, 4H), 7.19–7.16 (m, 1H), 7.11–7.07 (m, 2H), 7.05 (dt, *J* = 6.0, 2.3 Hz, 1H), 6.99 (dt, *J* = 3.3, 1.0 Hz, 1H), 6.90 (dd, *J* = 5.1, 3.4 Hz, 1H), 4.81 (s, 1H), 4.06 (qd, *J* = 13.8, 0.9 Hz, 2H), 3.04–2.90 (m, 2H), 2.87–2.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.0, 135.3, 134.0, 131.8, 129.0, 128.2, 128.1, 127.8, 127.0, 126.5, 126.2, 125.9, 125.2, 123.1, 87.3, 86.9, 54.3, 54.1, 45.7, 29.1; HRMS (ESI) calcd. for $C_{22}H_{20}NS$ (M^+ + H): 330.1316, found: 330.1302.

2-Methyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ha)[4b] Yellow oil (21 mg, 42% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.41 (m, 2H), 7.40–7.34 (m, 1H), 7.29 (tt, *J* = 3.8, 2.4 Hz, 3H), 7.22–7.17 (m, 2H), 7.16–7.11 (m, 1H), 4.72 (s, 1H), 3.11–3.01 (m, 1H), 2.94 (ddt, *J* = 21.2, 16.4, 5.4 Hz, 2H), 2.78–2.68 (m, 1H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.2, 133.5, 131.8, 128.9, 128.2, 128.1, 127.6, 127.0, 125.9, 123.2, 87.5, 86.3, 57.0, 48.7, 43.8, 28.9.

2-(2-Methylbutyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ia) Yellow oil (35 mg, 68% yield); IR (neat, cm^{-1}): 3226, 2921, 1560, 1406, 1247, 1036, 896; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 2H), 7.26–7.14 (m, 4H), 7.12–7.00 (m, 3H), 4.74 (s, 1H), 2.99–2.84 (m, 2H), 2.78–2.63 (m, 2H), 2.55 (ddd, *J* = 19.1, 12.4, 6.7 Hz, 1H), 2.45–2.31 (m, 1H), 1.68–1.57 (m, 1H), 1.45 (dddd, *J* = 21.0, 13.0, 7.4, 4.9 Hz, 1H), 1.09 (tt, *J* = 14.1, 7.3 Hz, 1H), 0.85 (ddt, *J* = 12.7, 7.4, 3.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.9, 134.4, 131.7, 129.0, 128.2, 127.9, 127.8, 127.8, 126.8, 125.7, 123.4, 88.1, 88.0, 86.1, 62.0, 61.9, 55.5, 54.9, 46.5, 45.9, 32.4, 32.3, 31.5, 29.2, 29.2, 28.0, 27.6, 18.0, 11.5, 11.3; HRMS (ESI) calcd. for $C_{22}H_{26}N$ (M^+ + H): 304.2065, found: 304.2065.

2-Phenethyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ja) Pale yellow oil (36 mg, 53% yield); IR (neat, cm^{-1}): 3060, 3025, 2922, 2823, 1702, 1648, 1600, 1489, 1451, 1262, 1095, 1027, 738, 697; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 2H), 7.27–7.02 (m, 12H), 4.92 (s, 1H), 2.99–2.71 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 135.4, 133.9, 131.8, 129.0, 128.9, 128.4, 128.2, 128.1, 127.9, 127.0, 126.1, 125.9, 123.2, 87.1, 86.6, 57.3, 54.6, 46.1, 34.2, 29.0; HRMS (ESI) calcd. for $C_{25}H_{24}N$ (M^+ + H): 338.1908, found: 338.1895.

2-Cyclohexyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3ka) Yellow oil (35 mg, 55% yield); IR (neat, cm^{-1}): 3027, 2926, 1560, 1401, 1248, 1030, 739, 691. ^1H NMR (400 MHz, $CDCl_3$) δ 7.34–7.30 (m, 2H), 7.26–7.22 (m, 1H), 7.21–7.17 (m, 3H), 7.10–7.07 (m, 2H), 7.06–7.01 (m, 1H), 5.03 (s, 1H), 3.06–2.97 (m, 1H), 2.96–2.83 (m, 2H), 2.80–2.72 (m, 1H), 2.65 (qd, *J* = 6.9, 4.3, 3.0 Hz, 1H), 2.18–2.02 (m, 2H), 1.81–1.70 (m, 2H), 1.63–1.54 (m, 1H), 1.30–1.21 (m, 4H), 1.16–1.09 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 134.4, 131.7, 128.9, 128.2, 127.9, 127.8, 126.8, 125.8, 123.4, 59.9, 52.3, 42.1, 31.1, 29.5, 29.5, 26.3, 25.7, 25.5; HRMS (ESI) calcd. for $C_{23}H_{26}N$ (M^+ + H): 316.2065, found: 316.2056.

2-Benzyl-6,7-dimethoxy-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (3la)[17] Blue gum (62 mg, 81% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (tdd, *J* = 6.0, 3.1, 1.6 Hz, 4H), 7.41–7.34 (m, 2H), 7.32 (dq, *J* = 4.8, 2.8 Hz, 4H), 6.77 (s, 1H), 6.63 (s, 1H), 4.72 (s, 1H), 4.00–3.90 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.09 (td, *J* = 10.5, 4.1 Hz, 1H), 2.99 (ddd, *J* = 16.0, 10.2, 5.7 Hz, 1H), 2.84 (dddd, *J* = 11.0, 5.5, 2.8, 1.0 Hz, 1H), 2.79–2.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.4, 138.4, 131.8, 129.3, 128.3, 128.3, 128.1, 127.4, 127.2, 126.1, 123.3, 111.4, 110.5, 87.6, 86.8, 59.6, 56.0, 55.9, 53.9, 46.0, 28.7.

1-((4-Chlorophenyl)ethynyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (3ml)[4b] Yellow oil (32 mg, 47% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.24 (m, 2H), 7.20–7.15 (m, 2H), 6.74 (s, 1H), 6.52 (s, 1H), 4.53 (s, 1H), 3.79 (s, 3H), 3.77 (s, 3H), 2.93 (ddd, *J* = 11.2, 8.5, 4.7 Hz, 1H), 2.87–2.78 (m, 1H), 2.72 (dt, *J* = 15.3, 4.2 Hz, 1H), 2.66–2.58 (m, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.2, 147.4, 134.1, 133.0, 128.5, 126.8, 125.6, 121.6, 111.3, 110.3, 88.7, 85.1, 56.5, 56.0, 55.9, 48.7, 43.7, 28.4.

Procedure for the Preparation of 13-Benzylidene-10,11-dimethoxy-5,8,13,13a-tetrahydro-6*H*-isoquinolino[3,2-*a*]isoquinoline (4) from 3ea

To a solution of **3ea** (90 mg, 0.19 mmol) in DMF (6 mL) and H_2O (2 mL) was added HCO_2Na (26 mg, 0.39 mmol). The solution was bubbled with a stream of dry nitrogen gas for 15 min before addition of $Pd(PPh_3)_4$ (11 mg, 0.01 mmol). The reaction mixture was heated at 100 ºC in an oil bath and stirred for 2 h under the nitrogen atmosphere. The reaction mixture was diluted with CH_2Cl_2 (10 mL). The organic phase was collected and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic fractions were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel using eluents (eluent: petroleum ether:EtOAc = 1:1) to provide the title compound (65 mg, 89% yield) as a yellow solid; m.p. 190–192°C; IR (neat, cm^{-1}): 2918, 2855, 1604, 1510, 1464, 1352, 1259, 1239, 1207, 1148, 1112, 1022, 830, 744, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.1 Hz, 2H), 7.24–7.01 (m, 9H), 6.33 (s, 1H), 5.23 (s, 1H), 3.88 (s, 3H), 3.79–3.60 (m, 5H), 3.48–3.37 (m, 1H), 3.29–3.10 (m, 2H), 2.69 (dd, *J* = 17.2, 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.0, 137.0, 134.7, 134.3, 133.8, 129.0, 128.5, 128.5, 127.6, 127.2, 127.1, 127.0, 126.4, 125.2, 124.7, 108.8, 107.1, 57.8, 56.0, 55.8, 49.6, 48.0, 22.7; HRMS (ESI) calcd. for $C_{26}H_{25}NO_2$ (M^+ + H): 384.1964, found: 384.1942.

Acknowledgements

This work was supported by a Discovery Project Grant (DP160101682) from the Australian Research Council.

References

[1] Selected reviews: a) M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, *Chem. Rev.* **2016**, *116*, 12369–12465; b) D. M. Flanigan, F. Romanov-Michailidis, N. A. White, T. Rovis, *Chem. Rev.* **2015**, 115, 9307–9387; c) M. Correia-da-Silva, E. Sousa, M. M. Pinto, *Med. Res. Rev.* **2014**, *34*, 223–279; d) *Progress in Heterocyclic Chemistry*, (Eds.: G. Gribble, J. Joule), Elsevier, **2012**; e) J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669–1730.

[2] Selected recent examples: a) L. Zeng, B. Huang, Y. Shen, S. Cui, *Org. Lett.* **2018**, *20*, 3460–3464; b) Y. Zhao, J. Jin, J. W. Boyle, B. R. Lee, D. P. Day, D. Susanti, G. J. Clarkson, P. W. H. Chan, *J. Org. Chem.* **2017**, *82*, 2826–2834; c) H. Zhou, Y. Liu, S. Yang, L. Zhou, M. Chang, *Angew. Chem. Int. Ed.* **2017**, *56*, 2725–2729; d) J. Zhu, H. Tan, L. Yang, Z. Dai, L. Zhu, H. Ma, Z. Deng, Z. Tian, X. Qu, *ACS Catal.* **2017**, *7*, 7003–7007; e) T. B. Nguyen, L. Ermolenko, A. Al-Mourabit, *Chem. Commun.* **2016**, *52*, 4914–4917.

[3] a) T. Huang, X. Liu, J. Lang, J. Xu, L. Lin, X. Feng, *ACS Catal.* **2017**, *7*, 5654–5660; b) I. Perepichka, S. Kundu, Z. Hearne, C. J. Li, *Org. Biomol. Chem.* **2015**, *13*, 447–451; c) S. Sun, C. Li, P. E. Floreancig, H. Lou, L. Liu, *Org. Lett.* **2015**, *17*, 1684–1687; d) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori, C. Vila, *Chem. Eur. J.* **2012**, *18*, 5170–5174; e) J. W. Tucker, Y. Zhang, T. F. Jamison, C. R. Stephenson, *Angew. Chem. Int. Ed.* **2012**, *51*, 4144–4147; f) D. B. Freeman, L. Furst, A. G. Condie, C. R. Stephenson, *Org. Lett.* **2012**, *14*, 94–97; g) Z. Li, C. J. Li, *Org. Lett.* **2004**, *6*, 4997–4999.

[4] a) K. N. Singh, P. Singh, A. Kaur, P. Singh, *Synlett* **2012**, 760–764; b) K. M. Jones, P. Karier, M. Klussmann, *ChemCatChem* **2012**, *4*, 51–54.

[5] a) S. Zhou, R. Tong, *Org. Lett.* **2017**, *19*, 1594–1597; b) E. V. Da-Cunha, I. M. Fechinei, D. N. Guedes, J. M. Barbosa-Filho, M. S. Da Silva, *Alkaloids Chem. Biol.* **2005**, *62*, 1–75.

[6] Selected reviews on photoredox-mediated reactions: a) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166; b) M. H. Shaw, J. Twilton, D. W. MacMillan, *J. Org. Chem.* **2016**, *81*, 6898–6926; c) J. R. Chen, X. Q. Hu, L. Q. Lu, W. J. Xiao, *Acc. Chem. Res.* **2016**, *49*, 1911–1923; d) E. C. Gentry, R. R. Knowles, *Acc. Chem. Res.* **2016**, *49*, 1546–1556; e) C. K. Prier, D. A. Rankic, D. W. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363; f) J. W. Tucker, C. R. Stephenson, *J. Org. Chem.* **2012**, *77*, 1617–1622.

[7] Selected reviews on gold catalysis: a) W. Li, J. Zhang, *Chem. Eur. J.* **2017**, *23*, 467–512; b) A. M. Asiri, A. S. K. Hashmi, *Chem. Soc. Rev.* **2016**, *45*, 4471–4503; c) D. P. Day, P. W. H. Chan, *Adv. Synth. Catal.* **2016**, *358*, 1368–1384; d) R. Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072; e) M. Jia, M. Bandini, *ACS Catal.* **2015**, *5*, 1638–1652; f) B. Alcaide, P. Almendros, *Acc. Chem. Res.* **2014**, *47*, 939–952; g) C. Obradors, A. M. Echavarran, *Acc. Chem. Res.* **2014**, *47*, 902–912; h) A. S. K. Hashmi, *Acc. Chem. Res.* **2014**, *47*, 864–876; i) *Gold Catalysis: An Homogeneous Approach*; F. D. Toste, V. Michelet, Eds.; Imperial College Press: London, 2014; j) C. D. Pina, E. Falletta, M. Rossi, *Chem. Soc. Rev.* **2012**, *41*, 350–369; k) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994–2009; l) A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2010**, *49*, 5232–5241; m) A. Corma, A. Leyva-Pérez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657–1712; n) A. Fürstner, *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; o) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180–3211.

[8] Selected reviews on $[Au_2(\mu\text{-dppm})_2]Cl_2$ catalysis: a) J. Xie, H. Jin, A. S. K. Hashmi, *Chem. Soc. Rev.* **2017**, *46*, 5193–5203; b) T. McCallum, S. Rohe, L. Barriault, *Synlett* **2017**, *28*, 289–305.

[9] G. Revol, T. McCallum, M. Morin, F. Gagosz, L. Barriault, *Angew. Chem. Int. Ed.* **2013**, *52*, 13342–13345.

[10] a) Z.-S. Wang, T.-D. Tan, C.-M. Wang, D.-Q. Yuan, T. Zhang, P. Zhu, C. Zhu, J.-M. Zhou, L.-W. Ye, *Chem. Commun.* **2017**, *53*, 6848–6851; b) B. Alcaide, P. Almendros, E. Busto, C. Lázaro-Milla, *J. Org. Chem.* **2017**, *82*, 2177–2186; c) M. Zidan, T. McCallum, L. Thai-Savarda, L. Barriault, *Org. Chem. Front.* **2017**, *4*, 2092–2096; d) J. Xie, J. Li, V. Weingand, M. Rudolph, A. S. K. Hashmi, *Chem. Eur. J.* **2016**, *22*, 12646–12650; e) T. McCallum, L. Barriault, *Chem. Sci.* **2016**, *7*, 4754–4758; f) H. Tran, T. McCallum, M. Morin, L. Barriault, *Org. Lett.* **2016**, *18*, 4308–4311; g) J. Xie, T. Zhang, F. Chen, N. Mehrkens, F. Rominger, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2016**, *55*, 2934–2938; h) A. Cannillo, T. R. Schwantje, M. Bégin, F. Barabé, L. Barriault, *Org. Lett.* **2016**, *18*, 2592–2595; i) C. D. McTiernan, M. Morin, T. McCallum, J. C. Scaiano, L. Barriault, *Catal. Sci. Technol.* **2016**, *6*, 201–207; j) J. Xie, S. Shi, T. Zhang, N. Mehrkens, M. Rudolph, A. S. K. Hashmi, *Angew. Chem. Int. Ed.* **2015**, *54*, 6046–6050; k) S. J. Kaldas, A. Cannillo, T. McCallum, L. Barriault, *Org. Lett.* **2015**, *17*, 2864–2866.

[11] The gold-catalyzed photoredox α-C(sp^3)–H alkynylation of tertiary aliphatic amines with 1-iodoalkynes was reported not to be applicable to the analogous reactions of a *N*-phenyl protected THIQ, see Ref [10j].

[12] a) D. Li, C.-M. Che, H.-L. Kwong, V. W.-W. Yam, *J. Chem. Soc., Dalton Trans.* **1992**, 3325–3329; b) C.-M. Che, H.-L. Kwong, K.-C. Poon, V. W.-W. Yam, *J. Chem. Soc., Dalton Trans.* **1990**, 3215–3219; c) C.-M. Che, H.-L. Kwong, V. W.-W. Yam, K.-C. Choc, *J. Chem. Soc., Chem. Commun.* **1989**, 885–886.

[13] Reactions involving selective light-mediated reductive dehalogenations, see Refs [9], [10j] and: a) C Le, T. Q. Chen, T. Liang, P. Zhang, D. W. MacMillan, *Science* **2018**, *360*, 1010–1014; b) K. Shimomaki, K Murata, R. Martin, N. Iwasawa, *J. Am. Chem. Soc.* **2017**, *139*, 9467–9470; c) III, J. J. Devery, J. D. Nguyen, C. Dai, C. R. J. Stephenson, *ACS Catal.* **2016**, *6*, 5962–5967.

[14] Selected examples of α-aminoalkyl radicals: a) R. Sakamoto, Y. Tomomi, H. Takada, K. Maruoka, *Org. Lett.* **2018**, *20*, 2080–2083; b) W. J. Zhou, G. M. Cao, G. Shen, X. Y. Zhu, Y. Y. Gui, J. H. Ye, L. Sun, L. L. Liao, J. Li, D. G. Yu, *Angew. Chem. Int. Ed.* **2017**, *56*, 15683–15687; c) J. Xuan, T. T. Zeng, Z. J. Feng, Q. H. Deng, J. R. Chen, L. Q. Lu, W. J. Xiao, H. Alper, *Angew. Chem. Int. Ed.* **2015**, *54*, 1625–1628; d) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle, D. W. MacMillan, *Science* **2014**, *345*, 437–440; e) P Kohls, D. Jadhav, G. Pandey, O. Reiser, *Org. Lett.* **2012**, *14*, 672–675; f) Y. Miyake, K. Nakajima, Y. Nishibayashi, *J. Am. Chem. Soc.* **2012**, *134*, 3338–3341.

[15] Rare examples of alkynyl radicals: a) K. Ni, L. G. Meng, K. Wang, L. Wang, *Org. Lett.* **2018**, *20*, 2245–2248; b) P. Boutillier, S. Z. Zard, *Chem. Commun.* **2001**, 1304–1305; c) M. S. Robinson, M. L. Polek, V. M. Bierbaum, C. H. DuPuy, W. C. Lineberger, *J. Am. Chem. Soc.* **1995**, *117*, 6766–6778; d) G. Martelli, P. Spagnolo, M. Tiecco, *J. Chem. Soc. B* **1970**, 1413–1418.

10.1002/adsc.201801289

[16] A. S.-K. Tsang, A. S. K. Hashmi, P. Comba, M. Kerscher, B. Chan, M. H. Todd, *Chem. Eur. J.* **2017**, *23*, 9313–9318.

[17] G. Shao, Y. He, Y. Xu, J. Chen, H. Yu, R. Cao, *Eur. J. Org. Chem.* **2015**, 4615–4619.

[18] Q. H. Zheng, W. Meng, G. J. Jiang, Z. X. Yu, *Org. Lett.* **2013**, *15*, 5928–5931.

10.1002/adsc.201801289

FULL PAPER

Gold Catalyzed Photoredox C1-Alkynylation of *N*-Alkyl-1,2,3,4-tetrahydroisoquinolines by 1-Bromoalkynes with Blue LED Light

Adv. Synth. Catal. **2018**, *Volume*, Page – Page

Yichao Zhao, Jianwen Jin, and Philip Wai Hong Chan*