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The A³ Redox-Neutral C1-Alkynylation of Tetrahydroisoquinolines: A Comparative Study between Visible Light Photocatalysis and Transition-Metal Catalysis

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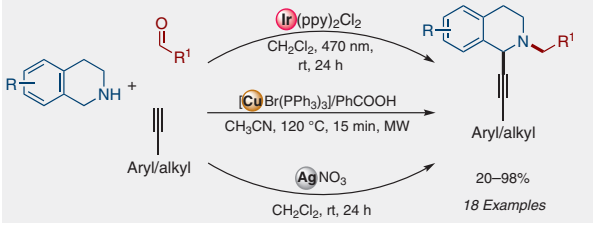

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Abstract Considering the current challenges of the A³ redox-neutral C1-alkynylation of tetrahydroisoquinolines (THIQs), we studied this synthetic tool under visible light photocatalysis and transition-metal catalysis in order to describe alternative reaction conditions and discuss possible improvements to this process. We demonstrated that 1-alkynylated THIQs can be readily obtained by three different approaches: iridium-based photocatalysis and copper ([CuBr(PPh$_3$)$_3$]) and silver ($AgNO_3$) catalysis under mild, selective and accessible reaction conditions. Among these approaches, the copper(I)-based methodology resulted in the most robust, optimal reaction conditions for the synthesis of a series of 18 1-alkynylated THIQs in moderate to excellent yields and with high selectivity for the *endo*-alkynylated products. Moreover, this reaction can be accelerated by microwave irradiation (120 °C, 15 min) affording a novel library of diverse THIQs with alkyne and *N*-substituent moieties, from unreactive and uncommon substrates, that could be further transformed into new compounds of interest.

Key words A³ coupling reaction, C1-alkynylation, tetrahydroisoquinolines, photocatalysis, transition-metal catalysis

Natural and synthetic C1-substituted tetrahydroisoquinolines (THIQs) have attracted considerable interest in drug research due to their remarkable biological properties,[1] including anticancer,[2] anti-HIV,[3] antimicrobial[4] and antiviral[5] activities. During the last decade, the cross-dehydrogenative coupling (CDC) of *N*-aryl THIQs has been the protocol of choice of many organic chemists to access functionalized THIQs.[6] Despite the success of the CDC strategy, this methodology still has two significant disadvantages: limited substrate scope to *N*-aryl THIQs and the stoichiometric use of oxidants.[7]

In 2008, Seidel and co-workers developed the A³ redox reaction for the a-C–H bond functionalization of secondary amines.[8] Later, Yu's group extended this approach to THIQs,[9] complementing the traditional A³ coupling process that gave propargylamines[10] and C1-substituted THIQs through the formation of tunable iminium ions.[11] Nowadays, this methodology stands as one of the key steps during the total synthesis of complex THIQ-based alkaloids and drug-like molecules,[12,13] such as the series of well-recognized biologically active 1-alkynyl THIQs **1**–**4** (Figure 1), which exhibit antitumor activity,[14] sirtuin inhibition against Hst2[15] and D3 dopamine receptor affinity,[16] compounds that can also be obtained through the A³ redox reaction.

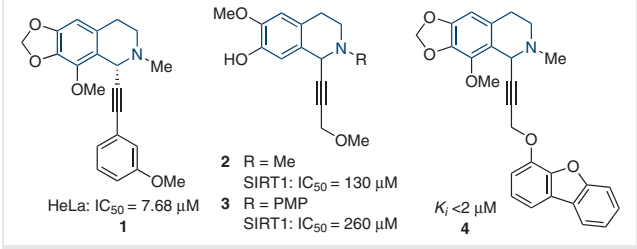


Figure 1 Representative bioactive C1-alkynyl THIQs

The A³ redox a-C–H bond functionalization of THIQs requires an *endo*-iminium ion as a reactive intermediate which is formed through the isomerization of the *exo*-iminium ion.[11,13,17] These species are rapidly formed by the condensation of THIQs with benzaldehydes, suggesting that the crucial step during this transformation will be the isomerization process prior to the alkyne addition.

Recently, some studies have established that this isomerization can be controlled by the nature of the catalyst (CuI-*endo*, CuBr-*exo*),[9] carbonyl substrates (steric hindrance, benzaldehydes-*endo*, alkyl aldehydes-*exo*),[18] additives (carboxylic acids-*endo*)[19] and temperature (>80 °C-*endo*, <60 °C-*exo*).[20] Moreover, aside from these reaction conditions,

a few outstanding approaches have studied the enantiocontrolled addition of alkynes to the *endo*-iminium ions, which resulted in the innovative enantioselective synthesis of naturally occurring THIQ alkaloids.[21]

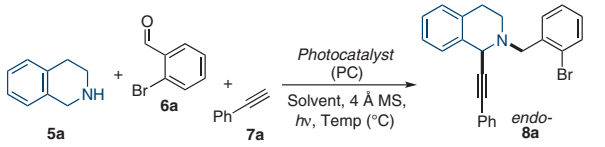
Although a variety of redox-neutral C–H alkynylations have been developed so far, this reaction has not been explored to the same extent as the CDC reaction under visible light and photocatalytic conditions. In addition, transition metals such as silver and copper have demonstrated their efficiency in A^3 redox transformations solely with reactive and common benzaldehydes and alkynes. For this reason, we decided to first explore and study whether excited photocatalysts could boost the formation of *exo*-iminium ions to facilitate their isomerization to *endo*-iminium ions and promote the subsequent alkyne addition with a variety of aldehydes and alkynes that have not been reported so far.

In this context, we began our study with the visible light photocatalytic approach for the synthesis of 1-alkynyl THIQ **8a** from THIQ (**5a**), 2-bromobenzaldehyde (**6a**) and phenylacetylene (**7a**) as model substrates (Table 1). This A^3 coupling reaction was first examined without any photoredox catalyst (PC) under blue LED irradiation and different temperatures, giving the desired *endo*-product **8a** in a very low yield at 50 °C. It is noteworthy that the reaction did not proceed at room temperature (Table 1, entries 1 and 2). Subsequently, a series of Ru, Cu and Ir photocatalysts were tested in this reaction at 50 °C (entries 3–5). In particular, the photoredox catalyst $Ir(ppy)_2Cl_2$ provided the desired THIQ **8a** in moderate 39% yield (entry 5), whereas the organophotocatalyst eosin Y did not allow the formation of the product (entry 6).

The effect of the Ir photocatalyst over the reaction temperature was determined by performing this process at room temperature, which did not afford the desired product in the absence of any catalyst (Table 1, entry 2). Interestingly, 1-alkynyl THIQ **8a** was obtained in 43% yield when $Ir(ppy)_2Cl_2$ (2 mol%) was used as a catalyst in dichloromethane for 24 hours at room temperature (entry 7). Aiming to further improve the efficiency of this approach, we tested acetonitrile as an alternative solvent for this reaction. Under these conditions, there was a significant decrease in the reaction yield when Ru and Cu photocatalysts were used (entries 8 and 9). On the other hand, there was a slightly increased yield of 1-alkynyl THIQ **8a** when Ir was employed as the photocatalyst (entry 10). Although eosin Y furnished the desired product at room temperature, the low yield in which **8a** was isolated (26%) did not encourage a further investigation of the reaction using this organophotocatalyst (entry 11).

In this sense, we focused our efforts on exploring this A^3 coupling reaction under the metal catalysis approach. First, and taking into account the successful silver-catalyzed coupling between aldehydes, alkynes and amines in the synthesis of propargylamines,[22] and C1-phosphonylated[23] and

Table 1 Optimization of Reaction Conditions for the Synthesis of 1-Alkynyl THIQ **8a** through A^3 Coupling under the Photocatalytic Approach[a]

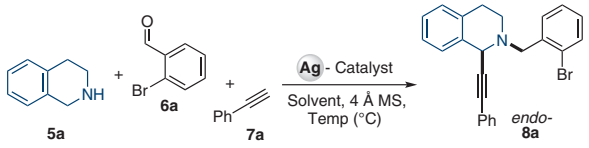


Entry	PC (2 mol%)	*hν* (nm)	Solvent	Temp (°C)	Yield (%)[b,c]
1	–	470	CH_2Cl_2	50	9
2	–	470	CH_2Cl_2	25	NR
3	$Ru(bpy)_3PF_6$	470	CH_2Cl_2	50	37
4	$Cu(dap)_2Cl_2$	470	CH_2Cl_2	50	25
5	$Ir(ppy)_2Cl_2$	470	CH_2Cl_2	50	39
6	eosin Y	530	DMF	50	NR
7	$Ir(ppy)_2Cl_2$	470	CH_2Cl_2	25	43
8	$Ru(bpy)_3PF_6$	470	CH_3CN	25	15
9	$Cu(dap)_2Cl_2$	470	CH_3CN	25	11
10	$Ir(ppy)_2Cl_2$	470	CH_3CN	25	47
11	eosin Y	530	DMF	25	26

[a] Reaction conditions: **5a** (1.4 mmol), **6a** (1.4 mmol), **7a** (1 mmol), solvent (0.2 M), molecular sieves (300 mg), 24 h.
[b] Isolated yield after silica gel column chromatography.
[c] NR: no reaction.

C1-alkynylated[24] THIQs, we used readily available silver catalysts in our model reaction between THIQ (**5a**), 2-bromobenzaldehyde (**6a**) and phenylacetylene (**7a**) to afford the desired 1-alkynyl THIQ **8a** (Table 2). When silver carbonate (Ag_2CO_3) was used as a catalyst, the raw materials reacted at room temperature to furnish *endo*-product **8a** in poor yield (17%) after 24 hours (Table 2, entry 1). Surprisingly, by changing the catalyst to silver nitrate ($AgNO_3$), a low cost and stable reagent,[25] the reaction yield was markedly improved and the desired 1-alkynyl THIQ **8a** was obtained in 98% yield (entry 2). This result is also much better than the one obtained by Shao and co-workers where the corresponding 1-alkynyl THIQ was obtained in 73% yield when silver acetate (AgOAc) was employed as a catalyst.[24] Anticipating that this reaction could be accelerated or performed in a more benign way or in an alternative reaction medium, we studied this process in green solvents such as polyethylene glycol (PEG-400) and propylene and in 1,4-dioxane (entries 3–5). With the exception of PEG-400, we found that this reaction could be promoted in these solvents, but the yield of THIQ product was significantly reduced, below 70%. The reaction yields in which product **8a** was obtained in experiments 3–6 (Table 2) were below 70%. Finally, in an attempt to reduce the reaction time, this transformation was performed at 40 °C for 12 hours, but the desired *endo*-product **8a** was isolated in 71% yield (entry 6).

Table 2 Optimization of Reaction Conditions for the Synthesis of 1-Alkynyl THIQ **8a** through A^3 Coupling Catalyzed by Silver Salts[a]



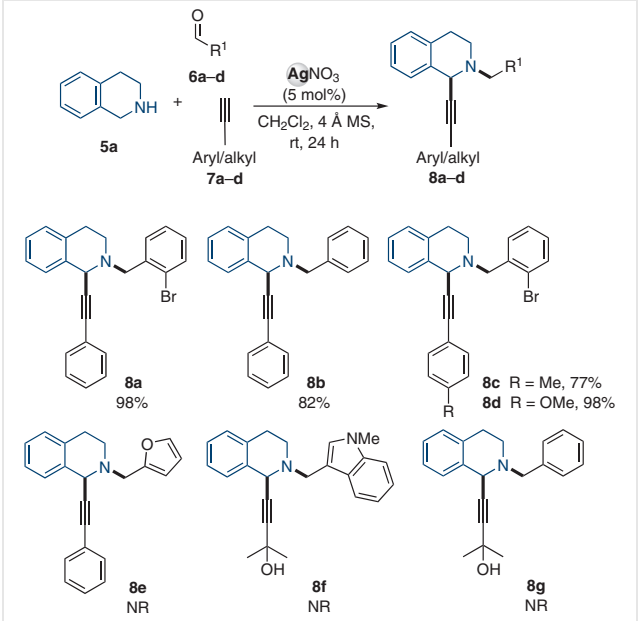
Entry	Ag salt (5 mol%)	Solvent	Temp (°C)	Yield (%)[b]
1	Ag_2CO_3	CH_2Cl_2	25	17
2	$AgNO_3$	CH_2Cl_2	25	98
3	$AgNO_3$	PEG-400	25	NR[c]
4	$AgNO_3$	propylene	25	38
5	$AgNO_3$	1,4-dioxane	25	6
6	$AgNO_3$	CH_2Cl_2	40	71[d]

[a] Reaction conditions: **5a** (1.4 mmol), **6a** (1.4 mmol), **7a** (1 mmol), solvent (0.2 M), molecular sieves (300 mg), 24 h.
[b] Isolated yield after silica gel column chromatography.
[c] NR: no reaction.
[d] Reaction time: 12 h.

Under these optimal reaction conditions (Table 2, entry 2), we explored the functional group tolerance and substrate applicability of this coupling reaction using a series of substituted, unreactive and uncommon aldehydes and phenylacetylenes. As shown in Scheme 1, benzaldehyde (**6b**) and phenylacetylenes **7b** and **7c** substituted with a Me or OMe group have little effect on the efficiency of the reaction and satisfactorily afforded the coupling products **8b–d** in 77–98% yield. However, when valuable heteroaldehydes, such as furfural (**6c**) and indole-3-carboxaldehyde **6d**, and alkynes like 2-hydroxy-2-methyl-3-butyne (**7d**) were employed as reactants, the reaction did not proceed under these reaction conditions and the substituted THIQs **8e**, **8f** and **8g** could not be isolated (Scheme 1).

At first, we speculated that this behavior could be attributed to the low reactivity of these aldehydes during the formation of the reactive intermediate, the corresponding iminium ion, at the initial step of this process. But considering that the formation of compound **8b** occurs through the respective iminium ion, it demonstrated that these species are readily formed when benzaldehyde reacts with THIQ (**5a**). In addition, the nonreactive character of compound **6b** towards 2-hydroxy-2-methyl-3-butyne to give compound **8g** indicates that the silver catalytic system is unable to activate this reagent for the nucleophilic attack and formation of the corresponding iminium ion.

Clearly, C–H activation in the terminal alkyne is essential for coupling with the iminium ion and formation of the new C–C bond. As a result, copper catalysts have allowed the smooth, facile and rapid formation of a copper(I) acetylide active species that can easily react with electrophilic intermediates such as the THIQ-iminium ion.[26–28] Thus, our study focused on screening some copper catalysts to promote the A^3 coupling between THIQ (**5a**), 2-bromobenzaldehyde (**6a**) and phenylacetylene (**7a**) to afford the desired 1-alkynyl THIQ **8a** under optimal, green, robust and rapid reaction conditions (Table 3). Our first attempt used copper iodide (CuI) based on Yu's report where toluene was employed as a solvent at different reaction temperatures.[9] We noticed that when this reaction was performed at room temperature, the desired product was obtained in only 15% yield. However, when the temperature was increased to 50 °C, the desired 1-alkynyl THIQ **8a** was isolated in moderate 58% yield (Table 3, entries 1 and 3). Aiming to conduct this process in a more polar solvent that allows dissolution of those reagents that are not soluble in toluene, and taking into account the success of dichloromethane in the silver-catalyzed process (Table 2), we performed this reaction in dichloromethane but, unfortunately, formation of THIQ **8a** was not observed, probably due to incompatibility of the copper(I) acetylide intermediate in this halogenated medium (Table 3, entry 2). Copper bromide (CuBr) was also tested as a catalyst, but although there was a high conversion of the reactants (96% yield), the *endo*-1-alkynyl THIQ **8a** was obtained along with the corresponding propargylamine **8a′** through the intermediate *exo*-THIQ-iminium ion in a 2.5:1 ratio, with *endo*-THIQ **8a** being preferred (entry 4). Copper catalysts containing phosphorus ligands have played an important role in some relevant organometallic transformations, since these complexes are more reactive, stable, and easily prepared and handled under laboratory conditions.[29] The commercially available [$CuBr(PPh_3)_3$] has demonstrated

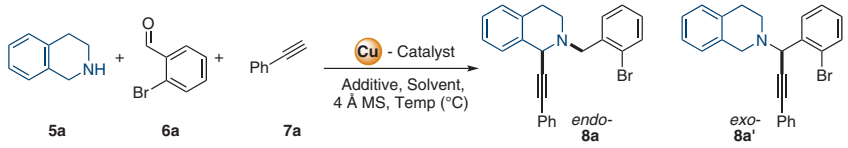


Scheme 1 Synthesis of 1-alkynyl THIQs **8a–d** through A^3 coupling catalyzed by silver nitrate. *Reagents and conditions*: **5a** (1.4 mmol), **6a–d** (1.4 mmol), **7a–d** (1 mmol), $AgNO_3$ (5 mol%), CH_2Cl_2 (0.2 M), molecular sieves (300 mg), rt, 24 h. NR: no reaction.

its ability to promote reactions at low catalyst loading and accelerate these processes under microwave irradiation.[30] After its rapid, efficient and scalable preparation,[31] [CuBr(PPh$_3$)$_3$] was employed as a catalyst (5 mol%) for our model reaction in toluene at 80 °C for 24 hours, to give the desired product **8a** in 48% yield (entry 5). To our delight, after changing the solvent for acetonitrile, under the same reaction conditions, the corresponding *endo*-THIQ **8a** was isolated as a single isomer in 92% yield (entry 6). Although this approach was highly efficient for the construction of THIQ **8a**, we encouraged ourselves to develop a greener protocol for this reaction by preparing and evaluating some biopolymers supported with copper species as heterogeneous catalysts. These kinds of materials have demonstrated a great utility for the construction of several heterocyclic compounds by allowing easy catalyst separation from the reaction mixture and reuse in successive small- and large-scale cycles.[32–34] In the particular case of C1-alkynylated THIQs, these compounds have been prepared through A^3 coupling using heterogeneous catalysts such as the MCM-41-supported copper(I) complex [MCM-41-2N-CuI][35] and CuO@Fe$_2$O$_3$ magnetic nanoparticles,[36] but the use of biopolymers as supporting materials has not been reported for this process. We first used two quantities of the copper sulfate catalyst immobilized over chitosan (Chit-CuSO$_4$), where a 0.5 g/mmol loading gave the desired 1-alkynyl THIQ **8a** in 70% yield; after increasing the catalyst loading to 1 g/mmol, a slightly increased product yield (80%) was observed (Table 3, entries 7 and 8). Surprisingly, the use of cellulose-supported CuI catalyst (Cell-CuI) at 0.5 g/mmol loading, which is based on Cu(I), gave the corresponding THIQ **8a** in 40% yield (entry 9), a lower value than the one obtained with Chit-CuSO$_4$, which is based on Cu(II). During our study, we had established 24 hours as the optimal reaction time under conventional heating but, being aware of this prolonged time, we next focused our efforts on accelerating this process from hours to minutes by assisting our reaction with microwave irradiation. In the first experiment, we applied the same reaction conditions depicted in entry 6 (Table 3) but with heating in a microwave reactor (Biotage Initiator+) for 10 minutes at 150 °C. Although conversion into the corresponding 1-alkynyl THIQ **8a** was observed (50%), formation of the respective propargylamine **8a′**, derived from the *exo*-THIQ-iminium ion, was also identified, in an 11:1 ratio (entry 10).

The presence of propargylamine **8a′** as a side product indicates that by shortening the reaction time, the *exo*-THIQ-iminium ion, which is the kinetic intermediate, is

Table 3 Optimization of Reaction Conditions for the Synthesis of 1-Alkynyl THIQ **8a** through A^3 Coupling Catalyzed by Copper Salts[a]

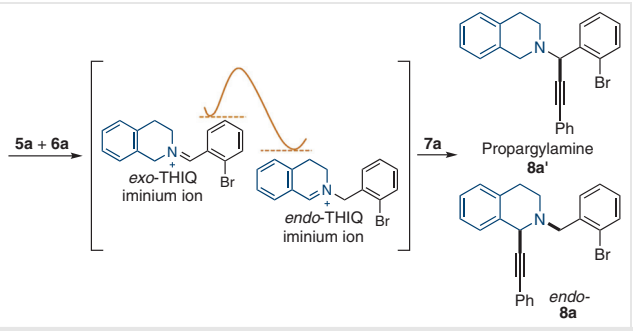


5a **6a** **7a**

Entry	Cu salt (5 mol%)	Additive (5 mol%)	Solvent	Temp (°C)	Time	Ratio *endo*/*exo*[b]	Yield (%)[c]
1	CuI	–	toluene	25	24 h	1:0	15
2	CuI	–	CH_2Cl_2	25	24 h	1:0	NR[d]
3	CuI	–	toluene	50	24 h	1:0	58
4	CuBr	–	toluene	50	24 h	2.5:1	96
5	[CuBr(PPh$_3$)$_3$]	–	toluene	80	24 h	1:0	48
6	[CuBr(PPh$_3$)$_3$]	–	CH_3CN	80	24 h	1:0	92
7	Chit-CuSO$_4$ (0.5 g/mmol)	–	CH_3CN	100	24 h	1:0	70
8	Chit-CuSO$_4$ (1 g/mmol)	–	CH_3CN	100	24 h	1:0	80
9	Cell-CuI (0.5 g/mmol)	–	CH_3CN	100	24 h	1:0	40
10[e]	[CuBr(PPh$_3$)$_3$]	–	CH_3CN	150	10 min	11:1	50
11[e]	[CuBr(PPh$_3$)$_3$]	PivOH	CH_3CN	150	10 min	1.5:1	40
12[e]	[CuBr(PPh$_3$)$_3$]	PhCOOH	CH_3CN	150	10 min	1:0	20
13[e]	[CuBr(PPh$_3$)$_3$]	PhCOOH	CH_3CN	120	15 min	1:0	98
14[e]	[CuBr(PPh$_3$)$_3$]	PhCOOH	CH_3CN	120	10 min	1:0	72

[a] Reaction conditions: **5a** (1.4 mmol), **6a** (1.4 mmol), **7a** (1 mmol), solvent (0.2 M), molecular sieves (300 mg).
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture.
[c] Isolated yield after silica gel column chromatography.
[d] NR: no reaction.
[e] Reaction assisted by microwave irradiation using Biotage Initiator+ equipment.

unable to reach equilibrium and be interconverted into the thermodynamic intermediate, the *endo*-THIQ-iminium ion, that furnishes the expected 1-alkynyl THIQ **8a** (Scheme 2).[9]



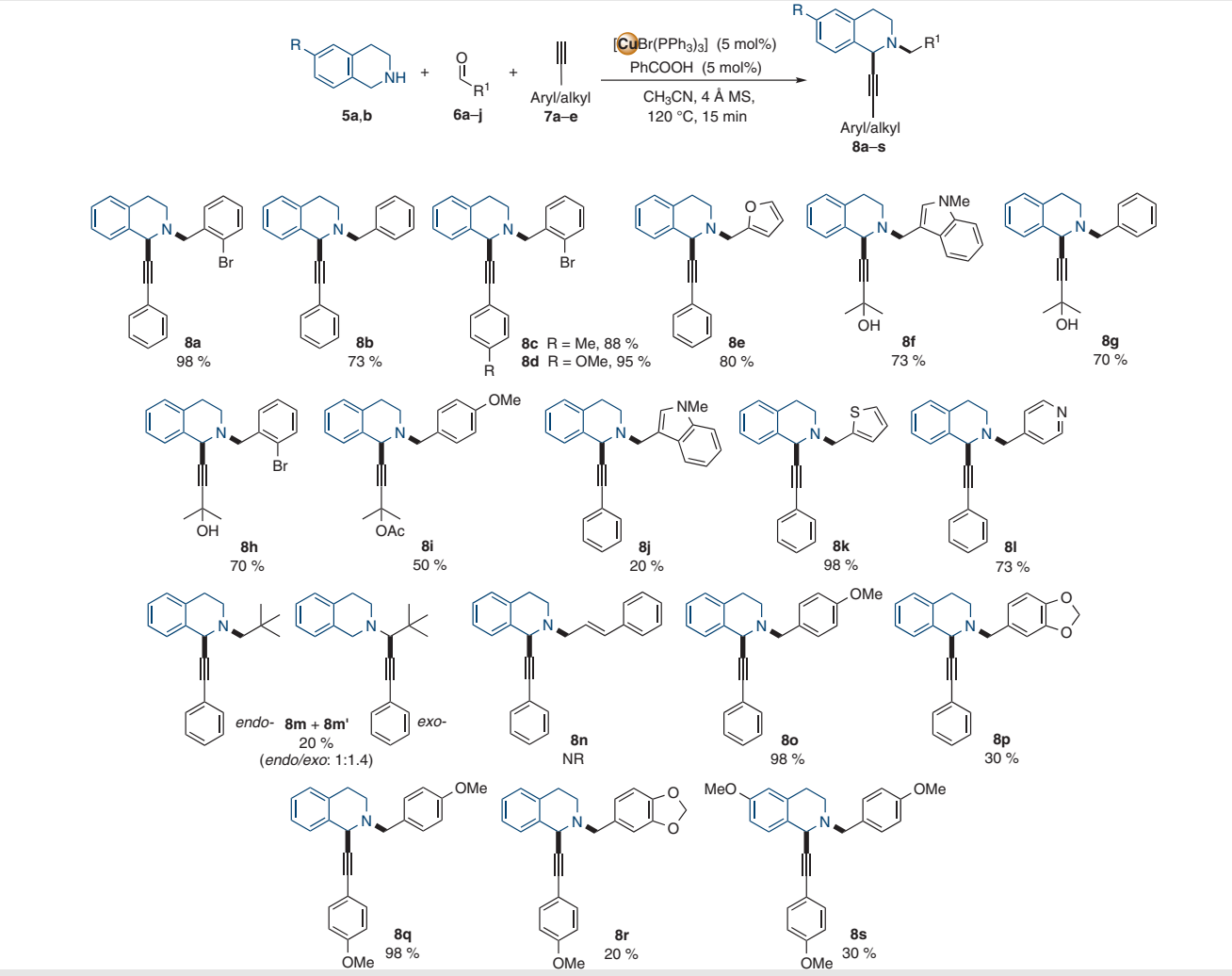
Scheme 2 Kinetic (propargylamine **8a′**) and thermodynamic (THIQ **8a**) products identified during microwave-assisted A^3 coupling

We noticed that Ma's group reported that the addition of carboxylic acids accelerated and improved the yields of C1-alkynylation of THIQs during the enantioselective version of this reaction, without evidence of the formation of the side propargylamine **8a′** derivative.[37] Based on this finding and also our previous experiences,[38] pivalic acid (5 mol%) was chosen as an additive but, under these reaction conditions, a low conversion into the desired **8a** was observed (40%) and the kinetic propargylamine product **8a′** was also identified, in a 1.5:1 ratio (Table 3, entry 11). Next, we used benzoic acid as an additive, and although the 1-alkynyl THIQ **8a** was isolated in poor yield (20%), the propargylamine was not identified and the desired **8a** was exclusively obtained (entry 12). The low yield in this last experiment would probably be due to the high reaction temperature that could result in decomposition of the reagents or intermediates involved over time; to prevent this issue, we then performed this reaction at 120 °C for 15 minutes. To our delight, under these reaction conditions, 1-alkynyl THIQ **8a** was isolated in excellent yield (98%) and, once again, without any evidence of the formation of the kinetic propargylamine product (entry 13). Finally, a decreased reaction time (10 min) gave exclusively product **8a** but in a lower yield (72%, entry 14).

With the optimal reaction conditions in hand, the main goal of our study was the scope evaluation of the A^3 redox C1-alkynylation of THIQs under our approach with unreactive or uncommon aldehydes and alkynes not tested before. We first noticed that this copper-catalyzed reaction proceeded well with those aldehydes and alkynes that had previously furnished the functionalized THIQs under silver catalysis (Scheme 1). Thus, C1-alkynylated THIQs **8b–d**, derived from benzaldehyde (**6b**) and phenylacetylenes **7b** and **7c** substituted with a Me or OMe group, were obtained in 73–95% yield (Scheme 3) in comparison with the silver approach that gave these products in 77–98% yield. Fortunately, under this copper-catalyzed approach, valuable *N*-substituted THIQs with a furfuryl (**8e**, 80%) or indolyl (**8f**, 73%) core, or with a butynol fragment at C1 (**8g**, 70%), were easily obtained, indicating that under the established conditions the respective *endo*-iminium ion is the preferred intermediate and that the Cu(I) catalyst is able to activate an alkyne moiety, besides other arylacetylene derivatives, towards electrophilic *endo*-THIQ-iminium species, an effect not achieved with the silver catalyst. Furthermore, the reactivity of 2-hydroxy-2-methyl-3-butyne (**7d**) and its *O*-acetylated analogue **7e** was explored with other benzaldehyde derivatives [2-bromobenzaldehyde (**6a**), *p*-anisaldehyde (**6e**)], affording the corresponding 1-alkynyl THIQs **8h** (70%) and **8i** (50%), respectively, in good to moderate yield (Scheme 3). Although the electronic effects of indole-3-carboxaldehyde **6d** exhibited an adverse effect on the efficiency of the reaction when phenylacetylene (**7a**) was used, with 1-alkynyl THIQ **8j** isolated in poor yield (20%), other heteroaromatic aldehydes, such as thiophenecarboxaldehyde (**6f**) and pyridine-4-carboxaldehyde (**6g**), were well tolerated in this reaction using alkyne **7a** and furnished the desired THIQs **8k** (98%) and **8l** (73%) in good yields. The limitations of our developed protocol were evident when aliphatic aldehydes were used; for example, when pivalaldehyde (**6h**) was employed, the desired THIQ **8m** was obtained in poor yield and with the corresponding propargylamine **8m′** as the major product (*endo*/*exo* ratio = 1:1.4, Scheme 3), suggesting that in this case the kinetic product will be more stable than the *endo*-THIQ-iminium ion. Unfortunately, cinnamaldehyde (**6i**) did not afford the desired THIQ **8n**. Finally, outstanding results were obtained with *p*-anisaldehyde (**6e**) and alkynes **7a** and **7c**, furnishing both THIQs **8o** and **8q** in 98% yield, while piperonal (**6j**) and 6-methoxy THIQ (**5b**) gave the corresponding THIQs **8p**, **8r** and **8s** in low yields (20–30%, Scheme 3). In particular, derivative **8s**, which is substituted with one methoxy group on each aromatic ring, could be of great interest for biological and pharmaceutical studies.

The C1-alkynylation of *N*-aryl THIQs, especially under visible light and photoredox catalysis, is a well-studied area but the *N*-aryl moiety limits its utility for the synthesis of complex, pharmaceutically active compounds since this fragment cannot be easily removed.[39,40] After having demonstrated that the A^3 redox a-C–H bond alkynylation of THIQs goes through two different mechanisms, photocatalyzed (Table 1) and copper-catalyzed (Table 3), where different reactive species are activated, we became interested in combining these approaches in one single strategy where those intermediates are simultaneously activated through these mechanisms to afford the coupling between THIQ (**5a**), 2-bromobenzaldehyde (**6a**) and phenylacetylene (**7a**) in what is called '*synergistic catalysis*'.[41]

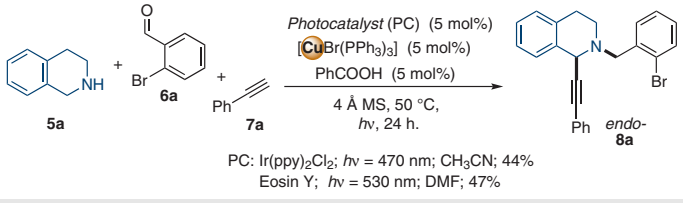
However, after having performed these experiments with the iridium and eosin Y photocatalysts, and with the optimal copper catalyst along with PhCOOH as an additive, we found that the efficiency of the process was quite similar to the one obtained solely with the $Ir(ppy)_2Cl_2$ catalyst



Scheme 3 Synthesis of 1-alkynyl THIQs **8a–s** through A^3 coupling catalyzed by [CuBr(PPh$_3$)$_3$] and assisted by microwave irradiation. *Reagents and conditions*: **5a,b** (1.4 equiv), **6a–j** (1.4 equiv), **7a–e** (1 equiv), [CuBr(PPh$_3$)$_3$] (5 mol%), PhCOOH (5 mol%), CH_3CN (0.2 M), molecular sieves (300 mg), MW, 120 °C, 15 min. NR: no reaction.

(Table 1, entry 10), while a promising synergic effect was observed when the reaction was performed using eosin Y as a photocatalyst where the reaction yield increased to 47% (Scheme 4); nevertheless, this approach did not reach the expected efficiency compared with the results obtained under the copper approach (Table 3, entry 13).

In summary, we have studied the A^3 redox-neutral C1-alkynylation of tetrahydroisoquinolines under visible light photocatalysis and transition-metal catalysis. To the best of our knowledge, this is the first approach in which the functionalization of THIQs through this coupling reaction has been studied under visible light and with metal catalysts and organophotocatalysts, besides the elegant works reported so far which focused on the photocatalytic coupling



Scheme 4 Synergic approach, between photocatalysis and copper catalysis, for the synthesis of 1-alkynyl THIQ **8a** through A^3 coupling

between aldehydes, alkynes and amines for the synthesis of propargylamines. Although, the moderate yields obtained did not encourage us to extend these conditions for the synthesis of a small library of 1-alkynyl THIQs.

Moreover, the transition-metal approach to the target compounds required the establishment of a mild and accessible protocol for the synthesis of THIQs from unreactive and uncommon substrates, a process that could be accelerated by microwave irradiation. After a series of silver catalysts were explored, copper salts were found to be more efficient and, by including an accessible additive to the reaction, the yields and selectivity were successfully improved in a simple and rapid methodology assisted by microwave irradiation. A few drawbacks of the already reported reaction conditions were overcome in our study; thus, the low catalyst and additive loading, mild reaction conditions, a substrate scope that includes unreactive aldehydes and alkynes, and the efficiency, speed and selectivity, in which valuable 1-alkynyl THIQs can be accessed, makes our protocol of broad interest to organic and medicinal chemists. Further studies are being actively pursued by our research group to apply this protocol with different nucleophiles instead of terminal alkynes, and to explore different synthetic manipulations of the alkyne and *N*-substituent moieties for the synthesis of more complex molecules.

Unless otherwise noted, all reactions were carried out with distilled and dried solvents and under atmospheric pressure. All workup and purification procedures were carried out with reagent grade solvents (purchased from Aldrich and Merck) in air. TLC was performed using Merck silica gel 60 F254 precoated plates (0.25 mm). Column chromatography was performed using spherical silica gel 70 Å, 40–75 mm. Infrared (FT-IR) spectra were recorded on a Shimadzu IR Prestige 21 spectrophotometer; the wavenumbers of the absorption peaks are listed in cm^{-1}. ^1H NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: d 7.26 ppm). Data are reported as follows: chemical shift, multiplicity (standard abbreviations), coupling constant(s) (Hz) and integration. ^{13}C NMR spectra were recorded on a Bruker Avance-400 (400 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: d 77.00 ppm). High-resolution mass spectra (HRMS) were measured on a Bruker ESI-micro Q-TOF III (Bruker Daltonics) apparatus. The photochemical experiments were performed with light sources of 470 and 530 nm driven by an Autolab LED driver kit operated with an electrochemical workstation (PGSTAT302, Metrohm).

1-Alkynyl THIQs 8a–s through A³ Coupling; General Procedure

A crimper vial equipped with a magnetic stir bar was charged with 1,2,3,4-tetrahydroisoquinoline **5a**,**b** (1.4 equiv), aldehyde **6a–j** (1.4 equiv), alkyne **7a–e** (1 equiv), [$CuBr(PPh_3)_3$] (5 mol%), PhCOOH (5 mol%) and 4 Å molecular sieves (300 mg). The vial was sealed and purged three times with argon, and degassed CH_3CN (0.2 M) was added. Then, the reaction mixture was heated at 120 °C for 15 min under microwave irradiation. After cooling to room temperature, the crude mixture was loaded directly onto Celite, then purified by column chromatography (silica gel) using petroleum ether (PE)/ethyl acetate (EA) mixtures as the eluent.

2-(2-Bromobenzyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (8a)

Yellow liquid; yield: 90 mg (0.22 mmol, 98%); R_f = 0.33 (PE/EA, 30:1).

IR (neat): 3060, 2093, 1708, 1694, 1600, 1574, 1338, 1239, 1160, 1113, 1024, 788, 744, 709, 646, 576 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 7.7, 1.5 Hz, 1 H), 7.64 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.56–7.51 (m, 2 H), 7.37 (m, 5 H), 7.27–7.24 (m, 2 H), 7.23–7.17 (m, 2 H), 4.97 (s, 1 H), 4.16 (d, *J* = 15.4 Hz, 1 H), 4.10 (d, *J* = 15.4 Hz, 1 H), 3.28–3.08 (m, 2 H), 2.89–2.83 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.8, 135.5, 134.1, 132.9, 131.8 (2 C), 130.7, 129.1, 128.5, 128.2, 128.1 (2 C), 127.8, 127.3, 127.0, 125.9, 124.9, 123.2, 87.7, 86.8, 58.9, 54.7, 45.8, 29.2.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{20}BrN$ $[M + H]^+$: 402.0852; found: 402.0901.

2-Benzyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (8b)

Colorless oil; yield: 73 mg (0.22 mmol, 73%); R_f = 0.3 (PE/EA, 30:1).

IR (neat): 3025, 2915, 2822, 2245, 1625, 1488, 734, 689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.55–7.49 (m, 4 H), 7.40 (t, *J* = 7.3 Hz, 3 H), 7.37–7.30 (m, 4 H), 7.24–7.18 (m, 3 H), 4.86 (s, 1 H), 4.03 (d, *J* = 13.3 Hz, 1 H), 3.98 (d, *J* = 13.3 Hz, 1 H), 3.21–3.02 (m, 2 H), 2.94–2.78 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.3, 135.5, 134.1, 131.8 (2 C), 129.3 (2 C), 129.0, 128.3 (2 C), 128.2 (2 C), 128.0, 127.8, 127.2, 126.9, 125.8, 123.3, 87.5, 86.9, 59.6, 54.4, 45.8, 29.0.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{21}N$ $[M + H]^+$: 324.1747; found: 324.1775.

2-(2-Bromobenzyl)-1-(*p*-tolylethynyl)-1,2,3,4-tetrahydroisoquinoline (8c)

Colorless oil; yield: 77 mg (0.18 mmol, 88%); R_f = 0.30 (PE/EA, 15:1).

IR (neat): 3060, 3024, 2115, 1693, 1651, 1604, 1436, 1023, 815, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.61 (dd, *J* = 7.7, 1.4 Hz, 1 H), 7.57 (dd, *J* = 8.0, 1.1 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 7.33–7.25 (m, 2 H), 7.20–7.17 (m, 2 H), 7.18–7.11 (m, 2 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 4.88 (s, 1 H), 4.11–3.99 (m, 2 H), 3.20–3.01 (m, 2 H), 2.89–2.75 (m, 2 H), 2.34 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.2, 138.0, 135.7, 134.1, 132.9, 131.8 (2 C), 130.8, 129.1, 129.0 (2 C), 128.5, 127.9, 127.3, 127.0, 125.9, 124.9, 120.2, 87.0, 86.9, 59.0, 54.8, 45.9, 29.3, 21.5.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}BrN$ $[M + H]^+$: 416.1008; found: 416.0993.

2-(2-Bromobenzyl)-1-((4-methoxyphenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (8d)

Colorless oil; yield: 98 mg (0.23 mmol, 95%); R_f = 0.33 (PE/EA, 15:1).

IR (neat): 3060, 2902, 2833, 2118, 1651, 1603, 1507, 1245, 1024, 830, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 7.6, 1.4 Hz, 1 H), 7.69 (dd, *J* = 7.9, 1.0 Hz, 1 H), 7.53 (d, *J* = 8.9 Hz, 2 H), 7.44–7.37 (m, 2 H), 7.34–7.26 (m, 2 H), 7.26–7.20 (m, 2 H), 6.93 (d, *J* = 8.9 Hz, 2 H), 5.02 (s, 1 H), 4.20–4.13 (m, 2 H), 3.86 (s, 3 H), 3.33–3.12 (m, 2 H), 2.98–2.88 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.4, 137.8, 135.7, 134.0, 133.2 (2 C), 132.8, 130.6, 129.0, 128.5, 127.8, 127.3, 126.9, 125.8, 124.8, 115.3, 113.8 (2 C), 86.6, 86.1, 58.9, 55.2, 54.8, 45.8, 29.2.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{22}BrNO$ [M + H]$^+$: 432.0958; found: 432.0940.

2-(Furan-2-ylmethyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (8e)

Yellow oil; yield: 80 mg (0.25 mmol, 80%); R_f = 0.33 (PE/EA, 15:1).

IR (neat): 3022, 2912, 2822, 2089, 1597, 1488, 1147, 729, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.46 (m, 2 H), 7.46–7.42 (m, 1 H), 7.34–7.31 (m, 4 H), 7.21–7.17 (m, 2 H), 7.14 (dd, *J* = 6.3, 2.7 Hz, 1 H), 6.39 (d, *J* = 1.6 Hz, 2 H), 4.85 (s, 1 H), 4.00 (q, *J* = 14.0 Hz, 2 H), 3.17–3.01 (m, 2 H), 2.94–2.84 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 151.7, 142.4, 135.1, 133.8, 131.8 (2 C), 128.9, 128.2 (2 C), 128.1, 127.8, 126.9, 125.8, 123.1, 110.1, 109.0, 87.1, 86.9, 54.3, 51.9, 45.9, 28.9.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{19}NO$ [M + H]$^+$: 314.1539; found: 314.1594.

2-Methyl-4-(2-((1-methyl-1*H*-indol-3-yl)methyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)but-3-yn-2-ol (8f)

Yellow oil; yield: 73 mg (0.20 mmol, 73%); R_f = 0.1 (PE/EA, 5:1).

IR (neat): 3357, 2977, 2922, 2825, 2242, 1565, 1436, 1258, 1162, 1133, 1023, 946, 745, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.9 Hz, 1 H), 7.34 (d, *J* = 8.2 Hz, 1 H), 7.26 (ddd, *J* = 8.1, 7.0, 1.0 Hz, 1 H), 7.20–7.10 (m, 6 H), 4.70 (s, 1 H), 4.11 (d, *J* = 13.2 Hz, 1 H), 4.03 (d, *J* = 13.5 Hz, 1 H), 3.80 (s, 3 H), 3.07–2.93 (m, 2 H), 2.89–2.76 (m, 2 H), 2.08 (s, 1 H), 1.60 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.0, 135.6, 134.2, 128.8, 128.6, 128.4, 127.7, 126.7, 125.6, 121.6, 119.8, 118.9, 111.0, 109.1, 91.2, 80.5, 65.3, 53.7, 50.3, 45.8, 32.7, 31.8, 31.7, 29.1.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{26}N_2O$ [M + H]$^+$: 359.2118; found: 359.2171.

4-(2-Benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-methylbut-3-yn-2-ol (8g)

Yellow oil; yield: 70 mg (0.23 mmol, 70%); R_f = 0.33 (PE/EA, 5:1).

IR (neat): 3384, 3061, 3025, 2978, 2823, 2242, 1624, 1492, 1452, 1359, 1163, 1132, 946, 908, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.48–7.44 (m, 2 H), 7.39–7.34 (m, 3 H), 7.19–7.11 (m, 4 H), 4.61 (s, 1 H), 3.92 (d, *J* = 13.1 Hz, 1 H), 3.82 (d, *J* = 13.1 Hz, 1 H), 3.02–2.96 (m, 2 H), 2.83–2.75 (m, 2 H), 2.02 (s, 1 H), 1.57 (s, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 138.2, 135.4, 134.0, 129.2 (2 C), 128.9, 128.3 (2 C), 127.7, 127.2, 126.8, 125.7, 91.4, 79.9, 65.3, 59.5, 53.7, 45.7, 31.7, 31.7, 28.9.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{23}NO$ [M + H]$^+$: 306.1852; found: 306.1883.

4-(2-(2-Bromobenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-methylbut-3-yn-2-ol (8h)

Yellow oil; yield: 70 mg (0.18 mmol, 70%); R_f = 0.23 (PE/EA, 5:1).

IR (neat): 3357, 2977, 2922, 2825, 2242, 1565, 1436, 1258, 1162, 1133, 1023, 946, 745, 729 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (ddd, *J* = 7.9, 3.2, 1.5 Hz, 2 H), 7.31 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.24–7.12 (m, 5 H), 4.71 (s, 1 H), 3.96 (s, 2 H), 3.12–2.97 (m, 2 H), 2.87–2.73 (m, 2 H), 1.98 (s, 1 H), 1.57 (d, *J* = 2.0 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.7, 135.3, 134.0, 132.8, 130.5, 128.9, 128.4, 127.6, 127.3, 126.9, 125.7, 124.7, 91.3, 80.0, 65.3, 58.7, 54.0, 45.6, 31.7, 31.7, 29.1.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{22}BrNO$ [M + H]$^+$: 384.0958; found: 384.0985.

4-(2-(4-Methoxybenzyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-2-methylbut-3-yn-2-yl Acetate (8i)

Yellow oil; yield: 50 mg (0.13 mmol, 50%); R_f = 0.33 (PE/EA, 5:1).

IR (neat): 3060, 2935, 2836, 1735, 1692, 1597, 1510, 1243, 1158, 1025, 831, 745 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.7 Hz, 2 H), 7.24–7.10 (m, 5 H), 6.91 (d, *J* = 8.7 Hz, 1 H), 4.59 (s, 1 H), 3.89 (d, *J* = 12.9 Hz, 1 H), 3.84 (s, 3 H), 3.80 (d, *J* = 12.9 Hz, 1 H), 3.04–2.94 (m, 2 H), 2.85–2.74 (m, 2 H), 2.06 (s, 3 H), 1.71 (d, *J* = 3.9 Hz, 6 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.2, 158.7, 135.4, 134.1, 130.5, 130.3 (2 C), 128.8, 127.8, 126.7, 125.7, 113.6 (2 C), 87.6, 82.2, 72.2, 58.6, 55.2, 53.5, 45.8, 29.3, 29.2, 29.0, 22.0.

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{27}NO_3$ [M + H]$^+$: 378.2064; found: 378.2102.

2-((1-Methyl-1*H*-indol-3-yl)methyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (8j)

Yellow oil; yield: 20 mg (0.05 mmol, 20%); R_f = 0.26 (PE/EA, 5:1).

IR (neat): 3054, 2909, 2818, 1326, 907, 734, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.87 (d, J= 7.9 Hz, 1 H), 7.51 (dd, J= 6.7, 3.0 Hz, 3 H), 7.36–7.32 (m, 4 H), 7.28–7.24 (m, 2 H), 7.20–7.14 (m, 4 H), 4.93 (s, 1 H), 4.18 (d, *J* = 2.1 Hz, 2 H), 3.80 (s, 3 H), 3.20–2.80 (m, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 137.2, 135.7, 134.3, 132.3, 132.2, 131.9 (2 C), 129.0, 128.9, 128.3 (2 C), 128.1, 127.9, 126.9, 125.8, 123.5, 121.7, 120.0, 119.1, 109.2, 88.1, 86.9, 54.3, 50.5, 46.0, 32.8, 29.2.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{24}N_2$ [M + H]$^+$: 377.2012; found: 377.2045.

1-(Phenylethynyl)-2-(thiophen-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (8k)

Yellow oil; yield: 98 mg (0.29 mmol, 98%); R_f = 0.33 (PE/EA, 15:1).

IR (neat): 2912, 2821, 2101, 1488, 737, 689 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58 (dd, *J* = 6.6, 3.0 Hz, 2 H), 7.40 (dd, *J* = 4.0, 2.6 Hz, 4 H), 7.37 (dd, *J* = 5.1, 1.0 Hz, 1 H), 7.31–7.27 (m, 2 H), 7.25 (q, *J* = 5.6 Hz, 1 H), 7.20 (d, *J* = 3.3 Hz, 1 H), 7.10 (dd, *J* = 5.0, 3.5 Hz, 1 H), 5.04 (s, 1 H), 4.28 (q, *J* = 13.8 Hz, 2 H), 3.26–3.11 (m, 2 H), 3.06–2.89 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 141.9, 135.2, 134.0, 131.8 (2 C), 129.0, 128.2 (2 C), 128.1, 127.8, 127.0, 126.5, 126.3, 125.9, 125.2, 123.1, 87.3, 86.9, 54.3, 54.0, 45.6, 29.1.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{19}NS$ [M + H]$^+$: 330.1311; found: 330.1343.

1-(Phenylethynyl)-2-(pyridin-4-ylmethyl)-1,2,3,4-tetrahydroisoquinoline (8l)

Yellow oil; yield: 73 mg (0.22 mmol, 73%); R_f = 0.26 (PE/EA, 15:1).

IR (neat): 3022, 2914, 2823, 2113, 1598, 1488, 1412, 732, 689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.57 (d, *J* = 2.2 Hz, 2 H), 7.45–7.41 (m, 2 H), 7.40 (d, *J* = 5.6 Hz, 2 H), 7.29 (ddt, *J* = 7.0, 5.7, 2.1 Hz, 4 H), 7.21–7.17 (m, 2 H), 7.14 (dd, *J* = 6.9, 2.1 Hz, 1 H), 4.79 (s, 1 H), 3.93 (d, *J* = 1.8 Hz, 2 H), 3.14–3.00 (m, 2 H), 2.85–2.75 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 149.8 (2 C), 147.8, 135.1, 133.7, 131.7 (2 C), 129.0, 128.2 (2 C), 128.2, 127.2 (2), 127.1, 125.9, 124.0, 122.9, 86.9, 86.9, 58.5, 54.6, 45.9, 29.0.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{20}N_2$ [M + H]$^+$: 325.1699; found: 325.1718.

2-Neopentyl-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (8m) + 8m′

Compound **8m** was very difficult to separate from its regioisomer (*exo*-form **8m′**). All spectra showed the signal features of the two isomers. Peak assignment in the ^1H NMR spectrum was simpler for the *endo*-form:

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.43 (m, 2 H), 7.39–7.27 (m, 4 H), 7.25–7.13 (m, 3 H), 4.87 (s, 1 H), 4.09–3.84 (m, 2 H), 3.21–2.97 (m, 2 H), 2.94–2.74 (m, 2 H), 1.00 (s, 9 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 136.2, 135.0, 134.4, 133.6, 132.1, 131.6, 129.0, 128.5, 128.2, 128.1, 127.7, 126.7, 125.4, 123.4, 87.5, 85.0, 67.4, 55.7, 48.6, 33.3, 29.6, 27.4.

HRMS (ESI): *m*/*z* calcd for $C_{22}H_{25}N$ [M + H]$^+$: 304.2060; found: 304.2095.

2-(4-Methoxybenzyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (8o)

Yellow liquid; yield: 98 mg (0.27 mmol, 98%); R_f = 0.23 (PE/EA, 30:1).

IR (neat): 2925, 2819, 2115, 1605, 1508, 1439, 1293, 1242, 1026, 817, 738, 688, 543 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.47 (m, 2 H), 7.43 (d, *J* = 8.6 Hz, 2 H), 7.35–7.28 (m, 4 H), 7.22–7.15 (m, 3 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 4.81 (s, 1 H), 3.93 (d, *J* = 12.9 Hz, 1 H), 3.89 (d, *J* = 12.8 Hz, 1 H), 3.85 (s, 3 H), 3.17–3.01 (m, 2 H), 2.91–2.80 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 158.8, 135.4, 134.1, 131.8 (2 C), 130.5, 130.2, 129.0, 128.2 (2 C), 128.0, 127.8, 126.9, 125.8, 123.2, 113.7 (2), 87.5, 86.9, 58.9, 55.3, 54.1, 45.7, 29.0.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{23}NO$ [M + H]$^+$: 354.1952; found: 354.1907.

2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-(phenylethynyl)-1,2,3,4-tetrahydroisoquinoline (8p)

Yellow oil; yield: 30 mg (0.082 mmol, 30%); R_f = 0.23 (PE/EA, 30:1).

IR (neat): 2894, 2828, 1687, 1650, 1601, 1486, 1440, 1241, 1035, 926, 736, 689 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.46 (m, 2 H), 7.34–7.28 (m, 4 H), 7.23–7.14 (m, 3 H), 7.03 (d, *J* = 1.5 Hz, 1 H), 6.96–6.92 (m, 1 H), 6.81 (d, *J* = 7.9 Hz, 1 H), 5.99–5.96 (m, 2 H), 4.82 (s, 1 H), 3.93–3.79 (m, 2 H), 3.14–3.02 (m, 2 H), 2.89–2.79 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 147.7, 146.7, 135.4, 134.1, 132.2, 131.8 (2 C), 129.0, 128.2 (2 C), 128.0, 127.8, 126.9, 125.8, 123.2, 122.3, 109.6, 107.9, 100.9, 87.4, 86.8, 59.3, 54.1, 45.6, 29.0.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{21}NO_2$ [M + H]$^+$: 368.1645; found: 368.1663.

2-(4-Methoxybenzyl)-1-((4-methoxyphenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (8q)

Yellow oil; yield: 98 mg (0.25 mmol, 98%); R_f = 0.23 (PE/EA, 15:1).

IR (neat): 3001, 2906, 2833, 1681, 1603, 1507, 1242, 1164, 1029, 830, 742 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.8 Hz, 4 H), 7.28–7.21 (m, 1 H), 7.17–7.09 (m, 3 H), 6.87 (d, *J* = 8.6 Hz, 2 H), 6.82 (d, *J* = 8.8 Hz, 2 H), 4.74 (s, 1 H), 3.85 (d, *J* = 6.5 Hz, 2 H), 3.80 (s, 3 H), 3.79 (s, 3 H), 3.11–2.93 (m, 2 H), 2.85–2.73 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5, 158.9, 135.8, 134.2, 133.3 (2 C), 130.5 (2 C), 129.1, 127.9, 126.9, 125.9, 115.5, 114.4, 113.9 (2 C), 113.8 (2 C), 86.7, 86.1, 59.0, 55.4, 55.4, 54.3, 45.7, 29.2.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{25}NO_2$ [M + H]$^+$: 384.1958; found: 384.1993.

2-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-1-((4-methoxyphenyl)-ethynyl)-1,2,3,4-tetrahydroisoquinoline (8r)

Colorless oil; yield: 20 mg (0.05 mmol, 20%); R_f = 0.16 (PE/EA, 30:1).

IR (neat): 2896, 2833, 1686, 1603, 1505, 1487, 1242, 1033 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.39 (m, 2 H), 7.31–7.27 (m, 1 H), 7.21–7.13 (m, 3 H), 7.02 (d, *J* = 1.4 Hz, 1 H), 6.94 (dd, *J* = 8.0, 1.3 Hz, 1 H), 6.87–6.83 (m, 2 H), 6.81 (d, *J* = 7.9 Hz, 1 H), 5.97 (d, *J* = 2.2 Hz, 2 H), 4.79 (s, 1 H), 3.86 (d, *J* = 3.7 Hz, 2 H), 3.83 (s, 3 H), 3.13–3.01 (m, 2 H), 2.88–2.79 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.4, 147.6, 146.7, 135.7, 134.0, 133.1 (2 C), 132.3, 128.9, 127.8, 126.8, 125.8, 122.3, 115.3, 113.8 (2 C), 109.6, 107.9, 100.8, 86.6, 85.9, 59.3, 55.3, 54.2, 45.6, 29.0.

HRMS (ESI): *m*/*z* calcd for $C_{26}H_{23}NO_3$ [M + H]$^+$: 398.1751; found: 398.1473.

6-Methoxy-2-(4-methoxybenzyl)-1-((4-methoxyphenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline (8s)

Colorless oil; yield: 30 mg (0.07 mmol, 30%); R_f = 0.33 (PE/EA, 30:1).

IR (neat): 2908, 2832, 1605, 1505, 1242, 1170, 1030, 830 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 7.5 Hz, 4 H), 7.20 (d, *J* = 8.5 Hz, 1 H), 6.91 (d, *J* = 8.7 Hz, 2 H), 6.86 (d, *J* = 8.9 Hz, 2 H), 6.76 (dd, *J* = 8.4, 2.7 Hz, 1 H), 6.68 (d, *J* = 2.5 Hz, 1 H), 4.73 (s, 1 H), 3.89 (d, *J* = 10.3 Hz, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.80 (s, 3 H), 3.12–2.96 (m, 2 H), 2.93–2.75 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.3, 158.8, 158.4, 135.3, 133.1 (2 C), 130.5 (2 C), 130.4, 128.8, 128.1, 115.5, 113.8 (2 C), 113.6 (2 C), 113.3, 112.3, 86.4, 86.2, 58.9, 55.2 (3), 53.7, 45.5, 29.3.

HRMS (ESI): *m*/*z* calcd for $C_{27}H_{27}NO_3$ [M + H]$^+$: 414.2064; found: 414.2113.

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Supporting Information

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