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ARTICLE TYPE

Efficient Merging of Copper and Photoredox Catalysis for the Asymmetric Cross-Dehydrogenative-Coupling of Alkynes and Tetrahydroisoquinolines

Inna Perepichka, Soumen Kundu, Zoë Hearne and Chao-Jun Li*

A highly efficient catalytic asymmetric alkynylation of prochiral CH$_2$ groups in tetrahydroisoquinoline was developed using copper catalyzed cross-dehydrogenative-coupling of sp^3 and sp C-H bonds with the assistance of a
10 photocatalyst and visible light.

Selective cross-coupling reactions for C–C bond formation via direct activation of C–H bonds under oxidizing conditions (cross-dehydrogenative-coupling, CDC) provide an atom economical and sustainable alternative to classical cross-coupling protocols.[1-8]
15 In the last decade, CDC methodologies formulated by us[9-16] and further developed by others[17-22] have provided a plethora of novel single-step routes to create C–C bonds, thus responding to the ever-growing demand for 'green' innovation in chemical design and synthesis. We have previously reported the CDC reaction for
20 alkynylation of tertiary amines, whereby an sp^3 C–H bond α to a tertiary nitrogen atom, and an sp C–H bond of a terminal alkyne were simultaneously activated by a CuBr/^{t}BuOOH catalyzed process.[9] This provides access to propargylic amines, which are valuable synthetic intermediates.[23-26] An enantioselective
25 variation of this reaction was realized in the presence of catalytic bis(oxazoline)-based PyBox chiral ligand (**L1**, Figure 1),[27, 28] in which direct activation of the prochiral CH$_2$ group in *N*-aryl-tetrahydroisoquinolines resulted in the synthesis of biologically active chiral C-1 substituted tetrahydroisoquinoline alkaloid
30 derivatives (Scheme 1A). This methodology has advantages over contemporary methods that require pre-synthesis of imine or iminium substrates.[29] Yu et al. performed this reaction under high-speed ball-milling under solvent free conditions, using recoverable copper balls with PyBox ligand and stoichiometric
35 2,3-dichloro-5,6-dicyanobenzoquinone as oxidant to synthesize optically active 1-alkynyl tetrahydroisoquinoline derivatives (Scheme 1B).[30] However, in both aforementioned cases, the optically active products were formed in only moderate yields[28, 30] and enantiomeric excesses (Scheme 1A and 1B)[28, 30]. This
40 motivated us to develop a novel concept to overcome these challenges.

Reaction temperature has a profound impact on the enantioselectivity of stereoselective reactions; lowering the temperature often results in better selectivity.[31] However, while
45 our previously reported CDC methodology is effective at 50 °C to produce optically active compounds, the desired coupling products are not observed at lower temperatures.[27]

On the other hand, following MacMillan and co-workers'

ground–breaking studies on photoredox organic reactions using
50 visible light,[32, 33] which have since been developed by Stephenson,[34, 35] Sanford,[36, 37] Yoon[38-40] and others,[41] metal (Ru and Ir) polypyridyl complexes[41-44] and metal-free organic dye-sensitizers[45-47] have been used to substitute *N*-aryl-tetrahydroisoquinolines at the C1 position with a variety of
55 nucleophiles (cyanide, nitroalkane, trifluoromethyl, dialkyl malonates, dialkyl phosphonates, terminal alkynes etc.). The most appealing feature of photoredox catalysis, for our current objectives, is the requirement of very mild conditions (room and low temperature), thereby providing great opportunities for
60 asymmetric synthesis.

Herein, *we report a highly efficient catalytic asymmetric alkynylation of prochiral CH$_2$ groups in N-aryl-tetrahydroisoquinolines by combining a photoredox process with a chiral copper catalyst*. The reaction produces optically active 1-
65 alkynyl tetrahydroisoquinoline derivatives in the highest yield and enantiomeric excess reported so far (Scheme 1) by using a photocatalyst ([Ru(bpy)$_3$](PF$_6$)$_2$ or [Ir(ppy)$_2$(d$t$bbpy)]PF$_6$) under visible light irradiation together with CuBr/chiral ligand (**L**, Figure 1) and benzoyl peroxide as the terminal oxidant. Such
70 merging of a photocatalyst and a metal catalyst (or organocatalyst) is an attractive alternative to traditional cross-coupling reactions; it produces valuable fine chemicals that cannot be accessed by independent use of these catalysts.[41, 48, 49] Enantioselective variations of such a dual catalysis approach is
75 still very rare.[49, 50]
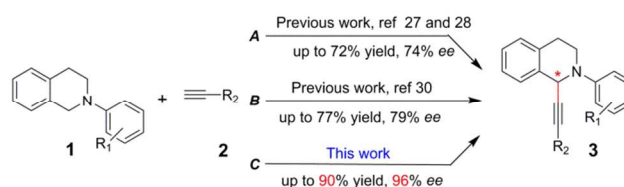
Scheme 1. Enantioselective alkynylation of *N*-aryl-tetrahydroisoquinoline

We started our investigation of the photocatalyzed
80 enantioselective oxidative CDC reaction between an alkyne and tertiary amine using prototype substrates *N*-phenyl-tetrahydroisoquinoline and phenylacetylene, and employing photosensitizer [Ru(bpy)$_3$](PF$_6$)$_2$[38] in CH$_3$CN under visible light irradiation, in the presence of CuOTf, ^{t}BuOOH , and bisoxazoline
85 chiral ligand **L1** at room temperature (RT). Desired product was

not observed under these conditions after 24 h. Changing the oxidant from ^{t}BuOOH to benzoyl peroxide, (BzO)$_2$, allowed the alkynylation reaction to proceed with good yield (70%), but poor enantioselectivity (*ee* 8%, Table 1, entry 1). Variation of chiral
₅ ligand (**L2** – **L4**) and copper salt (CuOTf and CuCl, Table 1, entries 2 – 5) resulted in a slight improvement in enantioselectivity (24% *ee*, Table 1, entry 5, **L4** and CuCl). Acetonitrile is a coordinating solvent,[51] and as such can hinder the chiral induction of ligands (**L**).[52] Our efforts to screen less
₁₀ coordinating solvents was hampered by the low solubility of [Ru(bpy)$_3$](PF$_6$)$_2$ in common organic solvents. Hence, we replaced [Ru(bpy)$_3$](PF$_6$)$_2$ by the more potent photoredox catalyst [Ir(ppy)$_2$(d$t$bbpy)]PF$_6$,[42] which is highly soluble in most organic solvents (Table 1, entries 6 – 17). Chiral ligand **L5** provided good
₁₅ enantioselectivities (*ee* 79 and 86%, Table 1 entries 9 and 11, respectively) at room temperature in THF using copper (I) catalysts CuBr and CuCl (Table 1, entries 9 and 11). However, these reactions resulted in only moderate yields of the desired products (41 and 30%, Table 1 entries 9 and 11, respectively) and
₂₀ low overall conversion of the starting material (ca. 50%). In CH$_3$CN with a CuBr catalyst the reaction yield considerably improved (87%, with 100% conversion) with concomitant lowering of enantioselectivity (*ee* 70%, Table 1, entry 10). Other combinations of chiral ligands (**L**), copper (I/II) salts, and
₂₅ solvents were ineffective in increasing enantioselectivities (Table 1, entries 6 – 8 and 12 – 17). The reaction did not proceed in the absence of copper salt (Supporting Information, SI). The product yield was drastically reduced when either the photosensitizer was omitted (24% yield, SI) or the reaction was conducted in dark
₃₀ (16% yield, SI). No improvement in enantioselectivity (*ee*) or product yield was observed upon increasing the amounts of phenylacetylene or chiral ligand **L** (SI).

Finally, the effect of temperature and solvent combination on the reaction enantioselectivity (*ee*) and yield was evaluated
₃₅ (Table 2). In THF and CH$_3$CN, predictably, the enantioselectivity (*ee*) of the reactions systematically increased with lowering of reaction temperature (Table 2, entries 1 – 6). At −20 °C, the reaction in THF provided the best enantioselectivity (97% *ee*) but the lowest yield (46%), whereas high yield (80%) but somewhat
₄₀ inferior enantioselectivity (93%) was obtained in CH$_3$CN (Table 2, entries 3 and 6). A compromise was achieved by using a solvent mixture of THF and CH$_3$CN (1:1) at −20 °C which resulted in 94% enantioselectivity and 64% yield (Table 2, entry 8). In the same solvent mixture, reaction at −40 °C resulted in
₄₅ further improvement of enantioselectivity (96%, Table 2, entry 9) and yield (75%, Table 2, entry 9). Although in this case the reaction time was twice as long (~ 4 d) compared to that at −20 °C.
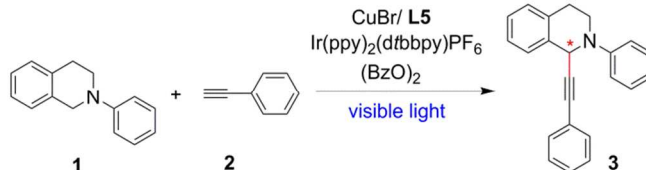
₅₀
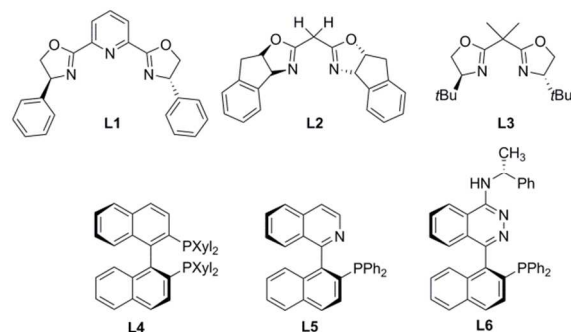
Figure 1. Chiral ligands (**L**) used. **L1** = (*S*)-PyBox, **L2** = (*S,S-R,R*)-Box1, **L3** = (*R*)-Box2, **L4** = (*R*)-XylBINAP, **L5** = (*R*)-QUINAP, **6** = (*R,R*)-N-PINAP.

₅₅ **Table 1**. Effect of Copper Salt and Chiral Ligand (**L**: Figure 1) on the Enantioselectivity of Coupling *N*-phenyl-tetrahydroisoquinoline with Phenylacetylene at RT[a]
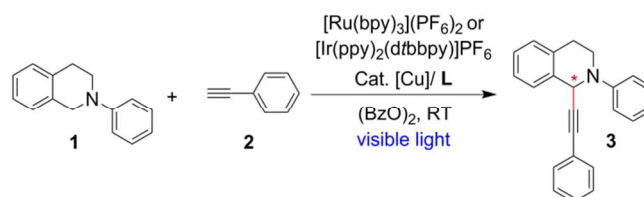
Entry	Cat.[Cu]	L	Solvent	*ee*[d] (%)
1 [b]	CuOTf	**L1**	CH$_3$CN	8
2 [b]	CuOTf	**L2**	CH$_3$CN	4
3 [b]	CuOTf	**L3**	CH$_3$CN	2
4 [b]	CuOTf	**L4**	CH$_3$CN	5
5 [b]	CuCl	**L4**	CH$_3$CN	24
6 [c]	CuCl	**L4**	DCM	1
7 [c]	CuCl	**L4**	THF	34
8 [c]	CuCl	**L5**	CH$_3$CN	22
9 [c]	CuCl	**L5**	THF	79(41)[e]
10 [c]	CuBr	**L5**	CH$_3$CN	70(87)[e]
11 [c]	CuBr	**L5**	THF	86(30)[e]
12 [c]	CuBr$_2$	**L5**	THF	17
13 [c]	CuI	**L5**	THF	27
14 [c]	CuBr	**L6**	THF	7
15 [c]	CuBr	**L6**	Toluene	8
16 [c]	CuBr	**L6**	DCM	2
17 [c]	CuBr	**L6**	CH$_3$CN	9

[a] Conditions: 0.1 mmol *N*-phenyl-tetrahydroisoquinoline, 0.1 mmol
₆₀ phenylacetylene, 10 mol % copper salt, 15 mol % chiral ligand (**L**), 1 mol % [Ru(bpy)$_3$](PF$_6$)$_2$ (entries 1-5) [b] or Ir(ppy)$_2$(d$t$bbpy)PF$_6$ (entries 6-17), [c] and 0.12 mmol (BzO)$_2$, 20 h reaction time, RT. [d] The *ee* values were determined with HPLC by using a Chiralcel OD-H column and 4:96 hexane/isopropanol as an eluent (SI). [e] The yields in parenthesis were
₆₅ calculated by ^{1}H NMR integration method using CH$_3$NO$_2$ as an internal standard (SI).

Table 2. Effect of Solvent and Temperature on the Enantioselectivity of Coupling of *N*-phenyl-tetrahydroisoquinoline with Phenylacetylene

Entry [a]	Solvent	T / °C	ee [b] / %
1		22	86
2	THF	4	92
3		−20	97 (46) [c]
4		22	70
5	CH₃CN	4	88
6		−20	93 (80) [c]
7		22	79 (75) [c]
8	THF/CH₃CN (1:1)	−20	94 (64) [c]
9		−40	**96 (75)** [c]

[a] Conditions: 0.1 mmol tetrahydroisoquinoline, 0.1 mmol phenylacetylene, 10 mol % CuBr, 15 mol % **L5**, 1 mol % [Ir(ppy)₂(d*t*bbpy)]PF₆, and 0.12 mmol (BzO)₂, reaction times and temperatures: 20 h/22 °C (RT), 46 h/4 °C, 48 h/−20 °C, 90 h/−40 °C. [b] The enantiomeric excess was determined as described in Table 1 (SI). [c] In parenthesis, the yield was calculated as described in Table 1 (SI)

With the optimized conditions in hand we investigated the effect that substituents on *N*-phenyl-tetrahydroisoquinoline (**1**, Table 3) and terminal alkyne (**2**, Table 3) had on the reaction enantioselectivity and yield (Table 3). To expedite the substrate scope analysis reactions were performed at −20 °C (for most substrates, Table 3), to reach a compromise between reaction time and enantioselectivity. Terminal alkynes with *n*-alkyl or aryl substituents all afforded the corresponding products (**3**, Table 3) in moderate to excellent yields (up to 90%) with high enantioselectivities (up to 94%). Moreover, functionalized aliphatic alkynes, such as TMS-acetylene (Table 3, entry 6), also produced the desired product (**3f**, Table 3) with good enantioselectivity and acceptable yield. The previously reported non-photoredox procedures either did not include this alkyne as substrates[28, 30] or produced the chiral product (**3f**, TMS) in very low yield (11%) and enantiomeric excess (30%).[28] Thus, this combination of photoredox catalysis and chiral metal catalysis further provides opportunities for attractive synthetic transformations tolerant of TMS functionality.[28, 30] Functional group variation of the alkyne had a moderate impact on the enantioselectivity (except TMS, Table 3, entries 1-6) but a more significant effect on reaction yields. Aliphatic alkynes resulted in chiral products with lower yields (Table 3, entries 4–6, 9, and 11) compared to aromatic alkynes. Lastly, we investigated the influence of substituents on the phenyl ring of the tetrahydroisoquinoline substrate (Table 3). Substituents at the *meta*- (OMe) and *para*- (Me) position had a minor influence on the enantioselectivities of the reaction (Table 3). However, *N*-(4-bromophenyl)-tetrahydroisoquinoline consistently afforded lower

yields with different alkynes (Table 3, entries 11 and 12). *N*-(2-methoxyphenyl)-tetrahydroisoquinoline was unstable under the oxidative reaction conditions[30, 41, 53] and instead of the desired CDC product produced the corresponding *N*-(2-methoxy)-tetrahydroisoquinoline amide (SI).[53] Gratifyingly, we found that changing the terminal oxidant from (BzO)₂ to O₂ (SI) (Scheme 3, entry 13) resulted in the formation of the desired product (**3m**) in good yield and enantiomeric excess.

Table 3. Enantioselectivity of Coupling between Tetrahydroisoquinolines with Terminal Alkynes in the Presence of a Photocatalyst and Visible Light.


Entry [a]	R₁	R₂	Compound	Yield [c] (%)	ee [d] / %
1	H	Ph	**3a**	64	94
2	H	4-MeOC₆H₄	**3b**	67	87
3	H	4-BrC₆H₄	**3c**	72	94
4	H	*n*-Bu	**3d**	48	87
5	H	*n*-Octyl	**3e**	57	82
6 [b]	H	TMS	**3f**	40	60
7	H	4-PhC₆H₄	**3g**	46	84
8	3-OMe	Ph	**3h**	55	94
9	3-OMe	*n*-Bu	**3i**	47	90
10	4-Me	4-MeOC₆H₄	**3j**	90	94
11	4-Br	*n*-Bu	**3k**	20	87
12	4-Br	4-MeOC₆H₄	**3l**	30	81
13 [e]	2-OMe	Ph	**3m**	80	80

[a] Conditions: 0.1 mmol tetrahydroisoquinoline, 0.15 mmol alkyne, 10 mol % CuBr, 15 mol % **L5**, 1 mol % [Ir(ppy)₂(d*t*bbpy)]PF₆ and 0.12 mmol (BzO)₂, visible light, reaction time 2 days at −20 °C. [b] Reaction time 2 days at 4 °C. [c] The yields are based on tetrahydroisoquinoline and were calculated as described in Table 1 (SI). [d] Determined as described in Table 1 (SI). [e] O₂ as a terminal oxidant in place of (BzO)₂. Reaction time 2 days at 4 °C. Yield was calculated based on conversion of **1** (SI).

Based on the well-established mechanism of photocatalyst Ru(bpy)₃/Ir(ppy)₂(d*t*bbpy) mediated organic reactions[32, 38, 40-42] and CDC reactions involving *N*-aryl-tetrahydroisoquinoline,[9, 27, 28, 54] we propose the following coupled pathways for product formation. In the photoredox catalytic cycle: upon interacting with visible light Ir^III is transformed to the redox-active photoexcited state Ir^III*, before being reductively quenched by single-electron-transfer (SET) from the nitrogen of *N*-aryl-tetrahydroisoquinoline (**1a**, Scheme 2) to generate Ir^II and an amine cation radical intermediate (**6a**, Scheme 2). Ir^II is re-oxidized to Ir^III by SET reduction of (BzO)₂ to the BzO⁻ anion and BzO• radical.[55] This benzoyloxy radical abstracts the benzylic hydrogen of **6a** to produce the reactive iminium ion intermediate (**7a**, Scheme 2). Deprotonation of α C-H in **6a**,

followed by 1-*e* oxidation of the generated α-amino radical can also produce **7a**.[41] The experimental data does not allow us to distinguish between these possibilities. In the CuBr mediated catalytic cycle, QUINAP (**L5**) binds to copper to form a chiral Cu-QUINAP (**Cu-1**) complex,[56, 57] which activates the terminal alkyne (**2a**, Scheme 2) to form a chiral Cu-QUINAP-acetylide species (**Cu-2**).[56, 57] Addition of nucleophilic, chiral acetylide (**Cu-2**) to electrophilic **7a** results in the formation of optically active 1-alkynyl tetrahydroisoquinoline (**3a**).[9, 27]
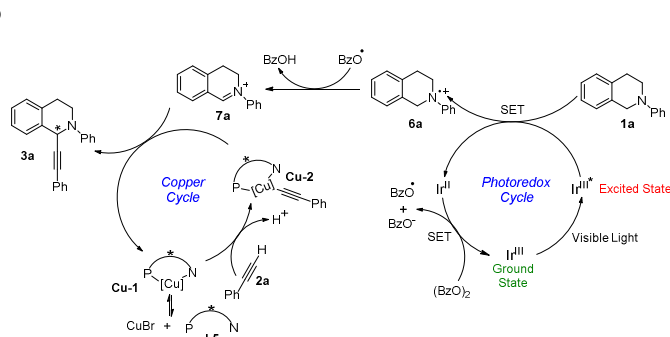
Scheme 2. Proposed mechanism

Conclusions

In summary, herein we report the first example of a highly efficient asymmetric cross-dehydrogenative-coupling reaction between tertiary amines and terminal alkynes. Synergistic photocatalytic and copper-catalyzed cycles cooperate to yield optically active 1-alkynyl tetrahydroisoquinolines in good yields (up to 90%) and excellent enantioselectivities (up to 96%). With *N*-aryl-tetrahydroisoquinolines as a 'proof-of-concept' substrate, we believe that this method can become a general approach to optically active propargylic amines. This combination of a photocatalyst and chiral copper catalysis provides an excellent low temperature alternate to the A³ coupling reactions developed by us[58] and others[59, 60] to produce chiral propargylic amines. Low photocatalyst loading (1 mol %), the convenience of visible light, and avoiding pre-functionalization of the starting material firmly places this reaction in the green chemist's synthetic toolbox.

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Notes and references

Department of Chemistry, McGill University, 801 Sherbrooke St. West, Montreal, Quebec H3A 0B8, Canada. *E-mail*: cj.li@mcgill.ca

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/
‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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