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C–H allylation of *N*-aryl-tetrahydroisoquinolines by merging photoredox catalysis with iodide catalysis

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A dual catalytic system, combing visible light photoredox catalysis and iodide catalysis, has been developed for the functionalization of inert C–H bonds. By doing so, radical allylation reactions of *N*-aryl-tetrahydroisoquinolines (THIQs) were realized under extremely mild conditions, affording a wide variety of allyl-substituted THIQs in up to 78% yields.

visible light photocatalysis, iodide catalysis, allylation, tetrahydroisoquinolines

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1 Introduction

The construction of C–C bonds in an efficient and sustainable way has attracted continuous attention from both industrial and academic community [1]. Among them, palladium-catalyzed allylation reactions (Tsuji-Trost reaction) play an important role in the C–C bond formation processes [2]. Despite advances, less progress has been made towards radical allylations with π-allylic palladium intermediates under reductive conditions [3]. Usually, only intramolecular radical addition reactions have been successfully developed in the presence of stoichiometric metal reducing reagents.

In recent years, photoredox catalysis has been identified as a green and mild method for C–C bond formations [4]. Particularly, direct functionalization of inert C–H bonds by merging photoredox catalysis with other catalysis modes has been largely explored [5]. As part of our ongoing efforts on heterocycle synthesis [6], we recently accomplished a redox-neutral α-C–H allylation of *N*-aryl-tetrahydroisoquinolines (*N*-aryl-THIQs) through the combination of palladium catalysis and photoredox catalysis (Pd/PC, Scheme 1(a)) [5c]. Critical to this success is the generation of the key allylic radical from a π-allyl palladium complex under visible light-mediated reduction conditions. Thereafter, the allylic radical species reacts with the α-amino radical, which is formed in a visible light-mediated event, to construct the C–C bond via a radical-radical cross coupling process. In the course of investigating the mechanism of this reaction, we found that the allylic bromide could be employed as an allylic source and this allylation reaction was able to proceed in the absence of the palladium catalyst, albeit with very low efficiency (allylic bromide: 9% GC yield, Scheme 1(a)). Thus, we speculated that allylic halide would serve as a suitable counterpart of π-allyl palladium complex. If so, it may enable the development of palladium catalyst-free, visible light-driven photocatalytic C–H allylation of *N*-aryl-THIQs.

Inspired by Stephenson's work [7] on the reduction cleavage of carbon-iodide under photoredox catalytic conditions, we presumed that allylic iodide would be more active than allylic bromide as an allylic source. With this hypothesis in mind, we initially examined the reaction of

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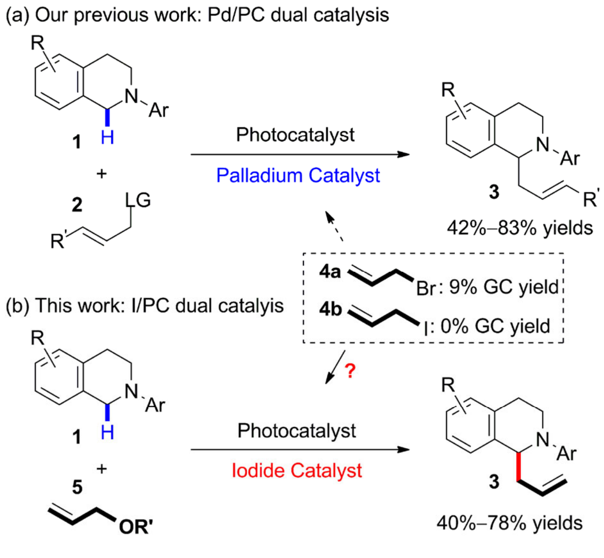


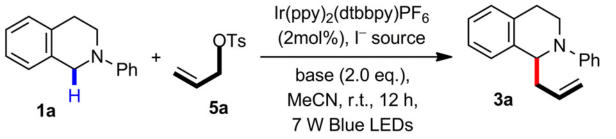
Scheme 1 Dual catalysis for C–H allylation of THIQs.

N-phenyltetrahydroisoquinoline **1a** and allylic iodide **4b** in the presence of Ir(ppy)$_2$(dtbbpy)PF$_6$ under the irradiation of 7 W blue LEDs. Unfortunately, no desired product was formed after 12 h, while the substrate **1a** was all consumed. Then, as depicted in Scheme 1(b), we envisioned that the iodide salt could be applied as the nucleophilic catalyst [8,9] to react with allylic ester to produce catalytic amount of allylic iodide *in situ*, so that allylic iodide would proceed with the desired reaction immediately, instead of oxidizing THIQs or decomposing under visible light photocatalysis conditions. Notably, the iodide anion could be regenerated during the oxidation step of Ir(II) catalyst by allylic iodide (see Scheme 2 for the detailed mechanism).

2 Results and discussion

Initially, we examined the dual I/PC catalytic system of Ir(ppy)$_2$(dtbbpy)PF$_6$ (ppy: 2-phenylpyridine; dtbbpy: 4,4-di-*tert*-butyl-2,2′-bipyridine) and potassium iodide (KI) for the photocatalytic radical allylation of THIQ **1a** with a wide range of allylic esters. To our delight, the combination of KI (0.5 equiv.) and allyl 4-methylbenzenesulfonate **5a** (1.2 equiv.) under the irradiation of 7 W blue LEDs afforded the desired allylation product in 52% GC yield (entry 1, Table 1). Encouraged by this result, we screened a representative set of iodide salts. We found that all the iodide salts were suitable for the reaction, though the desired product were given in moderate yields (24%–40%, entries 2–4). Employing different photoredox catalysts, light sources or reaction media, unfortunately, failed to improve the reaction efficiency [10]. Increasing the amount of the allylic ester **5a** gave a slightly better yield (55%, entry 5). To further enhance the yield, a wide range of bases were added to neutralize the byproduct *p*-toluenesulfonic acid (entries 6–13).

Table 1 Optimization of reaction conditions a)



Entry	I^- source	*x* (equiv.)	Ratio of **1a**:**5a**	Base	Yield (%) b)
1	KI	0.5	1:1.2	–	52
2	LiI	0.5	1:1.2	–	24
3	NaI	0.5	1:1.2	–	35
4	^{t}Bu$_4$NI	0.5	1:1.2	–	40
5	KI	0.5	1:1.5	–	55
6	KI	0.5	1:1.5	Cs_2CO_3	40
7	KI	0.5	1:1.5	^{t}BuONa	13
8	KI	0.5	1:1.5	^{t}BuOK	n.d.
9	KI	0.5	1:1.5	KOAc	50
10	KI	0.5	1:1.5	Na_2CO_3	58
11	KI	0.5	1:1.5	$NaCO_2CCl_3$	60
12	KI	0.5	1:1.5	$NaCO_2CF_3$	65
13	KI	0.5	1:1.5	KCO_2CF_3	52
14	**KI**	**0.2**	**1:1.5**	**$NaCO_2CF_3$**	**64 (53)** c)
15	–	0.2	1:1.5	$NaCO_2CF_3$	0
16 d)	KI	0.2	1:1.5	$NaCO_2CF_3$	0
17 e)	KI	0.2	1:1.5	$NaCO_2CF_3$	0

a) Reaction conditions: **1a** (0.2 mmol), Ir(ppy)$_2$(dtbbpy)PF$_6$ (2 mol%), **5a**, iodide salt (*x* equiv.), base (0.4 mmol) in MeCN (2 mL), 7 W blue LED irradiation at r.t., 12h; b) GC yield with tetradecane as the internal standard; c) isolated yield; d) without photocatalyst; e) in the dark.

Sodium trifluoroacetate ($NaCO_2CF_3$**)** was identified as the optimal choice, producing product **3a** in 65% yield. We were pleased to find that the loading of KI can be reduced to 0.2 equiv., with no erosive effect on the reaction efficiency. Under these conditions, the final allylation product **3a** was detected in 64% GC yield and 53% isolated yield (entry 14) [11]. Control experiments showed that iodide salt, photocatalyst and visible light were all essential for this radical allylation reaction (entries 15–17).

With the optimal reaction conditions identified, we then examined the generality of this dual catalysis system. As shown in Figure 1, this catalysis system appeared to be quite compatible with various THIQs. For example, variations of the aromatic substituents on the nitrogen atom were tolerant. Substrates with electron-donating (**1b**, **1c**) or electron-withdrawing groups (**1d**–**1f**) were converted to the corresponding allylation products (**3b**–**3f**) in 40%–66% yields. A variety of substituents on the benzene ring of THIQs can be successfully incorporated, delivering the allylation products in satisfactory yields (**3g**–**3i**: 34%–78% yields). We were delighted to find that *N*-2-naphthyltetrahydroisoquinoline can be also applied to this I/PC dual catalysis system and furnished the desired product **3j** in 48% yield. Notably, this was an unsuccessful example of our previous Pd/PC catalysis system. Moreover, this I/PC dual catalytic system can be significantly extended to other substituted allylic reagents, i.e. **5k** and **5l**, affording the corresponding product **3k** in 20% yield and **3l** in 50% yield.

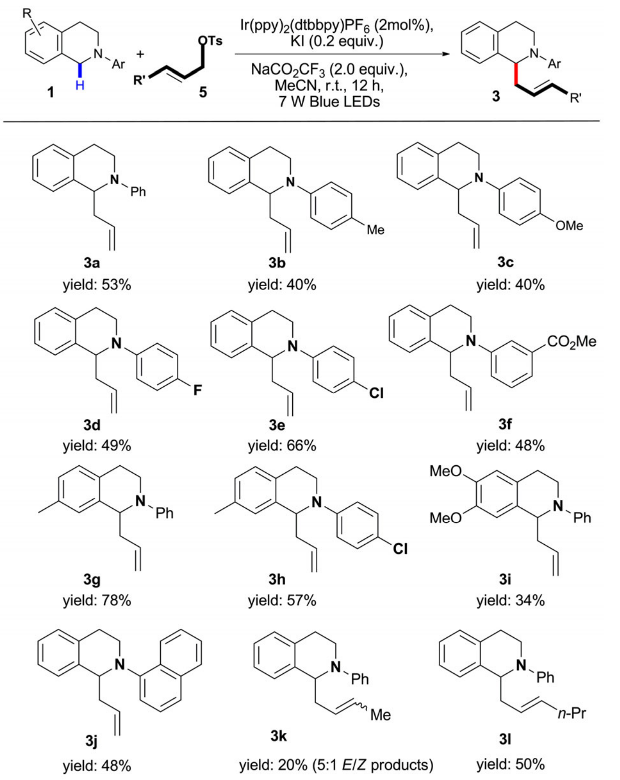
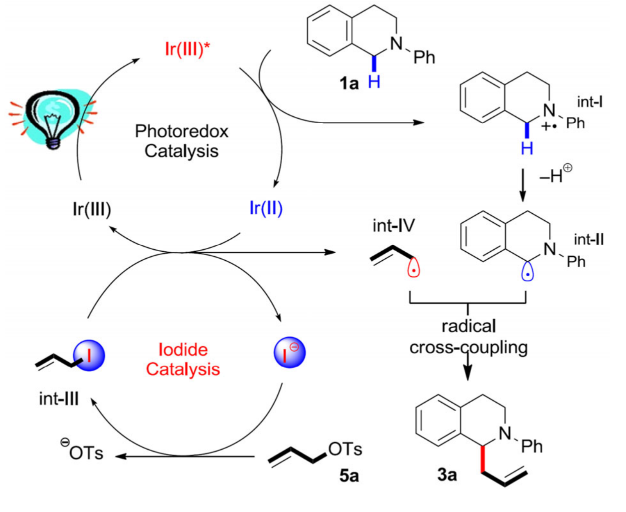


Figure 1 Generality of I/PC dual catalysis in the allylation of THIQs. Reaction conditions: **1** (0.5 mmol), $Ir(ppy)_2(dtbbpy)PF_6$ (2 mol%), **5** (0.75 mmol), KI (20 mol%), $NaCO_2CF_3$ (1.0 mmol) in MeCN (5 mL), 7 W blue LEDs at r.t., 12h; the yields are isolated yields.

Though great efforts have been made, this dual catalysis system failed to be applied to other tertiary amines.

A plausible mechanism was proposed to better understand the radical allylation process. As depicted in Scheme 2, excited state of photocatalyst Ir(III)* is firstly formed by the irradiation of the ground state of photocatalyst Ir(III). Then, this reactive catalyst species oxidizes THIQ **1a** to radical cation int-I while affording simultaneously the low-valent Ir(II). Deprotonation of int-I would deliver the α-amino alkyl radical int-II. Concurrently, the nucleophilic catalytic cycle is initiated by the iodide-substitution process of allylic esters. The allylic iodide int-III is subsequently reduced by Ir(II) to form allylic radical int-IV, and the iodide anion and ground-state Ir(III) are regenerated. Finally, the radical cross-coupling of int-II and int-IV provides the C–C bond formation and the desired α-amino allylation product is afforded.



Scheme 2 Proposed reaction mechanism (color online).

3 Conclusions

In conclusion, we have developed a dual catalytic system for the inert C–H functionalization by merging visible light photocatalysis and iodide catalysis. Compared with our prior dual catalytic system using palladium and photoredox catalysts, inexpensive and economical potassium iodide was utilized as the nucleophilic catalyst. Under these conditions, a direct allylation of sp^3 C–H of THIQs was realized under extremely mild conditions.

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Conflict of interest The authors declare that they have no conflict of interest.

Supporting information The supporting information is available online at http://chem.scichina.com and http://link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

1 For selected reviews and books on transition metal catalysis and C–H activation, see: a) Hickman AJ, Sanford MS. *Nature*, 2012, 484: 177–185; b) Yeung CS, Dong VM. *Chem Rev*, 2011, 111: 1215–1292; c) Ackermann L. *Chem Rev*, 2011, 111: 1315–1345; d) Davies HM, Du Bois J, Yu JQ. *Chem Soc Rev*, 2011, 40: 1855–1856; e) Yu JQ, Shi ZJ. *Topics in Current Chemistry*. Heidelberg: Springer, 2010; f) Dyker G. *Handbook of C–H Transformations*. Weinheim: Wiley-VCH, 2005; g) Beller M, Bolm C. *Transition Metals for Organic Synthesis: Building Blocks and Fine Chemicals*. Vol. 1 and 2. 2nd Ed, Weinheim: Wiley-VCH, 2004

2 For selected reviews and books, see: a) Zhuo CX, Zheng C, You SL. *Acc Chem Res*, 2014, 47: 2258–1856; b) Bandini M. *Angew Chem Int Ed*, 2011, 50: 994–995; c) Trost BM, Lee C. *Catalytic Asymmetric Synthesis*. 2nd Ed. New York: Wiley-VCH, 2010. 593–649; d) Lu Z, Ma S. *Angew Chem Int Ed*, 2008, 47: 258–297; e) Tsuji J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*. Chichester: Wiley, 2004: 431–518; f) Dai LX, Tu T, You SL, Deng WP, Hou XL. *Acc Chem Res*, 2003, 36: 659–667

3 For selected papers on reduction of π-allylpalladium complexes to allylic radicals, see: a) Millán A, Martín-Lasanta A, Miguel D, Cienfuegos LA, Cuerva JM. *Chem Commun*, 2011, 47: 10470–10472; b) Millán A, Campana AG, Bazdi B, Miguel D, Cienfuegos LA, Echavarren AM, Cuerva JM. *Chem Eur J*, 2011, 17: 3985–3994; c) Campana AG, Bazdi B, Fuentes N, Robles R, Cuerva JM. *Angew Chem Int Ed*, 2008, 47: 7515–7519; d) Sasaoka SI, Yamamoto T, Kinoshita H, Inomata K, Kotake H. *Chem Lett*, 1985, 315–318

4 For selected reviews, see: a) Narayanam JM, Stephenson CR. *Chem*

Soc Rev, 2011, 40: 102–113; b) Teplý F. *Collect Czech Chem Commun*, 2011, 76: 859–917; c) Shi L, Xia W. *Chem Soc Rev*, 2012, 41: 7687–7697; d) Xuan J, Xiao WJ. *Angew Chem Int Ed*, 2012, 51: 6828-6838; e) Prier CK, Rankic DA, MacMillan DW. *Chem Rev*, 2013, 113: 5322–5363; f) Ravelli D, Fagnoni M, Albini A. *Chem Soc Rev*, 2013, 42: 97–113; g) Xi Y, Yi H, Lei A. *Org Biomol Chem*, 2013, 11: 2387–2403; h) Schultz DM, Yoon TP. *Science*, 2014, 343: 1239176

5 For reviews and books on dual catalysis merging visible light photocatalysis with other catalytic manners, see: a) Hopkinson MN, SahooB, Li J, Glorius F. *Chem Eur J*, 2014, 20: 3874–3886; b) Zeitler K, Neumann M. Synergistic visible light photoredox catalysis. In: König B, Ed. *Chemical Photocatalysis.* Germany: Walter de Gruyter, 2013. 151–168. For recent examples with palladium catalysis, see: c) Xuan J, Zeng TT, Feng ZJ, Deng QH, Chen JR, Lu LQ, Xiao WJ. *Angew Chem Int Ed*, 2015, 54: 1625–1628; d) Lang SB, O'Nele K, Tunge JA. *J Am Chem Soc*, 2014, 136: 13606–13609. With gold catalysis, see: e) Hopkinson MN, Sahoo B, Glorius F. *Adv Synth Catal*, 2014, 356: 2794–2800; f) Shu XZ, Zhang M, He Y, Frei H, Toste FD. *J Am Chem Soc*, 2014, 136: 5844–5847. With nickel catalysis, see: g) Xuan J, Zeng TT, Chen JR, Lu LQ, Xiao WJ. *Chem Eur J*, 2015, 21: 4962–4965. With others, see: h) Feng ZJ, Xuan J, Xia XD, Ding W, Guo W, Chen JR, Zou YQ, Lu LQ, Xiao WJ. *Org Biomol Chem*, 2014, 12: 2037–2040; i) Bergonzini G, Schindler CS, Wallentin CJ, Jacobsen EN, Stephenson CRJ. *Chem Sci*, 2014, 5: 112–116

6 a) Zou YQ, Lu LQ, Fu L, Chang NJ, Rong J, Chen JR, Xiao WJ. *Angew Chem Int Ed*, 2011, 50: 7171–7175; b) Xuan J, Cheng Y, An J, Lu LQ, Zhang XX, Xiao WJ. *Chem Commun*, 2011, 47: 8337–8339; c) Zou YQ, Chen JR, Liu XP, Lu LQ, Davis RL, Jørgensen KA, Xiao WJ. *Angew Chem Int Ed*, 2012, 51: 784–788; d) Xuan J, Feng ZJ, Duan SW, Xiao WJ. *RSC Adv*, 2012, 2: 4065–4068; e) Xuan J, Xia XD, Zeng TT, Feng ZJ, Chen JR, Lu LQ, Xiao WJ. *Angew Chem Int Ed*, 2014, 53: 5653–5656, and Refs. [3c,3g,3k]

7 Nguyen JD, D'Amato EM, Narayanam JM, Stephenson CR. *Nat Chem*, 2012, 4: 854–859

8 For selected reviews, see: a) Wei Y, Shi M. *Acc Chem Res*, 2010, 43: 1005–1018; b) Dai LX, Hou XL. *Chiral Ferrocenes in Asymmetric Catalysis: Synthesis and Applications*. Weinheim: Wiley-VCH, 2010; c) List B. *Asymmetric Organocatalysis*. Heidlberg: Springer, 2010; d) Denmark SE, Beutner GL. *Angew Chem Int Ed*, 2008, 47: 1560–1638; f) Fu GC. *Acc Chem Res*, 2006, 39: 853–860

9 a) Carnes ME, Collins MS, Lindquist NR, Percástegui EG, Pluth MD, Johnson DW. *Chem Commun*, 2014, 50: 73–75; b) Patel K, Miljanić OS, Stoddart JF. *Chem Commun*, 2008, 44: 1853–1855; c) de Sousa AL, Resck IS. *J Braz Chem Soc*, 2002, 13: 233–237; d) Tipson RS, Clapp MA, Cretcher LH. *J Org Chem*, 1947, 12: 133–138

10 For detailed condition optimization, including the evaluation of photocatalysts, solvents, light sources and bases, see Supporting Information

11 General Procedure: In a 10 mL dry flask equipped with magnetic bar was charged with **1** (0.5 mmol, 1.0 equiv.) and $Ir(bpy)_2(dtbbpy)PF_6$ (2 mol%), **5** (0.75 mmol, 1.5 equiv.), KI (20 mol%), $NaCO_2CF_3$ (1.0 mmol, 2.0 equiv.) and MeCN (5 mL). The mixture was degassed via freeze-pump-thaw method (3 times) and then stirred under the irradiation of 7 W blue LEDs at room temperature for 12 h. The resultant mixture was filtered under vacuum to remove the solid. The filtrate was purified by flash chromatography on silica gel (petroleum ether/DCM=10:1) to afford the desired product **3**. Analytical data of 1-allyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (**3a**): light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.18 (m, 6H), 6.89 (d, J=8.2 Hz, 2H), 6.73 (t, J=7.1 Hz, 1H), 5.89–5.82 (m, 1H), 5.06 (t, J=13.1 Hz, 2H), 4.74 (t, J=6.7 Hz, 1H), 3.72–3.52 (m, 2H), 3.08–2.96 (m, 1H), 2.88 (dt, J=15.7, 5.2 Hz, 1H), 2.78–2.65 (m, 1H), 2.49 (dt, J=14.1, 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 149.4, 138.1, 135.6, 134.9, 129.2, 128.5, 127.3, 126.5, 125.7, 117.2, 117.0, 113.8, 59.3, 41.9, 40.9, 27.4; HRMS: m/z (ESI) calculated $[M+H]^+$ 250.1590, measured 250.1594.