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Highly efficient visible-light-induced aerobic oxidative C–C, C–P coupling from C–H bonds catalyzed by a gold(III)-complex†

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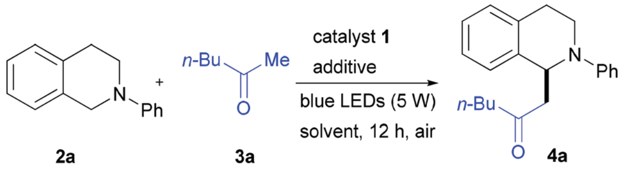
A novel and highly efficient gold(III)-complex catalyzed aerobic oxidative α-C–H functionalization of amines has been developed. The tertiary amines can be directly coupled with various nucleophiles using air as a sustainable oxidant.

The direct functionalization of C–H bonds has emerged as an attractive and challenging strategy, as C–H bonds are ubiquitous in organic molecules.[1] In recent years, gold-catalyzed C–H bond activation has aroused more and more interest.[2] For the methods reported, gold catalysts were commonly used as mild π-acids to activate unsaturated C–H bonds.[3] However, gold-catalyzed oxidative functionalization of the sp^3 C–H bond remains a great challenge,[4] since a sacrificial external oxidant is usually required.[5]

Visible light photoredox catalysis has become a promising strategy for the development of novel and sustainable sp^3 C–H activation reactions.[6] However, few efforts were dedicated to developing the other efficient photocatalysts relative to traditional Ru^{II},[6d,7] Ir^{III},[7k,8] or dye-liking catalysts[9] for chemical transformations. Since the 1990s, significant interest has been paid to developing the photochemical and photocatalytic properties of gold-complexes, but the successful case for the gold photocatalytic property is still elusive.[10] Very recently, Che and co-workers have disclosed the first organogold-catalyzed oxidative cyanation reaction enabled by irradiation with a 300 W xenon lamp under an oxygen atmosphere.[4a] As part of our ongoing interest in sp^3 C–H activation,[4b,c] we report a novel visible-light-induced sp^3 C–H bond functionalization protocol catalyzed by a gold(III)-complex.

To the best of our knowledge, the oxidative coupling of amines with unmodified ketones was usually limited to acetone, and the results are not satisfactory when unmodified long-chain ketones were employed as coupling partners.[7j,11] To address this challenge, our initial investigation was carried out on the reaction of *N*-phenyl tetrahydroisoquinoline **2a** with 2-hexanone **3a**. The oxidative coupling product **4a** could be formed using **1a** as a photoredox catalyst, and the yield could increase to 53% by the addition of 10 mol% of L-proline (Table 1, entry 1). Encouraged by this result, we investigated different photocatalysts, additives and solvents, and the results are summarized in Table 1. To compare the relative reactivity, all the reactions were also performed and stopped at 12 h. Among the gold catalysts screened in the dual catalytic process (Scheme 1), **1d** showed the best catalytic activity (Table 1, entry 4). L-Proline was found to play an important role in the catalytic process. Other additives such as pyrrolidine and piperidine gave less satisfactory yields (Table 1, entries 4–6). Subsequently, various solvents were evaluated in this

Table 1 Survey of different photocatalysts, additives and solvents[a]



Entry	Catalyst **1**	Additive	Solvent	Yield[b] (%)
1	**1a**	L-Proline	DMF	53
2	**1b**	L-Proline	DMF	51
3	**1c**	L-Proline	DMF	47
4	**1d**	L-Proline	DMF	61
5	**1d**	Pyrrolidine	DMF	15
6	**1d**	Piperidine	DMF	10
7	**1d**	L-Proline	CH_3OH	12
8	**1d**	L-Proline	CH_2Cl_2	Trace
9	**1d**	L-Proline	CH_3CN	34
10	**1d**	L-Proline	NMP	78
11	—	L-Proline	NMP	Trace
12	**1d**	—	NMP	Trace

[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.5 mmol), catalyst **1** (5 mol%), additive (10 mol%), solvent (1.0 mL), 5 W blue LEDs (λ_{max} = 455 nm), r.t., air, 12 h. [b] Isolated yield.

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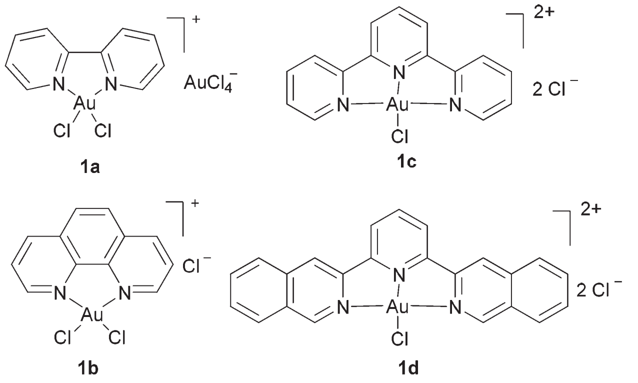
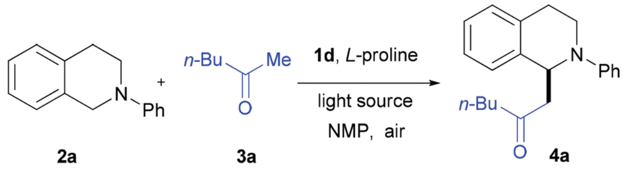


Scheme 1 Gold(III)-complexes screened.

Table 2 Further survey of the photocatalytic oxidative coupling conditions[a]



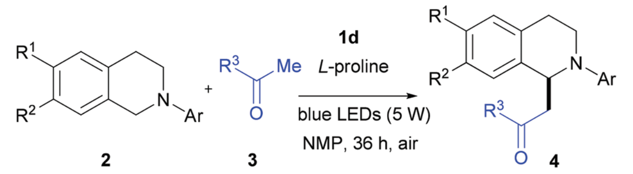
Entry	Light source	Time	Yield[b] (%)
1	Fluorescent light bulb (40 W)	12 h	66
2	White LEDs (5 W)	12 h	51
3	Red LEDs (5 W)	12 h	45
4	Yellow LEDs (5 W)	12 h	56
5	Blue LEDs (5 W)	12 h	78
6	Blue LEDs (5 W)	24 h	86
7	Blue LEDs (5 W)	36 h	91
8	—	36 h	Trace

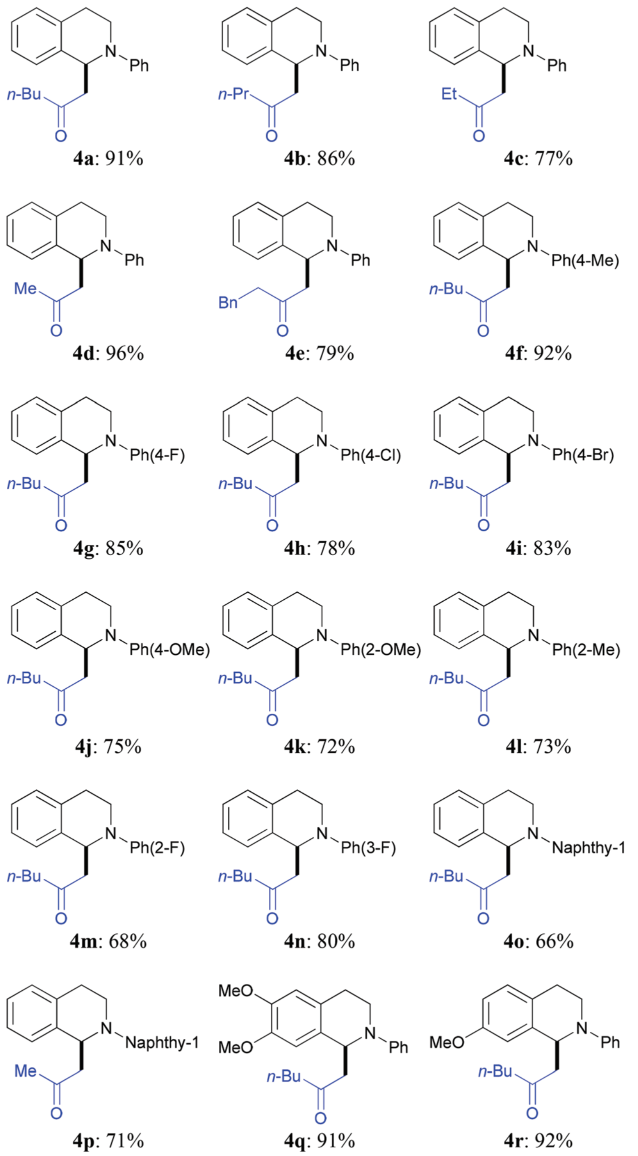
[a] Reaction conditions: **2a** (0.1 mmol), **3a** (0.5 mmol), **1d** (5 mol%), L-proline (10 mol%), NMP (1.0 mL), light source, r.t., air. [b] Isolated yield.

photooxidation coupling reaction. It was notable that when methanol or DCM was used as the solvent, the starting material **2a** was rapidly consumed but with a small amount of desired product, since enamine nucleophilic attack may be significantly slower than over-oxidative amide formation (Table 1, entries 7, 8). To our delight, the oxidative coupling reaction proceeded smoothly without generation of other by-products when it was conducted in NMP, providing the product **4a** with the highest isolated yield 78% (Table 1, entry 10). It should be pointed out that exclusion of the **1d** or L-proline gave trace amounts of **4a** (Table 1, entries 11, 12).

In order to maximize the yields, different light sources were also tested in the coupling reactions (Table 2). The results demonstrated that a fluorescent light bulb (40 W) resulted in decreased yield (66%) accompanied by the amide byproduct (Table 2, entry 1). Notably, the reaction led to the desired product in excellent yield with blue LEDs (5 W) as the light source (Table 2, entry 5). We observed that the yield could increase to 91% by prolonging the reaction time from 12 h to 36 h (Table 2, entry 7). In addition, the exclusion of the light gave unsatisfactory results (Table 2, entry 8).

Table 3 Scope of the photocatalytic oxidative coupling reaction[a]

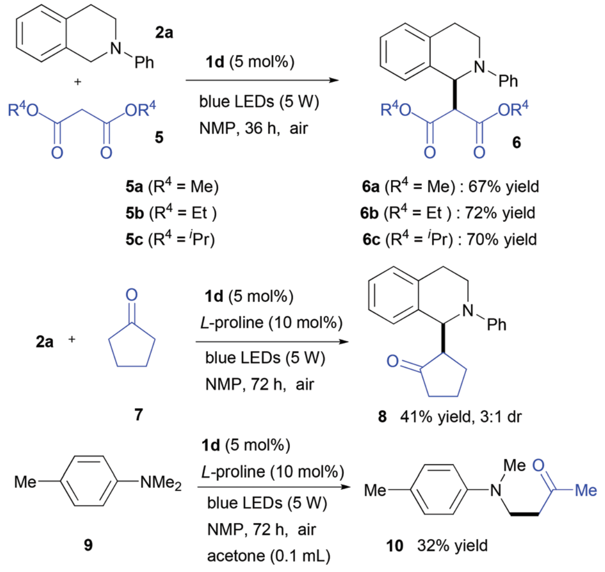




4a: 91%
4b: 86%
4c: 77%
4d: 96%
4e: 79%
4f: 92%
4g: 85%
4h: 78%
4i: 83%
4j: 75%
4k: 72%
4l: 73%
4m: 68%
4n: 80%
4o: 66%
4p: 71%
4q: 91%
4r: 92%

[a] Standard reaction conditions: **2** (0.1 mmol), **3** (0.5 mmol), **1d** (5 mol%), L-proline (10 mol%), NMP (1.0 mL), 5 W blue LEDs (λ_{max} = 455 nm), r.t., air, 36 h. Yields are of the isolated products.

With the optimized reaction conditions established (Table 2, entry 7), we investigated the scope of this protocol (Table 3). Firstly, a variety of unmodified ketones were subjected to the optimized conditions and they can afford the desired products in good to excellent yields. Intriguingly, it was found that long-chain ketones were still very effective in our catalytic system and can give good results (Table 3, **4a–e**).



Scheme 2 Extended scope of the oxidative C–C coupling reaction.

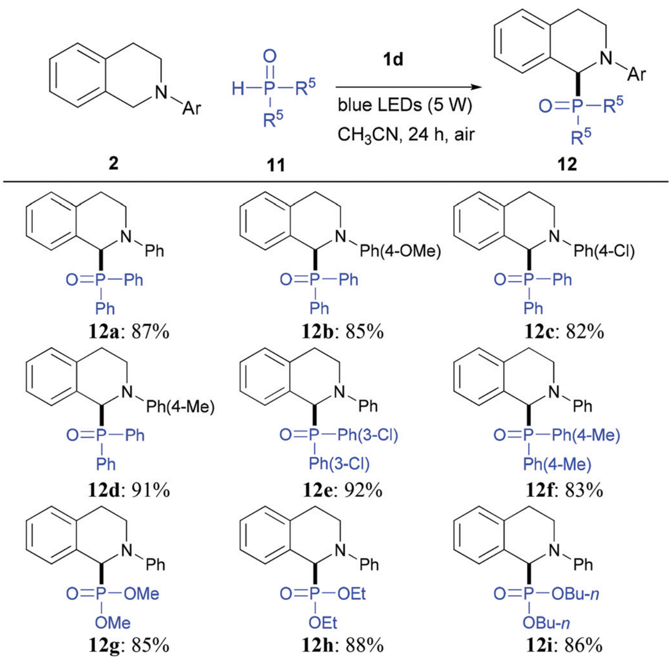
Subsequently, different *N*-aryltetrahydroisoquinolines were examined. All the tertiary amines could be coupled with 2-hexanone readily to afford the desired products **4f–n** in good yields under air. It was important to point out that electron-donating as well as electron-withdrawing groups on the aromatic rings were compatible in the aerobic oxidative C–C coupling reaction. The *N*-aryltetrahydroisoquinolines bearing bulky groups resulted in moderate yields (Table 3, **4o–p**). When 6 or 7-position substituted isoquinolines were employed, the reaction could proceed smoothly to furnish the C–C coupling products with excellent yields (Table 3, **4q–r**).

We applied this protocol to malonates, cyclic ketones, linear amines, and the corresponding results are listed in Scheme 2. Under visible-light irradiation in air, the desired products (**6a–c**), α-diester amine derivatives, were obtained in moderate yields. When cyclopentanone or *N*,*N*,4-trimethylaniline was used, an acceptable yield could also be obtained.

The success of C–C bond formation by using **1d** encouraged us to investigate C–P bond coupling reactions.[12] In this work, a variety of tertiary amines could react with phosphine oxides in the presence of **1d** to give the desired products in good yields after irradiation by blue light for 24 h (Table 4, **12a–f**). Both electron-donating and electron-withdrawing groups on the aromatic rings were compatible in the oxidative C–P coupling reaction. Moreover, different phosphites also could undergo the oxidative reaction to provide the desired products in good to excellent yields (Table 4, **12g–i**).

In conclusion, we have reported a novel gold(III)-complex catalyzed operationally simple method for the oxidative coupling of tertiary amines with unmodified long-chain methyl ketones, cycloketones, active methylene substrates, phosphine oxides and phosphites. Gold(III)-complex **1d** displayed high photocatalytic activity in the oxidative coupling reaction highlighting the richness of gold(III) photochemistry. The reaction proceeds in high isolated yield under air. The efficient, convenient and environmentally benign process, as well as broad substrate-scope, makes this protocol very practical. Further studies on exploration of the detailed mechanism of this transformation are currently underway in our laboratory.

Table 4 The oxidative coupling reaction of amines with phosphine oxides and phosphites[a]



[a] Standard reaction conditions: **2** (0.1 mmol), **11** (0.3 mmol), **1d** (5 mol%), CH_3CN (1.0 mL), 5 W blue LEDs (λ_{max} = 455 nm), r.t., air, 24 h. Yields are of the isolated products.

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Notes and references

1 For selected reviews and examples of C–H bond functionalization, see: (*a*) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215; (*b*) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.*, 2011, **111**, 1780; (*c*) E. Ferrer Flegeau, C. Bruneau, P. H. Dixneuf and A. Jutand, *J. Am. Chem. Soc.*, 2011, **133**, 10161; (*d*) P. B. Arockiam, C. Fischmeister, C. Bruneau and P. H. Dixneuf, *Angew. Chem., Int. Ed.*, 2010, **49**, 6629; (*e*) R. G. Bergman, *Nature*, 2007, **446**, 391; (*f*) K. Godula and D. Sames, *Science*, 2006, **312**, 67.

2 For recent reviews of gold-catalyzed C–H bond activation, see: (*a*) H. A. Wegner and M. Auzias, *Angew. Chem., Int. Ed.*, 2011, **50**, 8236; (*b*) M. N. Hopkinson, A. D. Gee and V. Gouverneur, *Chem.–Eur. J.*, 2011, **17**, 8248. T. C. Boorman and I. Larrosa, *Chem. Soc. Rev.*, 2011, **40**, 1910.

3 (*a*) T. D. Haro and C. Nevado, *J. Am. Chem. Soc.*, 2010, **132**, 1512; (*b*) A. Kar, N. Mangu, H. M. Kaiser and M. K. Tse, *J. Organomet. Chem.*, 2009, **694**, 524; (*c*) G. Lemière, V. Gandon, K. Cariou, A. Hours, T. Fukuyama, A. Dhimane, L. Fensterbank and M. Malacria, *J. Am. Chem. Soc.*, 2009, **131**, 2993.

4 (*a*) W. To, G. S. Tong, W. Lu, C. Ma, J. Liu, A. L. Chow and C. Che, *Angew. Chem., Int. Ed.*, 2012, **51**, 2654; (*b*) J. Xie, H. Li, J. Zhou, Y. Cheng and C. Zhu, *Angew. Chem., Int. Ed.*, 2012, **51**, 1252; (*c*) J. Xie, H. Li, Q. Xue, Y. Cheng and C. Zhu, *Adv. Synth. Catal.*, 2012, **354**, 1646.

5 For a review on F^+ oxidants in Au^I/Au^{III} catalysis, see: K. M. Engle, T. Mei, X. Wang and J. Yu, *Angew. Chem., Int. Ed.*, 2011, **50**, 1478.

6 For selected reviews: (*a*) J. Xuan and W. Xiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 6828; (*b*) J. W. Tucker and C. R. J. Stephenson, *J. Org. Chem.*, 2012, **77**, 1617; (*c*) J. M. R. Narayanam and C. R. J. Stephenson, *Chem. Soc. Rev.*, 2011, **40**, 102; (*d*) T. P. Yoon, M. A. Ischay and J. Du, *Nat. Chem.*, 2010, **2**, 527.

7 For selected examples of Ru species, see: (*a*) H. Rao, P. Wang and C. Li, *Eur. J. Org. Chem.*, 2012, **2012**, 6503; (*b*) D. B. Freeman, L. Furst, A. G. Condie and C. R. J. Stephenson, *Org. Lett.*, 2012, **14**, 94; (*c*) G. Zhao, C. Yang, L. Guo, H. Sun, C. Chen and W. Xia, *Chem. Commun.*, 2012, **48**, 2337; (*d*) P. Kohls, D. Jadhav, G. Pandey and O. Reiser, *Org. Lett.*, 2012, **14**, 672; (*e*) S. Cai, X. Zhao, X. Wang, Q. Liu, Z. Li and D. Z. Wang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8050; (*f*) M. Rueping, R. M. Koenigs, K. Poscharny, D. C. Fabry, D. Leonori and C. Vila, *Chem.–Eur. J.*, 2012, **18**, 5170; (*g*) M. Rueping, C. Vila, R. M. Koenigs, K. Poscharny and D. C. Fabry, *Chem. Commun.*, 2011, **47**, 2360; (*h*) M. Rueping, S. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 8679; (*i*) M. Rueping, D. Leonori and T. Poisson, *Chem. Commun.*, 2011, **47**, 9615; (*j*) Y. Zou, L. Lu, L. Fu, N. Chang, J. Rong, J. Chen and W. Xiao, *Angew. Chem., Int. Ed.*, 2011, **50**, 7171; (*k*) Z. Xie, C. Wang, K. E. DeKrafft and W. Lin, *J. Am. Chem. Soc.*, 2011, **133**, 2056; (*l*) J. Xuan, Y. Cheng, J. An, L. Lu, X. Zhang and W. Xiao, *Chem. Commun.*, 2011, **47**, 8337; (*m*) J. Xie, Q. Xue, H. Jin, H. Li, Y. Cheng and C. Zhu, *Chem. Sci.*, 2013, DOI: 10.1039/c2sc22131d.

8 For selected examples of Ir species, see: (*a*) Y. Miyake, K. Nakajima and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2012, **134**, 3338; (*b*) S. Zhu and M. Rueping, *Chem. Commun.*, 2012, **48**, 11960; (*c*) A. McNally, C. K. Prier and D. W. C. MacMillan, *Science*, 2011, **334**, 1114; (*d*) M. Rueping, S. Zhu and R. M. Koenigs, *Chem. Commun.*, 2011, **47**, 12709; (*e*) A. G. Condie, J. C. G. L. Mez and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2010, **132**, 1464.

9 For selected examples of dye-liking catalysts, see: (*a*) L. Möhlmann, M. Baar, J. Rieß, M. Antonietti, X. Wang and S. Blechert, *Adv. Synth. Catal.*, 2012, **354**, 1909; (*b*) Q. Liu, Y. Li, H. Zhang, B. Chen, C. Tung and L. Wu, *Chem.–Eur. J.*, 2012, **18**, 620; (*c*) D. P. Hari and B. König, *Org. Lett.*, 2011, **13**, 3852; (*d*) Y. Pan, S. Wang, C. W. Kee, E. Dubuisson, Y. Yang, K. P. Loh and C. Tan, *Green Chem.*, 2011, **13**, 3341.

10 (*a*) C. Bronner and O. S. Wenger, *Dalton Trans.*, 2011, **40**, 12409; (*b*) C. W. Chan, W. T. Wong and C. M. Che, *Inorg. Chem.*, 1994, **33**, 1266.

11 (*a*) A. Sud, D. Sureshkumar and M. Klussmann, *Chem. Commun.*, 2009, 3169; (*b*) Y. Shen, M. Li, S. Wang, T. Zhan, Z. Tan and C. Guo, *Chem. Commun.*, 2009, 953.

12 For optimization of the conditions see ESI.†