ARTICLE IN PRESS

Tetrahedron Letters xxx (xxxx) xxx

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Visible-light induced Cross-Dehydrogenative-Coupling (CDC) reactions of *N*-aryl tetrahydroisoquinolines under aerobic conditions

Chao Lin [a,*], Peiwu Li [a], Lin Wang [b,*]

[a] *Yantai Key Laboratory of Nanomedicine & Advanced Preparations, Yantai Institute of Materia Medica, Shandong 264000, China*
[b] *Key Laboratory of Molecular Pharmacology and Drug Evaluation (Yantai University), Ministry of Education, Yantai University, Yantai 264005, China*

ARTICLE INFO

Article history:
Received 22 February 2021
Revised 11 April 2021
Accepted 16 April 2021
Available online xxxx

Keywords:
Cross-dehydrogenative-coupling
N-aryl tetrahydroisoquinolines
Oxygen

ABSTRACT

A visible-light induced cross-dehydrogenative-coupling (CDC) reaction of *N*-aryl tetrahydroisoquinolines was developed under mild aerobic conditions. This protocol proceeded smoothly with a large range of nucleophiles (nitroalkane, dimethyl phosphite, dimethyl malonate, *N*-methyl indole, TMSCN) under metal-free conditions and an oxygen atmosphere, forming a new C—C bond. Visible-light played a significant acceleration effect in this reaction.

The development of methods for exploring C—C bond formation plays a central role in organic synthesis. Transition-metal catalyzed C—C bond coupling reactions and transition-metal catalyzed C—H activation with subsequent C—C bond formation have seen enormous progress in recent years [1]. However, these reactions typically require a pre-functionalized precursor. In the last decade, cross dehydrogenative coupling (CDC), which directly forms new C—C bonds by utilizing two different C—H bonds under oxidative conditions [2], have attracted considerable interest.

Among the reported CDC reactions, the oxidative coupling reactions of *N*-aryl tetrahydroisoquinolines with a number of nucleophiles have received considerable attention and significant advances have been made in this field. The pioneering work of Murahashi and Li demonstrated the utility of transition metal catalysts (Ru and Cu) for CDC reactions [3,4]. Recently, other transition metal catalysts, such as Fe [5], V [6], Rh [7], Au [8], Pt [9], Ru [10], Zr [11], and Mo [12] or photocatalysts, such as Ir(ppy)$_2$(dtbbpy) [13], Ru(bpy)$_3$ [14b], Co(II)-dmgh [15a], TiO$_2$ [15b], and eosin Y [16] have also been applied to these CDC reactions. In addition, transition-metal free methods using a stoichiometric amount of an oxidant, such as PhI(OAc)$_2$ [17], DDQ [18], *N*-ethoxy-2-methyl-pyridinium tetrafluoroborate [19], or the tropylium ion [19], have also been reported. Moreover, oxygen has been used in combination with catalytic amounts of a co-oxidant, such as DDQ, iodine, or sulfuryl chloride (Scheme 1, A-1) [20] or in the presence of acetic acid under metal-free conditions (Scheme 1, A-2) [21]. Recently, our group reported an efficient visible-light induced isoindole formation/Diels-Alder reaction, providing access to bridged-ring heterocycles [22]. To the best of our knowledge, there are no reports that only utilize visible-light to prompt CDC reactions. As an extension of our continued interest in the development of reactions induced by visible-light, herein, we describe the visible-light induced metal-free oxidative reactions of *N*-aryl tetrahydroisoquinolines with various nucleophiles in the presence of oxygen under ambient conditions (Scheme 1, B).

Our initial studies focused on the cross-coupling reaction of *N*-phenyl tetrahydroisoquinoline (**1a**) and nitromethane (**2a**) under irradiation with a 400–450 nm wavelength 6 W blue LED in the presence of oxygen at room temperature. To our delight, the desired cross-coupling product **3aa** was obtained in 41% yield after 72 h when MeOH was used as a solvent (Entry 1, Table 1). To enhance the reaction efficiency, different solvents were evaluated under otherwise identical conditions. When the reaction was conducted in DMF, the best yield of 69% yield was achieved (Entry 6, Table 1). The reaction under a nitrogen atmosphere did not proceed (Entry 7, Table 1). When the reaction was conducted under an air atmosphere, the yield decreased to 53% (Entry 8, Table 1). Compared with the reaction irradiated by the blue LED, the reaction under dark conditions or in sunlight afforded the desired product in only 5% and 22% yield, respectively (Entries 9, 10, Table 1). These findings indicate that the 400–450 nm wavelength of the blue LEDs and oxygen play critical roles in this oxidative cross-coupling reaction. Decreasing the amount of nitromethane to 1.5 equivalents resulted in a lower yield (Entry 12, Table 1). When

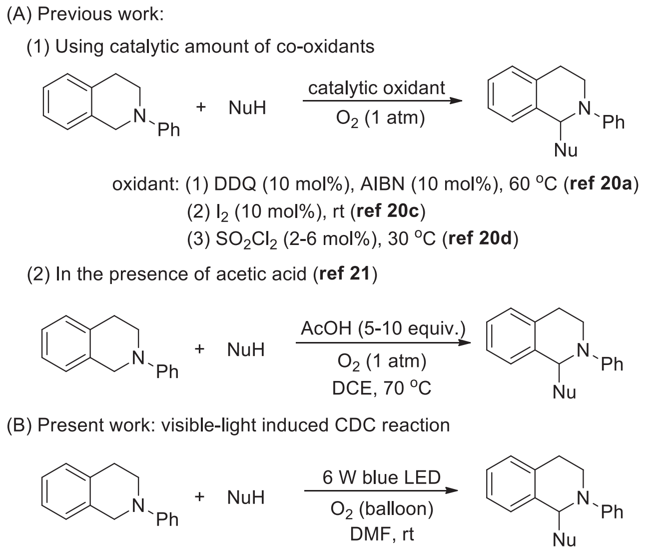
---

* Corresponding authors.

E-mail addresses: linchao46@163.com (C. Lin), rushanwanglin@126.com (L. Wang).

https://doi.org/10.1016/j.tetlet.2021.153102
0040-4039/© 2021 Elsevier Ltd. All rights reserved.

Please cite this article as: C. Lin, P. Li and L. Wang, Visible-light induced Cross-Dehydrogenative-Coupling (CDC) reactions of *N*-aryl tetrahydroisoquinolines under aerobic conditions, Tetrahedron Letters, https://doi.org/10.1016/j.tetlet.2021.153102



Scheme 1. O_2 as an oxidant in CDC reactions.

the amount of the nucleophile was increased to 1.0 mL, the best yield of 80% was achieved (Entry 13, Table 1).

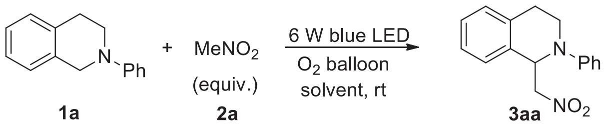
With the optimal reaction conditions in hand, we turned our attention to exploring the generality of the reaction. As shown in Table 2, a wide array of *N*-aryl tetrahydroisoquinolines **1** with different substituents on the phenyl ring proceeded smoothly in the oxidative CDC reaction. Electron-donating groups (Entries 2–5, Table 2) gave good yields (73–81% yields), while electron-withdrawing groups (Entries 6–8, Table 2) provided the desired products in lower yields (36–65%). When 1-naphthyl group was employed in the reaction, the corresponding product **3ia** was obtained in 47% yield (Entry 9, Table 2). Next, we evaluated the effect of different substituents on the tetrahydroisoquinoline. Substrates with electron-donating groups (Entries 10, 13) gave the corresponding products in good yields (76–80%). In contrast, substrates with electron-withdrawing groups (Entries 11–12) afforded the desired products in lower yields (54–63%).

The reaction scope using the different nucleophiles is shown in Scheme 2. The reaction with nitroethane provided the desired product **4a** in 57% yield as a diastereomeric mixture. Dimethyl phosphite could also be employed in the oxidative CDC reaction, affording the corresponding product **4b** in 71% yield. In addition, the reaction with dimethyl malonate gave the desired product **4c** in 57% yield. *N*-Methyl indole was also a suitable nucleophile for this reaction, providing product **4d** in 54% yield. Furthermore, the oxidative CDC reaction proceeded smoothly with using TMSCN as a nucleophile to give product **4e** in 75% yield.

A plausible mechanism for the formation of product **3aa** based on previous literature is shown in Scheme 3 [21,22]. Initially, visible-light irradiation of O_2 in the presence of *N*-phenyl tetrahydroisoquinoline **1a** generates radical cation **Int-1** and a superoxide radical anion ($O_2^{\cdot-}$). Hydrogen atom abstraction of **Int-1** by $O_2^{\cdot-}$ provides iminium ion **Int-2**. Finally, the desired product **3aa** was formed *via* nucleophilic substitution between **Int-2** and the nucleophile. A control experiment was performed in the presence of the radical inhibitor 2,6-di-*tert*-butyl-4-methylphenol. The conversion rate was lower than without 2,6-di-*tert*-butyl-4-methylphenol and product **3aa** was obtained in only 23% yield.

In conclusion, a visible-light induced oxidative CDC reaction of *N*-aryl tetrahydroisoquinolines with various nucleophiles under aerobic conditions has been developed. This protocol is compatible with a wide range of nucleophiles, including *N*-methyl indole. Significantly, the reaction only proceeds in the presence of visible-light and oxygen, and no metal catalyst or external oxidant is required. Further studies are ongoing to expand the synthetic utility of this transformation.

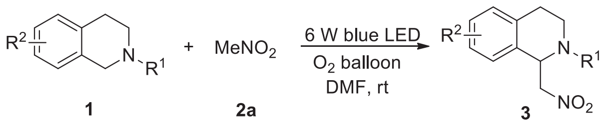
Table 1
Optimization of the reaction conditions.[a]



Entry	Nitromethane (equiv.)	Solvent	Time (h)	Yield **3aa** (%) [b]
1	10	MeOH	72	41
2	10	CH_2Cl_2	48	34
3	10	THF	24	21
4	10	DCE	48	43
5	10	toluene	24	19
6	10	DMF	48	69
7[c]	10	DMF	48	trace
8[d]	10	DMF	48	53
9[e]	10	DMF	48	5
10[f]	10	DMF	48	22
11	5	DMF	48	68
12	1.5	DMF	48	49
13[g]		**DMF**	**48**	**80**

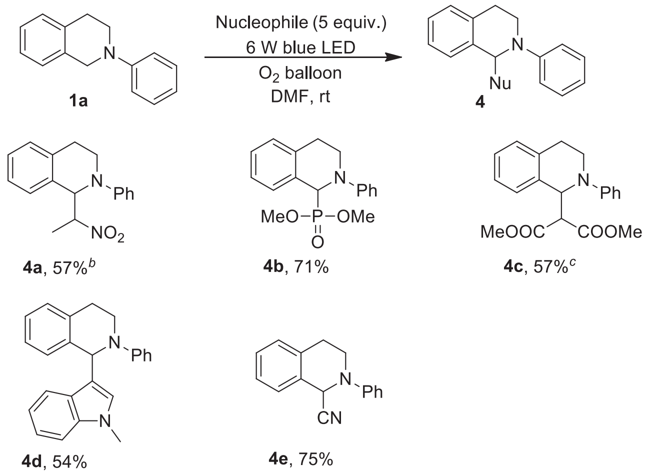
[a] Reagents and conditions: **1a** (0.3 mmol), solvent (3.0 mL), 6 W blue LED, room temperature.
[b] Isolated yields.
[c] Under a N_2 atmosphere.
[d] Under an air atmosphere.
[e] Under dark conditions.
[f] In sunlight.
[g] Using $MeNO_2$ (1.0 mL).

Table 2
Substrate scope of *N*-aryl tetrahydroisoquinolines.[a]

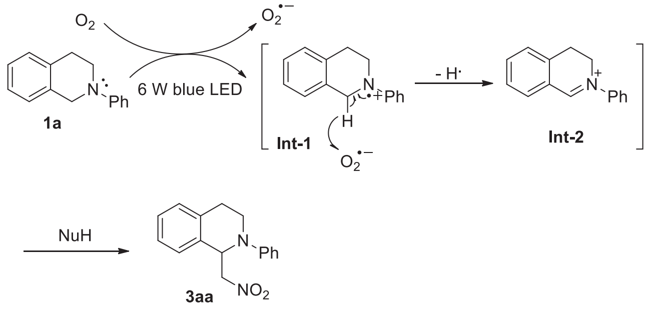


Entry	1	R¹	R²	3	Yield **3** (%)[b]
1	**1a**	Ph	H	**3aa**	80
2	**1b**	4-MeC$_6$H$_4$	H	**3ba**	81
3	**1c**	2-MeOC$_6$H$_4$	H	**3ca**	68
4	**1d**	3-MeOC$_6$H$_4$	H	**3da**	79
5	**1e**	4-MeOC$_6$H$_4$	H	**3ea**	73
6	**1f**	2-ClC$_6$H$_4$	H	**3fa**	36
7	**1g**	3-ClC$_6$H$_4$	H	**3ga**	65
8	**1h**	4-BrC$_6$H$_4$	H	**3ha**	61
9	**1i**	1-Naphthyl	H	**3ia**	47
10	**1j**	Ph	6-MeO	**3ja**	80
11	**1k**	Ph	6-Br	**3ka**	63
12	**1l**	Ph	7-NO$_2$	**3la**	54
13	**1m**	Ph	6,7-(MeO)$_2$	**3ma**	76

[a] Reagents and conditions: **1** (0.3 mmol), **2a** (1.0 mL), DMF (3.0 mL), 6 W blue LED, room temperature, 48 h.
[b] Isolated yields.



Scheme 2. Substrate scope of the reaction with different nucleophiles. [a] Reagents and conditions: **1a** (0.3 mmol), nucleophile (5.0 equiv.), DMF (3.0 mL), 6 W blue LED, room temperature. Isolated yields. [b] EtNO$_2$ (1.0 mL), Diastereomeric ratio (dr) was 2:1. [c] CH$_2$(CO$_2$Me)$_2$ (10.0 equiv.).



Scheme 3. Proposed reaction mechanism.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

The study was supported by the Science and Technology Innovation Development Planning Project of Yantai (2020MSGY057).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153102.

References

[1] (a) For selected reviews on C-H activation, see: K. Godula, D. Sames Science 312 (2006) 67;
(b) R.G. Bergman, Nature 446 (2007) 391;
(c) H.M.L. Davies, J.R. Manning, Nature 451 (2008) 417;
(d) X. Chen, K.M. Engle, D.-H. Wang, J.-Q. Yu, Angew. Chem., Int. Ed. 48 (2009) 5094;
(e) R.H. Carbtree, Chem. Rev. 110 (2010) 575;
(f) H.M.L. Davies, J. Du Bois, J.-Q. Yu, Chem. Soc. Rev. 2011 (1845) 40;
(g) P.B. Arockiam, C. Bruneau, P.H. Dixneuf, Chem. Rev. 112 (2012) 5879;
(h) M.-L. Louillat, F. Patureau, W, Chem. Soc. Rev. 43 (2014) 901;
(i) X.-X. Guo, D.-W. Gu, Z. Wu, W. Zhang, Chem. Rev. 115 (2015) 1622;
(j) T. Gensch, M.N. Hopkinson, F. Glorius, Chem. Soc. Rev. 45 (2016) 2900;
(k) Y. Yang, J. Lan, J. You, Chem. Rev. 117 (2017) 8787;
(l) C.-S. Wang, P.H. Dixneuf, J.-F. Soule, Chem. Rev. 118 (2018) 7532;
(m) Z. Chen, M.-Y. Rong, J. Nie, Chem. Soc. Rev. 48 (2019) 4921;
(n) Q. Zhao, G. Meng, S.P. Nolan, M. Szostak, Chem. Rev. 2020 (1981) 120;
(o) D.F. Fernandez, J.L. Mascarenas, F. Lopez, Chem. Soc. Rev. 49 (2020) 7378.

[2] (a) For selected reviews, see: C.-J. Li Acc. Chem. Res. 42 (2009) 335;
(b) C.S. Yeung, V.M. Dong, Chem. Rev. 111 (2011) 1215;
(c) S.A. Girard, T. Knauber, C.-J. Li, Angew. Chem., Int. Ed. 53 (2014) 74;
(d) C. Liu, J. Yuan, M. Gao, Chem. Rev. 115 (2015) 12138;
(e) K. Morimoto, T. Dohi, Y. Kita, Synlet. 28 (2017) 1680;
(f) K. Nagaraju, D. Ma, Chem. Soc. Rev. 47 (2018) 8018;
(g) Y. Yuan, A. Lei, Accounts. Chem. Res. 52 (2019) 3309;
(h) A.K. Bagdi, M. Rahman, D. Bhattacherjee, Green Chem. 22 (2020) 6632.

[3] (a) S.-I. Murahashi, N. Komiya, H. Terai, T. Nakae, J. Am. Chem. Soc. 125 (2003) 15312;
(b) S.-I. Murahashi, T. Nakae, H. Terai, N. Komiya, J. Am. Chem. Soc. 130 (2008) 11005;
(c) S.-I. Murahashi, D. Zhang, Chem. Soc. Rev. 37 (2008) 1490.

[4] (a) Z. Li, C.-J. Li, J. Am. Chem. Soc. 126 (2004) 11810;
(b) Z. Li, C.-J. Li, Org. Lett. 6 (2004) 4997;
(c) Z. Li, C.-J. Li, J. Am. Chem. Soc. 127 (2005) 6968;
(d) Z. Li, C.-J. Li, J. Am. Chem. Soc. 127 (2005) 3672;
(e) Z. Li, S. Bohle, C.-J. Li, Proc. Natl. Acad. Sci. U.S.A. 103 (2006) 8928;
(f) O. Baslé, C.-J. Li, Green Chem. 9 (2007) 1047;
(g) O. Baslé, C.-J. Li, Org. Lett. 10 (2008) 3661;

(h) E. Boess, D. Sureshkumar, A. Sud, C. Wirtz, C. Ferés, M. Klussmann, J. Am. Chem. Soc. 133 (2011) 8106;
(i) E. Boess, C. Schmitz, M. Klussmann, J. Am. Chem. Soc. 134 (2012) 5317;
(j) T. Sonobe, K. Oisaki, M. Kanai, Chem. Sci. 3 (2012) 3249.
[5] (a) Z. Li, L. Cao, C.-J. Li, Angew. Chem., Int. Ed. 46 (2007) 6505;
(b) P. Liu, Y. Liu, E.-L.-M. Wong, S. Xiang, C.-M. Che, Chem. Sci. 2 (2011) 2187;
(c) G. Kumaraswamy, A.N. Murthy, A. Pitchaiah, J. Org. Chem. 75 (2010) 3916;
(d) M.O. Ratnikov, X. Xu, M.P. Doyle, J. Am. Chem. Soc. 135 (2013) 9475.
[6] K.M. Jones, P. Karier, M. Klussmann, ChemCatChem 4 (2012) 51.
[7] (a) A.J. Catino, J.M. Nichols, B.J. Nettles, M.P. Doyle, J. Am. Chem. Soc. 128 (2006) 5648;
(b) M.O. Ratnikov, M.P. Doyle, J. Am. Chem. Soc. 135 (2013) 1549.
[8] (a) L. Cui, Y. Peng, L. Zhang, J. Am. Chem. Soc. 131 (2009) 8394;
(b) W.-P. To, G.-S.-M. Tong, W. Liu, C. Ma, J. Liu, A.-L.-F. Chow, C.-M. Che, Angew. Chem., Int. Ed. 51 (2012) 2654;
(c) J. Xie, H. Li, J. Zhou, Y. Cheng, C. Zhu, Angew. Chem., Int. Ed. 51 (2012) 1252.
[9] X.-Z. Shu, Y.-F. Yang, X.-F. Xia, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, Org. Biomol. Chem. 8 (2010) 4077.
[10] P. Rana, R. Gaur, R. Gupta, G. Arora, A. Jayashree, R.K. Sharma, Chem. Commun. 55 (2019) 7402.
[11] W.-Q. Zhang, Q.-Y. Li, Q. Zhang, Y. Lu, H. Lu, W. Wang, X. Zhao, X.-J. Wang, Inorg. Chem. 55 (2016) 1005.
[12] (a) K. Alagiri, K.R. Prabhu, Org. Biomol. Chem. 10 (2012) 835;
(b) F. Wang, W. Ueda, Chem. Eur. J. 15 (2009) 742.
[13] (a) A.G. Condie, J.C. Gonzá lez-Gómez, C.R.J. Stephenson, J. Am. Chem. Soc. 132 (2010) 1464;
(b) D.B. Freeman, L. Furst, A.G. Condie, C.R.J. Stephenson, Org. Lett. 14 (2012) 94.
[14] (a) C.-J. Wu, J.-J. Zhong, Q.-Y. Meng, T. Lei, X.-W. Gao, C.-H. Tung, L.-Z. Wu, Org. Lett. 17 (2015) 884;
(b) M. Rueping, J. Zoller, D.C. Fabry, K. Poscharny, R.M. Koenigs, T.E. Weirich, J. Mayer, Chem. Eur. J. 18 (2012) 3478.
[15] (a) D.P. Hari, B. König, Org. Lett. 13 (2011) 3852;
(b) T. Xiao, L. Li, G. Lin, Z.-W. Mao, L. Zhou, Org. Lett. 16 (2014) 4232.
[16] X.-Z. Shu, X.-F. Xia, Y.-F. Yang, K.-G. Ji, X.-Y. Liu, Y.-M. Liang, J. Org. Chem. 74 (2009) 7464.
[17] (a) A.S.-K. Tsang, M.H. Todd, Tetrahedron Lett. 50 (2009) 1199;
(b) W. Su, J. Yu, Z. Li, Z. Jiang, J. Org. Chem. 76 (2011) 9144;
(c) W. Muramatsu, K. Nakano, C.-J. Li, Org. Lett. 15 (2013) 3650.
[18] V. Quint, N. Chouchène, M. Askri, J. Lalevée, A.-C. Gaumont, S. Lakhdar, Org. Chem. Front. 6 (2019) 41.
[19] J.M. Allen, T.H. Lambert, J. Am. Chem. Soc. 133 (2011) 1260.
[20] (a) K. Alagiri, P. Devadig, K.R. Prabhu, Chem. Eur. J. 18 (2012) 5160;
(b) T. Nobuta, N. Tada, A. Fujiya, A. Kariya, T. Miura, A. Itoh, Org. Lett. 15 (2013) 574;
(c) J. Dhineshkumar, M. Lamani, K. Alagiri, K.R. Prabhu, Org. Lett. 15 (2013) 1092;
(d) A. Tanoue, W.-J. Yoo, S. Kobayashi, Org. Lett. 16 (2014) 2346.
[21] H. Ueda, K. Yoshida, H. Tokuyama, Org. Lett. 16 (2014) 4194.
[22] C. Lin, L. Zhen, Y. Cheng, H.-J. Du, H. Zhao, X. Wen, L.-Y. Kong, Q.-L. Xu, H. Sun, Org. Lett. 17 (2015) 2684.