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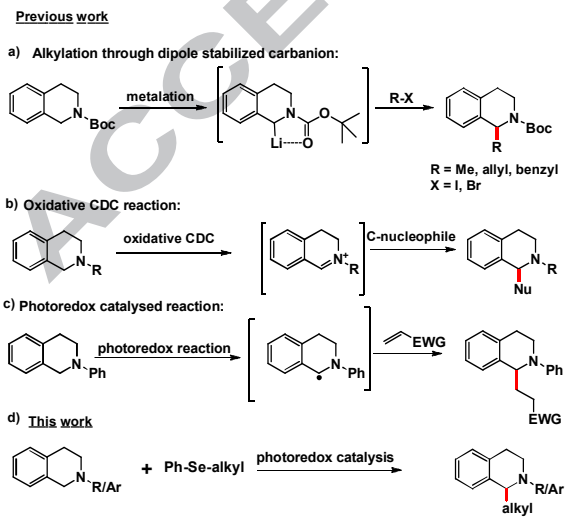
ABSTRACT

Direct α-alkylation of N-phenyl-tetrahydroisoquinoline with alkyl selenides of desired alkyl chain length and functionality is reported by photoredox catalysis. Construction of hexahydro pyrrolo- and pyrido-isoquinoline scaffolds along with indolines and tetrahydroquinolines is also described by intramolecular C(sp^3)-C(sp^3) cross-couplings.

1. Introduction

Developing new methodology for C-C bond forming reaction involving C(sp^3) C–H bond adjacent to nitrogen atom (α-aminoalkylation) represents an important and useful reaction[1] for synthesizing various pharmaceutically important and biologically active molecules [2].



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Usually, these reactions are achieved by the electrophilic substitution of the dipole-stabilized carbanion[3], however, this strategy is limited with only activated alkyl halides (R-X, R= Me, allyl and benzyl etc.). Oxidative cross-dehydrogenating coupling (CDC) reactions, another popular approach[4], mediated by metal catalyst [(Ru[5], Cu[6], Fe[7], V[8], Rh[9], Au[10] and Pt [11])], photoredox reactions [12] and organic oxidant[13-14] (stoichiometric) is limited to pronucleophiles such as nitroalkanes, enol silyl ethers etc. Ackermann[15] has reported alkylation of pyrrolidine at its α-position with alkenes [(C(sp^3)-C(sp^2) coupling], however, this strategy requires costly [Ru(II)] catalyst and pyridyl directed group.

Recently, we[16] and others[17] have reported α-aminoalkylation reaction by photoredox α-C-H functionalisation of *t*-amines to an α-aminoradical intermediate and its addition to olefins, but this reaction works with only activated olefins. To the best of our knowledge, there is no direct method of α-alkylation of tertiary amines[18] with desired carbon chain length and functionality. Therefore, we hypothesised a strategy as shown in **Fig.1** for α-alkylation of N-aryl tetrahydroisoquinolines (**1**).

The feasibility of the proposed photoredox cycle was established by estimating Gibbs free energy change for electron transfer processes ($-\Delta G_e$ = -31.01 kcal/M^{-1} and -28.88 kcal/M^{-1}) between excited DMA* (λmax = 410 *nm*) to alkyl phenyselenides as well as **1** to DMA$^{+\cdot}$ respectively[19]. Subsequent steps of mesolytic cleavage of **A** to produce an alkyl radical[20] and α-deprotonation from **B** to form α-amino radical (**C**)[16] was obvious from our earlier work. It was expected that cross-coupling of

these radicals would affect α-aminoalkylation reaction owing to well established persistent radical effect [21].

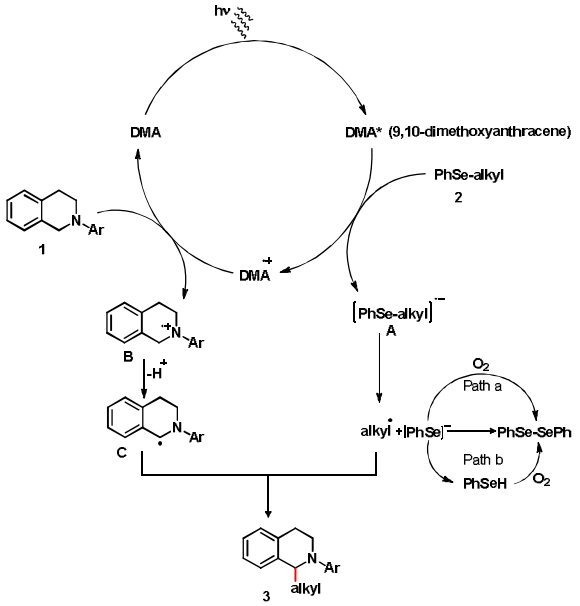


Figure 1. Proposed α-alkylation of tetrahydroisoquinoline with alkyl selenide.

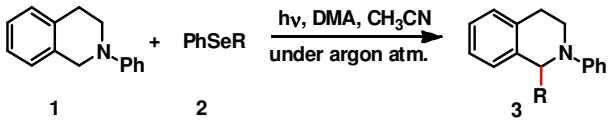
With these premises, we carried out first a reaction by irradiating a mixture of **1** (N-phenyltetrahydroisoquinoline, 0.098g, 0.47 mmol), butylphenylselenide (**2a**, 0.2g, 0.94 mmol) and a catalytic amount of DMA (0.034g, 0.140 mmol) in acetonitrile in the presence of argon atmosphere utilizing visible light (410 *nm*), obtained by using a combination of Pyrex and a $CuSO_4$:NH_3 solution filter[22] from a 450-W Hanovia medium pressure mercury lamp[23]. Progress of the reaction was monitored by following the disappearance of **1** by HPLC (C18 reverse phase, ACN: H_2O/75:25). It was pleasing to note that other than unreacted **1**, DMA and diphenyldisenide, there was only a single product peak observed on the chromatogram. There was no significant loss in DMA concentration during or after the reaction. After 8 h of photoirradiation, the solvent was removed and the product was purified by column chromatography to obtain **3a** in 40% yield along with diphenyl diselenide[24]. The maximum yield of **3a** was optimised to 70 % when **2a** was used 2.0 equivalents[25]. A control reaction without DMA and light did not produce any product.

This reaction may be rationalised by considering transient alkyl as well as persistent α-aminoalkyl radical **C** being generated at equal rates and initial build-up in the concentration of persistent radical **C**, due to self-termination of transient alky radical, allows radical-radical cross-coupling due to persistent radical effect.[21] Mcmillan et al.[26] has also reported similar coupling recently for the synthesis of β-aminoethers. Diphenydiselenide may be formed directly either by direct dimerization of $PhSe^-$ (Path a) or via PhSeH (Path b) due to presence of small impurity of oxygen[20].

Generality of the reaction was also established by irradiating **1** in the presence of a wide variety of **2** under optimized reaction condition and results are shown in **Table 1**. The yields mentioned in the Table is the isolated yield.

After successful demonstration of α-C-H alkylation of **1** with alkyl groups of varying chain length and functionality by visible light photoredox catalysis, we decided to explore this reaction for

Table 1: Alkylation of N-phenyltetrahydroisoquinoline by alkyl selenides



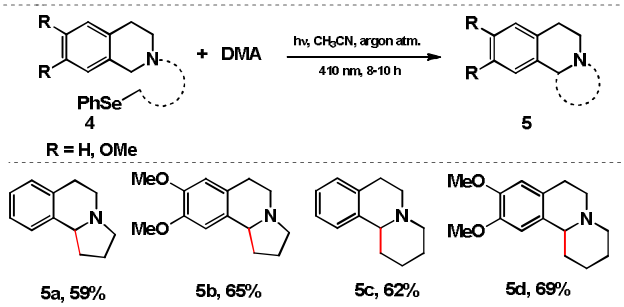
2 (eq.)	R	Entry	Time	Product[a]	Yield[b]
1.0	n-C_4H_9	1	10 h	**3a**	40%
1.5	n-C_4H_9	2	10 h	**3a**	50%
2	n-C_4H_9	3	8 h	**3a**	70%
2	n-C_2H_5	4	8 h	**3b**	52%
2	n-C_3H_7	5	8 h	**3c**	59%
2	n-$C_{10}H_{21}$	6	8 h	**3d**	73%
2	C_2H_5OH	7	8 h	**3e**	68%
2	CH_2Ph	8	8 h	**3f**	74%
2	$CH_3(CH)$ C2H5	9	8 h	**3g**	55%

a: characterised by NMR and mass spectrometry.

b: isolated by column chromatography.

the intramolecular cyclization of N-alkyl selenide substituted 1,2,3,4-tetrahydroisoquinolines **4** to prepare corresponding hexahydro pyrrolo- and pyrido-isoquinoline scaffolds (**5**). These heterocyclic scaffolds are known to possess wide range of biological and pharmacological activities. For example, hexahydropyrrolo [2.1-a] isoquinoline (**5a**) is known to be a 2-adrenoreceptor antagonist[27] and its 5-phenyl derivatives exhibit antidepressant-like activity[28]. Similarly, benzo[a]quinolizidine structural motifs (**5d**) have been found in numerous alkaloids that have shown potent biological activity[29]. In fact, most of the approaches for the construction of these structural frameworks have relied on C-N bond formation as an approach for the ring closing reaction[30] which suffers from the requirement of a number of steps, harsh reaction conditions and tedious work-up. Therefore, we envisioned the extension of this strategy for the synthesis of these heterocyclic scaffolds.

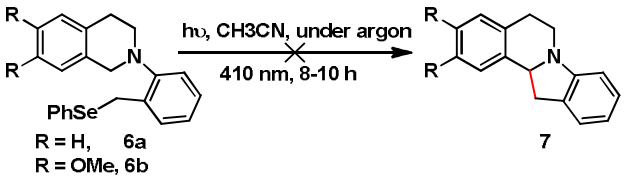
Thus, we proposed the synthesis of these compounds using a general strategy as shown in **Scheme 1**



Scheme 1. C(sp^3)-C(sp^3) intramolecular cyclization.

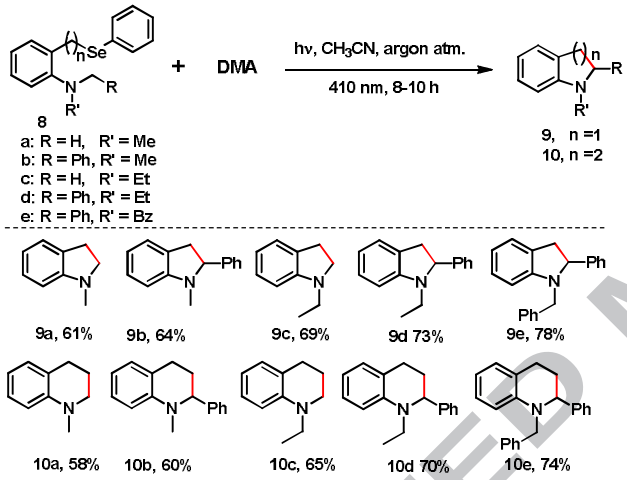
Usual photoredox reaction of **4** in CH_3CN in the presence of DMA under identical reaction conditions, as described above, gave corresponding cyclised products (**5**) in good yield. Crispine A (**5b**)[31], a naturally occurring alkaloid possessing hexahydropyrroloisoquinoline structural framework which displays high biological activity against SKOV3, KB and HeLa human cancer cell lines is also synthesized utilizing this approach to highlight the efficacy of the methodology (65%).

However, when this strategy is applied to synthesize tetrahydro-indolo[2,1-a] isoquinoline skeleton related to cryptaustoline alkaloid (**7**)[32] by the photoredox reaction of **6**, the reaction unfortunately failed and gave corresponding deselylated product (**Scheme 2).**



Scheme 2. C(sp3)-C(sp3) intramolecular cyclization.

After accomplishing these transformations successfully, we set out to explore further application of this reaction to synthesize indolines and 1,2,3,4-tetrahydroisoquinolines by intramolecular C(sp3)-C(sp3) coupling of 6 as shown in **Scheme 3**.



Scheme 3. Examples of indolines and tetrahydroquinolines.

The indolines **9** are found in numerous biologically active alkaloids[33] and pharmaceuticals[34]. Highly efficient indoline-based organic dyes for dye-sensitized solar cells have also been developed[35]. Similarly, tetrahydroquinoline derivatives **10** are also found to exihibit interesting biological activity. For example, 2-aryl-1,2,3,4-tetrahydroquinoline is a core structure of a molecule possessing 5-lipoxygenase inhibitory properties and potential therapeutic application in asthma[36]. Therefore, construction of these heterocyclic moieties have attracted the attention of organic chemists for a long time. A number of protocols for indoline synthesis involves C(sp^2)-H(x) functionalization for C-N bond formation or C-C bond formation by directed metalation[37].

On the other hand, construction of tetrahydroquinoline moiety have generally employed inverse electron-demand aza Diels-Alder reaction of azabutadiene with an electron-rich alkene[38]. Another interesting approach for the preparation of this moiety involves gold (**I**) catalysed reaction of 2-(2-propynyl) anilines through relay reaction[39]. Catalytic multiple cross-dehydrogenative-coupling reactions is also known[40] to synthesize this ring system. However, many of these approaches are transition metal based and specific to either indolines or tetrahydroquinolines. A general and metal free method is limited[17d] to synthesize substituted heterocycles of type **9** or **10**.

Easily synthesizable precursor **8** was subjected to usual photoredox reaction which produced corresponding cyclised products **9** or **10** in 58-78% yield. Regioselectivity of this reaction was also evaluated by studying the reaction of differently substituted aniline derivatives. For example, reaction of N-methyl N'-ethyl substituted precursor **8** underwent exclusively methyl activation giving rise to products like **9c**, whereas, N, N'-diethyl substituted **8** did not cyclise. In case of N-methyl-N-benzyl derivatives, the activation occurred at benzylic position producing compounds such as **9b**, **9d**, **9e**, **10b**, **10d** and **10e**. This observed regioselectivity is in tune with the observations made by us[12b] and others[41] earlier where α-deprotonation to generate α-aminoradical is dependent on the kinetic acidity of α-C-H subject to stereoelectronic factor. It is important to highlight that this strategy provides an opportunity to prepare 2-phenyl substituted indolines (**9b, 9d** and **9e**) and tetrahydroquinolines (**10b, 10d** and **10e**) directly which otherwise would require multiple steps.

Conclusion

In summary, we have developed a new strategy of visible light initiated photoredox reaction for α-alkylation of N-phenyltetrahydroisoquinoline with alkyl selenides of any chain length and functionality. The strategy is extended to carry out intramolecular C(sp3)-C(sp3) coupling reaction to synthesize the pyrolo-, pyrido-, and indolo tetrahydroquinoline frameworks. Indolines, tetrahydroquinolines and their 2-phenyl derivatives have also been synthesised directly utilizing this protocol.

Acknowledgments

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Supplementary Data

Supplementary data (experimental details and procedures, compound characterization data, copies of $_1$H, $_{13}$C spectra for new compounds) related to this article can be found at http://dx.doi.org/10.1016/j.tetlet.xxxxxxx

References and notes

1. (a) Campos, K. R. *Chem. Soc. Rev*. **2007**, *36*, 1069–1084; (b) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res*. **2015**, *48*, 1474.
2. (a) Corey, E. J.; Gin, D. Y.; Kania, R. S. J. *Am. Chem. Soc*. **1996**, *118*, 9202. (b) For a review, see: Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev*. **2004**, *104*, 3341 and references cited therein.
3. (a) Coppola, G. M. *J. Heterocyclic Chem*. **1991**, *28*, 1769-1; (b) Mitchell, E. A.; Peschiulli, A.; Lefevre, N.; Meerpoel, L.; Maes, B. U. W. *Chem. Eur. J*. **2012**, *18*, 10092; (c) Li, X.; Leonori, D.; Sheikh, N. S.; Coldham, I. *Chem. Eur. J*. **2013**, *19*, 7724.
4. (a) Pinter, A.; Sud, A.; Kumar, D. S.; Klussmann, M. *Angew. Chem. Int. Ed*. **2010**, *49*, 5004; (b) Chaput, B. S-; Sud, A.; Pinter, A.; Dehn, S.; Schulze, P.; Klussmann. M. *Angew. Chem. Int. Ed*. **2013**, *52*, 13228.
5. (a) Murahashi,S.-I.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc*. **2003**, *125*, 15312; (b) Murahashi, S.-I.; Nakae, T.; Terai, H.; Komiya, N. *J. Am. Chem. Soc*. **2008**, *130*, 11005; (c) Murahashi, S.-I.; Zhang, D. *Chem. Soc. Rev*. **2008**, *37*, 1490.
6. (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc*. **2004**, *126*, 11810; (b) Li, Z.; Li, C.-J. *Org. Lett*. **2004**, *6*, 4997; (c) Li, Z.; Li, C.-J. *J. Am. Chem.*

Soc. **2005**, *127*, 6968; (d) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672; (e) Li, Z.; Bohle, S.; Li, C.-J. *Proc. Natl. Acad. Sci. U.S.A.* **2006**, *103*, 8928; (f) O. Basle, C.-J. Li, *Green Chem.* **2007**, *9*, 1047; (g) Basle, O.; Li, C.-J. *Org. Lett*. **2008**, *10*, 3661; (h) Boess, E.; Kumar, D. S.; Sud, A.; Wirtz, C.; Feres, C.; Klussmann, M. *J. Am. Chem. Soc*. **2011**, *133*, 8106; (i) Boess, E.; Schmitz, C.; Klussmann, M. *J. Am. Chem. Soc*. **2012**, *134*, 5317; (j) Sonobe, T.; Oisaki, K.; Kanai, M. *Chem. Sci*. **2012**, *3*, 3249.

7. (a) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem. Int. Ed.* **2007**, *46*, 6505; (b) Liu, P.; Liu, Y.; Wong, E. L.-M.; Xiang, S.; Che, C.-M. *Chem. Sci*. **2011**, *2,* 2187; (c) Kumaraswamy, G.; Murthy, A. N.; Pitchaiah, A. *J. Org. Chem*. **2010**, *75*, 3916; (d) Ratnikov, M. O.; Xu, X.; Doyle, M. P. *J. Am. Chem. Soc*. **2013**, *135*, 9475.
8. Jones, K. M.; Karier, P.; Klussmann, M. *ChemCatChem* **2012**, *4*, 51.
9. (a) Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc*. **2006**, *128*, 5648; (b) Ratnikov, M. O.; Doyle, M. P. *J. Am. Chem. Soc*. **2013**, *135*, 1549.
10. (a) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc*. **2009**, *131*, 8394; (b) To, W.-P.; Tong, G. S.-M.; Liu, W.; Ma, C.; Liu, J.; Chow, A. L.-F.; Che, C.-M. *Angew. Chem. Int. Ed.* **2012**, *51*, 2654; (c) Xie, J.; Li, H.; Zhou, J.; Cheng, Y.; Zhu, C. *Angew. Chem. Int. Ed.* **2012**, *51*, 1252.
11. Shu, X.-Z.; Yang, Y.-F.; Xia, X.-F.; Ji, K.-G.; Liu, X.-Y.; Liang, Y.-M. *Org. Biomol. Chem.* **2010**, *8*, 4077.
12. (a) Pandey, G.; Kumaraswamy, G. *Tetrahedron Lett*. **1988**, *29*, 4153; (b) Pandey; G.; Kumaraswamy; G.; Reddy, P. Y. *Tetrahedron*, **1992**, *8*, 8295; (c) Pandey, G.; Sudha Rani, K.; Lakshamaiah, G. *Tetrahedron Lett*. **1992**, *33*, 5107.
13. (a) Pandey, G. *Synlett* **1992**, 546; (b) Yoon, U. C.; Mariano, P. S.; Givens, R. S.; Atwater, B. W. *In Advances in Electron Transfer Chemistry; P. S. Mariano, Ed.; JAI-Press: CT, Greenwich*, **1994**, *4,* 117. (c) Kumar, J. S. D.; Das, S. *Res. Chem. Intermed*. **1997**, *23*, 755; (d) Das, S.; Suresh, V. *In Electron Transfer in Chemistry; V. Balzani, Ed.; Wiley-VCH: New York*, **2001**, *2*, 379.
14. (a) Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc*. **2010**, *132*, 1464; (b) Xie, Z.; Wang, C.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc*. **2011**, *133*, 2056; (c) Xuan, J.; Cheng, Y.; An, J.; Lu, L.-Q.; Zhang, X.-X.; Xiao, W.-J. *Chem. Commun*. *2011*, *47*, 8337; (d) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem. Int. Ed*. **2011**, *50*, 7171; (e) Wang, C.; Xie, Z.; deKrafft, K. E.; Lin, W. *J. Am. Chem. Soc*. **2011**, *133*, 13445; (f) Hari, D. P.; Konig, B. *Org. Lett*. **2011**, *13*, 3852; (g) Maity, S.; Zhu, M.; Shinabery, R.; Zheng, N. *Angew. Chem. Int. Ed.* **2012**, *5*, 222; (h) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett*. **2012**, *14*, 94; (I) Liu, Q.; Li, Y.-N.; Zhang, H.-H.; Chen, B.; Tung, C.-H.; Wu, L.-Z. *Chem. Eur. J*. **2012**, *18*, 620; (j) Courant, T.; Masson, G. *Chem. Eur. J*. **2012**, *18*, 423; (k) Pan, Y.; Kee, C. W.; Chen, L.; Tan, C.-H. *Green Chem.* **2011**, *13*, 2682; (l) Pan, Y.; Wang, S.; Kee, C. W.; Dubuisson, E.; Yang, Y.; Loh, K. P.; Tan, C.-H. *Green Chem.* **2011**, *13*, 3341; (m) Mitkina, T.; Stanglmair, C.; Setzer, W.; Gruber, M.; Kisch, H.; Koenig, B. *Org. Biomol. Chem*. **2012**, *10*, 3556; (n) Möhlmann, L.; Baar, M.; Rieß, J.; Antonietti, M.; Wang, X.; Blechert, S. *Adv. Synth. Catal*. **2012**, *354*, 1909; (o) Wang, X.; Blechert, S.; Antonietti, M. *ACS Catal*. **2012**, *2*, 1596; (p) Cai, S.; Zhao, X.; Wang, X.; Liu, Q.; Li, Z.; Wang, D. Z. *Angew. Chem. Int. Ed*. **2012**, **51**, 8050; (q) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem. Int. Ed*. **2012**, *51*, 4144; (r) Neumann, M.; Zeitler, C. *Org. Lett*. **2012,** *14*, 2658; (s) Cherevatskaya, M.; Neumann, M.; Füldner, S.; Harlander, C.; Kümmel, S.; Dankesreiter, S.; Pfitzner, A.; Zeitler, K.; Koenig, B. *Angew. Chem. Int. Ed.* **2012**, *51*, 4062; (t) Zhao, G.; Yang; C.; Guo, L.; Sun, H.; Chen, C.; Xia, W. *Chem. Commun*. **2012**, *48*, 2337; (u) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc*. **2012**, *134*, 8094; (v) Xuan, J.; Feng, Z.-J.; Duan, S.-W.; Xiao, W.-J. RSC Adv. 2012, 2, 4065; w) Richter, H.; Frçhlich, R.; Daniliuc, C-G.; Mancheno, O-G. *Angew. Chem. Int. Ed*. **2012**, *51*, 8656. (x) Bergonzini, G. Schindler, C. S., Wallentin, C-J., Jacobsen, E. N., Stephenson. C. R. J, *Chem. Sci*. **2014**, *5*,112
15. Schinkel, M.; Wang, L.; Bielefeld, K.; Ackermann, L. *Org. Lett.* **2014**, *16*, 1876.
16. (a) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett*. **2012**, *14*, 672; (b) Pandey, G.; Jadhav, D.; Tiwari, S. K.; Singh, B. *Adv. Synth. Catal*. **2014**, *356*, 2813.
17. (a) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2012**, *134*, 3338; (b) Miyake, Y.; Ashida, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Commun*. **2012**, *48*, 6966; (c) Miyake, Y.; Nakajima, K.; Nishibayashi, Y. *Chem. Eur. J*. **2012**, *18*, 16473; (d) Liu, X.; Ye, X.; Bures, F.; Liu, H.; Jiang, Z. *Angew. Chem. Int. Ed*. **2015**, *54*, 11443.
18. Wang, T.; Schrempp, M.; Berndhauser, A.; Schiemann, O.; Menche, D.; *Org. Lett*. **2015**, *17*, 3982-3985. (In this reaction, the α-alkylation of THIQS is reported with alkylzinc).
19. For details, see supporting information.
20. (a) Pandey, G.; Rao, K. S. S. P.; SomaSekhar, B. B. V. *J. C. Soc., Chem. Comm.* **1993**,1636; (b) Pandey, G.; Rao, K. S. S. P.; Rao, K. V. N. *J. Org. Chem.* **1996**, *61*, 6799; (c) Rao, K. S. S. P.; Ph.D. Thesis entitled, ‘‘Photosensitized electron transfer (PET) reductive activation of –C-Se- and –Si-Se- bonds: mechanism and synthetic perspective” submitted to Pune University, Pune, India, 1997.
21. (a) Studer, A. *Chem. Euro. J*. **2001**, 1159, (b) Fischer, H. *Chem. Rev*. **2001**, *101*, 3581, and references cited therein, (c) Focsaneanu, K-S.; Scaiano J. C. *Helv. Chim. Acta*. **2006**, *89*, 2473.
22. Calvert, J. G.; Pitts, J. N. *Photochemistry Wiley, New York*, **1966**, p. 736.
23. This setup was used in the absence of a commercially available LED source in this wavelength range. Any lamp emitting at 410 nm with appropriate intensity (ca. 6.0×1015 photons per second) can be used.
24. Diphenyldiselenide can be reutilized for the preparation of 2.
25. Products were purified up to 95% pure as there was some difficulty in purification by column chromatography to get absolute pure compounds.
26. Hager, D.; MacMillan, D. W. C. *J. Am. Chem. Soc*. **2014**, *136*, 16986.
27. Chung, S.-H.; Yook, J.; Min, B. J.; Lee, J. Y.; Lee, Y. S.; Jin, C. *Arch. Pharm. Res*. **2000**, *23*, 353.
28. Maryanoff, B. E.; McComsey, D. F.; Gardocki, J. F.; Shank, R. P.; Costanzo, M. J.; Nortey, S. O.; Schneider, C. R.; Setler, P. E. *J. Med. Chem.* **1987**, *30*, 1433.
29. (a) Takada, K.; Uehara, T.; Nakao, Y.; Matsunaga, S.; van Soest, R. W. M.; Fusetani, N. *J. Am. Chem. Soc*. **2004**, *126*, 187; (b) The Alkaloids: Chemistry and Biology, Vol. *50* (Ed.: G. A. Cordell), Academic Press, New York, **1998**.
30. (a) Forró, E.; Schönstein, L.; Fülöp. F. *Tetrahedron: Asymmetry*, **2011** 1255. (b) Knolker, H-J.; Agarwal, S. *Tetrahedron Lett*, **2005** 1173; (c) Allin, S. M.; Gaskell, S. N.; Towler, J. M. R.; Page, P. C. B.; Saha, B.; McKenzie, M. J.; Martin, W. P. *J. Org. Chem*. **2007**, *72*, 8972. (d) Dhanasekaran, S.; Bisai, V.; Unhale, R. A.; Suneja, A.; Singh, V. K. *Org. Lett*., **2014**, *16*, 6068. (e) Gurram, M.; Gyimothy, B.; Wang, R.; Lam, S. Q.; Ahmed, F.; Herr, R. J. *J. Org. Chem.* **2011**, *76*, 1605.
31. Zhang, Q.; Tu, G.; Zhaoa, Y.; Cheng, T. *Tetrahedron*, **2002** 6795.
32. (a) Meyers, A. I.; Sielecki, T. M. *J. Am. Chem. Soc*. **1991**, *113*, 2789. b) Mahoney, S. J.; Fillion, E. *Chem. Eur. J*. **2012**, *18*, 68.
33. (a) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev*. **1997**, *97*, 787. (b) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi,; Komiyama, M. K.; Omura, S.; Smith, A. B. III *J. Am. Chem. Soc*. **2000**, *122*, 2122. (c) Dounay, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc*. **2005**, *127*, 10186.
34. (a) Gruenfeld, N.; Stanton, J. L.; Yuan, A. M.; F Ebetino,. H.; Browne, L. J.; Gude, C.; Huebner, C. F. *J. Med. Chem.* **1983**, *26*, 1277. (b) Bromidge, S. M.; Duckworth, M.; Forbes, I. T.; Ham, P.; King, F. D.; Thewlis, K. M.; Blaney, F. E.; Naylor, C. B.; Blackburn, T. P.; Kennett, G. A.; Wood, M. D.; Clarke, S. E. *J. Med. Chem*. **1997**, *40*, 3494. (c) Hobson, L. A.; Nugent, W. A.; Anderson, S. R.; Deshmukh, S. S.; Haley III, J. J.; Liu, P.; Magnus, N. A.; Sheeran, P.; Sherbine, J. P.; Stone, B. R. P.; Zhu, J. *Org. Process Res. DeV*. **2007**, *11*, 985.
35. Kuang, D.; Uchida, S.; Humphry-Baker, R.; Zakeeruddin, S. M.; Gratzel, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1923.
36. Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669.
37. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **1995**, *34*, 1348. (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 7421. (c) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett*, **2002**, 231. (d) Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett*. **2003**, *5*, 2311. (e) Minatti, A.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2721. f) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem*., **2010**, 3975.
38. Morita, H.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc*. **2006**, *128*, 13070.
39. Han, Z-Y.; Xiao, H.; Chen, X-H.; Gong, L-Z. *J. Am. Chem. Soc.* **2009**, *131*, 9182.

40. Sun, M.; Zhang, T.; Bao, W. *J. Org. Chem.* **2013**, *78*, 8155–8160.
41. (a) Lewis, F. D.; Ho, T. I.; Simpson, J. T. *J. Org. Chem.* **1981**, *46*, 1077 (b) Lewis, F. D.; Ho, T. I. *J. Am. Chem. Soc*., **1980**, *102*, 1751.

α-Alkylation of Tertiary Amines by C(sp^3) - C(sp^3) Cross-Coupling under Redox Neutral Photocatalysis

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1) This is also the first report of visible –light photoredox catalysed $C(sp)^3$ - $C(sp)^3$ cross-coupling reaction for C-C bond formation reaction.
2) This manuscript also described the construction of hexahydro pyrrolo- and pyrido-isoquinoline scaffolds by intramolecular $C(sp)^3$ - $C(sp)^3$ coupling.
3) The synthesis of **Crispine A (5b)** and **benzo[a]quinolizidine (5d)** is also described by this methodology.
4) The indolines and tetrahydroquinolines is also described by intramolecular $C(sp^3)$-$C(sp^3)$ cross-couplings.
5)