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Oxidative Dimerization of 2-Oxindoles Promoted by KO^{t}Bu-I_2: Total Synthesis of (±)-Folicanthine

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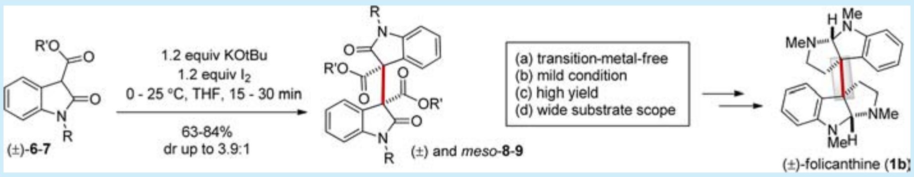
Supporting Information



ABSTRACT: A '*transition-metal-free*' oxidative coupling of 2-oxindoles has been demonstrated in the presence of 1.2 equiv each of potassium *tert*-butoxide and iodine. The method yields a diverse range of structurally different homo- and heterodimerized 2-oxindoles bearing vicinal all-carbon quaternary centers of great synthetic importance. A radical-driven pathway has been tentatively proposed.

C_2-Symmetric[1] dimeric cyclotryptamine alkaloids (**1a–c**, Figure 1) with a labile $C_{3a}–C_{3a'}$ σ-bond possess a diverse array of biological activities.[2] It is the presence of two vicinal all-carbon quaternary stereocenters in these alkaloids which are a challenge to the synthetic community, and hence they are attractive synthetic targets.[3] One of the plausible biogenetic pathways to achieve this involves a direct C–C bond formation via oxidative coupling[4,5] of two C–H bonds. Synthetic approaches in this direction are mainly concentrated toward the dimerization of 2-oxindoles such as **3a**[6a,b] and **3b**[6c] (Figure 1). However, these methods generally afford dimeric 2-oxindole products in poor to moderate yields, which might be due to the associated difficulty in the formation of a C–C bond containing a vicinal all-carbon quaternary center. Other approaches to dimeric cyclotryptamine alkaloids include direct oxidative dimerization of 3-substituted indoles.[7a–c,8]

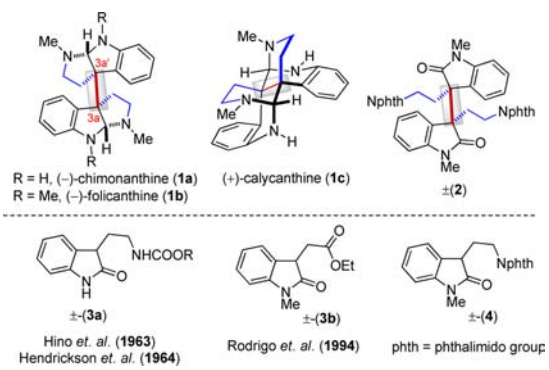
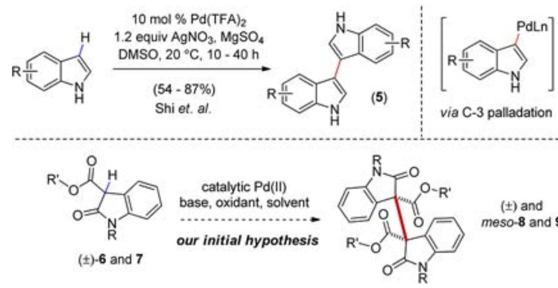


Figure 1. Selected bis-indole alkaloids (**1a–c**) with C_2-symmetry.

In 2010, Shi et al. demonstrated an oxidative homodimerization of indole derivatives toward 3,3′-linked bis-indole scaffolds (**5**) via Pd-catalysis,[9] where authors proposed formation of C-3 palladation of indole (Scheme 1). We envisioned that folicanthine **1b** and related cyclotryptamine alkaloids can be synthesized from a common intermediate (±)-**2** (Figure 1), which in turn can be accessed from a direct oxidative coupling of 2-oxindole (±)-**4** (Figure 1). Herein, we report an expeditious entry to dimeric 2-oxindoles bearing a variety of esters (**8** and **9**) and alkyl functionality (**2**) via a direct oxidative coupling of 3-substituted 2-oxindoles (**6**, **7**, and **4**) promoted by KO^{t}Bu-I_2, under mild conditions.

Scheme 1. Pd-Catalyzed Oxidative Dimerization



Initially, we thought to synthesize the dimeric 2-oxindoles[10] possessing bisesters functionalities (**8** and **9**) via a Pd-catalyzed oxidative coupling[11] of 2-oxindole derivatives (**6** and **7**) (Scheme 1). We envisioned that, in the presence of a suitable base, (±)-**6a** would generate enolate **10** (Scheme 2), which upon subsequent ligand exchange with $Pd(OAc)_2$ could lead to the formation of Pd(II) intermediate **11c** via the intermediacy of **11a** and **11b**. Ultimately, the direct coupling of two C–H bonds of 2-oxindoles (±)-**6a** could be achieved following a reductive elimination pathway. The process can be catalytic in the presence of a

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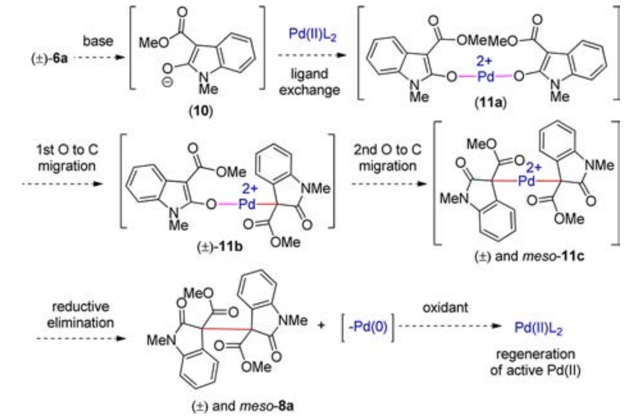
Scheme 2. Our Initial Hypothesis



sacrificial oxidant, which would help bring back the active catalyst Pd(II).

Preliminary experiments were performed with *N*-methyl-2-oxindole-3-methylcarboxylate (**6a**) in the presence of 1.2 equiv of ^{t}BuOK as base and 1.2 equiv of various oxidants using 10 mol % Pd(OAc)$_2$ as the catalyst in DMF at 0 °C−rt. Several oxidants such as FeCl$_3$, Cu(OAc)$_2$, iodosobenzene diacetate (PIDA), bis-trifluoroacetate iodoxybenzene (PIFA), and I$_2$ were screened in the coupling reaction. It was found that molecular iodine[12] was the best oxidant to afford (±)-and *meso*-**8a** in 61% isolated yield (dr 1.9:1) in 20 min (Table 1, entries 1−5). Switching to THF as solvent, the yield was further increased to 68% (dr 1.9:1) (entry 6). We observed that Pd(OAc)$_2$ and Pd(TFA)$_2$ were equally efficient to afford **8a** in 66−68% yields with dr 2.0:1 (entries 6 and 7). Also, ^{t}BuOK was found to be superior over other bases such as Cs$_2$CO$_3$ and ^{t}BuONa used in this reaction (entries 8−9).

Surprisingly, the same reaction, when performed in the absence of Pd(II) (entry 10, Table 1), afforded **8a** in 84% yield with dr 1.9:1. A brief solvent screening showed that nonpolar solvent such as toluene (entry 11) was inferior to polar aprotic solvents such as dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylformamide (DMF) (entries 12−13), yielding **8a** in 74% and 81% isolated yields, respectively, with almost similar dr. Optimization using different bases such as ^{t}BuONa, Na$_2$CO$_3$, K$_2$CO$_3$, and Cs$_2$CO$_3$ revealed that the product **8a** can be obtained in the range of 62−75% isolated yields with up to 2.4:1 dr (entries 14−17).[13] These results prompted us to revise our hypothesis of the Pd(II)-catalyzed sequence shown in Scheme 2. Since, palladium does not play a significant role in the reaction of **6a** to dimeric **8a**, we proposed a more reasonable alternative route involving a radical mediated intermolecular oxidative coupling. A single electron transfer (SET) from enolate **10** to an oxidant leads to the formation of radical intermediate **12a** (Scheme 3).[14] The latter has the resonating structure, a 3° radical (**12b**) at the pseudobenzylic position, which simply dimerizes to afford expected product **8a** (Scheme 3). In fact, a reaction between ^{t}BuOK and iodine is known to produce ^{t}BuOI,[15] which is reported to be a good radical initiator in a variety of organic transformations.[16,17]

In addition to iodine, simple oxidants such as *N*-halo succinimides such as NIS[18] and NBS also afforded product **8a** in 83% and 69% yields, respectively, with dr 1.6:1 (Table 2, entries 1−2) and we did not observe any traces of halides **13a−b**. Interestingly, well-known oxidizing agents, such as PIDA and PIFA,[19] which follow a radical mechanism, also afforded dimeric product **8a** in 45−52% yields (entries 3−4). Thus, based on this

Table 1. Optimization of Oxidative Coupling

sl. no.	solvent	base	oxidants	time	yield[a] (%)	dr[b]
1[c]	DMF	KO^{t}Bu	FeCl$_3$	1 h	–	–
2[c]	DMF	KO^{t}Bu	Cu(II)[e]	1 h	trace	–
3[c]	DMF	KO^{t}Bu	PIDA	30 min	43[f]	1.4:1
4[c]	DMF	KO^{t}Bu	PIFA	30 min	38[f]	1.3:1
5[c]	DMF	KO^{t}Bu	I$_2$	20 min	61	1.9:1
6[c]	THF	KO^{t}Bu	I$_2$	20 min	68	1.9:1
7[d]	THF	KO^{t}Bu	I$_2$	20 min	66	2.0:1
8[c]	THF	Cs$_2$CO$_3$	I$_2$	40 min	51[f]	2.0:1
9[c]	THF	NaO^{t}Bu	I$_2$	40 min	46[f]	1.2:1
10	**THF**	**KO^{t}Bu**	**I$_2$**	**15 min**	**84**	**1.9:1**
11	PhMe	KO^{t}Bu	I$_2$	30 min	31[f]	1.3:1
12	DMSO	KO^{t}Bu	I$_2$	15 min	74	1.7:1
13	DMF	KO^{t}Bu	I$_2$	15 min	81	1.9:1
14	THF	NaO^{t}Bu	I$_2$	15 min	62	1.1:1
15	THF	Na$_2$CO$_3$	I$_2$	15 min	68	1.5:1
16	THF	K$_2$CO$_3$	I$_2$	15 min	75	2.4:1
17	THF	Cs$_2$CO$_3$	I$_2$	15 min	72	1.9:1

[a]Reactions were carried out on a 0.25 mmol of **6a** in the presence of 0.30 mmol of base and oxidants in 1 mL of solvent at 0−25 °C, and isolated yields of **8a** are reported. [b]Dr determined from ^{1}H NMR of unpurified reaction mixture. [c]10 mol % Pd(OAc)$_2$ was used as catalyst. [d]10 mol % Pd (TFA)$_2$ was used as catalyst. [e]Cu(OAc)$_2$·H$_2$O was used as oxidant. [f]Mixture of products for rest of the mass balance.

Scheme 3. Revised Proposed Pathway of Dimerization

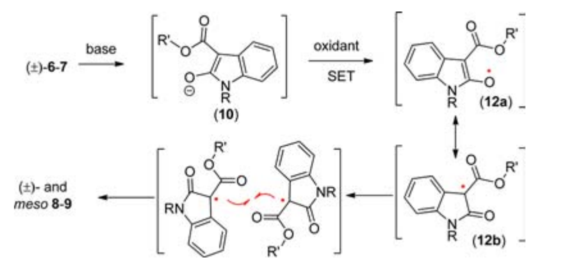
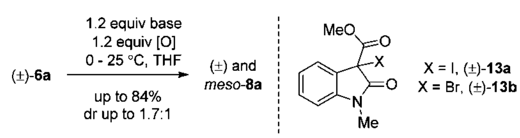


Table 2. Optimization of Intramolecular-Dehydrogenative Coupling



entry	oxidants	time	yield[a] (%)	dr[b]
1	NIS	15 min	83	1.5:1
2	NBS	15 min	69	1.6:1
3	PIDA	25 min	52[c]	1.7:1
4	PIFA	25 min	45[c]	1.4:1

[a]Isolated yields of **8a**. [b]Dr determined from ^{1}H NMR of unpurified reaction mixture. [c]Mixture of products for rest of the mass balance.

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evidence, it is quite reasonable to understand that our methodology follows a radical mediated process.

With the optimized conditions, we then explored the substrate scope using a variety of *N*-alkyl-2-oxindole-3-carboxylates (**6**, see Supporting Information for synthetic procedure) to afford dimeric 2-oxindoles. As evidenced from Figure 2, a variety of dimeric 2-oxindoles sharing vicinal all-carbon quaternary centers (**8a**−**r**) were obtained in 62−84% yields with a dr up to 3.9:1. The dr of the products can be further improved to >20:1 following recrystallization in a few cases to afford active isomer (±)-**8**.[20]

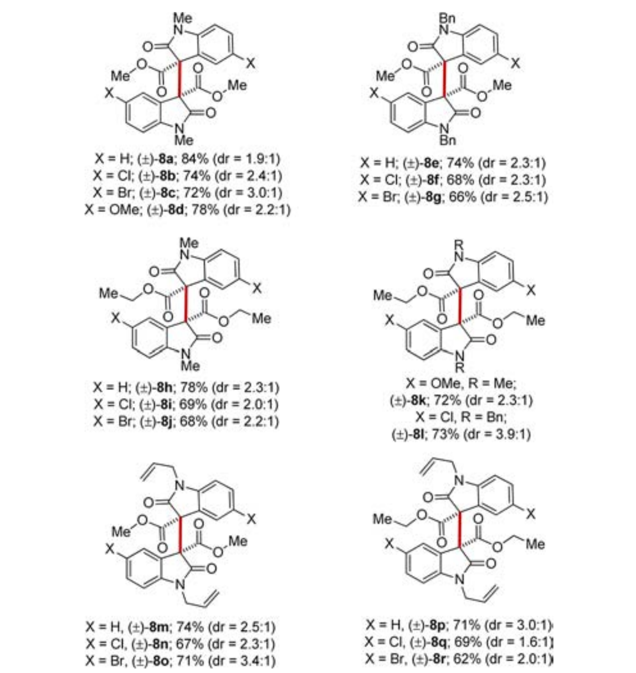


Figure 2. Substrate scope of oxidative dimerization.

To further extend the scope, a variety of *N*-methyl and benzyl substituted 2-oxindole-3-carboxylates (**7**, see Supporting Information for detailed method) having allyl, methallyl, prenyl, and geranyl esters with a diversely substituted 2-oxindole core were subjected to standard coupling conditions, and the results are shown in Figure 3.

Rewardingly, a variety of dimeric 2-oxindoles **9a**−**l** were prepared in good yields with a dr up to 2.8:1. Importantly, these dimeric 2-oxindoles are potential substrates that can provide access to enantioenriched bis-2-oxindoles with vicinal all-carbon quaternary stereocenters[21,22] under the influence of a catalytic nonracemic Pd-complex.[23] Later, a search for a more generalized dimerization protocol prompted us to carry out heterodimerization of two structurally different *N*-alkyl-2-oxindole-3-carboxylates (Scheme 4). Consequently, we observed that an efficient heterodimerization could also be realized under optimized conditions (see Supporting Information for details). When two different ester substrates were subjected to 1.2 equiv of each KO^{t}Bu and I_2, heterodimerized products **9m**−**n** were obtained in 50−52% yield with a moderate dr of 2.4:1. In addition, we also isolated homodimerized products in these processes in ∼10−13% yields (Scheme 4). We have also seen that an isolated yield of the heterodimerization product is dependent on the concentration of the reaction medium. With the dilution, an isolated yield of **9m** also increased (see Supporting Information for details). These heterodimerized skeletons represent an

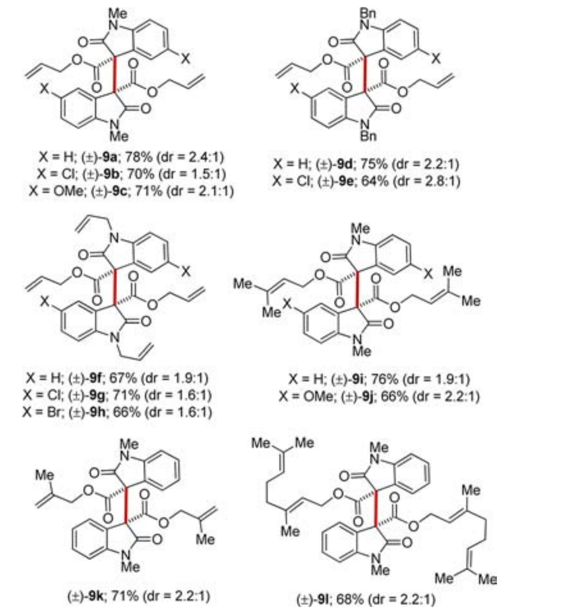
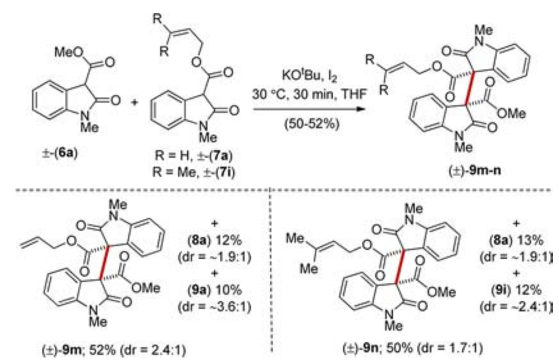


Figure 3. Substrate scope with various allylic type esters.

Scheme 4. Scope of Heterodimerization



efficient platform for the synthesis of unsymmetrical dimeric indole alkaloids.

Apart from this, different *N*-protected substrates, such as 3-methyl-*N*-Boc-2-oxindole **15a**, also undergo dimerization without an event to afford **14a** in 73% with an ∼1.1:1 dr (Figure 4) thus increasing the scope of the method even further. However, the reaction faced limitations with substrate **16a**, leading to 45−50% recovery of starting material along with decomposition of the rest of the mass balance (Figure 4). In the case of 2-oxindole **17**, the starting material was consumed but no expected product was isolated and always a multitude spots on TLC were observed. These results also suggested a tertiary radical is probably responsible for the oxidative coupling.

Notably, N_b-phth protected *N*-methyl-2-oxindole (±)-**4** afforded dimeric **2** in 56% yield with ∼1.2:1 dr, which on subsequent deprotection of the phthalimido group followed by carbamate protection afforded **19** in 70% yield with ∼1.2:1 dr. The major trans isomer was separated in column chromatography followed by Red-Al treatment affording (±)-folicanthine **1b** in 68% yield (see Supporting Information for details).

In summary, we have developed a novel and efficient oxidative coupling protocol which allows the synthesis of a structurally diverse range of dimeric 2-oxindoles with vicinal quaternary centers. The reaction is mediated by KO^{t}Bu and I_2 under mild conditions, and additional research will focus on the develop-

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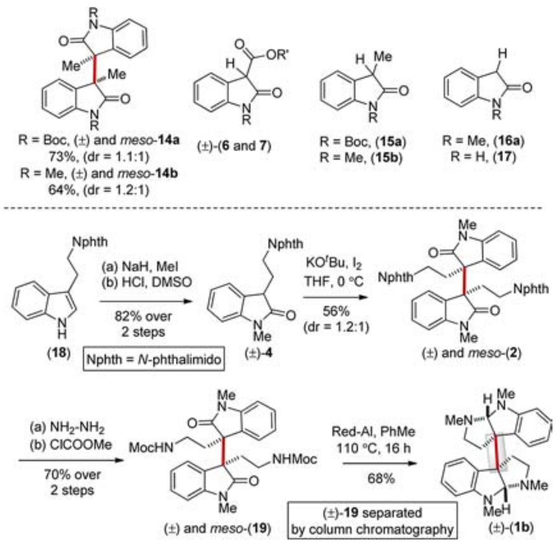

Figure 4. Further scope.

ment of catalytic versions of this method as well. The high synthetic value of oxidative coupling products ensures further improvement in this field and its applications in the total synthesis of dimeric cyclotryptamine alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) For an excellent review, see: Vrettou, M.; Gary, A. A.; Brewer, A. R. E.; Barrett, A. G. M. *Tetrahedron* **2007**, *63*, 1487 and references cited. (b) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953. (c) Ziegler, F. E.; Harran, P. G. *J. Org. Chem.* **1993**, *58*, 2768.

(2) For excellent reviews, see: (a) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262. (b) Steven, A.; Overman, L. E. *Angew. Chem., Int. Ed.* **2007**, *119*, 5584. (c) Schmidt, M. A.; Movassaghi, M. *Synlett* **2008**, 313.

(3) (a) Overman, L. E.; Paone, D. V.; Sterns, B. A. *J. Am. Chem. Soc.* **1999**, *121*, 7702. (b) Overman, L. E.; Larrow, J. F.; Stearns, B. A.; Vance, J. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 213. (c) Overman, L. E.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 9465.

(4) (a) Dyker, G., Ed. *Handbook of C−H Transformations: Applications in Organic Synthesis*; Wiley-VCH: Weinheim, 2005; Vol. 2. (b) Guo, F.; Clift, M. D.; Thomson, R. J. *Eur. J. Org. Chem.* **2012**, 4881.

(5) (a) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev.* **2009**, *38*, 3010. (b) Gaich, T.; Baran, P. S. *J. Org. Chem.* **2010**, *75*, 4657 and references cited.

(6) (a) Hino, T.; Yamada, S.-i. *Tetrahedron Lett.* **1963**, *4*, 1757. (b) Hendrickson, J. B.; Goschke, R.; Ress, R. *Tetrahedron* **1964**, *20*, 565. (c) Fang, C.-L.; Horne, S.; Taylor, N.; Rodrigo, R. *J. Am. Chem. Soc.* **1994**, *116*, 9480.

(7) (a) Scott, A. L.; Guo, L.; McCapra, F.; Hall, E. S. *J. Am. Chem. Soc.* **1964**, *86*, 302. (b) Ishikawa, H.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 5637. (c) Li, Y.-X.; Wang, H.-X.; Ali, S.; Xia, X.-F.; Liang, Y.-M. *Chem. Commun.* **2012**, 2343.

(8) (a) Tadano, S.; Mukaeda, Y.; Ishikawa, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 7990 and references cited. For radical mediated dimerization, see: (b) Movassaghi, M.; Schmidt, M. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725. (c) Kim, J.; Ashehurst, J. A.; Movassaghi, M. *Science* **2009**, *324*, 238. (d) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2010**, *132*, 14376.

(9) Li, Y.; Wang, W.-H.; Yang, S.-D.; Li, B.-J.; Feng, C.; Shi, Z. J. *Chem. Commun.* **2010**, *46*, 4553.

(10) Our one-pot synthesis of dimeric 2-oxindoles afforded product **3** only in 30−42% yields; see: Ghosh, S.; De, S.; Kakde, B. N.; Bhunia, S.; Adhikary, A.; Bisai, A. *Org. Lett.* **2012**, *14*, 5864.

(11) For direct oxidative coupling, see: (a) DeMartino, M. P.; Chen, K.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 11546 and references therein. (b) Jia, Y. X.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. (c) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249. (d) Guo, F.; Konkol, L. C.; Thomson, R. J. *J. Am. Chem. Soc.* **2011**, *133*, 18. (e) Bhunia, S.; Ghosh, S.; Dey, D.; Bisai, A. *Org. Lett.* **2013**, *15*, 2426.

(12) For iodine in homodimerization reactions, see: (a) Alvarez-Ibarra, C.; Csákÿ, A. G.; Colmenero, B.; Quiroga, M. L. *J. Org. Chem.* **1997**, *62*, 2478. (b) Kuo, W.-J.; Chen, Y.-H.; Jeng, R.-J.; Chan, L.-H.; Lin, W.-P.; Yang, Z.-M. *Tetrahedron* **2007**, *63*, 7086.

(13) We sincerely thank one of the reviewers for investigating the effect of simple bases, such as ^{t}BuONa, Na_2CO_3, K_2CO_3, and Cs_2CO_3, under the optimized conditions.

(14) The vinyloxy radical has been proposed earlier by Baran and co-workers: Richter, J. M.; Whitefield, B. W.; Maimone, T. J.; Lin, D. W.; Castroveijo, P. M.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 12857.

(15) (a) Montoro, R.; Wirth, T. *Org. Lett.* **2003**, *5*, 4729. (b) Akhtar, M.; Barton, D. H. R. *J. Am. Chem. Soc.* **1964**, *86*, 1528.

(16) We sincerely thank the reviewers for their valuable suggestions to validate the reactions using a preformed well-known radical generator ^{t}BuOI.

(17) We have also conducted the oxidative dimerization in the presence of *in situ* generated ^{t}BuOI (see Supporting Information for details) and found that oxidative dimerized products can be obtained in synthetically useful yields.

(18) For use of NIS as an oxidant in an oxidative bond-forming reaction, see: (a) West, S. P.; Bisai, A.; Lim, A. D.; Narayan, R. R.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 11187. (b) Foo, K.; Newhouse, T.; Mori, I.; Takayama, H.; Bran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2716.

(19) For a recent example, see: Wang, J.; Yuan, Y.; Xiong, R.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Org. Lett.* **2012**, *14*, 2210.

(20) The major diastereomer of our oxidative process is the active one, which was confirmed from HPLC analysis of one of the products (**9a**).

(21) The dimeric 2-oxindoles of the type **9a** can be converted to C_2-symmetric 2-oxindoles with vicinal all-carbon quaternary stereocenters. See our report: Ghosh, S.; Bhunia, S.; Kakde, B. N.; De, S.; Bisai, A. *Chem. Commun.* **2014**, *50*, 2434.

(22) For pioneering work on enantioselective double decarboxylative allylations, see: (a) Trost, B. M.; Osipov, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 9176. (b) Enquist, J. A., Jr.; Stoltz, B. M. *Nature* **2008**, *453*, 1228.

(23) For Pd-catalyzed asymmetric prenylations and geranylations, see: Trost, B. M.; Malhotra, S.; Chan, W. H. *J. Am. Chem. Soc.* **2011**, *133*, 7328.

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Org. Lett. 2015, 17, 1373−1376