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Integrated Catalytic C−H Transformations for One-Pot Synthesis of 1-Arylisoindoles from Isoindolines via Palladium-Catalyzed Dehydrogenation Followed by C−H Arylation

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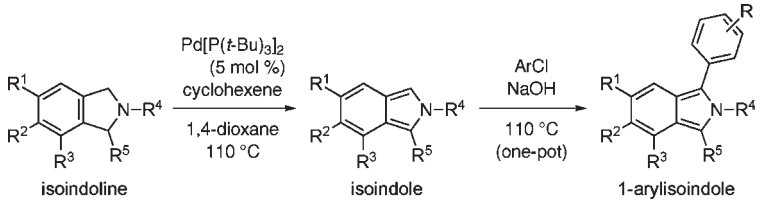
ABSTRACT



A one-pot conversion of isoindolines to 1-arylisoindoles was established from palladium-catalyzed cascade C−H transformations, that is, the dehydrogenation of isoindolines to give isoindoles, with subsequent C−H arylation of the isoindoles.

Organic compounds containing an aryl−heteroaryl conjugated π-system have received much interest across a wide range of research fields, including organic synthesis, medicinal chemistry, and materials sciences.[1] Among the various efficient synthetic methods for these compounds, transition-metal-catalyzed C−H arylation of heteroaromatic compounds has become an important synthetic method.[2,3] This method has an advantage over transition metal-catalyzed cross-coupling reactions,[4] in that the use of halogenated or metalated aromatic starting materials can be avoided. To make the strategy based on C−H arylation more useful and practical, its application to a cascade catalytic process, in

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(2) For recent reviews on catalytic C−H arylation of heteroaromatic compounds, see: (a) Satoh, T.; Miura, M. *Chem. Lett.* **2007**, *36*, 200. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173. (d) Bellina, F.; Rossi, R. *Tetrahedron* **2009**, *65*, 10269. (e) Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20.

(3) For examples on catalytic C−H arylation of pyrroles, indoles, and indolizines, see: (a) Akita, Y.; Itagaki, Y.; Takizawa, S.; Ohta, A. *Chem. Pharm. Bull.* **1989**, *37*, 1477. (b) Filippini, L.; Gusmeroli, M.; Riva, R. *Tetrahedron Lett.* **1992**, *33*, 1755. (c) Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1159. (d) Lane, B. S.; Sames, D. *Org. Lett.* **2004**, *6*, 2897. (e) Rieth, R. D.; Mankad, N. P.; Calimano, E.; Sadighi, J. P. *Org. Lett.* **2004**, *6*, 3981. (f) Lane, B. S.; Brown, M. A.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 8050. (g) Joucla, L.; Putey, A.; Joseph, B. *Tetrahedron Lett.* **2005**, *46*, 8177. (h) Touré, B. B.; Lane, B. S.; Sames, D. *Org. Lett.* **2006**, *10*, 1979. (i) Wang, X.; Gribkov, D. V.; Sames, D. *J. Org. Chem.* **2007**, *72*, 1476. (j) Roger, J.; Doucet, H. *Adv. Synth. Catal.* **2009**, *351*, 1977. (k) Gryko, D. T.; Vakuliuk, O.; Gryko, D.; Koszarna, B. *J. Org. Chem.* **2009**, *74*, 9517. (l) Roy, D.; Mom, S.; Beaupérin, M.; Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6650. See also refs 1a and 1d.

(4) (a) de Meijere, A., Diederich, F., Eds; *Metal-Catalyzed Cross-Coupling Reactions*; Wiley-VCH: Weinheim, 2004. (b) Li, J. J., Gribble, G. W., Eds. *Palladium in Heterocyclic Chemistry*, 2nd ed.; Elsevier: Oxford, 2007.

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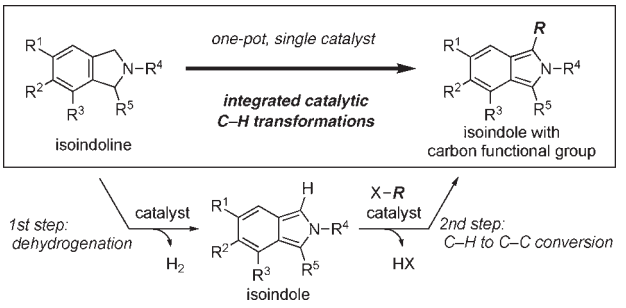
Scheme 1. Concept for Synthesis of Isoindoles with Carbon Functional Group Based on Catalytic C−H Transformations

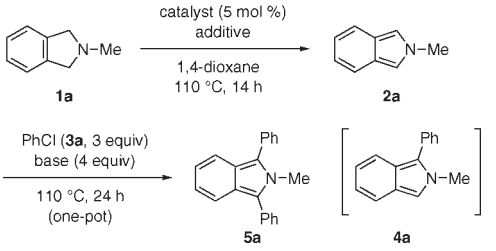


which two or more C−H transformations are achieved by a single catalyst, is highly attractive.[5]

Our recent interest has been directed to the development of a new concept for the synthesis of isoindole derivatives utilizing catalytic C−H transformations (Scheme 1).[6,7] To avoid isolation of the air-sensitive isoindoles that are subjected to functionalization,[8] we particularly focused on cascade transformations starting from isoindolines, which are easy to handle and are easily available via several synthetic methods.[9] In this regard, we have established a palladium-catalyzed conversion of isoindolines to 1-boryl- and 1,3-diborylisoindoles via sequential dehydrogenation and C−H borylation.[10] Herein, we describe the conversion of isoindolines to 1-arylated isoindoles via integrated catalytic C−H transformations. The dehydrogenation of isoindolines and the C−H arylation of the isoindoles was achieved in one-pot using a single palladium catalyst.

The reaction of 2-methylisoindoline (**1a**) was initially examined in 1,4-dioxane at 110 °C in the presence of phosphine-free $Pd(dba)_2$ (5 mol %), which was found to be effective for the dehydrogenation/C−H borylation sequence in a previous study (entry 1, Table 1).[10,11] Dehydrogenation of **1a** took place efficiently to give 2-methylisoindole (**2a**) in 56% yield after 14 h. Chlorobenzene (**3a**, 3 equiv) and NaOH (4 equiv) were then added to the reaction mixture, and the resulting solution was stirred at 110 °C for 24 h. However, no phenylated products were observed under these reaction conditions. We tested several phosphorus ligands to find a catalyst for C−H arylation while maintaining the catalyst activity for dehydrogenation (entries 2−6). We found that palladium catalysts generated in situ from $Pd(dba)_2$ with PCy_3 or $P(t\text{-}Bu)_3$ (Pd/P = 1/2) were effective for both dehydrogenation and C−H phenylation (entries 5 and 6). The phenylation took place at both the C1 and C3 positions of **2a** to afford double-phenylated **5a** in 61−69% yields. The formation of monophenylated **4a** was observed during the course of the reaction, indicating that **5a** was formed via a stepwise double C−H phenylation of **2a**.[12] It is important to note that **3a** and NaOH were required to be

Table 1. Optimization of Reaction Conditions for Palladium-Catalyzed One-Pot Dehydrogenation/C−H Phenylation of **1a**[a]



entry	catalyst	additive	yield of **2a** (%)[b]	base	yield of **5a** (%)[b]
1	$Pd(dba)_2$	–	56	NaOH	0
2	$Pd(dba)_2$/DPPF	–	10	NaOH	4
3	$Pd(dba)_2$/$2PPh_3$	–	11	NaOH	2
4	$Pd(dba)_2$/2SPhos	–	62	NaOH	9
5	$Pd(dba)_2$/$2PCy_3$	–	60	NaOH	61
6	$Pd(dba)_2$/ $2P(t\text{-}Bu)_3$	–	59	NaOH	69
7	$Pd[P(t\text{-}Bu)_3]_2$	Me_2S[c]	55	NaOH	27
8	$Pd[P(t\text{-}Bu)_3]_2$	norbornene[d]	58	NaOH	48
9	$Pd[P(t\text{-}Bu)_3]_2$	t-BuCH=CH_2[d]	68	NaOH	73
10	$Pd[P(t\text{-}Bu)_3]_2$	cyclohexene[d]	92[e]	NaOH	98 (97)[f]
11	$Pd[P(t\text{-}Bu)_3]_2$	cyclohexene[d]	–	K_2CO_3	0
12	$Pd[P(t\text{-}Bu)_3]_2$	cyclohexene[d]	–	K_3PO_4	29
13	$Pd[P(t\text{-}Bu)_3]_2$	cyclohexene[d]	–	KOAc	3
14	$Pd[P(t\text{-}Bu)_3]_2$	cyclohexene[d]	–	KF	0
15[g]	$Pd[P(t\text{-}Bu)_3]_2$	cyclohexene[d]	–	NaOH	42[h]
16[i]	$Pd[P(t\text{-}Bu)_3]_2$	cyclohexene[d]	–	NaOH	59[h]

[a] Pd complex (0.010 mmol), additive, and **1a** (0.20 mmol) were reacted in 1,4-dioxane (0.3 mL) at 110 °C for 14 h. **3a** (0.60 mmol) and base (0.80 mmol) were then added to the mixture and the resulting mixture was stirred at 110 °C for 24 h. [b] GC yield based on **1a**. [c] 2.0 μmol. [d] 1.0 mmol. [e] Average of entries 10−16. [f] Isolated yield based on **1a** in 0.4 mmol scale reaction. [g] Bromobenzene was used instead of **3a**. [h] Cyclohexenylbenzenes, products via Heck reaction of cyclohexene with aryl halide, were formed as side products. [i] Iodobenzene was used instead of **3a**.

(5) (a) Müller, T. J. J., Ed. *Metal Catalyzed Cascade Reactions*; Springer: Berlin, 2006. For general statement of reaction integration, see: (b) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett*. **2010**, *39*, 404.

(6) For reviews on isoindole, see: (a) Jones, G. B.; Chapman, B. J. In *Comprehensive Heterocyclic Chemistry II*, Katrizky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; Vol 2, p 1. (b) Donohoe, T. J. In *Science of Synthesis*; Thomas, E. J., Ed.; Georg Thieme Verlag; Stuttgart, 2000; Vol 10, p 653.

(7) For examples on transition-metal-catalyzed synthesis of isoindoles, see: (a) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardía, M.; Bonjoch, J. *J. Am. Chem. Soc*. **2003**, *125*, 1587. (b) Kadzimirsz, D.; Hildebrandt, D.; Merz, K.; Dyker, G. *Chem. Commun*. **2006**, 661. (c) Ding, Q.; Ye, Y.; Fan, R.; Wu, J. *J. Org. Chem*. **2007**, *72*, 5439. (d) Heugebaert, T. S. A.; Stevens, C. V. *Org. Lett*. **2009**, *11*, 5018. (e) Solé, D.; Serrano, O. *Org. Biomol. Chem*. **2009**, 3382. (f) Shimizu, H.; Igarashi, T.; Murakami, M. *Bull. Korean Chem. Soc*. **2010**, *31*, 1461. (g) Solé, D.; Serrano, O. *J. Org. Chem*. **2010**, *75*, 6267.

(8) Ahmed, M.; Kricka, L. J.; Vernon, J. M. *J. Chem. Soc., Perkin 1* **1975**, 71.

(9) For examples, see: (a) Sakuragi, A.; Shirai, N.; Sato, Y.; Kurono, Y.; Hatano, K. *J. Org. Chem*. **1994**, *59*, 148. (b) Ebden, M. R.; Simpkins, N. S.; Fox, D. N. A. *Tetrahedron* **1998**, *54*, 12923. (c) Hou, D.-R.; Hsieh, Y.-D.; Hsieh, Y.-W. *Tetrahedron Lett*. **2005**, *46*, 5927. (d) Yamamoto, Y.; Saigoku, T.; Nishiyama, H.; Ohgai, T.; Itoh, K. *Org. Biomol. Chem*. **2005**, *3*, 1768. (e) Hou, D.-R.; Wang, M.-S.; Chung, M.-W.; Hsieh, Y.-D.; Tsai, H.-H. G. *J. Org. Chem*. **2007**, *72*, 9231.

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(11) For limited example on palladium-catalyzed dehydrogenation of isoindoline to give isoindole, see: Grigg, R.; Somasunderam, A.; Sridharan, V.; Keep, A. *Synlett* **2009**, 97. See also ref 7g.

(12) All attempts for selective synthesis of **4a** from **1a** failed because reactivity of **2a** and **4a** in the C−H phenylation was similar under the palladium-catalyzed conditions.

added *after* the first dehydrogenation step, as the addition of these reagents to the initial reaction mixture resulted in low conversion of **1a**. It should also be noted that use of electron-rich and sterically bulky trialkylphosphines is critical for the one-pot, two-step conversion. Slower dehydrogenation was observed in the reactions with Pd/DPPF and Pd/PPh_3 catalysts (entries 2 and 3), whereas a palladium complex bearing SPhos (2-dicyclohexylphosphino-2′,6′-dimethoxy-1, 1′-biphenyl) was effective for dehydrogenation, but was inefficient for C−H phenylation (entry 4).

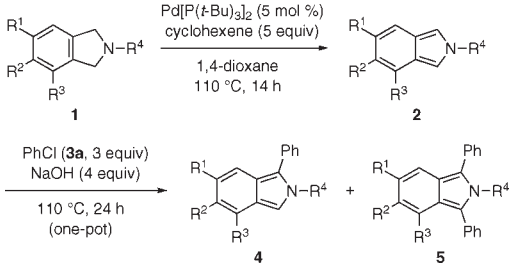
Several additives were examined with $Pd[P(t\text{-}Bu)_3]_2$ catalyst to improve the reaction (entries 7−10). The addition of a catalytic amount of Me_2S (1 mol %), which was found to be effective for the synthesis of 1-borylisoindoles via dehydrogenation/C−H borylation of isoindolines,[10] did not result in a significant improvement in dehydrogenation with an inefficient C−H arylation (entry 7). In contrast, effective dehydrogenation took place on addition of an alkene as a hydrogen acceptor (entries 8−10). Finally, we found that an efficient conversion of **1a** to **2a** was achieved in the presence of cyclohexene (5 equiv), leading to the formation of the final product **5a** in high yield (entry 10).

The second step (C−H phenylation) was also optimized (entries 10−14). The C−H phenylation proceeded efficiently with use of NaOH as a base (entry 10), whereas other bases such as K_2CO_3, K_3PO_4, KOAc, and KF gave poor results (entries 11−14). Bromo- and iodobenzene could also be employed in the C−H phenylation of **2a**, although the yields of **5a** were lower than that obtained using chlorobenzene (**3a**), because of the competing Heck reaction with the remnant cyclohexene (entries 15 and 16).

The optimized reaction conditions were then employed for the dehydrogenation/C−H phenylation of various isoindolines **1** (Table 2). Although dehydrogenation of *N*-Et-, *N*-*i*-Pr-, and *N*-*t*-Bu-substituted isoindolines **1b**−**d** took place smoothly to give the corresponding isoindoles **2b**−**d** in high yields, the C−H phenylation was sensitive to the steric bulkiness of the alkyl groups (entries 1−3). Selective formation of **5b** was achieved in the reaction of *N*-Et-substituted **2b** (entry 1), whereas the phenylation of *N*-*i*-Pr-substituted **2c** resulted in a slow formation of a mixture of mono- and double-phenylated products (entry 2). A much more sluggish phenylation was observed in the reaction of *N*-*t*-Bu-substituted **2d** (entry 3). *N*-Me-substituted isoindolines **1e-i** were then subjected to the sequential reaction (entries 4−8). Methyl, methoxy, and trifluoromethyl groups on the benzene ring did not affect the reactivity in either the dehydrogenation or the C−H phenylation, giving double phenylated products **5e**−**h** in high yields. The second C−H phenylation of **2i** proceeded smoothly, despite the presence of the sterically demanding 4-methyl group (entry 8).

2-Methylisoindolines **1j**−**m** bearing a substituent at the C1 position were then subjected to the reactions with various aryl chlorides **3** (1.5 equiv) (Table 3). Dehydrogenation of 1-aryl-2-methylisoindolines **1j**−**l** and 1,2-dimethylisoindoline (**1m**) took place cleanly under the optimized conditions to give the corresponding isoindoles **4a** and **2k**−**m** in high yields (entries 1−12). Isoindole **4a** underwent subsequent C−H phenylation with **3a** to afford **5a** in 97% yield (entry 1).

Table 2. Palladium-Catalyzed One-Pot Dehydrogenation/C−H Phenylation of Isoindolines **1**[a]



entry	R^1	R^2	R^3	R^4		yield of **2** (%)[b]	yield of **4** and **5** (%)[c]
1	H	H	H	Et	**1b**	96 (**2b**)	82 (**5b**)
2[d]	H	H	H	*i*-Pr	**1c**	99 (**2c**)	66[e] (**4c**), 13[e] (**5c**)
3	H	H	H	*t*-Bu	**1d**	99 (**2d**)	32[f] (**4d**), 0[f] (**5d**)
4	Me	H	H	Me	**1e**	91 (**2e**)	84 (**5e**)
5	MeO	H	H	Me	**1f**	92 (**2f**)	92 (**5f**)
6	F_3C	H	H	Me	**1g**	97 (**2g**)	99 (**5g**)
7	Me	Me	H	Me	**1h**	88 (**2h**)	85 (**5h**)
8	H	H	Me	Me	**1i**	92 (**2i**)	81 (**5i**)

[a] $Pd[P(t\text{-}Bu)_3]_2$ (0.020 mmol), cyclohexene (2.0 mmol), and **1** (0.40 mmol) were reacted in 1,4-dioxane (0.6 mL) at 110 °C for 14 h. **3a** (1.2 mmol) and NaOH (1.6 mmol) were then added to the mixture and the resulting mixture was stirred at 110 °C for 24 h. [b] Determined by ^{1}H NMR and GC. [c] Isolated yield based on **1**. [d] **3a** (5 equiv) and NaOH (5 equiv) were used. [e] ^{1}H NMR yield after 48 h. [f] ^{1}H NMR yield after 71 h.

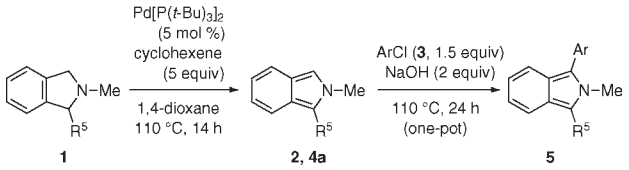
Electron-rich aryl chlorides **3b** and **3c**, as well as electron-deficient **3d**, reacted with **4a** to give **5j**−**l** in high yields (entries 2−4), although the reaction of sterically demanding **3e** with **4a** was slow, resulting in the formation of **5m** in a moderate yield (entry 5). 3-Chloropyridine (**3f**) successfully took part in the C−H arylation, yielding **5n** in good yield (entry 6). The C−H phenylation of 4-methoxyphenyl-substituted isoindole **2k** and 4-trifluoromethylphenyl-substituted **2l** gave the corresponding 1,3-diarylisoindoles **5k** and **5l**, respectively, in good yields (entries 7 and 8). 1,2-Dimethylisoindole (**2m**) was more reactive than **4a**, **2k**, and **2l** in the C−H arylation, leading to a reaction with sterically demanding **3e** to give **5q** in high yield (entry 11). However, the reaction of **2m** with the more hindered **3h** was slow under the conditions used (entry 12). An application of the dehydrogenation/C−H arylation sequence is demonstrated in the reaction with 1,4-dichlorobenzene (**3i**), which led to an efficient synthesis of phenylene-linked isoindole **5s** (Scheme 2).

Isoindoles have attracted much interest in applications such as fluorescent and electroluminescent materials[13,14]

(13) For study on utilization of isoindoles as fluorescent and electroluminescent materials, see: (a) Zweig, A.; Metzler, G.; Maurer, A.; Roberts, B. G. *J. Am. Chem. Soc.* **1967**, *89*, 4091. (b) Ding, Y.; Hay, A. S. *J. Pom. Sci. Part A: Polym. Chem.* **1999**, *37*, 3293. (c) Gauvin, S.; Santerre, F.; Dodelet, J. P.; Ding, Y.; Hlil, A. R.; Hay, A. S.; Anderson, J.; Armstrong, N. R.; Gorjanc, T. C.; D'Iorio, M. *Thin Solid Films* **1999**, *353*, 218. (d) Mi, B.-X.; Wang, P.-F.; Liu, M.-W.; Kwong, H.-L.; Wong, N.-B.; Lee, C.-S.; Lee, S.-T. *Chem. Mater.* **2003**, *15*, 3148. (e) Jiao, L.; Yu, C.; Lin, M.; Wu, Y.; Cong, K.; Meng, T.; Wang, Y.; Hao, E. *J. Org. Chem.* **2010**, *75*, 6035.

(14) Photophysical properties of 1-arylated isoindoles obtained in this study are summarized in Supporting Information.

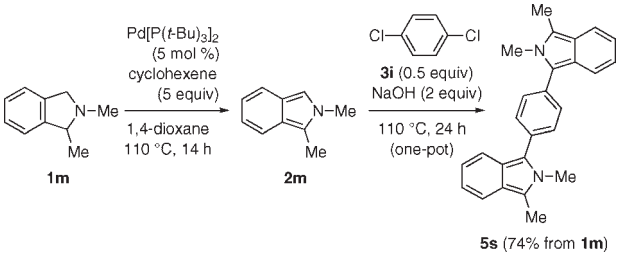
Table 3. Palladium-Catalyzed One-Pot Dehydrogenation/C−H Arylation of 1-Substituted Isoindolines[a]



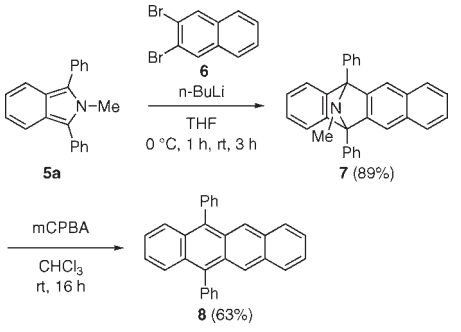
entry	1	yield of **2** or **4a** (%)[b]	ArCl	yield of **5** (%)[c]
1	**1j** (R^5 = Ph)	99[d] (**4a**)	**3a** (Ar = Ph)	97 (**5a**)
2	**1j**	− (**4a**)	**3b** (Ar = 4-MeC_6H_4)	93 (**5j**)
3[e]	**1j**	− (**4a**)	**3c** (Ar = 4-$MeOC_6H_4$)	77 (**5k**)
4[f]	**1j**	− (**4a**)	**3d** (Ar = 4-$F_3CC_6H_4$)	85 (**5l**)
5	**1j**	− (**4a**)	**3e** (Ar = 2-MeC_6H_4)	48[g] (**5m**)
6[h]	**1j**	− (**4a**)	**3f** (Ar = 3-pyridyl)	74[g] (**5n**)
7	**1k** (R^5 = 4-$MeOC_6H_4$)	99 (**2k**)	**3a**	66 (**5k**)
8	**1l** (R^5 = 4-$F_3CC_6H_4$)	99 (**2l**)	**3a**	71 (**5l**)
9	**1m** (R^5 = Me)	93[i] (**2m**)	**3a**	90 (**5o**)
10	**1m**	− (**2m**)	**3g** (Ar = 3-MeC_6H_4)	97 (**5p**)
11	**1m**	− (**2m**)	**3e**	86 (**5q**)
12	**1m**	− (**2m**)	**3h** (Ar = 2,6-$Me_2C_6H_3$)	25[j] (**5r**)

[a] $Pd[P(t\text{-}Bu)_3]_2$ (0.020 mmol), cyclohexene (2.0 mmol), and **1** (0.40 mmol) were reacted in 1,4-dioxane (0.6 mL) at 110 °C for 14 h. **3** (0.60 mmol) and NaOH (0.80 mmol) were then added to the mixture and the resulting mixture was stirred at 110 °C for 24 h. [b] Determined by ^1H NMR and GC. [c] Isolated yield based on **1**. [d] Average of entries 1−6. [e] **3c** (0.80 mmol) was used. [f] **3d** (0.80 mmol) was used. [g] Yield after 48 h. [h] **3f** (1.0 mmol) and NaOH (1.0 mmol) were used. [i] Average of entries 9−12. [j] ^1H NMR yield after 72 h.

Scheme 2. Synthesis of Phenylene-Linked Isoindole **5s**



Scheme 3. Synthesis of 5,12-Diphenylnaphthacene (**8**) Utilizing Isoindole **5a**



as well as synthetic intermediates.[15] A synthetic application of the arylated isoindoles is demonstrated by the Diels−Alder reaction of **5a** with naphthalyne, which was generated in situ from 2,3-dibromonaphthalene (**6**) with *n*-butyllithium (Scheme 3).[16] The reaction proceeded cleanly to give amine **7** in a high yield. Amine **7** served as a useful precursor of 5,12-diphenyltetracene (**8**),[17] which afforded **8** in a good yield on treatment with mCPBA.[18]

(15) For examples of Diels−Alder reaction of isoindoles, see: (a) Chen, Y.-L.; Lee, M.-H.; Wong, W.-Y.; Lee, A. W. M. *Synlett* **2006**, 2510. (b) Duan, S.; Sinha-Mahapatra, D. K.; Herndon, J. W. *Org. Lett.* **2008**, *10*, 1541.

(16) For related tetracene synthesis utilizing 1,3-unsubstituted isoindoles, see: (a) LeHoullier, C. S.; Gribble, G. W. *J. Org. Chem.* **1983**, *48*, 2364. (b) Chen, Z.; Müller, P.; Swager, T. M. *Org. Lett.* **2006**, *8*, 273.

(17) For another route to **8**, see: Zhou, L.; Nakajima, K.; Kanno, K.; Takahashi, T. *Tetrahedron Lett.* **2009**, *50*, 2722.

(18) Gribble, G. W.; Allen, R. W.; Anderson, P. S.; Christy, M. E.; Colton, C. D. *Tetrahedron Lett.* **1976**, *17*, 3673.

In conclusion, we have established an efficient route to 1-aryl-substituted isoindoles via the palladium-catalyzed dehydrogenation of isoindolines and subsequent C−H arylation of the resulting isoindoles. The synthesis of dehydrogenation products in high yields is achieved by the addition of cyclohexene as a hydrogen acceptor. A wide range of aryl chlorides is applicable to the C−H arylation. Further development of the isoindole synthetic method based on the dehydrogenation/C−H functionalization is now being undertaken in this laboratory.

Supporting Information Available. Experimental details and characterization data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.