Synthesis of *N*-Arylisoindolin-1-ones via Pd-Catalyzed Intramolecular Decarbonylative Coupling of *N*-(2-Bromobenzyl)oxanilic Acid Phenyl Esters

Yu Zheng,^a Gongli Yu,^a Jinlong Wu,^a Wei-Min Dai*^{a,b}

^b Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, P. R. of China

Fax +85223581594; E-mail: chdai@ust.hk

Received 23 December 2009

Abstract: Ethyl and phenyl oxanilates were readily prepared from N-(2-bromobenzyl)anilines and oxalyl chloride monoethyl and monophenyl esters, respectively. It was found that the ethyl oxanilate survived in the presence of K₂CO₃ in DMA at 120 °C and underwent an intramolecular direct arylation using Pd(OAc)₂–dppf, furnishing the 5,6-dihydrophenanthridine derivative. In contrast, the corresponding phenyl oxanilates decomposed upon exposure to K₂CO₃ in DMA at 120 °C and were transformed into *N*-arylisoindo-lin-1-ones via Pd(OAc)₂–dppf-catalyzed intramolecular decarbony-lative coupling. Except for the 4-methoxy-substituted oxanilic acid phenyl ester, other phenyl oxanilates possessing electron-withdrawing (NO₂, Cl) and weak electron-donating (Me) substituents provided the *N*-arylisoindolin-1-ones in 43–80% yields.

Key words: decarbonylative coupling, direct arylation, isoindolin-1-ones, oxanilates, palladium

In the last few years, decarbonylative cross-coupling reactions under palladium catalysis (or with copper) have become an attractive synthetic methodology which promises use of carboxylic acids as a new source of nucleophilic coupling partners.¹ As compared to the organometallic reagents widely used in conventional cross-coupling reactions, such as Negishi, Suzuki-Miyaura, and Stille protocols, use of aryl and heteroaryl carboxylic acids in decarbonylative cross-coupling reactions^{2,3} is advantageous in the aspects of availability and low cost of diverse reagents and stability for reagent storage and handling. In an analogous manner, several groups have reported syntheses of diaryl ketones 3^4 , 3-indolyl ynones 5^5 , and aryl carboxylates 8⁶ via Pd- or Pd–Cu-catalyzed decarbonylative coupling of 1,2-dicarbonyl derivatives (Scheme 1). Gooβen et al.⁴ used a bimetallic catalyst system consisting of $Pd(F_6-acac)_2 - P(o-Tol)_3$ and CuBr-1, 10-phenanthroline for promoting decarbonylative coupling of α-oxocarboxvlates 1 with aryl bromides 2, affording ketones 3 in 45– 99% yields except for those products possessing a 2,6-

SYNLETT 2010, No. 7, pp 1075–1080 Advanced online publication: 10.03.2010 DOI: 10.1055/s-0029-1219580; Art ID: W20409ST © Georg Thieme Verlag Stuttgart · New York



Scheme 1 Pd-catalyzed decarbonylative coupling of α -oxocarboxylates 1, indole-3-glyoxylyl chlorides 4, potassium oxalate monoesters 7, and phenyl oxanilates 9

dimethyl-substituted phenyl group. When bulky (*o*-biphenyl)P(*t*-Bu)₂ was used as the ligand, aryl chlorides could replace aryl bromides **2** for the formation of **3**. It was suggested that **1** was first converted into an acyl copper species, ArC(=O)[Cu], which underwent acyl group transfer to a Pd species, leading to the formation of ketones **3**.^{3e,4} Müller and co-workers generated indole-3-glyoxylyl chlorides **4** from the indoles and oxalyl chloride via a Friedel– Crafts acylation and used them, without purification, for the decarbonylative Sonogashira coupling with terminal alkynes to form alkynones **5** in 43–85% overall yields.^{5,7} An acyl palladium species was proposed by direct oxidative addition of the C(=O)Cl bond in **4** followed by decarbonylative elimination, indicating no function of copper in the decarbonylation.⁵ Furthermore, a copper-free inter-

^a Laboratory of Asymmetric Catalysis and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, P. R. of China Fax +86(571)87953128; E-mail: chdai@zju.edu.cn

molecular coupling of potassium oxalate monoesters **7** with aryl bromides **6** was reported by Fu and Liu's groups,⁶ affording aromatic esters **8** in 52–98% yields. By using 1,3-bis(dicyclohexylphosphino)propane (dCypp) instead of dppp, decarbonylative coupling of aryl chlorides with **7** was successfully realized. A five-coordinated Pd(II) transition state with an energy barrier of ca. 30 kcal/ mol was obtained for the rate-limiting decarbonylation from standard density functional theory calculations. We report here on an intramolecular decarbonylative coupling of *N*-(2-bromobenzyl)oxanilic acid phenyl esters **9** under palladium catalysis (Scheme 1). It should serve as the first example of formation of bioactive heterocycles via Pd-catalyzed decarbonylative coupling of oxalic acid derivatives

Isoindolin-1-ones are not only the core structural motif of alkaloids but also the proven 'privileged scaffold'.8 A number of synthetic methods has been developed for the synthesis of isoindolin-1-ones.⁹ Among them, the Pdcatalyzed carbonylative heteroannulation enables an efficient three-component reaction cascade starting with 2halobenzyl halides, amines, and gaseous carbon monoxide.¹⁰ For investigating our proposed novel synthesis of isoindolin-1-ones by intramolecular decarbonylative coupling we obtained N-(2-bromobenzyl)oxanilates 15 from substituted anilines 11 and 2-bromobenzaldehyde 12 (Scheme 2). (2-Bromo- α -methylbenzyl)aniline 13 was prepared by condensation of 11a with 12 followed by reaction of the resultant imine with MeLi¹¹ in 72% yield (entry 9, Table 1). Alternatively, a reductive alkylation of anilines 11 with aldehyde 12 in the presence of



Scheme 2 Synthesis of aniline derivatives 13 and 14, and the corresponding ethyl/phenyl oxanilates 15

NaBH(OAc)₃ in 1,2-dichloroethane¹² gave **14** in 62–94% yields (entries 1, 4, 5, 7, and 8, Table 1). Some of the products **14** were contaminated with inseparable byproduct(s) and were used for the next step (entries 2, 3, and 6, Table 1). Treatment of **13** and **14** with NaH and subsequently with oxalyl chloride monophenyl¹³ and monoethyl esters, respectively, afforded phenyl oxanilates **15a**-i (entries 1–9, Table 1) and ethyl oxanilate **15j** (entry 10, Table 1) in 68–90% yields.¹⁴

The thermal stability of phenyl and ethyl oxanilates 15a and 15j was first examined in the presence of 2 equivalents of K₂CO₃ in DMA¹⁵ at 120 °C for 2 hours. It was found that phenyl oxanilate 15a decomposed presumably via cleavage of the phenyl ester moiety while ethyl oxanilate 15j remained intact with recovery of most materials. Upon exposure of 15j to $Pd(OAc)_2$ -dppf^{12c} (K₂CO₃, DMA, 120 °C, 2 h), an intramolecular direct arylation took place to furnish the 5,6-dihydrophenanthridine derivative 16 in 71% yield along with the minor inseparable debromination byproduct (Scheme 3).¹⁶ On the other hand, it was interesting to find that under the identical catalysis conditions phenyl oxanilate 15a underwent a novel intramolecular decarbonylative coupling to provide N-phenylisoindolin-1-one $(17a)^{10b}$ in 80% isolated yield. In a similar manner, N-phenyl-3-methylisoindolin-1-one (17i) was formed from 15i in 48% yield (Scheme 3).

Table 2 summarizes some results obtained after screening reaction conditions for the decarbonylative coupling of **15i**. We found that prolonged reaction time did not improve the product yield (entries 10-12) and in some cases lower yields were observed (entry 1 vs. entry 2), indicating that the product might be unstable under the heating conditions. The reaction at $100 \,^{\circ}$ C was not beneficial even after extension of the reaction time (entry 3). The base

Table 1Structures and Yields of Aniline Derivatives 13 and 14 andthe Corresponding Ethyl/Phenyl Oxanilates 15

Entry	\mathbb{R}^1	R ²	R ³	\mathbb{R}^4	R ⁵	Aniline (%) ^a	Oxanilate (%) ^a
1	Н	Н	Н	Н	Ph	14a 94	15a 81
2	Cl	Н	Н	Н	Ph	14b – ^b	15b 68°
3	Н	Cl	Н	Н	Ph	14c - ^b	15c 76 ^c
4	Me	Н	Н	Н	Ph	14d 92	15d 89
5	Н	Me	Н	Н	Ph	14e 81	15e 87
6	Me	Н	Me	Н	Ph	14f – ^b	15f 75°
7	Н	OMe	Н	Н	Ph	14g 68	15g 81
8	NO_2	Н	Н	Н	Ph	14h 62	15h 90
9	Н	Н	Н	Me	Ph	13 72	15i 81
10	Н	Н	Н	Н	Et	_	15j 90

^a Isolated yield.

^b Inseparable mixture which was used for next step.

^c Overall yield of two steps from 11.

Synlett 2010, No. 7, 1075-1080 © Thieme Stuttgart · New York



Scheme 3 Pd-catalyzed intramolecular direct arylation of ethyl oxanilate 15j and decarbonylative coupling of phenyl oxanilates 15a,i

 Table 2
 Screening for Decarbonylative Coupling of 15i^a

Entry	Pd	Ligand	Base	Temp (°C)	Time (h)	17i (%)
1	Pd(OAc) ₂	dppf	K ₂ CO ₃	120	2	48
2	Pd(OAc) ₂	dppf	K ₂ CO ₃	120	5	38
3	Pd(OAc) ₂	dppf	K ₂ CO ₃	100	7	<40 ^c
4	Pd(OAc) ₂	dppf	K ₃ PO ₄ ^b	120	2	<40 ^c
5	Pd(OAc) ₂	dppb	K ₂ CO ₃	120	2	<45°
6	Pd(OAc) ₂	BINAP	K ₂ CO ₃	120	2	<50°
7	PdCl ₂	BINAP	K ₂ CO ₃	120	7	47
8	Pd(OAc) ₂	Aphos ^d	K ₂ CO ₃	120	20	23
9	$Pd(PPh_3)_4$	_	K ₂ CO ₃	120	20	<38°
10	Pd(OAc) ₂	dppp	K ₂ CO ₃	120	5	47
11	Pd(OAc) ₂	dppp	K ₂ CO ₃	120	7	52
12	Pd(OAc) ₂	dppp	K ₂ CO ₃	120	20	50
13 ^e	Pd(OAc) ₂	dppp	K ₂ CO ₃	120	20	48
14	Pd(OAc) ₂ ^f	dppp	K ₂ CO ₃	120	20	25
15	Pd(TFA) ₂	dppp	K ₂ CO ₃	120	3.5	51
16	Pd(OAc) ₂	dppp	KOt-Bu	120	7	54
17	Pd(OAc) ₂	dppp	Cs ₂ CO ₃	120	7	47

^a Pd and ligand (10 mol% each), base (1.5 equiv), and DMA were used unless otherwise stated.

^b The hydrate form, K₃PO₄·3H₂O, was used.

^c Some starting materials remained.

^d The structure of Aphos is found in Scheme 4.

^e NMP was used as the solvent.

^f Pd(OAc)₂ and dppp (5 mol% each) were used.

 $K_3PO_4 \cdot 3H_2O$ gave somewhat poor result than K_2CO_3 (entry 4 vs. entry 1). We examined several common ligands

and found that the bidentate ligands, dppb, BINAP,¹⁷ and dppp⁶ were equally efficient as dppf (entries 5, 6, 10 vs. entry 1) but the monodentate ligands, Aphos¹⁸ and Ph₃P were much less preferred (entries 8 and 9). Influence of palladium precursors on the catalysis was not apparent because Pd(OAc)₂, PdCl₂, and Pd(TFA)₂⁶ gave similar results (entries 6, 7, and 15) but reduction in palladium loading to 5 mol% caused a sharp drop in the product yield to 25% (entry 14). For the Pd(OAc)₂-dppp catalyst system, change of the solvent to NMP (entry 13) and the base to KOt-Bu and Cs₂CO₃ (entries 16 and 17) did not significantly alter the results of the intramolecular decarbonylative coupling. Therefore, the optimized catalytic conditions using a mild base are: Pd(OAc)₂-dppf (10 mol% each) as the precatalyst with K_2CO_3 as the base in DMA at 120 °C for 2 hours.

Table 3 lists other examples of *N*-arylisoindolin-1-ones **17b–h** synthesized via the Pd-catalyzed intramolecular decarbonylative coupling of phenyl oxanilates **15b–h**. The weak electron-donating methyl group was tolerated to form the products **17d–f** in 43–52% yields (entries 4–6, Table 3) while the methoxy-substituted substrate **15g** gave a low yield of 27% for **17g** (entry 7). In contrast, both weak and strong electron-withdrawing groups (Cl and NO₂) were compatible for the catalytic reaction, and the corresponding products **17b,c,h** were generated in 50– 75% yields (entries 2, 3, and 8). In particular, the chloro functionality allows a second cross-coupling reaction for introducing structural diversity. Some examples are given in Scheme 4.



Scheme 4 Synthesis of isoindolin-1-ones 18a–c via Suzuki–Miyaura coupling of 17b,c

Synlett 2010, No. 7, 1075-1080 © Thieme Stuttgart · New York

Table 3Synthesis of N-Arylisoindolin-1-ones 17^a



R^3	Ó			
Entry	R ¹	\mathbb{R}^2	R ³	Yield (%)
1	Н	Н	Н	17a 80 (62) ^b
2	Cl	Н	Н	17b 68 (53) ^b
3	Н	Cl	Н	17c 75 (40) ^b
4	Me	Н	Н	17d 52 (45) ^b
5	Н	Me	Н	17e 46
6	Me	Н	Me	17f 43
7	Н	OMe	Н	17g 27 (50) ^b
8	NO ₂	Н	Н	17h 50

^a The reaction conditions shown in Scheme 3 for formation of **17a**,i were used.

^b The numbers in parentheses were reported in ref. 10b via Pd-catalyzed carbonylative coupling using CO.

By using our Pd(OAc)₂–Aphos catalyst system, the aryl chlorides **17b,c** underwent Suzuki–Miyaura cross-coupling with aryl and vinyl boronic acids under mild conditions to afford **18a–c** in excellent yields.^{18,19}

Mechanistically, Pd-catalyzed oxidative cleavage of the C(=O)OPh bond is considered,²⁰ it seems much more appropriate to follow a pathway initiated by cleavage of the phenyl ester moiety in oxanilates **15a–i** on exposure to K_2CO_3 in DMA¹⁵ at 120 °C. Then, the resultant potassium oxanilate enters a similar catalytic cycle proposed for the intermolecular decarbonylative coupling of potassium oxalate monoesters **7** (Scheme 1).⁶ However, a definite mechanism awaits for further evidences.

In summary, we have established a novel intramolecular decarbonylative coupling of functionalized phenyl oxanilates by using Pd(OAc)₂-dppf as the precatalyst under mild reaction conditions (K_2CO_3 , DMA, 120 °C). This protocol enables access to a number of *N*-arylisoindolin-1-ones in moderate to good yields. Studies on application of this methodology to heterocycle synthesis are in progress in our laboratories.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The Laboratory of Asymmetric Catalysis and Synthesis is established under the Cheung Kong Scholars Program of The Ministry of Education of China. This work is supported in part by the research grants from The National Natural Science Foundation of China (Grant No. 20672092), Zhejiang University, and Zhejiang University Education Foundation.

References and Notes

- (1) Baudoin, O. Angew. Chem. Int. Ed. 2007, 46, 1373.
- (2) For selected examples of Heck reaction using aryl carboxylic acids, see: (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* 2002, *124*, 11250.
 (b) Tanaka, D.; Myers, A. G. *Org. Lett.* 2004, *6*, 433.
 (c) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* 2005, *127*, 10323. (d) Hu, P.; Kan, J.; Su, W.; Hong, M. *Org. Lett.* 2009, *11*, 2341.
- (3) For selected examples of biaryl coupling reaction using aryl carboxylic acids, see: (a) Gooßen, L. J.; Deng, G.; Levy, L. M. Science 2006, 313, 662. (b) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. J. Am. Chem. Soc. 2006, 128, 11350. (c) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. J. Am. Chem. Soc. 2007, 129, 4824. (d) Becht, J.-M.; Catala, C.; Le Drian, C.; Wagner, A. Org. Lett. 2007, 9, 1781. (e) Gooβen, L. J.; Zimmermann, B.; Keauber, T. Angew. Chem. Int. Ed. 2008, 47, 7103. (f) Becht, J.-M.; Le Drian, C. Org. Lett. 2008, 10, 3161. (g) Shang, R.; Fu, Y.; Wang, Y.; Xu, Q.; Yu, H.-Z.; Liu, L. Angew. Chem. Int. Ed. 2009, 48, 9250. (h) Wang, Z.; Ding, Q.; He, X.; Wu, J. Tetrahedron 2009, 65, 4635. (i) Moon, J.; Jang, M.; Lee, S. J. Org. Chem. 2009, 74, 1403. See also: (j) Duan, Z.; Ranjit, S.; Zhang, P.; Liu, X. Chem. Eur. J. 2009, 15, 3666. (k) Dicktein, J. S.; Mulrooney, C. A.; O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. Org. Lett. 2007, 9, 2441.
- (4) Gooβen, L. J.; Rudolphi, F.; Oppel, C.; Rodríguez, N. Angew. Chem. Int. Ed. 2008, 47, 3043; see also ref. 3e.
- (5) Merkul, E.; Oeser, T.; Müller, T. J. J. Chem. Eur. J. 2009, 15, 5006.
- (6) Shang, R.; Fu, Y.; Li, J.-B.; Zhang, S.-L.; Guo, Q.-X.; Liu, L. J. Am. Chem. Soc. 2009, 131, 5738.
- (7) For Cu-catalyzed reaction of zirconacyclopentenes with oxalyl chloride, see: (a) Chen, C.; Xi, C.; Jiang, Y.; Hong, X. J. Am. Chem. Soc. 2005, 127, 8024. (b) Chen, C.; Liu, Y.; Xi, C. Tetrahedron Lett. 2009, 50, 5434.
- (8) For selected recent examples, see: (a) Lee, S.; Shinji, C.; Ogura, K.; Shimizu, M.; Maeda, S.; Sato, M.; Yoshida, M.; Hashimoto, Y.; Miyachi, H. *Bioorg. Med. Chem. Lett.* 2007, *17*, 4895. (b) Hughes, T. V.; Emanuel, S. L.; O'Grady, H. R.; Connolly, P. J.; Rugg, C.; Fuentes-Pesquera, A. R.; Karnachi, P.; Alexander, R.; Middleton, S. A. *Bioorg. Med. Chem. Lett.* 2008, *18*, 5130. (c) Lawson, E. C.; Luci, D. K.; Ghosh, S.; Kinney, W. A.; Reynolds, C. H.; Qi, J.; Smith, C. E.; Wang, Y.; Minor, L. K.; Haertlein, B. J.; Parry, T. J.; Damiano, B. P.; Maryanoff, B. E. *J. Med. Chem.* 2009, *52*, 7432.
- (9) Couture, A.; Deniau, E.; Lamblin, M.; Lorion, M.; Grandclaudon, P. Synthesis 2007, 1434.
- (10) For examples of palladium-catalyzed carbonylative heteroannulation, see: (a) Mori, M.; Chiba, K.; Ban, Y. J. Org. Chem. 1978, 43, 1684. (b) Shim, S. C.; Jiang, L. H.; Lee, D. Y.; Cho, C. S. Bull. Korean Chem. Soc. 1995, 16, 1064. (c) Cho, C. S.; Shim, H. S.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. Synth. Commun. 2002, 32, 1821. (d) Grigg, R.; Zhang, L.; Collard, S.; Keep, A. Tetrahedron Lett. 2003, 44, 6979. (e) Grigg, R.; Gai, X.; Khamnaen, T.; Rajviroongit, S.; Sridharan, V.; Zhang, L.; Collard, S.; Keep, A. Can. J. Chem. 2005, 83, 990. (f) G rigg, R.; Sridharan, V.; Shah, M.; Mutton, S.; Kilner, C.; MacPherson, D.; Milner, P. J. Org. Chem. 2008, 73, 8352. (g) Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, T.; Tokuda, M. J. Org. Chem. 2006, 71, 5951. (h) Cao, H.; McNamee, L.; Alper, H. Org. Lett. 2008, 10, 5281.

- (11) For addition of MeLi with imines, see: Strekowski, L.;
 Wydra, R. L.; Cegla, M. T.; Czarny, A.; Patterson, S. J. Org. Chem. 1989, 54, 6120.
- (12) (a) Abdel-Magid, A. F.; Carson, K. G.; Harris, B. D.; Maryanoff, C. A.; Shah, R. D. *J. Org. Chem.* **1996**, *61*, 3849. (b) Feng, G.; Wu, J.; Dai, W.-M. *Tetrahedron* **2006**, *62*, 4635. (c) Wu, J.; Nie, L.; Luo, J.; Dai, W.-M. *Synlett* **2007**, 2728.
- (13) Mao, C. H.; Wang, Q. M.; Huang, R. Q.; Bi, F. C.; Chen, L.; Liu, Y. X.; Shang, J. J. Agric. Food Chem. 2004, 52, 6737.
- (14) Representative Procedure for Synthesis of Oxanilates 15 To a solution of phenol (235.0 mg, 2.0 mmol) and pyridine (0.31 mL, 3.0 mmol) in dry CH₂Cl₂ (5 mL) cooled in an icewater bath was added oxalyl chloride (0.33 mL, 3.0 mmol) followed by stirring at r.t. for 30 min. The reaction mixture was evaporated, and hexane was added to the residue. The pyridinium salt was removed by quick filtration with washing by hexane. The combined filtrate was condensed under reduced pressure in a nitrogen atmosphere, and the crude oxalyl chloride monophenyl ester was used for next step without purification.¹³

To a separate dry flask was added NaH (60.0 mg, 1.5 mmol) and dry THF (5 mL). To the resultant suspension cooled in an ice–water bath was added a solution of **14e** (276.0 mg, 1.0 mmol) in dry THF (5 mL). After stirring at the same temperature for 1 h, a solution of oxalyl chloride monophenyl ester prepared above in dry THF (5 mL) was added. After stirring at r.t. for 1 h, the reaction was quenched by H₂O. The reaction mixture was extracted with EtOAc (3×15 mL), and the combined organic layer was washed with brine, dried over anhyd Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with elution by 10% EtOAc in PE (60–90 °C) to give the phenyl oxanilate **15e** (367.0 mg, 87%). The results are listed in Table 1.

Characterization Data for Compound 15e

White crystalline solid; mp 92–93 °C (CH₂Cl₂–hexane); $R_f = 0.59$ (20% EtOAc in PE). IR (KBr): 1763, 1668, 1511, 1403, 1163 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.52$ (d, J = 8.0 Hz, 1 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.31–7.25 (m, 3 H), 7.21–7.12 (m, 6 H), 6.67 (d, J = 7.6 Hz, 2 H), 5.16 (s, 2 H), 2.35 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 161.4$, 160.8, 149.4, 139.1, 136.5, 134.8, 132.9, 130.1 (3×), 129.4 (2×), 129.3, 127.8, 127.6 (2×), 126.4, 123.8, 120.9 (2×), 51.7, 21.1. MS (ESI⁺): m/z (%) = 448 (75) [M + 2 + Na⁺], 446 (100) [M + Na⁺]. Anal. Calcd for C₂₂H₁₈BrNO₃: C, 62.28; H, 4.28; N, 3.30. Found: C, 62.31; H, 4.31; N, 3.37.

- (15) We used N,N-dimethylacetamide (DMA) as received from commercial supplies. The anhydrous grade has 99.8% purity with <0.005% water content. In all of our experiments described in this work, water was not added. Upon heating phenyl oxanilate **15a** in DMA at 120 °C in the presence of K₂CO₃, all materials in the reaction mixture remained on the base line of the TLC plate while ethyl oxanilate **15j** could be developed up on the TLC plate.
- (16) **Representative Procedure for Formation of 16 and 17** A 10 mL flask was charged with Pd(OAc)₂ (13.5 mg, 6.0×10^{-2} mmol), dppf (33.0 mg, 6.0×10^{-2} mmol), and K₂CO₃ (166.0 mg, 1.2 mmol). The loaded flask was evacuated and backfilled with N₂ (repeated for three times). To the degassed flask was added a solution of phenyl oxanilate **15e** (255.0 mg, 0.6 mmol) in degassed DMA (3 mL). The resultant mixture was heated at 120 °C for 2 h under a nitrogen atmosphere. After cooling to r.t., the reaction was quenched by adding CH₂Cl₂ (20 mL), and the resultant mixture was washing with H₂O (3 × 10 mL) to remove

DMA. The organic layer was washed with brine, dried over anhyd Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with elution by 20% EtOAc in PE (60–90 °C) to give *N*-(*p*-tolyl)isoindolin-1-one (**17e**, 61.0 mg, 46%). The results are given in Scheme 3 and Table 3.

Compound **16** was prepared in 71% yield from **15**j (Scheme 3) under the same conditions as described above for **17e**. The sample of **16** contains two atropisomers along with a minor inseparable debromination byproduct in the ratio of 75:15:10. The result was confirmed by independent synthesis as found in Supporting Information.

Characterization Data for Compound 16

Pale yellow oil; $R_f = 0.27$ (20% EOAc in PE). IR (film): 2928, 1742, 1667, 1185 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.83$ (d, J = 7.2 Hz, 1 H), 7.81 (d, J = 8.0 Hz, 1 H), 7.43– 7.19 (m, 6 H), 4.95 (s, 2 H), 4.16 (q, J = 6.8 Hz, 2 H), 1.12 (t, J = 7.2 Hz, 3 H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 162.5$, 160.4, 135.6, 133.2, 131.1, 129.0, 128.4, 128.4, 128.1, 127.3, 126.4, 124.7, 123.5, 121.8, 62.1, 44.5, 13.6. MS (ESI⁺): m/z (%) = 304 (100) [M + Na⁺]. HRMS (ESI⁺): m/zcalcd for C₁₇H₁₅NO₃Na [M + Na⁺]: 304.0944; found: 304.0953.

Characterization Data for Compound 17e

White crystalline solid; mp 126–128 °C (CH₂Cl₂–hexane). $R_f = 0.38$ (20% EtOAc in PE). IR (KBr): 2921, 1683, 1513, 1447, 1390, 1305, 1159 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): $\delta = 7.92$ (d, J = 7.2 Hz, 1 H), 7.74 (d, J = 8.4 Hz, 2 H), 7.60– 7.48 (m, 3 H), 7.23 (d, J = 8.0 Hz, 2 H), 4.83 (s, 2 H), 2.35 (s, 3 H). ¹³C NMR (100 MHz, CDCl₃): $\delta = 167.3$, 140.1, 136.9, 134.2, 133.3, 131.9, 129.7 (2×), 128.3, 124.1, 122.5, 119.6 (2×), 50.8, 20.8. MS (ESI⁺): m/z (%) = 246 (35) [M + Na⁺], 224 (100) [M + H⁺]. Anal. Calcd for C₁₅H₁₃NO: C, 80.69; H, 5.87; N, 6.27. Found: C, 80.56; H, 5.79; N, 6.28.

- (17) Pd(OAc)₂–BINAP were used for catalyzing intramolecular amidation to form 2-oxindoles, see: Xing, X.; Wu, J.; Luo, J.; Dai, W.-M. *Synlett* **2006**, 2099.
- (18) For Pd–Aphos-catalyzed Suzuki–Miyaura coupling, see:
 (a) Dai, W.-M.; Li, Y.; Zhang, Y.; Lai, K. W.; Wu, J. *Tetrahedron Lett.* 2004, *45*, 1999. (b) Dai, W.-M.; Zhang, Y. *Tetrahedron Lett.* 2005, *46*, 1377. (c) Jin, J.; Chen, Y.; Li, Y.; Wu, J.; Dai, W.-M. Org. Lett. 2007, *9*, 2585.
 (d) Dai, W.-M.; Li, Y.; Zhang, Y.; Yue, C.; Wu, J. Chem. Eur. J. 2008, *14*, 5538.

(19) Representative Procedure for Suzuki–Miyaura Coupling of Aryl Chlorides 17b,c

A 10 mL flask was charged with the aryl chloride 17b (24.4 mg, 0.1 mmol), phenyl boronic acid (19.0 mg, 0.15 mmol), and K₃PO₄·3H₂O (80.0 mg, 0.3 mmol). The loaded flask was evacuated and backfilled with N₂ (repeated for three times). To the degassed flask was added degassed H₂O (0.1 mL) and a stock THF (1 mL) solution containing Pd(OAc)₂ (0.23 mg, 1.0×10⁻³ mmol) and Aphos (0.80 mg, 2.0×10⁻³ mmol). The resultant mixture was heated at 60 °C for 24 h under a nitrogen atmosphere. After cooling to r.t., the reaction was quenched by H_2O , and the resultant mixture was extracted with EtOAc $(3 \times 5 \text{ mL})$. The combined organic layer was washed with brine, dried over anhyd Na₂SO₄, filtrated, and concentrated under reduced pressure. The residue was purified by column chromatography over silica gel with elution by 15% EtOAc in PE (60–90 °C) to give the coupling product 18a (27.0 mg, 95%). The results are found in Scheme 4.

Characterization Data for Compound 18a

White crystalline solid; mp 126–128 °C (CH₂Cl₂–hexane). $R_f = 0.38$ (20% EtOAc in PE). IR (KBr): 1691, 1600, 1483, 1429, 1376 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 8.13 (dd, *J* = 2.0, 2.0 Hz, 1 H), 7.93 (d, *J* = 7.2 Hz, 1 H), 7.85 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.65 (d, *J* = 7.2 Hz, 2 H), 7.60 (ddd, *J* = 6.4, 6.4, 1.2 Hz, 1 H), 7.52 (d, *J* = 7.6 Hz, 2 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.48–7.35 (m, 4 H), 4.90 (s, 2 H). ¹³C NMR (100 MHz, CDCl₃): δ = 167.6, 142.2, 140.8, 140.0, 139.9, 133.1, 132.1, 129.5, 128.7 (2×), 128.4, 127.5, 127.2 (2×), 124.1, 123.2, 122.6, 118.2, 118.2, 50.8. MS (ESI⁺): *m/z* (%) = 308 (95) [M + Na⁺], 286 (100) [M + H⁺]. Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91. Found: C, 84.22; H, 5.32; N, 4.96.

(20) For Pd- and Ni-catalyzed oxidative cleavage of aryl esters, see: (a) Gooβen, L. J.; Paetzold, J. *Angew. Chem. Int. Ed.* **2002**, *41*, 1237. (b) Li, Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. J. Am. Chem. Soc. **2009**, *131*, 8815.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.