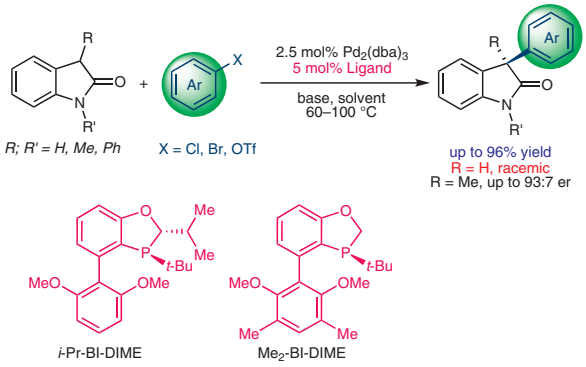
Synthesis H. P. Mangunuru et al. Paper

Enantioselective Arylation of Oxindoles Using Modified BI-DIME Ligands

Hari P. R. Mangunuru[1]
Christian A. Malapit[2]
Nizar Haddad*
Jonathan T. Reeves
Bo Qu
Sonia Rodriguez
Heewon Lee
Nathan K. Yee
Jinhua J. Song
Carl A. Busacca
Chris H. Senanayake*

Chemical Development, Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT, 06877-0368, USA
nizar.haddad@boehringer-ingelheim.com

Published as part of the *Special Section dedicated to Scott E. Denmark on the occasion of his 65th birthday*



Received: 13.03.2018
Accepted after revision: 27.04.2018
Published online: 28.06.2018
DOI: 10.1055/s-0036-1591590; Art ID: ss-2018-c0180-op

Abstract The Pd-catalyzed 3-arylation of 2-oxindoles with aryl bromides, chlorides and triflates is found to proceed using *i*-Pr-BI-DIME and Me_2-BI-DIME ligands. The mono-arylation of 3-unsubstituted oxindoles is accomplished using a $Pd_2(dba)_3$/*i*-Pr-BI-DIME catalyst system, and gives good yields of 3-aryloxindoles from aryl bromides and chlorides. The arylation of 3-substituted oxindoles is also possible using this catalyst/ligand system. The asymmetric arylation of 3-substituted oxindoles is accomplished using Me_2-BI-DIME to furnish oxindoles bearing a quaternary C-3 stereocenter in enantiomeric ratios of up to 93:7.

Key words arylation, oxindoles, Pd catalysis, asymmetric, BI-DIME

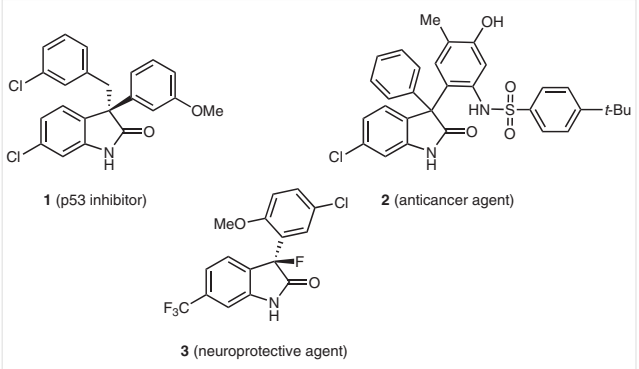


Figure 1 Biologically active 3-aryloxindoles

3-Substituted and 3,3-disubstituted oxindoles are common structural motifs found both in pharmaceuticals and natural products.[3] Oxindoles bearing a 3-aryl substituent have been found to exhibit diverse biological activity, such as p53 inhibition (**1**),[4] anticancer activity (**2**),[5] and neuroprotection (**3**)[6] (Figure 1). The methods reported for the synthesis of 3-aryloxindoles can roughly be divided into two categories: those which build the oxindole unit last after incorporation of the 3-aryl group in a precursor substrate,[6,7] and those which install the 3-aryl group onto an already assembled oxindole core.[8,9] The latter process has been demonstrated primarily by Pd-catalyzed arylation of oxindole enolates.[9]

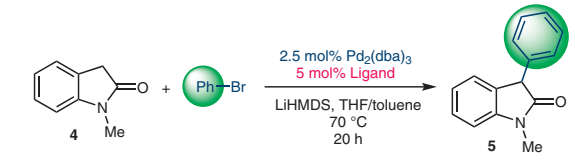
The Pd-catalyzed arylation of oxindoles was first demonstrated by the pioneering reports of Willis[9a] and Buchwald[9b] in 2008, and for the asymmetric arylation by Buchwald[9c] in 2009.

Over the last several years, we have developed a class of P-chiral phosphine ligands bearing a dihydrobenzooxaphosphole core structure.[10] As part of our continuing efforts to apply these ligands to useful methodologies and to explore their potential for catalytic efficiency and asymmetric induction,[11] we examined the utility of our ligands in the 3-arylation and asymmetric 3-arylation of oxindoles. Herein we report our results.

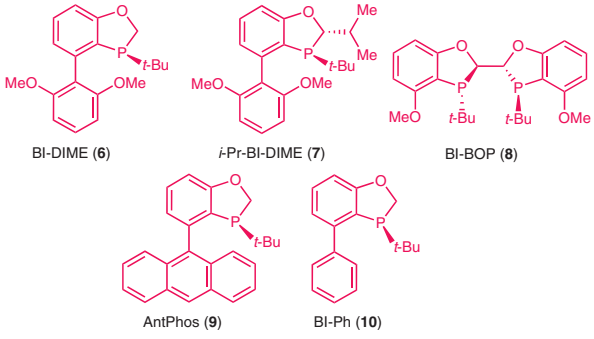
As a system for ligand screening we chose the arylation of *N*-methyloxindole (**4**) with bromobenzene using LiHMDS as base and THF/toluene as solvent at 70 °C (Table 1). The use of our in-house-developed BI-DIME ligand **6** gave a modest 25% assay yield of the product **5** (entry 1). When

the isopropyl-substituted analog, *i*-Pr-BI-DIME **7**, was used, a dramatic improvement to a 95% assay yield and a 91% isolated yield was obtained (entry 2).

Table 1 Ligand Screening for the 3-Arylation of Oxindole **4**[a]



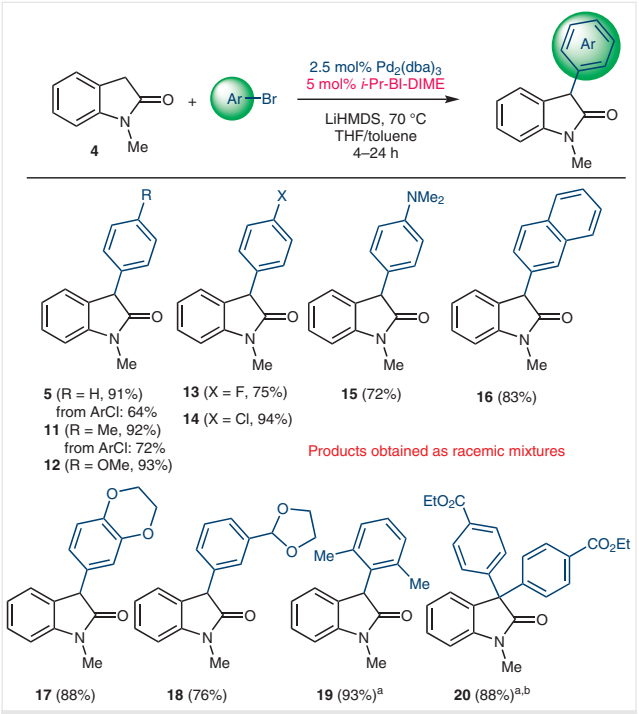
Entry	Ligand (conditions)[b]	Yield (%)[c]
1	BI-DIME	25
2	***i*-Pr-BI-DIME**	**95 (91)**
3	BI-BOP	0
4	AntPhos	<5
5	BI-Ph	0
6	BINAP	0
7	PCy_3	0
8	$Pt\text{-}Bu_3{\cdot}HBF_4$	10
9	BI-DIME (1.1 equiv NaHMDS)	12
10	*i*-Pr-BI-DIME (1.1 equiv NaHMDS)	86
11	*i*-Pr-BI-DIME (2 equiv K_2CO_3, dioxane, 100 °C)	93 (91)



[a] Typical reaction conditions: 0.5 mmol oxindole, 1.1 equiv LiHMDS (1 M in toluene), 1.1 equiv ArX, 2.5 mol% $Pd_2(dba)_3$, 5.0 mol% ligand, 0.5 mL THF, 70 °C, 20 h.
[b] Parameters in parentheses denote a change from the typical reaction conditions.
[c] HPLC assay yields, values in parentheses are isolated yields.

The bidentate BI-BOP **8** gave no product (entry 3). The use of the less electron-rich ligands AntPhos **9** and BI-Ph **10** gave little to no conversion into **5** (entries 4 and 5). BINAP and tricyclohexylphosphine (PCy_3) were not effective ligands for this process (entries 6 and 7), while tri-*tert*-butylphosphonium tetrafluoroborate ($Pt\text{-}Bu_3{\cdot}HBF_4$) gave a low assay yield of 10% (entry 8). The use of NaHMDS in place of LiHMDS gave slightly decreased yields when **6** or **7** were used as ligands (entries 9 and 10). When conditions similar to those developed by Buchwald and co-workers were employed (K_2CO_3, dioxane, 100 °C) with **7** as ligand, high assay (93%) and isolated (91%) yields were obtained (entry 11). We chose the use of *i*-Pr-BI-DIME **7** as the ligand and the conditions of entry 2 as optimal for an exploration of the reaction scope.

The scope of the 3-arylation of oxindole **4** with respect to the aryl halide was examined next (Scheme 1).

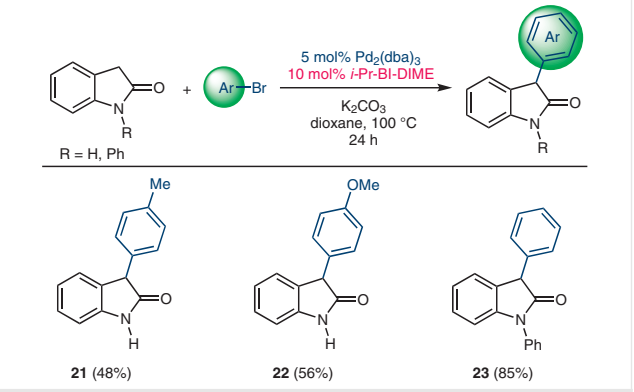


Scheme 1 Scope of the 3-arylation of *N*-methyloxindole (**4**). *Reagents and conditions*: 1–2 mmol oxindole, 1.1 equiv LiHMDS (1 M in toluene), 1.1 equiv ArX, 2.5 mol% $Pd_2(dba)_3$, 5.0 mol% *i*-Pr-BI-DIME, 1–2 mL THF, 70 °C, 4–24 h. Yields are those of isolated products. [a] Reaction was performed using 2 equiv K_2CO_3, 2.5 mol% $Pd_2(dba)_3$, 5.0 mol% *i*-Pr-BI-DIME, dioxane, 110 °C, 24 h. [b] 2.2 Equivalents of ArBr were used.

Chlorobenzene provided **5** in a reduced yield (64%) compared with bromobenzene (91%). This trend held for the coupling with 4-bromotoluene to give **11** (92%) versus with 4-chlorotoluene (72%). The reaction with 4-bromoanisole gave **12** in 93% yield. 4-Fluoro and 4-chloro substituents on the aryl bromide were tolerated and gave the products **13** and **14** in good yields, respectively. A 4-dimethylamine group was tolerated, giving **15** in 72% yield. 2-Bromonaphthalene coupled smoothly giving **16** in 83% yield. Aryl bromides containing benzodioxane and dioxolane groups were tolerated, giving the products **17** and **18** in good yields. For coupling of the sterically hindered 2,6-dimethylbromobenzene to give **19**, the reaction conditions were modified to K_2CO_3 in dioxane at 110 °C; under these conditions **19** was obtained in excellent yield (93%).[12] The arylation of **4** with 1.1 equivalents of ethyl 4-bromobenzoate under the modified conditions used for preparation of

19 provided bisarylated oxindole **20** as the major product, presumably due to the enhanced acidity of the product. Effective 3,3-diarylation of **4** using 2.2 equivalents of the aryl bromide was demonstrated, providing **20** in 88% yield.

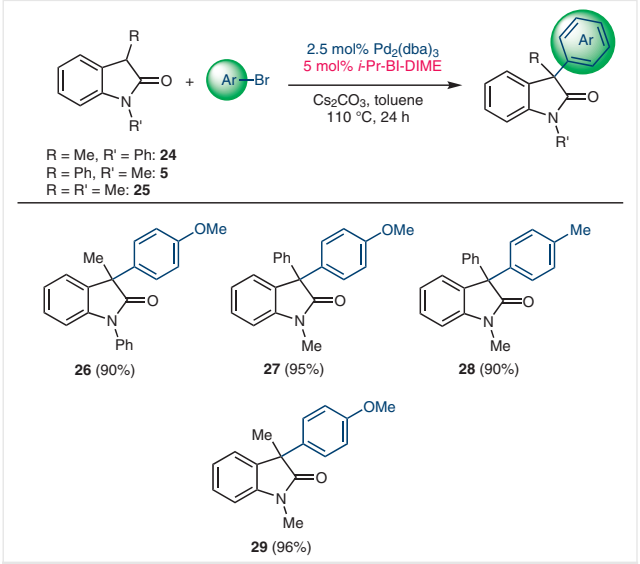
The 3-arylation of *N*-H oxindole and *N*-phenyloxindole is described in Scheme 2. These reactions required a higher temperature and thus the K_2CO_3/dioxane conditions were employed. The arylation of oxindole with 4-bromotoluene and 4-bromoanisole gave products **21** and **22** bearing an unprotected nitrogen in moderate yields of 48% and 56%, respectively. The arylation of *N*-phenyloxindole with bromobenzene gave **23** in 85% yield. Chiral analysis of products **11**, **19** and **21** indicated formation of racemic mixtures, presumably due to racemization under the reaction conditions.[12]



Scheme 2 3-Arylation of *N*-H and *N*-phenyloxindoles. *Reagents and conditions*: 1 mmol oxindole, 3 equiv K_2CO_3, 1.1 equiv ArBr, 5 mol% $Pd_2(dba)_3$, 10 mol% *i*-Pr-BI-DIME, 1 mL dioxane, 100 °C, 24 h. Yields are those of isolated products.

The 3-arylation of oxindoles already bearing a 3-substituent would provide products bearing a fully substituted 3-carbon. The exploration of this reaction using 3-methyl-*N*-phenyloxindole (**24**) and 3-phenyl-*N*-methyloxindole (**5**) is detailed in Scheme 3. In this case, reaction conditions of Cs_2CO_3 in toluene at 110 °C for 24 hours proved optimal for high conversions. The arylation of **24** with 4-bromoanisole gave **26** in high yield (90%). The arylation of **5** to give **27** and **28** also proceeded in excellent yields. Finally, arylation of 3-methyl-*N*-methyloxindole (**25**) with 4-bromoanisole gave **29** in 96% yield.

Given that the products shown in Scheme 3 bear a quaternary stereocenter, we examined if the 3-arylation of 3-substituted oxindoles could proceed with enantioselectivity (Table 2). For ligand screening the arylation of **24** with 4-bromoanisole was employed. While the use of BI-DIME (**6**) or Me-BI-DIME (**30**) gave little conversion into **26** (entries 1 and 2), *i*-Pr-BI-DIME (**7**) gave a 76% yield of **26** and an enantiomeric ratio (er) of 80:20 with the (*R*)-enantiomer as the major product[13] (entry 3).



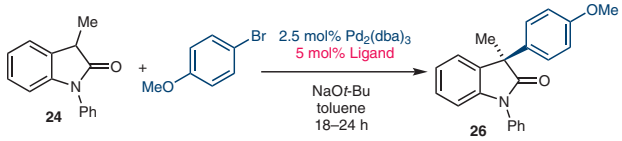
Scheme 3 3-Arylation of 3-substituted oxindoles. *Reagents and conditions*: 1 mmol oxindole, 2 equiv Cs_2CO_3, 1.1 equiv ArBr, 2.5 mol% $Pd_2(dba)_3$, 5.0 mol% *i*-Pr-BI-DIME, 1 mL toluene, 110 °C, 24 h. Yields are those of isolated products.

Reducing the temperature to 30 °C increased the er to 84:16, but the yield dropped to 38% (entry 4). The cyclohexyl-substituted ligand CyHx-BI-DIME (**31**) gave a reduced er of 69:31 (entry 5). Interestingly, the use of Me_2-BI-DIME (**32**), bearing *ortho*-methyl groups on the lower arene moiety, resulted in a significant increase of er to 93:7, albeit in a modest 41% yield (entry 6). Increasing the temperature to 110 °C gave a higher yield of 68% but with a concurrent reduction in er to 85:15 (entry 7).

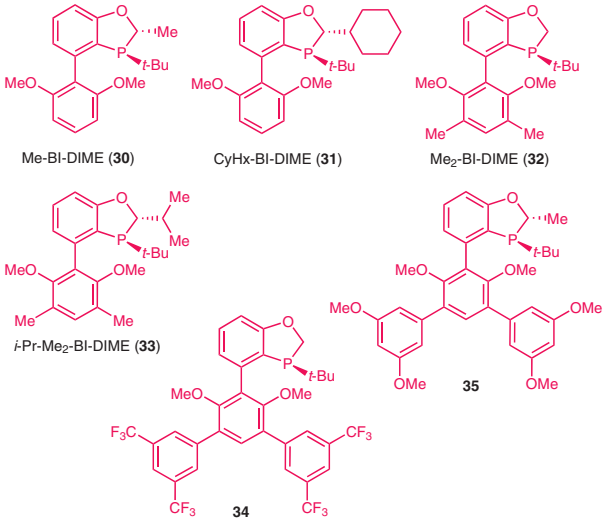
Somewhat surprisingly, the 'hybrid' of *i*-Pr-BI-DIME (**7**) and Me_2-BI-DIME (**32**), *i*-Pr-Me_2-BI-DIME (**33**), was not as effective as **32** for asymmetric induction, though it did provide the product in higher yields (entries 8 and 9). The replacement of the *ortho*-methyl groups in **32** with aryl groups (ligands **34** and **35**) resulted in good yields of **26** with enantiomeric ratios of up to 80:20 (entries 10 and 11).

With Me_2-BI-DIME (**32**) identified as the optimal ligand for asymmetric induction, the scope of the asymmetric arylation of **24** and **25** was explored with different aryl bromides (Scheme 4). The arylation of **24** with 4-bromoanisole at 110 °C gave **26** in 68% yield and 85:15 er, while the reaction at 60 °C proceeded in 93:7 er and 41% yield. Arylation of **25** with 4-bromoanisole at 60 °C gave **29** in 68% yield and 87:13 er. The use of 3-bromoanisole gave **36** in 56% yield and 81:19 er. The reaction with the electron-deficient aryl bromide 4-bromobenzotrifluoride gave **37** in 48% yield and 82:18 er. The arylation with 3,5-bis(trifluoromethyl)-bromobenzene gave **38** in 51% yield and 87:13 er.

Table 2 Ligand Screen for the Asymmetric 3-Arylation of 3-Methyl-*N*-phenyloxindole (**24**)[a]



Entry	Ligand	Temp (°C)	Yield (%)[b]	er[c]
1	BI-DIME (**6**)	60	<5	n.d.
2	Me-BI-DIME (**30**)	60	<5	n.d.
3	*i*-Pr-BI-DIME (**7**)	60	76	80:20
4	*i*-Pr-BI-DIME (**7**)	30	38	84:16
5	CyHx-BI-DIME (**31**)	60	65	69:31
6	**Me_2-BI-DIME (32)**	**60**	**41**	**93:7**
7	Me_2-BI-DIME (**32**)	110	68	85:15
8	*i*-Pr-Me_2-BI-DIME (**33**)	60	79	66:34
9	*i*-Pr-Me_2-BI-DIME (**33**)	30	41	78:22
10	**34**	60	74	80:20
11	**35**	60	95	70:30

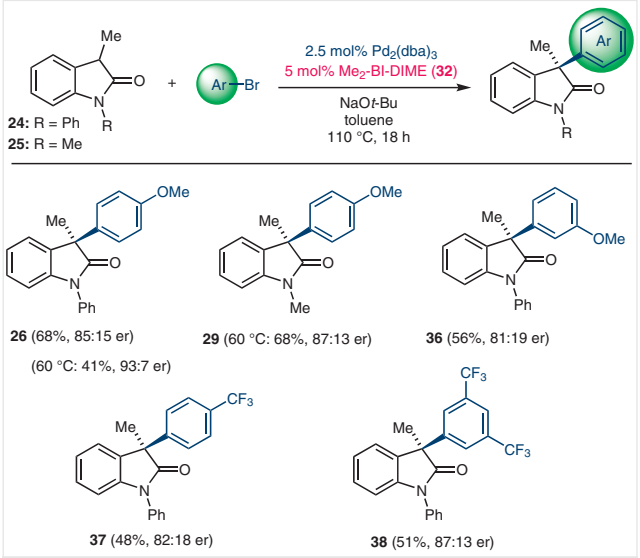


[a] Reaction conditions: 1 mmol oxindole **24**, 1.1 equiv NaO*t*-Bu, 1.1 equiv 4-bromoanisole, 2.5 mol% $Pd_2(dba)_3$, 5.0 mol% ligand, 1 mL toluene, temperature indicated in the table, 24 h.
[b] Enantiomeric ratio determined by chiral HPLC or SFC.

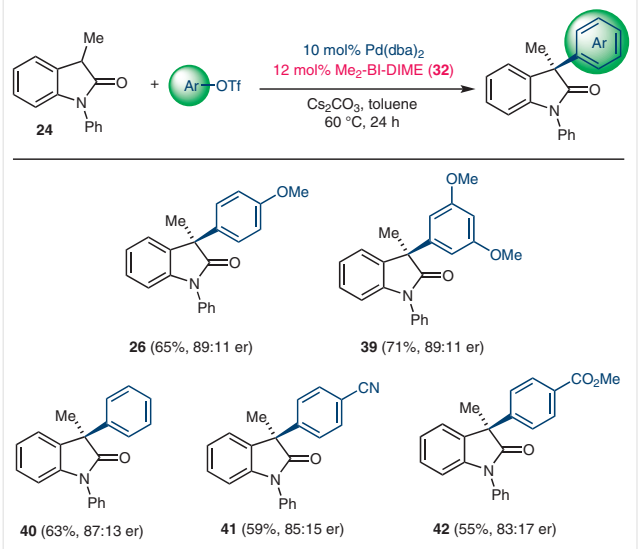
In an attempt to improve the conversion, while maintaining good enantioselectivity, the asymmetric arylation was examined with aryl triflates under milder conditions (Scheme 5).

Indeed, coupling of the aryl triflates under milder conditions with Cs_2CO_3 as the base resulted in higher yields while maintaining good enantioselectivity.[8e] The arylation of **24** with 4-methoxyphenyltriflate at 60 °C provided **26** in 65% yield and 89:11 er. Different aryl triflates resulted in similar yields and enantioselectivities. 3,5-Dimethoxyphenyltriflate provided **39** in the highest yield (71%) and good enantioselectivity (89:11 er).

In conclusion, the Pd-catalyzed 3-arylation of oxindoles using the in-house-developed ligands *i*-Pr-BI-DIME (**7**) and Me_2-BI-DIME (**32**) has been demonstrated. The arylation of 3-unsubstituted oxindoles bearing *N*-methyl or *N*-phenyl



Scheme 4 Scope of the asymmetric 3-arylation of oxindoles with aryl bromides. *Reagents and conditions*: 1 mmol oxindole, 1.1 equiv NaO*t*-Bu, 1.1 equiv ArBr, 2.5 mol% $Pd_2(dba)_3$, 5.0 mol% Me_2-BI-DIME, 1 mL toluene, 110 °C, 18 h. Yields are those of isolated products. Enantiomeric ratios determined by chiral HPLC or SFC.



Scheme 5 Scope of the asymmetric 3-arylation of oxindoles with aryl triflates. *Reagents and conditions*: 0.45 mmol oxindole **24**, 2 equiv Cs_2CO_3, 1.1 equiv ArOTf, 10 mol% $Pd(dba)_2$, 12 mol% Me_2-BI-DIME, 1 mL toluene, 60 °C, 24 h. Yields are those of isolated products. Enantiomeric ratios determined by chiral HPLC or SFC.

groups with aryl bromides proceeded in excellent yields when *i*-Pr-BI-DIME was employed as the ligand. When aryl chlorides were utilized, the reaction proceeded, albeit in reduced yields. The chemoselective *C*-arylation of *N*-H oxindole was possible but proceeded in reduced yields compared to the N-substituted oxindoles. The 3-arylation of 3-substituted oxindoles to give products bearing a quaternary carbon was possible using *i*-Pr-BI-DIME as the ligand, giving excellent yields of products for C3-alkyl and C3-aryl oxindole starting materials. A screen of the most effective ligands for the asymmetric C3-arylation of 3-methyl-3-phenyloxindole showed Me_2-BI-DIME to be superior to *i*-Pr-BI-DIME, giving enantiomeric ratios of up to 93:7. When aryl triflates were utilized, the reaction proceeded with high yields and good enantioselectivities. The utility of these ligands in other catalytic and asymmetric processes is currently under investigation.

All starting materials and reagents were purchased from commercial sources and used as received unless otherwise noted. Ligands were prepared according to our reported procedures.[10a,11b] Flash chromatography was performed on a CombiFlash-*Rf* automated system with 12g silica columns. SFC (suppercritical fluid chromatography) was performed on an Agilent Technologies 1260 instrument equipped with 1260 infinity SFC control module. Melting points were recorded using a MELT-TEMP 3.0 apparatus and are uncorrected. NMR spectra were recorded on Bruker 400 or 500 MHz instruments. All ^{1}H and ^{13}C NMR data were referenced to the internal deuterated solvent relative to TMS. High-resolution mass spectrometry (HRMS) was performed on a Agilent LC/MSD TOF (time-of-flight) instrument with ESI in positive ionization mode.

Arylation of *N*-Methyloxindole (4); General Procedure

All reactions were conducted in 10 mL glass vials fitted with crimp-cap septum caps. The reaction vial, equipped with a magnetic stir bar, was charged under an N_2 atmosphere with 1-methylindolin-2-one (**4**) (73.6 mg, 0.5 mmol), $Pd_2(dba)_3$ (10 mg, 0.011 mmol, 2.5 mol%), *i*-Pr-BI-DIME (**7**) (0.022 mmol, 5 mol%), LiHMDS (1 M in toluene, 0.55 mL, 0.55 mmol) and the aryl halide (1.1 equiv), then sealed with a crimp-cap septum. THF (0.5 mL) and toluene (0.5 mL) were added via syringe and the reaction was heated to 70 °C for 4–24 h. The reaction mixture was cooled to room temperature then filtered through a Celite pad with EtOAc (5 mL) as eluent. The filtered solution was washed with H_2O (3 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. The crude residue was purified using a 12 g silica column (30% EtOAc/hexanes) to afford the corresponding oxindole product.

1-Methyl-3-phenylindolin-2-one (5)[14a]

Prepared following the general arylation procedure and isolated as a light yellow solid in 91% yield; mp 110.0–112.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.23 (m, 4 H), 7.19 (d, *J* = 7.0 Hz, 2 H), 7.14 (d, *J* = 7.4 Hz, 1 H), 7.04 (t, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 7.8 Hz, 1 H), 4.58 (s, 1 H), 3.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 144.5, 136.7, 128.9, 128.5, 127.6, 125.1, 122.8, 108.2, 52.1, 26.5.

1-Methyl-3-(*p*-tolyl)-indolin-2-one (11)[14a]

Prepared following the general arylation procedure and isolated as a light yellow solid in 92% yield; mp 80.0–82.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (t, *J* = 7.8 Hz, 1 H), 7.01–6.95 (m, 5 H), 6.90 (t, *J* = 7.5 Hz, 1 H), 6.73 (d, *J* = 7.7 Hz, 1 H), 4.39 (s, 1 H), 3.07 (s, 3 H), 2.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 144.3, 136.9, 133.5, 129.4, 128.9, 128.19, 128.15, 124.8, 122.5, 108.0, 51.5, 26.2, 20.9.

3-(4-Methoxyphenyl)-1-methylindolin-2-one (12)[9b]

Prepared following the general arylation procedure and isolated as a light yellow solid in 93% yield; mp 88.0–90.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27 (t, *J* = 7.7 Hz, 1 H), 7.11–7.06 (m, 3 H), 7.02–6.98 (dt, *J* = 7.6, 0.7 Hz, 1 H), 6.84–6.80 (m, 3 H), 4.47 (s, 1 H), 3.69 (s, 3 H), 3.16 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 158.8, 144.3, 129.3, 128.9, 128.5, 128.2, 124.8, 122.5, 114.1, 108.0, 55.0, 51.0, 26.2.

3-(4-Fluorophenyl)-1-methylindolin-2-one (13)[14a]

Prepared following the general arylation procedure and isolated as a pale yellow solid in 75% yield; mp 134.0–136.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.8 Hz, 1 H), 7.29–7.26 (m, 2 H), 7.15–7.12 (m, 3 H), 7.06 (dt, *J* = 7.6, 0.8 Hz, 1 H), 6.91 (d, J=7.8 Hz, 1H), 4.56 (s, 1 H), 3.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 163.7, 161.2, 144.6, 132.5, 130.2, 125.1, 123.0, 116.0, 115.8, 108.5, 51.3, 26.6.

3-(4-Chlorophenyl)-1-methylindolin-2-one (14)[14a]

Prepared following the general arylation procedure and isolated as a light yellow solid in 94% yield; mp 160.0–162.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J* = 7.8 Hz, 1 H), 7.29–7.26 (m, 2 H), 7.15–7.12 (m, 3 H), 7.06 (dt, *J* = 7.6, 0.8 Hz, 1 H), 6.88 (d, 7.7 Hz, 1H), 4.56 (s, 1 H), 3.22 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.6, 144.6, 135.1, 133.6, 129.9, 129.0, 128.8, 128.3, 125.0, 123.0, 108.4, 51.4, 26.6.

3-[4-(Dimethylamino)phenyl]-1-methylindolin-2-one (15)[14b]

Prepared following the general arylation procedure and isolated as a yellow solid in 72% yield; mp = 83–85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 1 H), 7.17 (d, *J* = 7.4 Hz, 1 H), 7.07–7.03 (m, 2 H), 7.04–7.02 (m, 1 H), 6.87 (d, *J* = 7.7 Hz, 1 H), 6.70–6.67 (m, 2 H), 4.51 (s, 1 H), 3.23 (s, 3 H), 2.91 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 150.3, 144.7, 129.7, 129.2, 128.3, 125.2, 124.4, 122.8, 113.2, 108.2, 51.4, 40.8, 26.6.

1-Methyl-3-(naphthalen-2-yl)-indolin-2-one (16)[14b]

Prepared following the general arylation procedure and isolated as a light yellow solid in 83% yield; mp 95.0–97.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80–7.76 (m, 3 H), 7.70 (d, *J* = 1.0 Hz, 1 H), 7.46–7.43 (m, 2 H), 7.37–7.32 (m, 1 H), 7.25 (dd, *J* = 8.5, 1.8 Hz, 1 H), 7.18 (d, *J* = 7.4 Hz, 1 H), 7.07 (dt, *J* = 7.6, 1.0 Hz, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 4.76 (s, 1 H), 3.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.1, 144.7, 134.2, 133.7, 133.0, 129.0, 128.9, 128.7, 128.0, 127.8, 127.7, 126.4, 126.3, 126.1, 125.3, 123.0, 108.4, 52.4, 26.7.

3-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-1-methylindolin-2-one (17)

Prepared following the general arylation procedure and isolated as a light brown semi-solid in 88% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.29 (m, 1 H), 7.16 (d, *J* = 7.3 Hz, 1 H), 7.07–7.03 (m, 1 H), 6.87 (d, *J* = 7.9 Hz, 1 H), 6.81 (d, *J* = 7.9 Hz, 1 H), 6.70–6.67 (m, 2 H), 4.48 (s, 1 H), 4.20 (s, 4 H), 3.23 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 144.6, 143.8, 143.2, 129.9, 129.1, 128.5, 125.1, 122.9, 121.6, 117.8, 117.3, 108.3, 64.5, 51.5, 26.6.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{16}NO_3$: 282.1130; found: 282.1122.

3-[3-(1,3-Dioxolan-2-yl)phenyl]-1-methylindolin-2-one (18)

Prepared following the general arylation procedure and isolated as a light brown semi-solid in 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.31 (m, 4 H), 7.20 (d, *J* = 7.5 Hz, 1 H), 7.15 (d, *J* = 7.2 Hz, 1 H), 7.05 (dd, *J* = 7.5, 7.5 Hz, 1 H), 6.89 (d, *J* = 7.9 Hz, 1 H), 5.79 (s, 1 H), 4.63 (s, 1 H), 4.11–4.07 (m, 2 H), 4.04–3.98 (m, 2 H), 3.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 144.7, 138.7, 136.9, 129.5, 129.1, 128.8, 128.6, 126.8, 125.8, 125.7, 122.9, 108.4, 103.6, 65.5, 65.3, 52.1, 26.7.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{18}NO_3$: 296.1287; found: 296.1281.

3-(2,6-Dimethylphenyl)-1-methylindolin-2-one (19)

Prepared following the general arylation procedure and isolated as a light yellow solid in 93% yield; mp 106.0–108.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 7.6, 7.6 Hz, 1 H), 7.12 (d, *J* = 7.3 Hz, 1 H), 7.08 (dd, *J* = 7.4, 7.4 Hz, 1 H), 6.98 (dd, *J* = 7.4, 7.4 Hz, 1 H), 6.97–6.90 (m, 2 H), 6.89 (d, *J* = 7.8 Hz, 1 H), 5.03 (s, 1 H), 3.30 (s, 3 H), 2.54 (s, 3 H), 1.64 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 144.1, 138.1, 137.3, 133.7, 129.6, 128.6, 128.4, 128.1, 127.7, 123.7, 122.8, 108.1, 48.5, 26.6, 21.5, 19.1.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}NO$: 252.1388; found: 252.1382.

Diethyl 4,4′-(1-Methyl-2-oxoindoline-3,3-diyl)dibenzoate (20)

Prepared following the general arylation procedure using ethyl 4-bromobenzoate (2.2 equiv). The product was isolated as a light brown solid in 88% yield; mp 101.0–103.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (d, *J* = 8.5 Hz, 4 H), 7.35 (dt, *J* = 7.8, 0.7 Hz, 1 H), 7.31 (d, *J* = 8.5 Hz, 4 H), 7.23 (d, *J* = 7.3 Hz, 1 H), 7.11 (t, *J* = 7.5 Hz, 1 H), 6.97 (d, *J* = 7.8 Hz, 1 H), 4.35 (q, *J* = 7.1 Hz, 4 H), 3.31 (s, 3 H), 1.36 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.5, 166.3, 146.4, 143.2, 131.7, 129.93, 129.90, 129.1, 128.6, 126.1, 123.3, 109.1, 62.7, 61.1, 27.0, 14.5.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{26}NO_5$: 444.1811; found: 444.1804.

3-Arylation of *N*-H and *N*-Phenyloxindoles; General Procedure

All reactions were conducted in 10 mL glass vials fitted with crimp-cap septum caps. The reaction vial, equipped with a magnetic stir bar, was charged under an N_2 atmosphere with the oxindole (2.25 mmol), $Pd_2(dba)_3$ (51 mg, 0.056 mmol, 2.5 mol%), *i*-Pr-BI-DIME (**7**) (41 mg, 0.112 mmol, 5 mol%), K_2CO_3 (932 mg, 6.75 mmol) and the aryl bromide (1.1 equiv), then sealed with a crimp-cap septum. Dioxane (5.0 mL, degassed) was added via syringe and the reaction was stirred in an oil bath at 100 °C for 24 h. The reaction mixture was then cooled to room temperature and filtered through a Celite pad using EtOAc (15 mL) as eluent. The filtered solution was washed with H_2O (5 mL), dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude residue was purified using a 12 g silica column (30% EtOAc/hexanes) to afford the desired oxindole product.

3-(*p*-Tolyl)-indolin-2-one (21)[8d]

Prepared following the general arylation procedure and isolated as a yellow solid in 48% yield; mp 160.0–162.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (s, 1 H), 7.24–6.96 (m, 6 H), 6.90 (t, *J* = 7.5 Hz, 1 H), 6.73 (d, *J* = 7.7 Hz, 1 H), 4.39 (s, 1 H), 2.17 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.9, 144.3, 136.9, 133.5, 129.4, 128.9, 128.19, 128.15, 124.8, 122.5, 108.0, 51.5, 26.2, 20.9.

3-(4-Methoxyphenyl)indolin-2-one (22)[8d]

Prepared following the general arylation procedure and isolated as a yellow solid in 56% yield; mp 152–154 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.27 (s, 1 H), 7.28–7.21 (m, 1 H), 7.17–6.95 (m, 3 H), 7.02 (t, *J* = 7.6 Hz, 1 H), 6.92 (d, *J* = 7.8 Hz, 1 H), 6.87 (d, *J* = 7.7 Hz, 2 H), 4.58 (s, 1 H), 3.78 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.7, 159.3, 141.7, 130.0, 129.9, 128.7, 128.5, 125.6, 122.9, 114.6, 109.9, 55.5, 52.0.

1,3-Diphenylindolin-2-one (23)[14c]

Prepared following the general arylation procedure and isolated as a light yellow solid in 85% yield; mp 119–121 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.51 (t, *J* = 7.7 Hz, 2 H), 7.46–7.42 (m, 2 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 7.35 (d, *J* = 7.2 Hz, 2 H), 7.33–7.28 (m, 3 H), 7.26–7.20 (m, 2 H), 7.08 (t, *J* = 7.4 Hz, 1 H), 6.88 (d, *J* = 7.2 Hz, 1 H), 4.79 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.5, 144.6, 137.0, 134.8, 129.8, 129.1, 128.9, 128.7, 128.5, 128.2, 127.9, 126.8, 125.6, 123.4, 109.7, 52.3.

3-Arylation of 3-Methyl/phenyl-*N*-methyl/phenyloxindoles; General Procedure

All reactions were conducted in 10 mL glass vials fitted with crimp-cap septum caps. The reaction vial, equipped with a magnetic stir bar, was charged under an N_2 atmosphere with the oxindole (1 mmol), the aryl bromide (1.1.equiv), $Pd_2(dba)_3$ (10 mg, 0.011 mmol), ligand (8 mg, 0.022 mmol), Cs_2CO_3 (2 mmol) or NaO*t*-Bu (1.1 mmol). Degassed (Ar sparge) toluene or cyclohexane (1.0 mL) was charged to the vial which was then sealed with a crimp-cap septum. The vial was heated at 30–110 °C for 24 h. The reaction mixture was cooled to room temperature and filtered through a Celite pad with EtOAc (5 mL) as eluent. The filtered solution was washed with H_2O (5 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. The crude residue was purified using a 12 g silica column (30% EtOAc/hexanes) to afford the desired product.

3-(4-Methoxyphenyl)-3-methyl-1-phenylindolin-2-one (26)

Prepared following the general arylation procedure and isolated as a light green oil in 41% yield; 84% ee.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.52–7.47 (m, 2 H), 7.43–7.37 (m, 3 H), 7.31–7.28 (m, 2 H), 7.25–7.22 (m, 2 H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.8 Hz, 1 H), 6.85–6.82 (m, 2 H), 3.78 (s, 3 H), 1.88 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1, 159.0, 143.3, 135.0, 134.9, 133.2, 129.7, 128.1, 128.0, 126.8, 124.7, 123.4, 114.2, 109.8, 55.5, 51.8, 24.4.

Chiral HPLC conditions: Chiralpak OJ-3 column, 4.6 × 250 mm, 10 µ; isopropanol/heptane (4:96); 1.0 mL/min; 220 nm; t_{major} = 16.7 min, t_{minor} = 19.8 min.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}NO_2$: 330.1489; found: 330.1472.

3-(4-Methoxyphenyl)-1-methyl-3-phenylindolin-2-one (27)[14d]

Prepared following the general arylation procedure and isolated as a light green oil in 95% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.22 (m, 4 H), 7.26–7.22 (m, 7 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 6.91 (d, *J* = 7.6 Hz, 1 H), 6.80 (d, *J* = 8.4 Hz, 2 H), 3.76 (s, 3 H), 3.28 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.9, 158.9, 143.1, 142.3, 133.9, 129.7, 128.5, 128.4, 128.3, 127.3, 126.1, 122.9, 113.9, 108.8, 55.4, 26.8.

1-Methyl-3-phenyl-3-(*p*-tolyl)-indolin-2-one (28)[14d]

Prepared following the general arylation procedure and isolated as a light green oil in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.29 (m, 2 H), 7.28–7.23 (m, 6 H), 7.13 (m, 1 H), 7.08–7.05 (m, 3 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 3.28 (s, 3 H), 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 143.2, 142.2, 129.3, 128.6, 128.5, 128.4, 127.4, 126.2, 122.9, 108.6, 29.9, 21.1.

3-(4-Methoxyphenyl)-1,3-dimethylindolin-2-one (29)[9c]

Prepared following the general arylation procedure and isolated as a light greenish semi-solid in 96% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.32 (t, *J* = 7.9 Hz, 1 H), 7.23–7.16 (m, 3 H), 7.09 (t, *J* = 7.1 Hz, 1 H), 6.90 (d, *J* = 8.2 Hz, 1 H), 6.82 (m, 2 H), 3.76 (s, 3 H), 3.23 (s, 3 H), 1.75 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.9, 158.6, 143.5, 135.2, 128.2, 127.9, 124.4, 122.9, 114.2, 108.5, 55.5, 51.7, 26.6, 24.1.

3-(3-Methoxyphenyl)-3-methyl-1-phenylindolin-2-one (36)

Prepared following the general arylation procedure and isolated as a light green oil in 56% yield; 74% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50 (m, 2 H), 7.41 (m, 3 H), 7.23 (m, 3 H), 7.11 (m, 1 H), 6.96 (m, 2 H), 6.90 (m, 1 H), 6.80 (m, 1 H), 3.77 (s, 3 H), 1.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 159.8, 143.2, 142.6, 134.7, 129.73, 129.70, 128.17, 128.13, 126.7, 124.6, 123.4, 119.2, 113.4, 112.3, 109.8, 55.3, 52.3, 24.1.

Chiral HPLC conditions: Chiralpak OD-H column, 4.6 × 250 mm, 10 µ; isopropanol/heptane (10:90); 1.0 mL/min; 222 nm; t_{major} = 8.83 min, t_{minor} = 7.45 min.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{20}NO_2$: 330.1489; found: 330.1473.

3-Methyl-1-phenyl-3-[4-(trifluoromethyl)phenyl]indolin-2-one (37)

Prepared following the general arylation procedure and isolated as a light red solid in 48% yield; 64% ee; mp 110.0–112.0 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58 (m, 2 H), 7.54–7.50 (m, 4 H), 7.43–7.40 (m, 3 H), 7.27 (m, 1 H), 7.24 (m, 1 H), 7.15 (t, *J* = 7.4 Hz, 1 H), 6.83 (d, *J* = 8.0 Hz, 1 H), 1.93 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2, 145.0 (d, *J* = 1.2 Hz), 143.3, 134.5, 133.9, 129.8, 128.6, 128.3, 127.4, 126.7, 125.7 (q, *J* = 4.1 Hz), 124.7, 123.6, 110.1, 52.4, 24.4.

Chiral HPLC conditions: Chiralpak AD-H column, 4.6 × 250 mm, 10 µ; isopropanol/heptane (10:90); 1.0 mL/min; 222 nm; t_{major} = 4.18 min, t_{minor} = 5.03 min.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}F_3NO$: 368.1257; found: 368.1242.

3-[3,5-Bis(trifluoromethyl)phenyl]-3-methyl-1-phenylindolin-2-one (38)

Prepared following the general arylation procedure and isolated as a light green solid in 51% yield; 75% ee; mp 94.0–96.0 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (m, 2 H), 7.81 (m, 1 H), 7.53 (m, 2 H), 7.43 (m, 3 H), 7.32 (m, 1 H), 7.27 (m, 1 H), 7.20 (m, 1 H), 6.96 (m, 1 H), 1.95 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.4, 143.6, 143.3, 134.2, 132.6, 132.3, 131.9, 129.9, 129.2, 128.6, 127.4 (q, *J* = 3.2 Hz), 126.7, 124.3 (d, *J* = 3.2 Hz), 123.2 (d, *J* = 272.0 Hz), 121.7 (q, *J* = 3.8 Hz), 110.5, 52.1, 25.1.

Chiral HPLC conditions: Chiralcel OD-H column, 4.6 × 250 mm, 10 µ; isopropanol/hexane (90:10); 1.0 mL/min; 222 nm; t_{major} = 3.44 min, t_{minor} = 3.63 min.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{16}F_6NO$: 436.1131; found: 436.1122.

3-Arylation of 3-Methyl-*N*-phenylindolin-2-one with Aryl Triflates; General Procedure

All reactions were conducted in 10 mL glass vials fitted with crimp-cap septum caps. The reaction vial, equipped with a magnetic stir bar, was charged under an N_2 atmosphere with 3-methyl-*N*-phenylindolin-2-one (**24**) (100 mg, 0.45 mmol), the aryl triflate (1.1 equiv), $Pd(dba)_2$ (25 mg, 0.045 mmol), Me_2-BI-DIME (**32**) (18 mg, 0.053 mmol), Cs_2CO_3 (291 mg, 0.894 mmol). Degassed (Ar sparged) toluene (1.0 mL) was charged to the vial which was then sealed with a crimp-cap septum. The vial was heated at 60 °C for 24 h. The reaction mixture was then cooled to room temperature and filtered through a Celite pad with EtOAc (5 mL) as eluent. The filtered solution was washed with H_2O (5 mL), dried over $MgSO_4$ and then concentrated under reduced pressure. The crude product was purified using a 12 g silica column (30% EtOAc/hexanes) to afford the desired product.

3-(3,5-Dimethoxyphenyl)-3-methyl-1-phenylindolin-2-one (39)

Prepared following the general arylation procedure and isolated as a brown liquid in 71% yield; 78% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.48 (m, 2 H), 7.44–7.35 (m, 3 H), 7.27–7.20 (m, 3 H), 7.13–7.08 (m, 1 H), 6.88 (m, 1 H), 6.55 (d, *J* = 2.1 Hz, 1 H), 6.36 (s, 1 H), 3.75 (s, 6 H), 1.86 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 161.0, 143.5, 143.2, 134.9, 134.7, 129.8, 128.3, 126.9, 124.8, 123.5, 109.9, 105.7, 99.0, 55.6, 52.4, 24.2.

Chiral SFC conditions: Lux Cel1, 4.6 × 150 mm, particle size: 3 µm, temperature: 30 °C, A: CO_2, B: MeOH, isocratic: A/B: 50:50, v/v, flow rate: 3.0 mL/min, t_{major} = 5.11 min, t_{minor} = 4.73 min.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{22}NO_3$: 360.1600; found: 360.1592.

3-Methyl-1,3-diphenylindolin-2-one (40)

Prepared following the general arylation procedure and isolated as a yellow solid in 63% yield; 74% ee; mp 135–137 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53–7.48 (m, 2 H), 7.45–7.43 (m, 1 H), 7.42–7.36 (m, 4 H), 7.35–7.29 (m, 2 H), 7.28–7.21 (m, 3 H), 7.11 (dt, *J* = 7.6, 1.0 Hz, 1 H), 6.92–6.89 (m, 1 H), 1.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.9, 143.3, 141.1, 134.9, 134.8, 129.7, 128.8, 128.1, 127.5, 126.9, 126.8, 124.7, 123.4, 109.9, 52.6, 24.2.

Chiral SFC conditions: Lux Cellulose1, 4.6 × 150 mm, particle size: 3 µm, temperature: 30 °C, A: CO_2, B: MeOH, isocratic: A/B: 50:50, v/v, flow rate: 3.0 mL/min, t_{major} = 4.60 min, t_{minor} = 4.42 min.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{18}NO$: 300.1388; found: 300.1382.

4-(3-Methyl-2-oxo-1-phenylindolin-3-yl)benzonitrile (41)

Prepared following the general arylation procedure and isolated as a yellow solid in 59% yield; 70% ee; mp 133–135 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63–7.60 (m, 2 H), 7.54–7.50 (m, 4 H), 7.43–7.39 (m, 3 H), 7.28 (t, *J* = 7.7 Hz, 1 H), 7.23 (m, 1 H), 7.16 (t, *J* = 7.5 Hz, 1 H), 6.93 (d, *J* = 7.7 Hz, 1 H), 1.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.8, 146.4, 143.3, 134.4, 133.4, 132.6, 129.9, 128.8, 128.5, 127.9, 126.9, 126.7, 124.7, 123.8, 118.9, 111.6, 110.2, 52.6, 24.4.

Chiral SFC conditions: ES-CCC, 4.6 × 150 mm, particle size: 3 µm, temperature: 30 °C, A: CO_2, B: MeOH, isocratic: A/B: 50:50, v/v, flow rate: 3.0 mL/min, t_{major} = 5.40 min, t_{minor} = 5.11 min.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{22}H_{17}N_2O$: 325.1341; found: 325.1335.

Methyl 4-(3-Methyl-2-oxo-1-phenylindolin-3-yl)benzoate (42)

Prepared following the general arylation procedure and isolated as a brown liquid in 55% yield; 66% ee.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (m, 2 H), 7.54–7.49 (m, 2 H), 7.49–7.45 (m, 2 H), 7.44–7.38 (m, 3 H), 7.29–7.26 (m, 1 H), 7.25–7.21 (m, 1 H), 7.14 (dt, *J* = 7.5, 1.0 Hz, 1 H), 6.92–6.89 (m, 1 H), 3.90 (s, 3 H), 1.93 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.3, 166.9, 146.1, 143.3, 134.6, 134.2, 130.0, 129.8, 129.4, 128.5, 128.3, 127.0, 126.8, 124.7, 123.6, 110.0, 52.6, 52.3, 24.2.

Chiral SFC conditions: Lux Cellulose 2, 4.6 × 150 mm, particle size: 3 µm, temperature: 30 °C, A: CO_2, B: MeOH, isocratic: A/B: 50:50, v/v, flow rate: 3.0 mL/min, t_{major} = 6.04 min, t_{minor} = 5.44 min.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{23}H_{20}NO_3$: 358.1443; found: 358.1436.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591590.

References

(1) Current address: Department of Chemical and Life Science Engineering, Virginia Commonwealth University, 737 N. 5th St., Richmond, VA 23219, USA.
(2) Current address: Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, USA.
(3) (a) Cao, Z.-Y.; Wang, Y.-H.; Zeng, X.-P.; Zhou, J. *Tetrahedron Lett.* **2014**, *55*, 2571. (b) Shen, K.; Liu, X.; Lin, L.; Feng, X. *Chem. Sci.* **2012**, *3*, 327. (c) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381. (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748. (e) da Silva, J. F. M.; Garden, S. J.; Pinto, S. C. *J. Braz. Chem. Soc.* **2001**, *12*, 273.
(4) Richmond, E.; Ling, K. B.; Duguet, N.; Manton, L. B.; Celebi-Olcum, N.; Lam, Y.-H.; Alsancak, S.; Slawin, A. M. Z.; Houk, K. N.; Smith, A. D. *Org. Biomol. Chem.* **2015**, *13*, 1807.
(5) Natarajan, A.; Guo, Y.; Harbinski, F.; Fan, Y.-H.; Chen, H.; Luus, L.; Diercks, J.; Aktas, H.; Chorev, M.; Halperin, J. A. *J. Med. Chem.* **2004**, *47*, 4979.
(6) Hewawasam, P.; Gribkoff, V. K.; Pendri, Y.; Dworetzky, S. I.; Meanwell, N. A.; Martinez, E.; Boissard, C. G.; Post-Munson, D. J.; Trojnacki, J. T.; Yeleswaram, K.; Pajor, L. M.; Knipe, J.; Gao, Q.; Perrone, R.; Starrett, J. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1023.
(7) Lim, J. W.; Kim, K. H.; Moon, H. R.; Kim, J. N. *Tetrahedron Lett.* **2016**, *57*, 784.
(8) For recent publications, see: (a) Mai, C.-K.; Sammons, M. F.; Sammakia, T. *Org. Lett.* **2010**, *12*, 2306. (b) Li, P.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2011**, *50*, 6396. (c) Pietruszka, J.; Wang, C. *ChemCatChem* **2012**, *4*, 782. (d) Xiao, Z. K.; Yin, H. Y.; Shao, L.-X. *Org. Lett.* **2013**, *15*, 1254. (e) Jin, Y.; Chen, M.; Ge, S.; Hartwig, J. F. *Org. Lett.* **2017**, *19*, 1390. (f) Moghaddam, F. M.; Tavakoli, G.; Latifi, F.; Saeednia, B. *Catal. Commun.* **2016**, *75*, 37. (g) Zhai, C.; Xing, D.; Jing, C.; Zhou, J.; Wang, C.; Wang, D.; Hu, W. *Org. Lett.* **2014**, *16*, 2934. (h) Duan, J.; Kwong, F. Y. *J. Org. Chem.* **2017**, *82*, 6468. (i) Yu, J.-S.; Zhou, F.; Liu, Y.-L.; Zhou, J. *Synlett* **2015**, *26*, 2491. (j) Kaur, J.; Chimni, S. S.; Mahajan, S.; Kumar, A. *RSC Adv.* **2015**, *5*, 52481. (k) Zhou, L.-J.; Zhang, Y.-C.; Jiang, F.; He, G.; Yan, J.; Lu, H.; Zhang, S.; Shi, F. *Adv. Synth. Catal.* **2016**, *358*, 3069. (l) Guo, W.; Liu, Y.; Li, C. *Org. Lett.* **2017**, *19*, 1044. (m) Jiang, F.; Zhao, D.; Yang, X.; Yuan, F.-R.; Mei, G.-J.; Shi, F. *ACS Catal.* **2017**, *7*, 6984.
(9) (a) Durbin, M. J.; Willis, M. C. *Org. Lett.* **2008**, *10*, 1413. (b) Altman, R. A.; Hyde, A. M.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 9613. (c) Taylor, A. M.; Altman, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 9900.
(10) (a) Tang, W.; Qu, B.; Capacci, A. G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, *12*, 176. (b) Tang, W.; Capacci, A. G.; Wei, X.; Li, W.; White, A.; Patel, N. D.; Savoie, J.; Gao, J.; Rodriguez, S.; Qu, B.; Haddad, N.; Lu, B. Z.; Krishnamurthy, D.; Yee, N. K.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 5879. (c) Tang, W.; Patel, N. D.; Xu, G.; Xu, X.; Savoie, J.; Ma, S.; Hao, M.-H.; Keshipeddy, S.; Capacci, A. G.; Wei, X.; Zhang, Y.; Gao, J.; Li, W.; Rodriguez, S.; Lu, B. Z.; Yee, N. K.; Senanayake, C. H. *Org. Lett.* **2012**, *14*, 2258.
(11) For selected publications, see: (a) Wei, X.; Qu, B.; Zeng, X.; Savoie, J.; Fandrick, K. R.; Desrosiers, J.-N.; Tcyrulnikov, S.; Marsini, M. A.; Buono, F. G.; Li, Z.; Yang, B.-S.; Tang, W.; Haddad, N.; Gutierrez, O.; Wang, J.; Lee, H.; Ma, S.; Campbell, S.; Lorenz, J. C.; Eckhardt, M.; Himmelsbach, F.; Peters, S.; Patel, N. D.; Tan, Z.; Yee, N. K.; Song, J. J.; Roschangar, F.; Kozlowski, M. C.; Senanayake, C. H. *J. Am. Chem. Soc.* **2016**, *138*, 15473. (b) Haddad, N.; Mangunuru, H. P. R.; Fandrick, K. R.; Qu, B.;

Sieber, J. D.; Rodriguez, S.; Desrosiers, J.-N.; Patel, N. D.; Lee, H.; Kurouski, D.; Grinberg, N.; Yee, N. K.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal.* **2016**, *358*, 3522. (c) Sieber, J. D.; Qu, B.; Rodríguez, S.; Haddad, N.; Grinberg, N.; Lee, H.; Song, J. J.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2016**, *81*, 729. (d) Sieber, J. D.; Angeles-Dunham, V. V.; Chennamadhavuni, D.; Fandrick, D. R.; Haddad, N.; Grinberg, N.; Kurouski, D.; Lee, H.; Song, J. J.; Yee, N. K.; Mattson, A. E.; Senanayake, C. H. *Adv. Synth. Catal.* **2016**, *358*, 3062. (e) Fandrick, K. R.; Li, W.; Zhang, Y.; Tang, W.; Gao, J.; Rodriguez, S.; Patel, N. D.; Reeves, D. C.; Wu, J.-P.; Sanyal, S.; Gonnella, N.; Qu, B.; Haddad, N.; Lorenz, J. C.; Sidhu, K.; Wang, J.; Ma, S.; Grinberg, N.; Lee, H.; Tsantrizos, Y.; Poupart, M.-A.; Busacca, C. A.; Yee, N. K.; Lu, B. Z.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2015**, *54*, 7144. (f) Qu, B.; Samankumara, L. P.; Ma, S.; Fandrick, K. R.; Desrosiers, J.-N.; Rodriguez, S.; Li, Z.; Haddad, H.; Han, Z. S.; McKellop, K.; Pennino, S.; Grinberg, N.; Gonnella, N. C.; Song, J. J.; Senanayake, C. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 14428. (g) Qu, B.; Samankumara, L. P.; Savoie, J.; Fandrick, D. R.; Haddad, N.; Wei, X.; Ma, S.; Lee, H.; Rodriguez, S.; Busacca, C. B.; Yee, N. K.; Song, J. J.; Senanayake, C. H. *J. Org. Chem.* **2014**, *79*, 993.

(12) Chiral analysis of the arylation products **11**, **19** and **21** indicated formation of racemic mixtures. The low er might be attributed to possible racemization of the monoarylation product under the reaction conditions.

(13) The configuration of the major enantiomer was determined by comparison to the literature data of compound **29**.[7c] Please refer to the Supporting Information for more details.

(14) (a) Trost, B. M.; Zhang, Y. *Angew. Chem. Int. Ed.* **2005**, *44*, 308. (b) Trost, B. M.; Zhang, Y. *J. Am. Chem. Soc.* **2007**, *129*, 14548. (c) Matloubi, M. F.; Ghazal, T.; Fatemeh, L.; Borna, S. *Catal. Commun.* **2016**, *75*, 37. (d) Bernhard, B.; Richard, S. R. *Chem. Ber.* **1985**, *118*, 1726.