Palladium-Catalyzed Inter- and Intramolecular α-Arylation of Amides. Application of Intramolecular Amide Arylation to the Synthesis of Oxindoles

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2A palladium-catalyzed α-arylation of amides is reported. Intermolecular arylation of *N*,*N*-dimethylamides and lactams occurs using aryl halides, silylamide base, and a palladium catalyst. Intramolecular arylation of *N*-(2-halophenyl)amides occurs using alkoxide base and a palladium catalyst. The palladium catalyst was formed in situ from $Pd(dba)_2$ (dba = *trans*,*trans*-dibenzylidene acetone) and BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthalene). Although the intermolecular arylation of amides is less general than that reported previously for ketones, unfunctionalized and electron-rich aryl halides gave α-arylamides in 48−75% yield and *N*-methyl-α-phenylpyrrolidinone in 49% yield. These reactions provided the highest yields yet reported for regioselective amide arylations. Intramolecular amide arylation of 2-bromoanilides gave oxindoles in 52−82% yield. Mono- and disubstituted acetanilides gave 1,3-di- and 1,3,3-trisubstituted oxindoles. The use of dioxane, rather than THF, solvent was important for some of the amide arylations.

Introduction

Palladium-catalyzed couplings of aryl and vinyl halides or pseudohalides with organometallic reagents are widely used in modern synthetic organic chemistry.[1] Despite the wide variety of organometallic reagents which mediate these types of cross coupling reactions, examples of enolate additions to aryl and vinyl halides have been limited in scope.[2−15] Only recently have reports by us,[16] Buchwald,[17,18] and Satoh[19] shown that the palladium-catalyzed, intermolecular coupling of aryl halides and ketone enolates is a useful methodology for the synthesis of α-aryl ketones. On the basis of our success with ketone arylations, we have begun to explore the arylation of other substrates such as carboxylic acid derivatives.

α-Arylamides have potential medical and agricultural applications, but few general methods for their preparation have been reported. Classical methods for the amide α-arylation have involved Friedel−Crafts or photoinitiated addition of α-haloamides to arenes.[20] These reactions give poor regioselectivity and variable yields. Enolates formed from *N*-methylpyrrolidinone (NMP) have been coupled with aryl halides to give 3-arylpyrrolidinones in low to moderate yields (15−50%) in the presence of an excess of strong base.[21] Since this reaction occurs through a benzyne intermediate, addition to substituted arenes often gives mixtures of regioisomers. Coupling of aryl halides and amide enolates via an $S_{RN}1$ mechanism initiated photochemically was the first and only reported example of a regioselective amide arylation.[22,23] However, this methodology required enolate to aryl halide ratios of 15:1 to achieve > 2:1 mono:diarylation selectivities. In view of the limited number of methodologies for the selective arylation of amides, we have explored the extension of the palladium-catalyzed ketone arylation methodology to amide arylation.

Oxindoles are important substructures in numerous biologically active molecules.[24] Considering the potential to conduct intermolecular amide arylations, it seemed likely that an intramolecular variant of the amide arylation could be developed for oxindole syntheses. A number of methods for the synthesis of oxindole compounds have been reported. Friedel−Crafts cyclizations of α-haloacetanilides and variations on the Fischer indole synthesis are the classical methods of oxindole synthesis.[25] Cyclizations of 2-haloacryloylanilide derivatives by a variety of radical initiators have been reported more

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recently.[26−31] Metal-catalyzed routes to oxindoles include cyclocarbonylations of 2-aminostyrenes catalyzed by palladium,[32] rhodium catalyzed carbonylations of 2-alkynylanilines,[33] rhodium- and Nafion-H-catalyzed cyclizations of α-diazoamides,[34,35] and intramolecular Heck couplings of 2-haloacryloylanilides.[36,37] Photochemical,[38,39] Ullman-type,[40] and radical[41] promoted cyclizations of saturated 2-haloanilide derivatives have also been reported.

Although there are a variety of methods for synthesizing these structures, methods which form oxindoles with complete regioselectivity are rare. Friedel−Crafts methods and more recent variations do not allow control of arene regiochemistry.[25,40,41] Most other methodologies involve cyclization by addition of reactive intermediates to olefin or alkynyl moieties. Often these additions occur with poor regioselectivity producing mixtures of oxindole and 3,4-dihydroquinolin-2-one products.[26,28−31,33,36] Regioselectivity becomes particularly poor when attempting to prepare 3,3-disubstituted oxindoles. Preparation of oxindoles via intramolecular amide arylation of 2-haloanilide substrates would be expected to occur with complete regioselectivity regardless of the substrate's substitution pattern.

Although extension of the palladium-catalyzed ketone arylation methodology to the arylation of amides appeared conceptually simple, the significantly higher pK_a of amides compared to that of ketones appears to affect the rate of many of the steps of the catalytic cycle. Thus, it was necessary to find modified reaction conditions for both inter- and intramolecular amide arylation. Herein, we report the first example of a palladium-catalyzed, intermolecular arylation of dialkylamides and pyrrolidinones, along with intramolecular versions of this reaction that produce oxindoles.

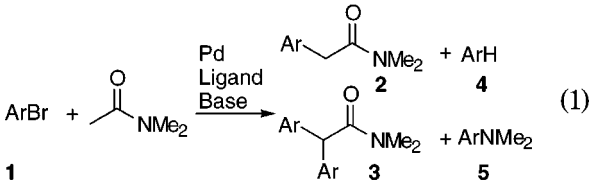
Results

Intermolecular Arylation of *N*,*N*-Dialkylamides. In a simple, one-pot procedure, aryl halides were coupled with *N*,*N*-dialkylamides in the presence of an excess amount of potassium hexamethyldisilazide (KHMDS) and a catalytic amount of $Pd(dba)_2$ and chelating phosphine ligand (eq 1). A series of reactions carried out on a 0.10 mmol scale were used to determine a suitable ligand, base, and solvent for the amide arylation reaction. Use of either DPPF or *rac*-BINAP[42] resulted in an active catalyst system. BINAP gave higher yields of arylated amide (Table 1, entries 1−2). Other chelating phosphines such as bis(di-*o*-tolylphosphino)ferrocene (DTPF), which was effective in ketone arylations, and bis(diphenylphosphino)xanthene produced catalysts with low activity for the amide arylation reaction. We do not understand the difference between the activity of DTPF-ligated palladium in the ketone and amide arylations.

Table 1. Optimization of Ligand, Base, and Solvent in Amide Arylation[a]

entry	ligand	base	solvent	yield of **2a**[b] %	yield of **4a**[b] %
1	DPPF	KHMDS	THF	22	22
2	BINAP	KHMDS	THF	32	8
3	DPPF	LiTMP	THF	5	4
4	DPPF	KHMDS	dioxane	48	2
5	DPPF	LiTMP	dioxane	38	5

[a] Reactions run with 0.1 mmol of substrate, 7.5 mol % of $Pd(OAc)_2$, 9% ligand, 1.2 equiv of base at 85 °C for 2 h. [b] Yields determined by GC.



(1)

a: Ar = 4-*t*-Bu-phenyl
b: Ar = 2-naphthyl
c: Ar = 4-biphenyl
d: Ar = 4-tolyl
e: Ar = 2-tolyl
f: Ar = 4-methoxyphenyl
g: Ar = 4-$CF_3C_6H_4$
h: Ar = 4-*n*-Bu-C_6H_4

KHMDS was the most effective base for the amide arylation. Reactions employing KHMDS gave significantly higher yields than did reactions run with lithium tetramethylpiperidine (LiTMP) (Table 1, entries 2−5). Use of sodium *tert*-butoxide resulted in very slow conversion and high levels of undesired side products, while lithium diisopropylamide appeared to deactivate the catalyst system. THF and dioxane were suitable solvents for amide arylation, but reactions in dioxane consistently gave higher yields than those for reactions in THF.

Using BINAP as ligand, KHMDS as base, and dioxane as solvent, a series of preparative scale reactions were conducted. The coupling of 2-bromonaphthalene (**1b**) with *N*,*N*-dimethylacetamide (DMA) using palladium acetate as metal source gave coupled product **2b** in 44% yield (eq 1, Table 2, entry 2). Use of $Pd(dba)_2$, rather than $Pd(OAc)_2$, under identical conditions gave **2b** in 57% yield (Table 2, entry 1). Arene (**4b**) formed from hydrodehalogenation of the aryl halide was a common side product in the arylation chemistry. The amount of this side product was essentially unchanged between these two reactions, but the amount of product resulting from amide cleavage to form amine followed by aryl halide

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(42) DPPF = 1,1′-bis(diphenylphosphino)ferrocene. *rac*-BINAP = *rac*- 2,2′-bis(diphenylphosphino)-1,1′-binaphthalene.

Table 2. Effect of Pd Source and Reaction Concentration on Arylamide Yield[a]

entry	Pd source	[**1b**], M	yield of **2b**[b] %	yield of **3b**[b] %	yield of **4b**[b] %	yield of **5b**[b] %
1	$Pd(dba)_2$	0.45	57	n.d.[d]	(5)	(1)
2	$Pd(OAc)_2$	0.45	44	n.d.	(6)	(7)
3	$Pd(dba)_2$	0.10	70	9	(5)	(1)
4	$Pd(dba)_2$	0.01	75	n.d.	(3)	(1)
5	$Pd(dba)_2$	0.10	52[c]	24	n.d.	n.d.

[a] Reactions run with 2 mmol of substrate, 5% Pd, 7.5% BINAP, 2 equiv of KHMDS, in dioxane at 100 °C for 2 h. [b] Isolated yields except those in parentheses which indicate GC yields. [c] 1.5 equiv of KHMDS. [d] n.d. = not determined.

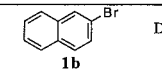
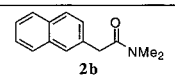
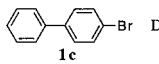
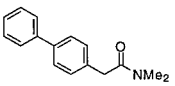
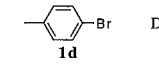
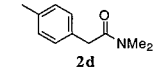
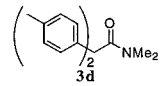
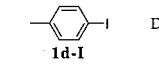
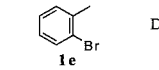
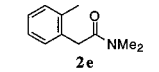
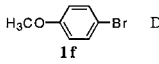
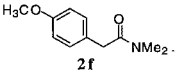
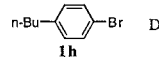
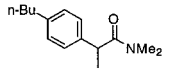
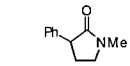
amination was different. The palladium acetate-catalyzed reaction gave a significantly higher amount of dimethylaminonaphthalene (7% vs 1%).

Reaction concentration and quantity of base also appeared to affect the reaction yields. Decreasing the reaction concentration from [ArBr] = 0.45 to 0.10 M resulted in an increase in the yield from 57% to 70% (Table 2, entries 1 and 3), while a further decrease in the reaction concentration to 0.01 M gave **2b** in 75% yield (Table 2, entry 4). The use of at least 2 equiv of base was necessary for good yields. Reactions employing 1.5 equiv of base resulted in only 52% yield of **2b**, and these conditions led to formation of diarylated product in 24% yield (Table 2, entry 5). Thus, it was important to use 2 equiv of base in order to conduct selective monoarylations of DMA. Increasing the amount of DMA eliminated the formation of diarylated product but had no effect on the yield of monoarylamide.

A variety of aryl halides were, therefore, coupled with DMA using 5 mol % $Pd(dba)_2$, 7.5 mol % BINAP, and 2 equiv of KHMDS at 0.10 M concentration in dioxane at 95−100 °C as shown in eq 1 and Table 3. Arenes **1b**−**d** gave good yields of the desired α-arylacetamides (66−72%). Undesired side products were principally diarylated amides (**3b**−**d**) formed in approximately 10% yield, along with arenes **4b**−**d** (5%) and dimethylaminoarenes **5b**−**d** (1%). The dimethylaminoarene side products formed from reactions using substrates **1c** and **1d** were observed as 1:1 mixtures of two isomers. Although dimethylaminoarenes are minor side products, their formation and reactivity are interesting. The 1:1 mixture of isomers in this case and others presented below shows that the aminoarenes are not formed by the palladium-catalyzed amination of aryl halide, which is regiospecific.[43−45] Rather, the aminoarene more likely forms through the trapping of an aryne species by dimethylamine, presumably formed in the reaction mixture through transamination of DMA with KHMDS.

The sterically hindered 2-bromotoluene (**1e**) gave a 72% yield of arylamide **2e**. This yield is identical to that observed with the unhindered substrate 4-bromotoluene. However, the amount of diarylated product was reduced to 4%. Iodotoluene reacted with DMA to give **2d** in 70% yield (Table 3, entry 5). 4,4′-Dimethylbiphenyl was observed as the major side product (13%) from this reaction, while the diarylated product was produced in only 4% yield. Coupling of **1d** with 0.5 equiv of DMA using 1.25 equiv of KHMDS per aryl halide gave diarylated amide **3d** in 74% yield and the monoarylated product **2d** in 24% yield.

Table 3. Intermolecular Arylation of *N*,*N*-Dialkylamides

Entry	ArX	Amide	Time	Major Product	Mono-aryl Yield[a]	Diaryl Yield[a]
1	 **1b**	DMA	2h	 **2b**	70 %	9 %
2	 **1c**	DMA	2h	 **2c**	66 %	13 %
3	 **1d**	DMA	1.5 h	 **2d**	72 %	10 %
4	**1d**	DMA[b]	1.5	 **3d**	24 %	74 %
5	 **1d-I**	DMA	1 h	**2d**	70 %	(4 %)[c]
6	 **1e**	DMA	1.5 h	 **2e**	72 %	(4 %)
7	 **1f**	DMA	4 h	 **2f**	48 %	18 %
8	 **1h**	DMP[d]	3 h	 **6**	(16 %)[e]	n.d.
9	PhBr	NMP	3 h	 **7**	49 %	9 %

[a] Yields are isolated yields for the average of at least two independent runs. Yields in parentheses are GC yields. All isolated products were fully characterized spectroscopically (^1H and ^{13}C NMR, FTIR, and LRMS) and are consistent with previously reported values. [b] 0.5 equiv of DMA used. [c] 4,4′-dimethylbiphenyl observed in 13% yield by GC. [d] P(*t*-Bu)$_3$ used as ligand. [e] Butylbenzene was produced in 78% yield by GC.

Methoxy-substituted bromoarene **1f** gave α-arylacetamide **2f** in lower yield (48%) and produced larger amounts of diarylated product (18%), arene (13% by GC), and dimethyaminoarene (16% by GC) (Table 3, entry 7). Again, dimethylaminoanisole was observed as a 1:1 mixture of isomers. Electron-poor arene **1g** (eq 1) gave only trace amounts of α-aryl amide under the standard reaction conditions. The major products identified by GCMS were trifluoromethyl-*N*,*N*-dimethylaniline and trifluoromethyl-*N*,*N*-bis(trimethylsilyl)aniline, which were produced in approximately a 1:1 ratio (20% combined yield by GC). Both aminated products were observed as 1:1 mixtures of isomers by GC. Electron-deficient arenes such as 4-bromobenzonitrile reacted directly with KHMDS. Attempts to carry out the amide arylation using the weaker base sodium *tert*-butoxide resulted in a 57% yield of 4-*tert*-butoxybenzonitrile, which has been shown previously to form from palladium-catalyzed conversion of the aryl halide to an aryl ether.[46,47]

Attempted arylation of *N*,*N*-dimethylpropionamide (DMP) with 4-bromotoluene under the standard conditions resulted principally in the reduction of the aryl halide to toluene. Use of tri(*o*-tolyl)phosphine in place of BINAP gave similar results. Coupling of 4-bromobutylbenzene with DMP using tri(*tert*-butyl)phosphine as

(43) Louie, J.; Hartwig, J. *Tetrahedron Lett.* **1995**, *36*, 3609−3612.
(44) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216.
(45) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218.
(46) Mann, G.; Hartwig, J. *J. Am. Chem. Soc.* **1996**, *118*, 13109−13110.
(47) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 3395−3396.

Table 4. Optimization of Intramolecular Amide α-Arylation[a]

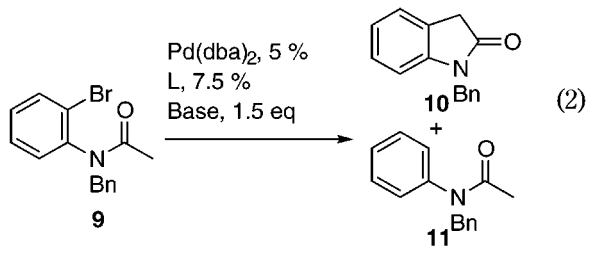
entry	ligand	base	solvent	temp, °C	time, h	convn.[b] %	yield of **10**[b] %	yield of **11**[b] %
1	DPPF	KHMDS	THF	75	19	100	trace	14[c]
2	DPPF	NaO-*t*-Bu	THF	75	19	100	56	13
3	BINAP	NaO-*t*-Bu	THF	75	23	85	65	2
4	DPPF	NaO-*t*-Bu	dioxane	75	23	40	10	1
5	BINAP	NaO-*t*-Bu	dioxane	75	23	95	50	1
6	DPPF	NaO-*t*-Bu	THF	100	3	96	53	9
7	BINAP	NaO-*t*-Bu	THF	100	3	100	57	2
8	DPPF	NaO-*t*-Bu	dioxane	100	3	96	43	10
9	P(*o*-tol)$_3$	NaO-*t*-Bu	dioxane	100	4	18	6	n.d.[d]
10	BINAP	NaO-*t*-Bu	dioxane	100	3	100	64	1

[a] Reactions run with 3.5 μmol of Pd(dba)$_2$, 5.3 μmol of ligand, 105 μmol of base, and 70 μmol of substrate in 1.5 mL of solvent at the indicated temperature. [b] Reaction yields determined by GC. [c] Also observed N-benzylaniline (40%). [d] Not detected.

ligand gave 2-(4-butylbenzene)propionamide **6** in 16% yield and butylbenzene in 78% yield as determined by GC (Table 3, entry 8). Attempted arylation of *N*,*N*-dimethylisobutyramide resulted exclusively in hydrodehalogenation of the aryl halide.

Arylations of lactams such as NMP were more successful than arylations of secondary carbon sites in acyclic amides. For example, bromobenzene reacted with NMP to give the arylation product **7** in 49% yield (Table 3, entry 9). The diarylation product diphenylpyrrolidinone **8** was formed competitively in 9% yield. Although the yield is lower than that for DMA, this reaction yield is comparable to the only other reported synthesis of 3-arylpyrrolidinones, and the previous method provided regioisomeric mixtures of products for reactions conducted with substituted arenes.[21]

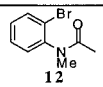
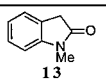
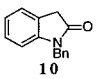
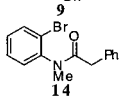
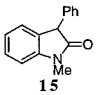
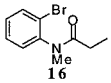
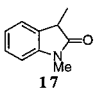
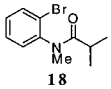
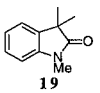
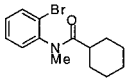
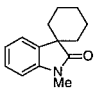
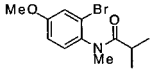
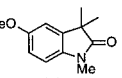
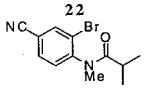
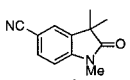
Oxindole Synthesis via Intramolecular Amide Arylation. The ability to conduct intermolecular α-arylation of amides led us to investigate an intramolecular variant of this reaction that would generate oxindoles. We investigated the use of 2-bromoanilides as substrates for cyclization to oxindoles. *N*-(2-Bromophenyl)-*N*-alkylamides are readily prepared by coupling 2-bromoaniline to an acid chloride followed by *N*-alkylation of the resulting amide. Treatment of *N*-benzyl-2-bromoacetanilide (**9**) with sodium *tert*-butoxide (1.5 equiv) in the presence of Pd(dba)$_2$ (5 mol %) and a chelating phosphine such as BINAP or DPPF resulted in the formation of 1-benzyloxindole **10** in up to 66% yield (eq 2, Table 5, entry 2).



(2)

As was the case for intermolecular amide arylations, the choice of base was important (Table 4). In this case, reactions run with sodium *tert*-butoxide gave clean conversion to the oxindole product with no side products observed in the reaction mixture other than arene **11** from hydrodehalogenation. In contrast, reactions conducted with KHMDS as the base resulted in significant deacylation of the acetanilide substrate giving *N*-benzylaniline in approximately 40% yield and only a trace of the desired oxindole **10**. No conversion was observed for reactions employing cesium carbonate as base.

Table 5. Formation of Oxindoles from 2-Bromoanilides

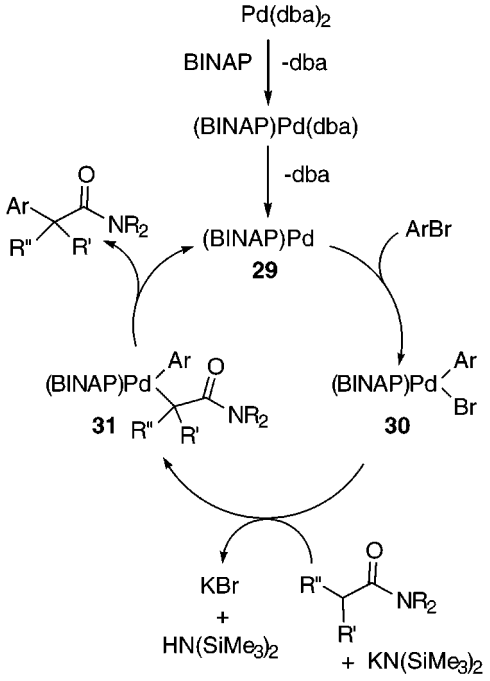
Entry	Substrate	Time[a]	Product	Yield[b]	Reduced Arene[c]
1	 **12**	2 h	 **13**	60 %	1 %
2	 **9**	3 h	 **10**	66 %	1 %
3	 **14**	10 h	 **15**	63 %	2 %
4	 **16**	1.5 h	 **17**	52 %	8 %
5	 **18**	3 h	 **19**	75 %	2 %
6	 **20**	4 h	 **21**	82 %	1 %
7	 **22**	12 h	 **23**	80 %	2 %
8	 **24**	4 h[d]	 **25**	83 %	<1 %

[a] Reaction times were not optimized. [b] Isolated yields from the average of at least two runs. All compounds were fully characterized spectroscopically (^{1}H and ^{13}C NMR, FTIR, and LRMS) and are consistent with previously reported values. [c] Reduced arene yields determined by GC. [d] 10 mol % of Pd used.

Reactions run with BINAP typically gave higher yields than those run with DPPF or P(*o*-tolyl)$_3$ (Table 4). Only trace amounts of hydrodehalogenation product were observed in reactions employing BINAP. When DPPF was used as ligand, **10** was observed in 40−50% yield, along with hydrodehalogenation product **11** that was formed in approximately 10% yield. The use of tri(*o*-tolyl)phosphine as ligand gave much lower yields. Only 18% conversion and 6% yield of oxindole **10** was observed from reactions using this ligand. Reactions run at 75 °C with BINAP as ligand required at least 19 h for complete consumption of starting material, but reactions run at 100 °C provided complete reaction in less than 3 h without decrease in the selectivity of the arylation chemistry. Reactions run in dioxane solvent gave slightly higher yields than those run in THF.

In addition to *N*-benzyloxindole, cyclization to form *N*-alkyl versions of the parent oxindole core occurred in

Scheme 1. Proposed Mechanism of Amide Enolate Arylation



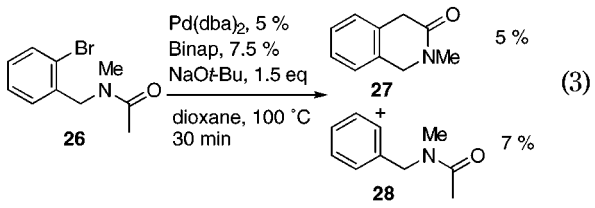
good yields. The ability to produce 1-substituted oxindoles by this route avoids alkylation of oxindole that often occurs with poor regioselectivity.[48] 1-Methyloxindole **13** was produced in 60% yield from *N*-methyl-2-bromoacetanilide (**12**) (Table 5, entry 1). However, the use of *N*-methyl-2-iodoacetanilide (**12-I**) resulted in only a 40% yield of **13** as determined by GC.

Substrates with secondary C−H bonds α to the carbonyl also gave oxindole products. α-Arylacetanilide **14** was converted to the corresponding oxindole **15** in yields comparable to those for unsubstituted substrates (Table 5, entry 3). However, this reaction was significantly slower (10 h compared to 2−4 h) than arylation of the alkyl-substituted substrates. Intramolecular amide arylation of **16** gave oxindole **17** in a lower 52% yield with an increase in the amount of hydrodehalogenation product to 8% (Table 5, entry 4). Although the yield of this cyclization was lower than that for unsubstituted and disubstituted (see below) 2-bromoacetanilide substrates, it was much higher than that observed for the intermolecular α-arylation of DMP.

As noted in the Introduction, the importance of 3,3-disubstituted oxindoles as pharmaceuticals makes the development of new synthetic routes to this core important. In contrast to the attempted *inter*molecular arylation of secondary and tertiary amide enolates, *N*-(2-bromophenyl)isobutyramide **18** underwent clean *intra*molecular arylation to form 1,3,3-trimethyloxindole in 75% yield. The spirocyclic oxindole **21** was also produced in excellent yield (82%). These reactions demonstrate that the intramolecular amide arylation should be a useful methodology for generating this type of core in biologically active oxindoles.

Both electron-withdrawing and electron-donating substituents are tolerated on the aromatic ring of the 2-bromoanilide substrate. Methoxy-substituted substrate **22** gave 5-methoxy-1,3,3-trimethyloxindole (**23**) in 80% yield. This cyclization of substrate **22** required 12 h, compared to the 4 h reaction time necessary for the unsubstituted **18**. Cyano-substituted substrate **24** also underwent clean, high-yielding (83%) conversion to 5-cyano-1,3,3-trimethyloxindole (**25**), but required 10 mol % palladium catalyst for complete conversion. These results contrast those for our *inter*molecular amide arylation, in which both electron rich and electron poor aromatic systems gave lower yields than those of electron neutral systems.

Attempted intramolecular arylation to generate six-membered rings has so far been unsuccessful. The reaction of *N*-(2-bromobenzyl)amide **26** under the conditions described above resulted in rapid consumption (<30 min) of the substrate but provided only 5% yield of the isoquinolinone product **27** (eq 3). *N*-Benzylacetamide **28** (7%) was also observed by GC. Variation of reaction temperature and concentration had little effect on the yield of **27**, and the fate of the remaining material has not been determined.



(3)

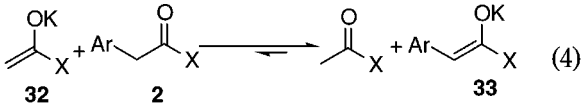
Discussion

We have now extended the palladium-catalyzed intermolecular arylation of ketone enolates developed by us[16] and Buchwald[17,18] to the arylation of amides. While little mechanistic work has been conducted on the amide arylation at this time, we propose that the reaction occurs by the catalytic cycle shown in Scheme 1 in analogy to proposed catalytic cycles for ketone arylation[16,17] and experimentally verified cycles in the related amination chemistry.[43−45] Oxidative addition of aryl halide to palladium(0) complex **29** would give arylpalladium halide complex **30**. Addition of the amide enolate would form arylpalladium enolate complex **31**, which could reductively eliminate product. By using the less acidic amide in place of ketones, the rates of palladium enolate formation, α-aryl amide formation by reductive elimination, and arene formation by *β*-hydride elimination from the palladium enolate will be altered. The cumulative effect of these changes on the relative rates for different steps of this cycle are difficult to predict. Thus, we conducted a series exploratory synthetic experiments to find conditions for the use of amides as substrates. Several aspects of the reaction conditions and types of reaction products warrant discussion.

First, the selection and quantity of base was crucial to obtaining good reaction yields. The higher pK_a of amides apparently makes the use of the strong base KHMDS necessary. Two equivalents of base are presumably required to deprotonate both the substrate amide and the more acidic monoarylamide product (eq 4). In the absence of a second equivalent of base, the concentration of enolate **32a** becomes low since the pK_a of the amide corresponding to enolate **32a** is approximately 9 pK_a units higher than that of the product amide corresponding to

(48) Kende, A. S.; Hodges, J. C. *Synth. Comm.* **1982**, *12*, 1−10 and references therein.

enolate **33a** (33.5 vs 24.5 in THF).[49] Thus, the slower arylation of product enolate **33a** becomes a competitive pathway when 1 equiv of base is used.



In contrast to the requirement of 2 equiv of base in the amide arylations, 1.2 equiv of base was used in the ketone arylations.[16,17] The pK_as of α-aryl ketones (**33b**) and alkyl ketones (**32b**) are lower and more similar to each other than those of the corresponding amides (pK_as of **32b** and **33b** = 24.7 and 17.65 in DMSO, respectively).[50] The greater selectivity for monoarylation of ketones may therefore be due to the higher relative concentration of **32b** in the equilibrium mixture compared to **32a**. It also is possible that **33b** undergoes arylation very slowly due to its more highly stabilized anion.

Enolate stability also seems to control reaction rates for the intramolecular arylations. The slower conversion of the phenyl-substituted substrate **14** (Table 5, entry 3) appears to result from the amide pK_a rather than from steric factors, considering that the disubstituted substrates **18** and **20** underwent ring closure at approximately the same rate as the unsubstituted substrates. Interestingly, the intramolecular arylation of an α-arylamide takes approximately twice as long as the intermolecular arylation of an α-arylamide. For example, **3d** was produced in approximately 4 h in the reaction of **1d** with 0.5 equiv of DMA, while cyclization of **14** required 10 h.

Attempts to arylate homologous amides such as DMP under our standard conditions resulted in the formation of trace amounts of desired α-arylamide plus numerous side products. Bulky monophosphines such as tri(*o*-tolyl)phosphine and tri(*tert*-butyl)phosphine gave high yields in the coupling of secondary amines and aryl halides.[43,45] Considering the similar steric demand and basicity of secondary amines and secondary amide enolates, one might have expected these ligands to provide improved, or at least competitive, yields in comparison to those obtained using chelating phosphines. However, tri(*o*-tolyl)phosphine gave a short-lived, inactive catalyst and tri(*tert*-butyl)phosphine gave low yields of α-aryl amides. Clearly our understanding of the factors governing this reaction at this time are not sufficient to rationally select or design ligands for this process.

Perhaps the most synthetically valuable amide arylation is the formation of 3,3-disubstituted oxindole cores. In contrast to the intermolecular amide arylation of α,α-disubstituted substrates, which occurred in low yields, the intramolecular arylation of α,α-disubstituted substrates occurred in the highest yields. The ability to cleanly produce 3,3-disubstituted oxindoles is significant due to the difficulty in preparing these structures by other methods and the importance of 3,3-disubstituted oxindoles as biologically active compounds. Examples of biologically active 3,3-disubstituted oxindoles that may be accessible by this methodology are horsfiline (**34**),[51] vasopressin binder **35**,[52] and compound **36** which has been proposed as a treatment of cognitive or neurological dysfunction (Figure 1).[53]

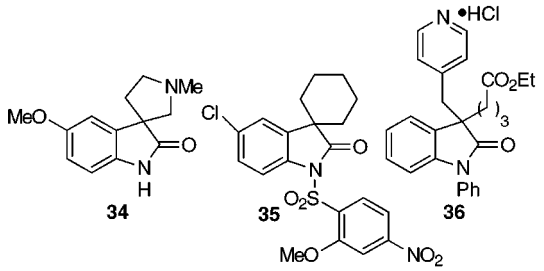


Figure 1. Examples of simple, biologically active compounds with 3,3′-disubstituted oxindole cores.

Conclusion

Palladium-catalyzed coupling of unfunctionalized aryl halides and DMA is a simple and efficient synthesis of α-arylamides. Unlike the analogous ketone arylation, amide arylation was less effective with homologous amides. Reactions of electron-deficient arenes gave products from nucleophilic attack by base, while electron-rich arenes gave moderate yields of arylamide. Although the intermolecular reaction was somewhat limited in scope, it still represents the most selective and general method yet reported for the direct arylation of alkylamides.

Intramolecular amide arylation of 2-haloanilides now represents a versatile methodology for preparing substituted oxindoles. The intramolecular reaction was significantly more tolerant of both electronic and steric modifications of the substrate than was the intermolecular reaction. Particularly significant was the ability to prepare 3,3-disubstituted oxindoles in high yield with complete regioselectivity. This methodology should prove useful in the synthesis of biologically interesting oxindole structures.

Experimental Section

General Considerations. All coupling reactions were set up in a nitrogen drybox and run in sealed reaction flasks under a nitrogen atmosphere. $Pd(dba)_2$ was prepared by a literature procedure.[54] BINAP, DPPF, tri(*o*-tolyl)phosphine, tri(*tert*-butyl)phosphine, KHMDS, NaO-*t*-Bu, aryl halides, *N*,*N*-dimethylamides, and NMP were obtained from commercial sources and used as received. THF was distilled from sodium/benzophenone. Anhydrous grade dioxane was purchased from Aldrich and was used and stored in a nitrogen glovebox. 2-Bromoanilide substrates for oxindole synthesis (**9**, **12**, **14**, **16**, **18**, **20**, **22**, **24**) were prepared from 2-bromoanilines by coupling to the appropriate acid chloride followed by *N*-alkylation of the resulting amide. 4-Amino-3-bromoanisole was prepared from 3-bromophenol by literature methods.[55,56] 4-Amino-3-bromobenzonitrile was prepared by the previously

(49) Krom, J. A.; Streitwieser, A. *J. Org. Chem.* **1996**, *61*, 6354−6359.
(50) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(51) Jossang, A.; Josssang, P.; Hadi, H. A.; Sévenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527−6530.
(52) Foulon, L.; Garcia, G.; Misato, D.; Roux, R.; Seradeil-Legal, C.; Valette, G.; Wagnon, J. WO 15, 051, 1993.
(53) Wilkerson, W.; Wilkie, E.; Richard, A.; Voss, M. E. WO 14, 085, 1993.
(54) Rettig, M. F.; Maitlis, P. M. *Inorg. Synth. 28*, 110−111.
(55) Hodgson, H. H.; Moore, F. H. *J. Chem. Soc.* **1926**, *128*, 155−161.
(56) Frank, H. R.; Fanta, P. E.; Tarbell, D. S. *J. Am. Chem. Soc.* **1948**, *70*, 2314−2320.

reported bromination of 4-aminobenzonitrile.[57] Naphthalene was used as a standard in quantitative GC experiments using response factors determined from isolated products. ^{1}H and ^{13}C NMR data are reported in ppm from TMS and were referenced to residual solvent protons or internal TMS. Low-resolution mass spectral data was obtained on a Hewlett-Packard 5890 series II gas chromatograph interfaced with a Hewlett-Packard 5989 A mass spectrometer. Electron impact ionization was used for all samples. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

General Procedure for Intermolecular Arylation of Amides. In the drybox, $Pd(dba)_2$ (57.5 mg, 0.10 mmol), BINAP (93.4 mg, 0.15 mmol), and KHMDS (796 mg, 4.00 mmol) were combined in a small round-bottom flask followed by addition of 18 mL of dioxane. Aryl halide (2.00 mmol) and amide (2.15 mmol) were then added, and the flask was sealed with a septum. The reaction flask was placed in an oil bath preheated to 100 °C. Once the aryl halide was completely consumed as determined by GC, the reaction mixture was poured into 50 mL of saturated NH_4Cl solution and extracted 3 × 30 mL with ether. The combined ether extracts were washed with brine (50 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude oil was flash chromatographed on silica gel. The product was eluted with a 15−45% solvent gradient of ethyl acetate in hexanes (200 mL, 15% increments).

***N,N*-Dimethyl-2-(2-naphthyl)acetamide (2b).** 2-Bromonaphthalene (420 mg, 2.03 mmol) was coupled with DMA (0.20 mL, 2.15 mmol) at 100 °C for 2 h to give 305 mg (70%) of **2b** as a tan solid after chromatography. Recrystallization from hexanes gave pale yellow needles (mp 93.5−94 °C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.82−7.77 (m, 3H), 7.69 (s, 1H), 7.46−7.26 (m, 3H), 3.88 (s, 2H), 3.01 (s, 3H), 2.99 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 170.9, 133.5, 132.6, 132.3, 128.3, 127.6, 127.5, 127.1, 127.0, 126.0, 125.6, 41.2, 37.7, 35.6 ppm. FTIR (KBr pellet): 1647 cm^{-1}. Anal. Calcd for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.56. Found: C, 78.69; H, 6.94; N, 6.39.

***N,N*-Dimethyl-2,2-di(2-naphthyl)acetamide (3b).** This material was isolated from an experiment conducted as described above for **2b**, but using only 3.00 mmol of KHMDS. After chromatography, **3b** (82 mg, 24%) was recovered as a white solid (mp 159−161 °C). ^{1}H NMR (500 MHz, $CDCl_3$): 7.81−7.78 (m, 6 H), 7.72 (s, 2H), 7.45−7.42 (m, 6 H), 5.55 (s, 1H), 3.08 (s, 3H), 3.06 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 171.2, 137.0, 133.4, 132.5, 128.2, 127.9, 127.6, 127.5, 127.4, 126.0, 125.8, 55.1, 37.7, 36.1 ppm. MS (EI): 339 *m*/*z*.

***N,N*-Dimethyl-2-(4-biphenyl)acetamide (2c).**[49] 4-Bromobiphenyl (470 mg, 2.02 mmol) was coupled with DMA (0.20 mL, 2.15 mmol) at 100 °C for 2 h to give 319 mg (66%) of **2c** as a tan solid after chromatography. Recrystallization from hexanes gave fine, colorless needles (mp 88−89 °C, lit. mp 88−89 °C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.59−7.53 (m,4H), 7.43 (t, J = 7.50 Hz, 2H), 7.36−7.32 (m, 3H), 3.75 (s, 2H), 3.03 (s, 3H), 2.99 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 170.9, 140.8, 139.6, 134.1, 129.2, 128.7, 127.3, 127.2, 127.0, 40.6, 37.7, 35.6 ppm. FTIR (KBr pellet): 1633 cm^{-1}. Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.03; H, 7.01; N, 5.71.

***N,N*-Dimethyl-2-(4-tolyl)acetamide (2d).**[23] 4-Bromotoluene (0.25 mL, 2.04 mmol) and DMA (0.20 mL, 2.15 mmol) were heated at 100 °C for 1.5 h to give 271 mg (75%) of **2d** as a yellow oil after chromatography. Recrystallization from hexanes gave colorless needles which melted at approximately room temperature (lit. mp 24−25 °C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.13 (brs, 4H), 3.67 (s, 2H), 2.98 (s, 3H), 2.95 (s, 3H), 2.32 (s,3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 171.2, 136.1, 131.9, 129.2, 128.5, 40.5, 37.6, 35.5, 20.9 ppm. FTIR (KBr pellet): 1640 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.80; H, 8.63; N, 7.88.

***N,N*-Dimethyl-2,2-di(4-tolyl)acetamide (3d).**[23] 4-Bromotoluene (0.25 mL, 2.04 mmol) was coupled with DMA (0.93 mL, 1.00 mmol) to give **2d** (85 mg, 24%) and **3d** (139 mg, 52%) as a pale yellow, waxy solid after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): 7.12 (brs, 8H), 5.14 (s, 1H), 2.99 (s, 3H), 2.98 (s, 3H), 2.30 (s, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 171.9, 136.7, 136.3, 129.0, 129.0, 53.9, 37.4, 35.9, 2089 ppm. MS (EI): 267 *m*/*z*.

***N,N*-Dimethyl-2-(2-tolyl)acetamide (2e).**[58] 2-Bromotoluene (0.24 mL, 2.00 mmol) and DMA (0.20 mL, 2.15 mmol) were heated at 100 °C for 1.5 h to give 254 mg (72%) of **2e** as a pale yellow solid after chromatography. Recrystallization from hexanes gave fine, colorless needles (mp 53−54 °C, Lit mp 54−55 °C). ^{1}H NMR (300 MHz, $CDCl_3$): 7.16−7.11 (m, 4H), 3.66 (s, 2H), 2.99 (s, 3H), 2.98 (s, 3H), 2.27 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 170.8, 136.3, 133.7, 130.1, 128.6, 126.7, 126.0, 38.4, 37.4, 35.4, 19.5 ppm. FTIR (KBr pellet): 1640 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.51; H, 8.37; N, 7.95.

***N,N*-Dimethyl-2-(4-methoxyphenyl)acetamide (2f).**[23] 4-Bromoanisole (0.24 mL, 0.20 mmol) was coupled with DMA (0.20 mL, 2.15 mmol) at 100 °C for 4 h to give 186 mg (50%) of **2f** as a pale yellow oil after chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): 7.17 (d, J = 8.55 Hz, 2H), 6.85 (d, J = 8.58 Hz, 2H), 3.78 (s, 3H), 3.65 (s, 3H), 2.99 (s, 3H), 2.95 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 171.3, 158.3, 129.7, 127.0, 114.0, 55.3, 40.0, 37.6, 35.5 ppm. FTIR (neat, NaCl plate): 1642 cm^{-1}.

1-Methyl-3-phenylpyrrolidin-2-one (7).[21] Bromobenzene (0.21 mL, 1.99 mmol) and NMP (0.21 mL, 2.19 mmol) were heated at 100 °C for 3 h to give 172 mg (49%) of **7** as a tan solid after chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): 7.34−7.29 (m, 2H), 7.27−7.22 (m, 3H), 3.64 (t, J = 8.77 Hz, 1H), 3.48−3.38 (m, 2H), 2.93 (s, 3H), 2.54−2.48 (m, 1H), 2.15−2.07 (m, 1H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 174.8, 139.9, 128.6, 127.8, 126.8, 47.4, 47.6, 30.0, 27.9 ppm. FTIR (KBr pellet): 1682 cm^{-1}.

General Procedure for Oxindole Synthesis. In the drybox, $Pd(dba)_2$ (57.5 mg, 0.10 mmol), BINAP (93.4 mg, 0.15 mmol), and sodium *tert*-butoxide (288 mg, 3.00 mmol) were combined in a small round-bottom flask. Dioxane (18 mL) was added, and the flask was sealed with a septum. After removing the flask from the box, 2-bromoanilide (2.00 mmol) was added. The flask was placed in an oil bath at 100 °C until the starting material was consumed as determined by GC. The reaction was poured into 50 mL of saturated NH_4Cl solution and extracted (3 × 30 mL) with ether. The combined ether extracts were washed with brine (50 mL), dried over $MgSO_4$, and filtered. The solvent was removed under vacuum, and the resulting crude product was flash chromatographed on silica gel. The product was eluted with 15% ethyl acetate in hexanes.

1-Benzyloxindole (10).[34,38] Heating of 2-bromo-*N*-benzylacetanilide **9** (609 mg, 2.00 mmol) at 100 °C for 3 h gave 297 mg (66%) of **10** as a pale yellow oil after chromatography. Recrystallization from hexanes gave a pale yellow needles (mp 66.5−67, lit. mp 50−52,[34] 66−67,[59] 76−77 °C[38]). ^{1}H NMR (500 MHz, $CDCl_3$): 7.33−7.34 (m, 3H), 7.26−7.30 (m, 2H), 7.19 (t, J = 7.75, 7.84 Hz, 1H), 7.03 (t, J = 7.12, 7.31 Hz, 1H), 6.75 (d, J = 7.55 Hz, 1H), 4.94 (s, 2H), 3.65 (s, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 175.3, 144.4, 135.9, 128.8, 127.9, 127.7, 127.4, 124.5, 124.5, 122.5, 109.2, 43.8, 35.8 ppm. FTIR (neat, NaCl plate): 1717 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.68; H, 5.87; N, 6.27. Found: C, 80.59; H, 5.92; N, 6.16.

1-Methyloxindole (13).[34,60,61] Heating 2-bromo-*N*-methylacetanilide **12** (466 mg, 2.04 mmol) at 100 °C for 2 h gave 186 mg (62%) of **13** as a pale yellow oil after chromatography. Recrystallization from hexane gave pale orange needles (mp

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86.5−87 °C, lit. mp 86−87 °C). ^{1}H NMR (500 MHz, $CDCl_3$): 7.25−7.20 (m, 2H), 7.02 (t, J = 7.66, 7.25 Hz, 1H), 6.80 (d, J = 8.05 Hz, 1H), 3.50 (s, 2H), 3.19 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 175.0, 145.2, 127.8, 124.5, 124.3, 122.3, 108.0, 35.7, 26.1 ppm. FTIR (neat, NaCl plate): 1701 cm^{-1}. Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.51. Found: C, 73.52; H, 6.01; N, 9.25.

1-Methyl-3-phenyloxindole (15).[62] Heating of *N*-(2-bromophenyl)-*N*-methyl-2-phenylacetamide (615 mg, 2.02 mmol) at 100 °C for 10 h gave **15** (296 mg, 66%) as pale yellow needles after chromatography. Recrystallization from hexanes gave colorless, fine needles (mp 119.5−120 °C, lit. mp 119−120 °C). ^{1}H NMR (500 MHz, $CDCl_3$): 7.36−7.32 (m, 3H), 7.30−7.29 (m, 1H), 7.222−7.21 (m, 2H), 7.18 (d, J = 7.35 Hz, 1H), 7.07 (t, J = 7.47 Hz, 1H), 6.91 (d, J = 7.94 Hz, 1H), 4.62 (s, 1H), 3.26 (s, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 176.0, 144.5, 136.6, 128.8, 128.4, 127.5, 125.0, 122.7, 108.1, 52.0, 26.4 ppm. FTIR (KBr pellet) 1705 cm^{-1}. Anal. Calcd for $C_{15}H_{13}NO$: C, 80.68; H, 5.87; N, 6.27. Found: C, 80.52; H, 5.82; N, 6.05.

1,3-Dimethyloxindole (17).[63] Heating of *N*-(2-bromophenyl)-*N*-methylpropionamide **16** (495 mg, 2.04 mmol) at 100 °C for 1.5 h gave **17** (165 mg, 50%) as a yellow oil after chromatography. Recrystallization from hexanes gave a pale yellow crystalline material (mp 55−56 °C, lit. mp 54−55 °C). ^{1}H NMR (500 MHz, $CDCl_3$): 7.30 (t, J = 7.83 Hz, 1H), 7.27 (d, J = 6.72 Hz, 1H), 7.09 (t, J = 7.52 Hz, 1H), 6.85 (d, J = 7.78 Hz, 1H), 3.45 (q, J = 7.54 Hz, 1H), 3.23 (s, 3H), 1.50 (d, J = 7.93, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 178.6, 143.9, 130.6, 127.8, 123.4, 122.3, 107.9, 40.5, 26.1, 15.3 ppm. FTIR (KBr pellet): 1712 cm^{-1}. Anal. Calcd for $C_{10}H_{11}NO$: C, 74.50; H, 6.88; N, 8.69. Found: C, 74.20; H, 6.72; N, 8.39.

1,3,3-Trimethyloxindole (19).[38,63] Heating of *N*-(2-bromophenyl)-*N*-methylisobutyramide (524 mg, 2.05 mmol) at 100 °C for 3 h gave **19** (286 mg, 80%) as a yellow oil after chromatography. Recrystallization from hexanes gave pale yellow needles (mp 54−55 °C, lit. mp 49−50 °C[63]). ^{1}H NMR (500 MHz, $CDCl_3$): 7.24−7.28 (m, 1H), 7.20 (d, J = 7.37 Hz, 1H), 7.06 (t, J = 7.69, 7.23 Hz, 1H), 6.84 (d, J = 7.77 Hz, 1H), 3.22 (s, 3H), 1.33 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): 181.3, 142.6, 135.8, 127.6, 122.4, 122.2, 107.9, 44.1, 26.1, 24.3 ppm. FTIR (neat, NaCl plate): 1710, cm^{-1}. Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.30; H, 7.29; N, 7.83.

1-Methyl-3-spirocyclohexyloxindole (21).[64] Heating of *N*-(2-bromophenyl)-*N*-methylcyclohexanecarboxamide **20** (595 mg, 2.01 mmol) at 100 °C for 4 h gave 356 mg (82%) of **21** as a viscous, pale yellow oil after chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): 7.46 (d, J = 7.23, 1H0, 7.28 (t, J = 7.70 Hz, 1H), 7.49 (t, J = 7.56 Hz, 1 H), 6.85 (d, J = 7.73 Hz, 1H), 3.21 (s, 3H), 1.98−1.92 (m, 2H), 1.88−1.81 (m, 2H), 1.79−1.71 (m, 4H), 1.69−1.61 (m, 1H), 1.59−1.55 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 180.6, 142.8, 135.4, 127.4, 123.8, 121.9, 107.8, 47.4, 33.0, 26.1, 25.2, 21.2 ppm. FTIR (neat, NaCl plate): 1711 cm^{-1}. Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.90; N, 6.50. Found: C, 77.87; H, 7.83; N, 6.35.

5-Methoxy-1,3,3-trimethyloxindole (23).[65] Heating of *N*-(2-bromo-4-methoxyphenyl)-*N*-methylisobutyramide **22** (583 mg, 2.04 mmol) at 100 °C for 12 h gave 350 mg (84%) of **21** as a viscous, pale yellow oil after chromatography. ^{1}H NMR (500 MHz, $CDCl_3$): 6.84 (d, J = 2.33 Hz, 1H), 6.80 (dd, J = 2.22, 7.43 Hz, 1H), 6.76 (d, J = 8.71 Hz, 1H), 3.81 (s, 3H), 3.20 (s, 3H), 1.37 (s, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 183.9, 156.0, 137.1, 136.0, 111.5, 109.9, 108.1, 55.7, 44.5, 26.2, 24.3 ppm. FTIR (neat, NaCl disk): 1709 cm^{-1}.

5-Cyano-1,3,3-trimethyloxindole (25). Heating of *N*-(2-bromo-4-cyanophenyl)-*N*-methylisobutyramide **24** (567 mg, 2.02 mmol) at 100 °C for 4 h with 10 mol % of $Pd(dba)_2$ and 15 mol % BINAP gave 338 mg (84%) of **21** as an orange solid after chromatography. Recrystallization from hexanes gave light orange needles (mp 138−139 °C). ^{1}H NMR (500 MHz, $CDCl_3$): 7.61 (dd, J = 1.82, 8.08 Hz, 1H), 7.46 (d, J = 1.18 Hz, 1H), 6.92 (d, J = 8.08 Hz, 1H), 3.26 (s, 3H), 1.40 (s, 6H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): 180.8, 146.5, 136.7, 133.1, 125.7, 119.2, 108.4, 105.6, 44.0, 26.4, 24.1 ppm. FTIR (KBr pellet): 2218, 1716 cm^{-1}. Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04; N, 13.99. Found: C, 72.14; H, 5.94; N, 13.61.

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