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Transition-Metal-Free Synthesis of Oxindoles by Potassium *tert*-Butoxide-Promoted Intramolecular α-Arylation

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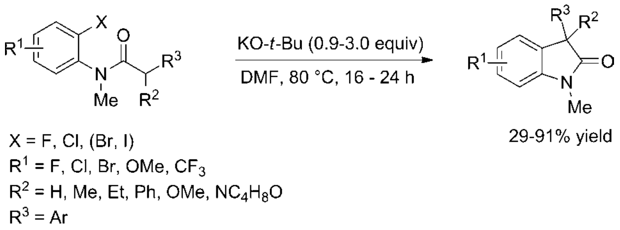
ABSTRACT



Potassium *tert*-butoxide-mediated intramolecular α-arylations of fluoro- and chloro-substituted anilides provide oxindoles in DMF at 80 °C. In this manner, diversely substituted products have been obtained in moderate to high yields.

Oxindoles represent an important heterocyclic scaffold that can be found in many natural products.[1] Several of them show significant bioactivities.[2] In the past decades, a wide range of synthetic methods have been developed, giving access to oxindoles with a variety of functionalities. In particular, palladium-catalyzed cyclization reactions, including Mizoroki–Heck couplings,[3] arylations,[4] and alkylations[5] were shown to be useful. Metal-catalyzed oxindole syntheses by direct C_{sp2}–H/C_{sp3}–H couplings have also been reported.[6] A few other methods are known,[7] and most of them require the presence of a palladium complex in combination with a suitable ligand.[8] Recently, transition-metal-free processes for the formation of C–C, C–N, C–O, and C–S bonds have gained importance.[9] Our interest has been focused on base-promoted arylation reactions,[10] and in particular, on intramolecular

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(1) For reviews on total syntheses of oxindole natural products, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003. For a review on transition-metal-mediated routes to 3,3-disubstituted oxindoles, see: (c) Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, *34*, 6821. For a review on 3-alkenyloxindoles, see: (d) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527.

(2) For a review on pyrrolidinylspirooxindoles, see: Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748.

(3) Dounay, A. B.; Hatanaka, K.; Kodanko, J. J.; Oestreich, M.; Overman, L. E.; Pfeifer, L. A.; Weis, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 6261 and references cited therein.

(4) (a) Shaughnessy, K. H.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1998**, *63*, 6546. For asymmetric arylations, see: (b) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402. (c) Kündig, E. P.; Seidel, T. M.; Jia, Y.-X.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 8484. For a recent example, see: (d) Wu, L.; Falivene, L.; Drinkel, E.; Grant, S.; Linden, A.; Cavallo, L.; Dorta, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 2870.

(5) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

(6) For a Pd-catalyzed C–H Ar–H coupling, see: (a) Jia, Y.-K.; Kündig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. For Cu-promoted C–H Ar–H couplings, see: (b) Perry, A.; Taylor, R. J. K. *Chem. Commun.* **2009**, 3249.

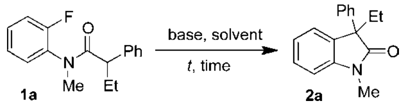
(7) For an aryl radical cylization, see: (a) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977. (b) Khan, T. A.; Tripoli, R.; Crawford, J. J.; Martin, C. G.; Murphy, J. A. *Org. Lett.* **2003**, *16*, 2971. (c) Lidong, C.; Chaozhong, L. *Chin. J. Chem.* **2010**, *28*, 1640. For a $PhI(OAc)_2/I_2$-promoted cyclization, see: (d) Wei, H.-L.; Piou, T.; Dufour, J.; Neuville, L.; Zhu, J. *Org. Lett.* **2011**, *13*, 2244. For the synthesis of nitrooxindoles by vicarious nucleophilic substitution (VNS), see: (e) Makosza, M.; Paszewski, M. *Synthesis* **2002**, 2203. (f) Makosza, M. *Pure Appl. Chem.* **1997**, *69*, 559.

(8) For some selected asymmetric examples, see: (a) Franckevicius, V.; Cuthbertson, J. D.; Pickworth, M.; Pugh, D. S.; Taylor, R. J. K. *Org. Lett.* **2011**, *13*, 4264. (b) Liu, L.; Ishida, N.; Ashida, S.; Murakami, M. *Org. Lett.* **2011**, *13*, 1666. (c) Luan, X.; Wu, L.; Drinkel, E.; Mariz, R.; Gatti, M.; Dorta, R. *Org. Lett.* **2010**, *12*, 1912. (d) Jia, Y.-X.; Katajev, D.; Bernardinelli, G.; Seidel, T. M.; Kündig, E. P. *Chem.—Eur. J.* **2010**, *16*, 6300. (e) Ackermann, L.; Vicente, R.; Hofmann, N. *Org. Lett.* **2009**, *11*, 4274. (f) Würtz, S.; Lohre, C.; Fröhlich, R.; Bergander, K.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 8344.

(9) For a review on transition-metal-free coupling reactions of aryl halides, see: (a) Shirakawa, E.; Hayashi, R. *Chem. Lett.* **2012**, *41*, 130. For an overview of *tert*-butoxide mediated reactions, see: (b) Yanigasawa, S.; Itami, K. *ChemCatChem* **2011**, *3*, 827. (c) Wang, Y. *Synlett* **2011**, 2901.

10.1021/ol301704z

Table 1. Optimization of the Reaction Conditions



entry	base (equiv)	solvent	temp (°C)	time (h)	yield[a] (%)
1	KOH (3.0)	DMSO	80	24	traces
2	KO-*t*-Bu (3.0)	DMSO	80	24	23
3	KO-*t*-Bu (3.0)	dioxane	80	24	s.m.
4	KO-*t*-Bu (3.0)	toluene	80	24	s.m.
5	KO-*t*-Bu (3.0)	DMA	80	24	65
6	KO-*t*-Bu (3.0)	MeCN	80	24	s.m.
7	KO-*t*-Bu (3.0)	DMF	80	24	78
8	KOH (3.0)	DMF	80	24	s.m.
9	NaO-*t*-Bu (3.0)	DMF	80	24	47
10	LiO-*t*-Bu (3.0)	DMF	80	24	s.m.
11	NaOEt (3.0)	DMF	80	24	s.m.
12	LiOH (3.0)	DMF	80	24	s.m.
13	KO-*t*-Bu (3.0)	DMF	60	24	70
14	KO-*t*-Bu (3.0)	DMF	40	24	59
15	KO-*t*-Bu (2.0)	DMF	80	24	82
16	KO-*t*-Bu (1.5)	DMF	80	24	83
17	KO-*t*-Bu (1.2)	DMF	80	24	80
18	KO-*t*-Bu (1.5)	DMF	80	16	82
19	KO-*t*-Bu (1.5)	DMF	80	14	78

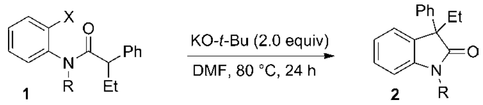
[a] After column chromatography; s.m. = starting material.

N-arylations for the synthesis of benzimidazol-2-ones[11] and *N*-substituted phenoxazines.[12] In this context, we now developed a transition-metal-free protocol for the intramolecular cyclization of anilides to generate substituted oxindoles. It takes place in the presence of simple KO-*t*-Bu in DMF at 80 °C and is applicable to a wide range of functionalized substrates.

Fluoro-substituted anilide **1a** was chosen as model substrate for the initially attempted intramolecular α-arylation using the superbasic medium KOH/DMSO (Table 1, entry 1).[13] However, to our disappointment, only traces of the cyclized product were formed. Most of the starting material could be recovered after 24 h at 80 °C. When the base was changed to KO-*t*-Bu, the desired oxindole **2a** was obtained in 23% yield (entry 2). Encouraged by this result, various base/solvent combinations were screened (entries 3–12), and it was found that KO-*t*-Bu in DMF gave the best result. After a reaction time of 24 h at 80 °C, oxindole **2a** was obtained in 78% yield (entry 7). Among the other solvents tested, only DMA gave a comparable result (entry 5). All other solvents proved to be ineffective, and in most cases, no conversion of the starting material was observed (entries 3, 4, and 6).

To further optimize the reaction parameters, the base quantity, reaction time, and temperature were varied. Lowering the temperature led to a decrease in conversion and, thus, to lower yields of oxindole **2a** (entries 13 and 14). By using less base the yield of **2a** could be slightly increased, and the best result was obtained with 1.5 equiv of KO-*t*-Bu (83%, entry 16). A similar yield was obtained when the reaction time was shortened from 24 to 16 h (entry 18).

Table 2. Screening of Halo- and *N*-Substituents



entry	substrate	X	R	product	yield of **2**[a] (%)
1	**1b**	Cl	Me	**2a**	76[b]
2	**1c**	Br	Me	**2a**	55
3	**1d**	I	Me	**2a**	44[c]
4	**1e**	F	H	**2b**	
5	**1f**	F	Ts	**2c**	
6	**1g**	F	Bn	**2d**	

[a] After column chromatography. [b] Use of 1.5 equiv of KO*t*-Bu; 16 h reaction time. [c] Use of 3.0 equiv of KO-*t*-Bu at 100 °C.

Using the chloro, bromo, and iodo analogues of **1a** also yielded oxindole **2a** (Table 2, entries 1–3). Hence, a comparable yield (76%) was obtained when chloro-substituted anilide **1b** was applied. In the reactions of the bromo- and iodo-substituted anilides **1c** and **1d**, lower yields of **2a** (55% and 44%, respectively) were observed. No conversion occurred in the attempt to cyclize NH-amide **1e** (entry 4). *N*-Tosylanilide **1f** decomposed upon treatment with KO-*t*-Bu in DMF under the given reaction conditions (entry 5),[14] and *N*-benzyl derivative **1g** remained uncyclized because of the formation of a rather stable anion formed by a competing deprotonation at the benzyl group (enty 6). Thus, none of those starting materials (**1e**–**g**) led to the corresponding products (**2b**–**d**).

To extend the substrate scope of the cyclization reaction, various anilides were synthesized[15] and submitted to the KO-*t*-Bu/DMF system. The results of this study are shown in Table 3. Varying the α-substituent from ethyl to methyl and phenyl led to full substrate conversions providing products **2e** and **2f** in high yields (entries 1 and 2). When anilide **1k** having only a single phenyl substituent in the α-position was applied, the use of less base (0.9 equiv) increased the yield and the corresponding product **2g** was obtained in 61% (entry 4). α-Heteroatom-substituted anilides **1l** and **1m** gave oxindoles **2h** and **2i** in moderate yields of 35 and 29%, respectively. In addition, substrates with various aryl substituents were tested, and in most cases, high yields of the corresponding oxindoles were achieved (entries 7–18). In general, anilides with both

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(10) (a) Yuan, Y.; Thomé, I.; Kim, S. H.; Chen, D.; Beyer, A.; Bonnamour, J.; Zuidema, E.; Chang, S.; Bolm, C. *Adv. Synth. Catal.* **2010**, *352*, 2892. For a related study, see: (b) Cano, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2011**, *76*, 654.

(11) Beyer, A.; Reucher, C. M. M.; Bolm, C. *Org. Lett.* **2011**, *13*, 2876.

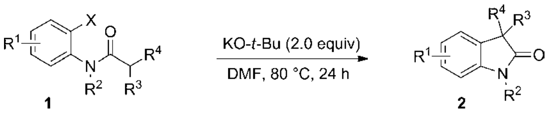
(12) Thomé, I.; Bolm, C. *Org. Lett.* **2012**, *14*, 1892.

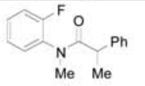
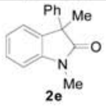
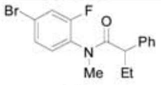
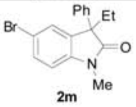
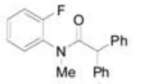
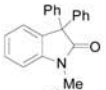
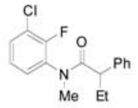
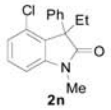
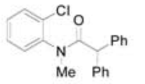
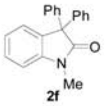
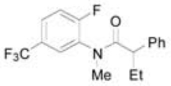
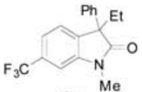
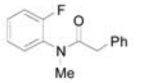
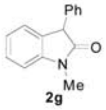
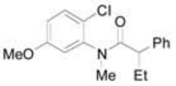
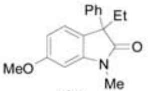
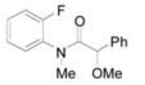
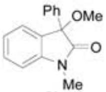
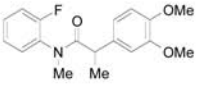
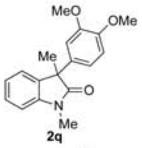
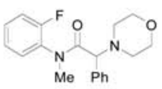
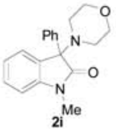
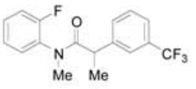
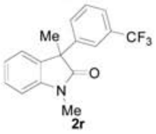
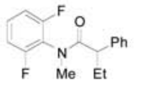
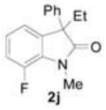
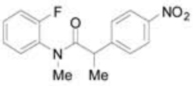
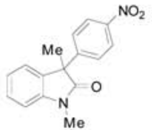
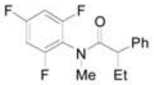
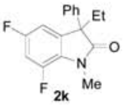
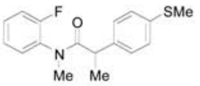
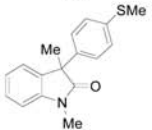
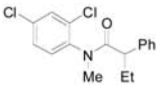
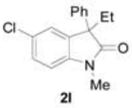
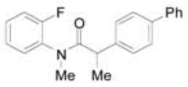
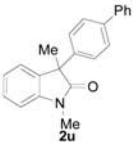
(13) KOH in DMSO is known as a "super base" and has proven to be effective in arylation reactions, as shown in ref 10.

(14) The formation of *N*-(2-fluorophenyl)-4-methylbenzenesulfonamide was observed.

(15) For more details on the synthesis of starting materials, see the Supporting Information.

Table 3. Scope of the Intramolecular α-Arylation for the Synthesis of Oxindoles



entry	substrate	product	yield %[a]	entry	substrate	product	yield %[a]
1	 **1h**	 **2e**	77	10	 **1q**	 **2m**	59[e]
2	 **1i**	 **2f**	91[b]	11	 **1r**	 **2n**	54
3	 **1j**	 **2f**	89	12	 **1s**	 **2o**	77
4	 **1k**	 **2g**	61[c]	13	 **1t**	 **2p**	54
5	 **1l**	 **2h**	35[b]	14	 **1u**	 **2q**	76[b]
6	 **1m**	 **2i**	29[b]	15	 **1v**	 **2r**	86[b]
7	 **1n**	 **2j**	74[b]	16	 **1w**	 **2s**	29[b]
8	 **1o**	 **2k**	73[d]	17	 **1x**	 **2t**	82[b]
9	 **1p**	 **2l**	47	18	 **1y**	 **2u**	91[f]

[a] After column chromatography. [b] Use of 1.5 equiv of KO-*t*-Bu; 16 h reaction time. [c] Use of 0.9 equiv of KO-*t*-Bu; 24 h reaction time. [d] Use of 1.2 equiv of KO-*t*-Bu; 16 h reaction time. [e] Use of 1.5 equiv of KO-*t*-Bu; 24 h reaction time. [f] Use of 2.0 equiv of KO-*t*-Bu; 20 h reaction time.

electron-withdrawing and -donating groups on the nitrogen-substituted aryl ring afforded satisfactory yields of cylized products (entries 7–13). In this series, the highest yield was obtained in a reaction of anilide **1s** bearing a trifluoromethyl group in the 4-position to the fluoro substituent. Here, the corresponding oxindole **2o** was isolated in 77% yield (entry 12). Cyclization reactions of compounds with non-hydrogen substituents on the phenyl ring in α-position to the amide carbonyl gave good to excellent yields as well (entries 14–18). The best result was observed in the conversion of 4-phenyl-substituted anilide **1y**, which provided oxindole **2u** in 91% yield (entry 18). One exception was 4-nitro-substituted anilide **1w**, which gave oxindole **2s** in only 29% yield (entry 16).

Attempted reactions of the substrates **3a**–**f** (Figure 1) revealed the limitations of the method. First, it became apparent that the aryl substituent at the α-position of the amide moiety was crucial. In its absence, no cyclization occurred as seen, for example, in the attempted reaction of cyclohexyl derivative **3a**. Analogous observations were made when **3b**–**f** were treated with KO-*t*-Bu in DMF. In addition, no cyclizations occurred.

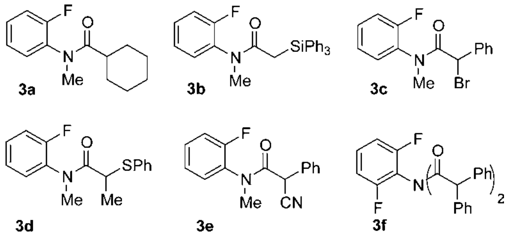


Figure 1. Unreactive substrates in the intramolecular α-arylation with KO-*t*-Bu in DMF.

We assume that for most substrates the reactions follow an S_N-Ar mechanism. This hypothesis is substantiated by the following observations: The highest yields were obtained with fluoro-substituted anilides, and the leaving group activity decreases in the following order: F > Cl > Br ≈ I.[16] In the cases of the fluoro-substituted anilides, the formation of arynes was considered unlikely because *N*-(3-fluorophenyl)-*N*-methyl-2-phenylbutanamide (the 3-fluoro-substituted isomer of **1a**) did not give any oxindole **2a** when treated under the standard reaction conditions. Instead, the starting material was almost completely recovered. Furthermore, the successful cyclization of **1r** to give **2n** (Table 3, entry 11) excluded the involvement of an aryne. For other substrates with different substituents, however, alternative or even more than one mechanism could be relevant. Thus, the possible intermediacy of aryl radicals (formed by electron transfer) should also not be ruled out.[17,18] Support for this mechanism stems from a reaction with an iodo-substituted anilide **1d**, which upon treatment with KO-*t*-Bu (3.0 equiv) in DMF at 40 °C provided a mixture of oxindole **2a** and dehalogenated starting material [*N*-methyl-2,*N*-diphenylbutanamide; **1** with X = H and R = Me (Table 1)]. This result could be interpreted as evidence for the intermediacy of radicals or arynes, and perhaps those were generally the predominant intermediates when starting from iodo-substituted substrates.

In summary, we have developed a protocol for the transition-metal-free synthesis of oxindoles starting from readily available anilides. The cylization reactions are promoted by KO-*t*-Bu and occur in DMF at 80 °C. Many functional groups are tolerated, giving access to a wide range of synthetically relevant heterocycles.

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Supporting Information Available. Experimental procedures, full characterization of new products, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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[16] For kinetic studies on nucleophilic aromatic substitution reactions with carbanions and nitranions in DMSO, see: (a) Bordwell, F. G.; Hughes, D. L. *J. Am. Chem. Soc.* **1986**, *108*, 5991. For a general review on equilibrium acidities in DMSO, see: (b) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456. For a review on nucleophilic substitutions of compounds with nitro, fluoro and chloro groups, see: (c) Vlasov, V. M. *Russ. Chem. Rev.* **2003**, *72*, 681.

[17] For a comment on radical and electron transfer reactions, see: Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5018.

[18] For nucleophilic substitution reactions involving electron transfer, see: (a) Bunnett, J. F. *Acc. Chem. Res.* **1978**, *11*, 413. (b) Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. *Chem. Rev.* **2003**, *103*, 71.