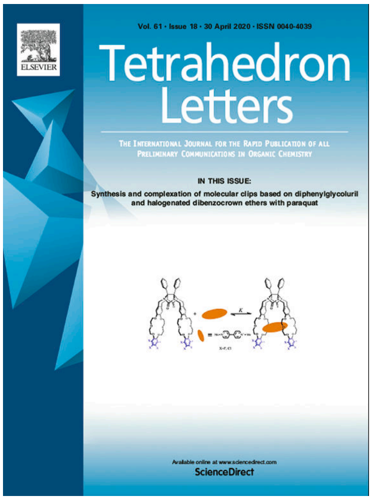

Ionic Liquid Catalyzed Ritter Reaction/Pd-Catalyzed Directed *Ortho*-Arylation; Facile Access to Diverse Libraries of Biaryl-amides from Aryl-nitriles

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PII: S0040-4039(20)31046-7
DOI: https://doi.org/10.1016/j.tetlet.2020.152553
Reference: TETL 152553

To appear in: *Tetrahedron Letters*

Received Date: 7 August 2020
Revised Date: 3 October 2020
Accepted Date: 8 October 2020

Please cite this article as: Sutar, S.M., Savanur, H.M., Kalkhambkar, R.G., Borosky, G.L., Aridoss, G., Laali, K.K., Ionic Liquid Catalyzed Ritter Reaction/Pd-Catalyzed Directed *Ortho*-Arylation; Facile Access to Diverse Libraries of Biaryl-amides from Aryl-nitriles, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152553

Ionic Liquid Catalyzed Ritter Reaction/Pd-Catalyzed Directed *Ortho*-Arylation; Facile Access to Diverse Libraries of Biaryl-amides from Aryl-nitriles

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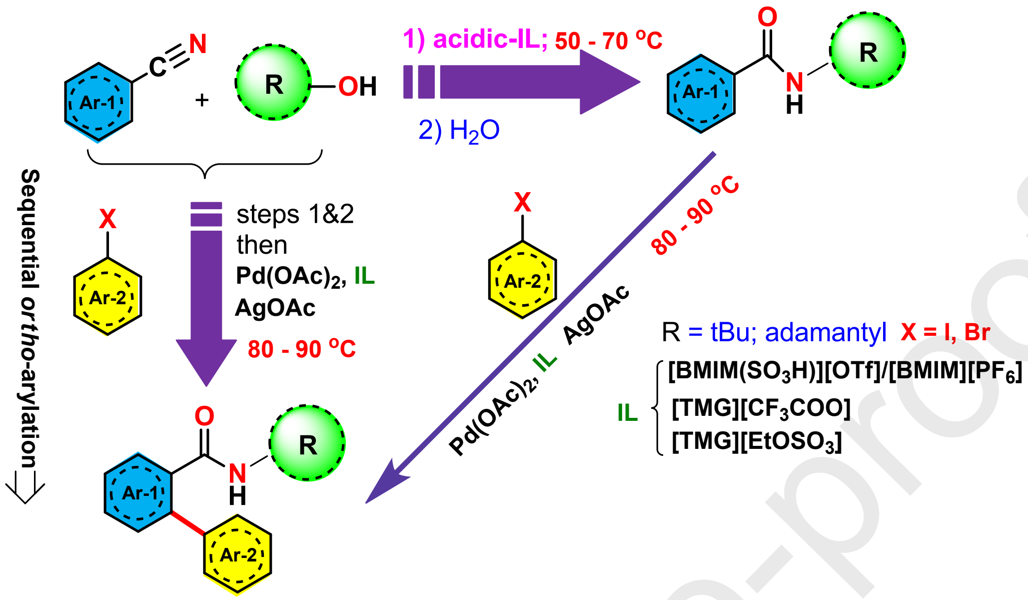
E-mail: Kenneth.Laali@UNF.edu (K.K. Laali) (senior corresponding author)

Graphical Abstract



Abstract

Diverse libraries of biaryl-amides bearing *N-t*-butyl and *N*-adamantyl groups were synthesized in two steps by the Ritter reaction of aryl-nitriles, using tBuOH and AdaOH as carbocation precursors, and employing [BMIM(SO_3H)][OTf] (neat or with [BMIM][PF_6] as co-solvent) or tetramethyl guanidinium-ILs [TMG][X] (X = CF_3COO, EtOSO_3) as dual catalyst/solvent, followed by a Pd-catalyzed directed regioselective *ortho*-C-H arylation of the Ritter amides with Ar-X (X = I, Cl). The feasibility to perform the two-steps in sequence is also demonstrated, and potential for recycling/reuse of the ILs is also shown. Preference for [Pd] coordination to the amide carbonyl versus amide nitrogen is borne out by DFT computations.

Keywords: Biarylamides from arylnitriles; Ritter reaction; Pd-catalyzed directed *ortho*-arylation; imidazolium and guanidiniumILs

Functionalized biaryls are high value small molecules that serve as building blocks in medicinal and natural products chemistry as well as in material science.[1,2] There is a vast literature on transition-metal catalyzed cross-coupling reactions in which Ar-M couples to ArX to yield biaryls.[1]Another strategy for the synthesis of biaryls is direct arylation involving coupling of ArH to ArX.[1-3]

Metal-mediated directed C-H arylation enables the biaryl moiety to be assembled in a regioselective manner by introducing the aryl moiety selectively *ortho* to a directing substituent to which the metal pre-coordinates. Among various directing groups that have been employed, the amide functionality has played an important role.[4-8] Apart from simple primary benzamides and aryl-acetamides,[4-5] bidentate versions of sec-benzamides in which -CO-N(H)-*Ph-NHR* or -CO-N(H*)-Ph-pyrazole* moieties provide additional metal coordination sites have also been utilized.[6-8] Reactions were catalyzed by $Pd(OAc)_2$ with Ag or Mn salts as additive in acetic acid or toluene as solvent at high temperatures. The PIP (2-pyridylisopropyl) group in -CO-N(H)-*PIP* acted as a removable auxiliary for directed *ortho*-arylation in Ni (II) catalyzed reactions using triethoxy(aryl)silanes, KF and other additives.[9]

In continuation of our studies on metal-mediated cross-coupling reactions in ILs[10-18] and our earlier report on synthesis of amides via the Ritter chemistry in ILs,[19] we report here a facile method for the synthesis of diverse libraries of biaryl-amides from arylnitriles.

Expanding upon our earlier report,[19] libraries of arylnitriles were synthesized by the Ritter reaction, using tBuOH and AdaOH as carbocation precursors, in imidazolium as well as in tetramethylguanidium (TMG) ILs (Figure 1 and Table 1).

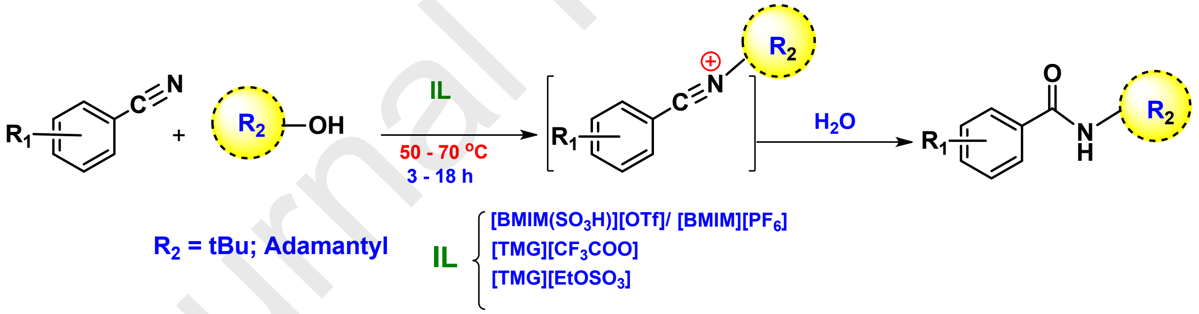


Figure 1. Synthesis of Ritter amides in ILs

Isolated yields of the amides when using fresh [BMIM(SO_3H)][OTf], [TMG][CF_3COO], and [TMG][$EtOSO_3$] were in 92% to 89% range (for R = tBu), and 90% to 84% range (for R = Ada) respectively. Slightly lower yields were obtained by using [BMIM(SO_3H)][OTf]/[BMIM][PF_6]. The use of this IL mixture was advantageous allowing lesser quantities of the Brønsted acidic IL to be used. The isolated yields gradually decreased when recycled/reused ILs were employed in subsequent runs (Table 1). The feasibility to employ recycled BMIM-ILs and TMG-ILs was gauged by repeating selected model reactions from Tables 1 and 2, and the data are shown in graphical format in Figures S1-S3.

With a library of the arylamides at hand, attention was then focused on the *ortho*-arylation step. Reactions were carried out in [BMIM(SO_3H)][OTf], [BMIM(SO_3H)][OTf]/[BMIM][PF_6], [TMG][CF_3COO], and [TMG][EtOSO_3] solvents, with aryl-iodides and aryl-bromides, and with Pd$(OAc)_2$ as catalyst and AgOAc as additive, under mild heating (Figure 2 and Table 2), with isolated yields in 67%-54% range when fresh ILs were used. Use of recycled/reused ILs resulted in gradual decrease in conversions.

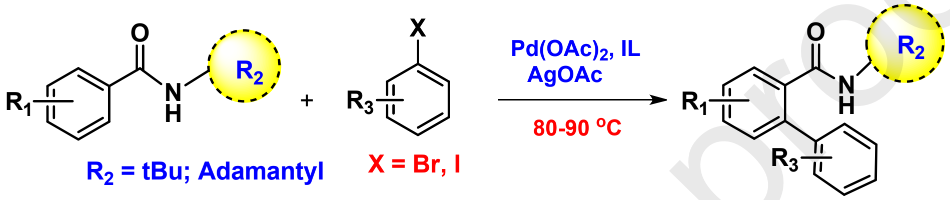


Figure 2. Synthesis of biarylamides by regioselective *ortho*-arylation

The next phase of the study focused on developing a sequential version (Figure 3). At the onset, a comparative study was undertaken to determine relative efficacy of various IL systems in a model reaction (Table 3), showing neat [BMIM(SO_3H)][OTf] to be most effective (run 1). Adding small volumes of [BMIM][PF_6] to [BMIM(SO_3H)][OTf] resulted in small yield reductions (runs 6-7), but use of excess [BMIM][PF_6] resulted in drastic drop in yields (runs 9-12). Based on this survey, [BMIM(SO_3H)][OTf]/[BMIM][PF_6] (2:1) was selected for the sequential reactions, allowing the recovered [BMIM][PF_6] from the Ritter step to be used in the arylation step. Table 4 summarizes these reactions, with isolated yields based on two steps in the 47% to 39% range.

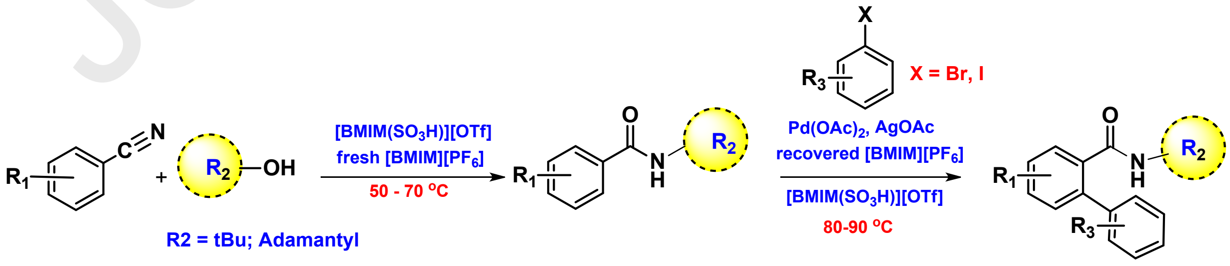
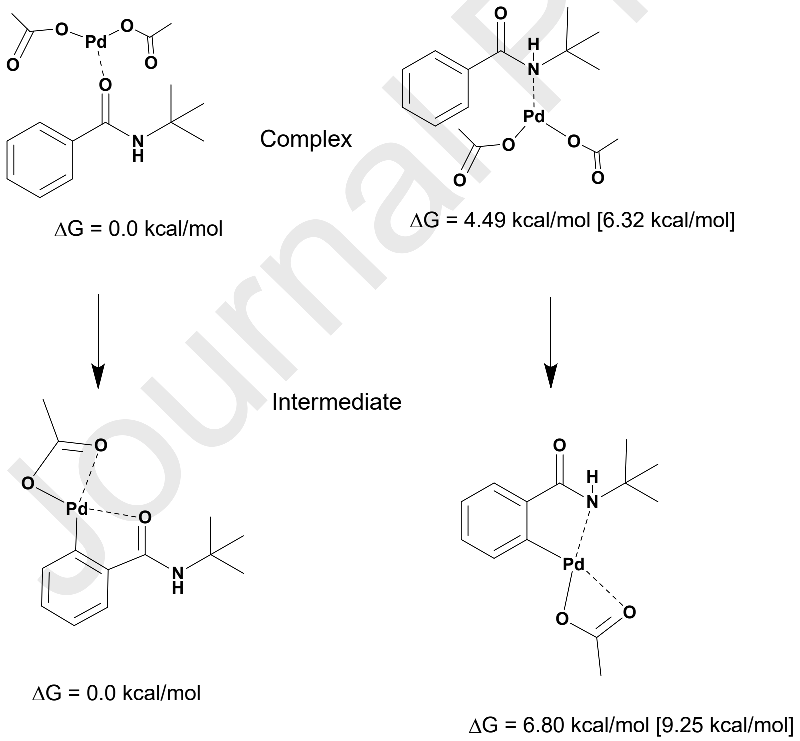


Figure 3. Sequential Ritter reaction/*ortho* arylation in ILs

To shed light on the relative preference for Pd coordination to carbonyl oxygen versus amide nitrogen, structures of the corresponding complexes and the intermediates were studied by density functional theory (DFT) computations using *N*-*t*-butyl-benzamide as model (Table 1, run 1). For both pairs, Pd coordination to carbonyl oxygen was favored (Figure 4). This preference increased when acetic acid was used as solvent by polarized continuum model (PCM) calculations. These findings are in line with those reported for aryl-acetamides (ref.5). The DFT-optimized structures are shown in Figure S4.

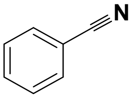
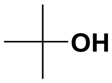
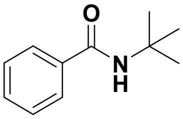
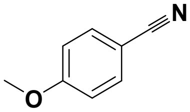
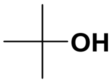
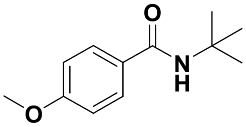
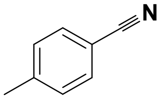
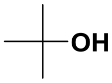
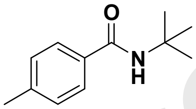
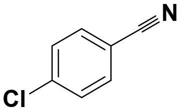
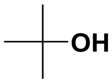
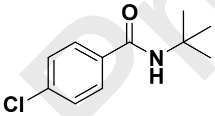
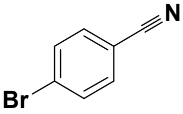
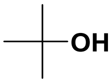
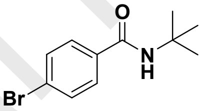
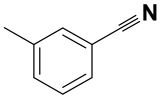
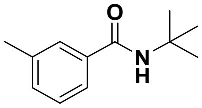
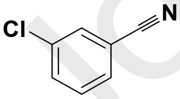
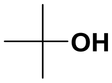
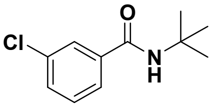
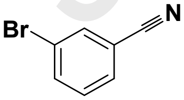
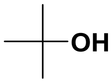
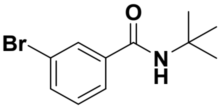
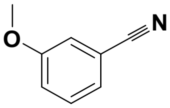
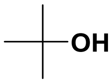
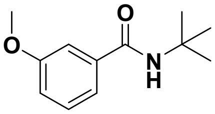
In summary, the *N*-*t*-butyl- and *N*-adamantyl-arylamides prepared from aryl-nitriles by the Ritter reaction in imidazolium and guanidinium ILs undergo Pd-catalyzed directed *ortho*-arylation to furnish libraries of biaryl-amides in good yields. A sequential version of this chemistry is feasible albeit in moderate yields. The recycling and reuse of the ILs employed in this study was also demonstrated. DFT computations using *N*-*t*-butyl-benzamide as model suggested that the complex formed by Pd coordination to the carbonyl oxygen and the resulting Pd-insertion intermediate are energetically favored over those arising from amide-nitrogen coordination.

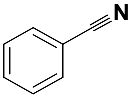
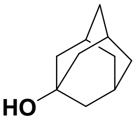
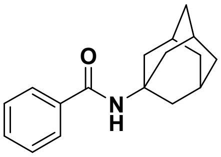
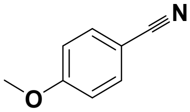
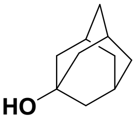
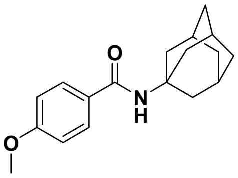
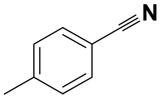
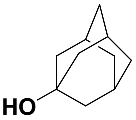
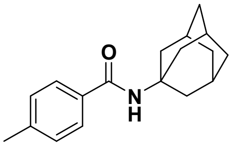
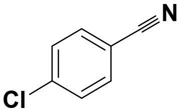
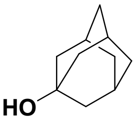
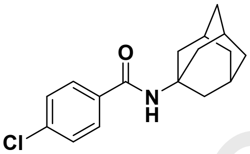
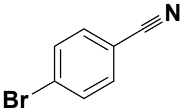
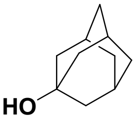
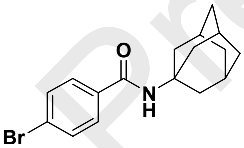
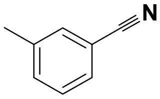
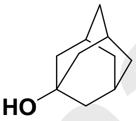
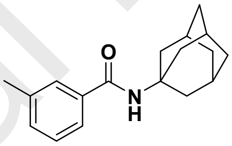
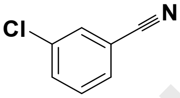
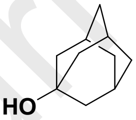
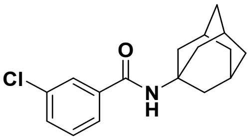
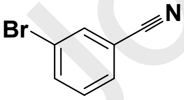
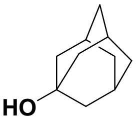
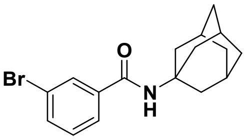
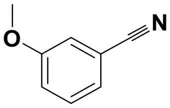
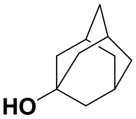
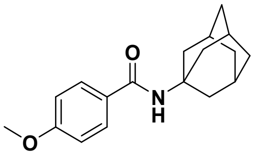


Relative free energies [PCM acetic acid]

Figure 4. Computed relative energiesfor the [Pd] coordination complexes and the resulting intermediates.

Table 1: Scope of the Imidazolium and Tetramethylguanidium ILs Catalyzed Ritter Reaction[a]

Entry	**Aryl-nitrile**	**ROH**	**Aryl-amide**	**IL**	**Time (h)**	**Yield[b] (%)**
1				[BMIM(SO_3H)][OTf]	9	90[c]
2				[TMG][CF_3COO]	13	92[c]
3				[TMG][EtOSO_3]	14	89[c]
4				[TMG][CF_3COO]	16	91[c]
5				[BMIM(SO_3H)][OTf]	9	88[d]
6*				[BMIM(SO_3H)][OTf]/ [BMIM][PF_6]	13	82[c]
7				[TMG][CF_3COO]	12	85[d]
8				[BMIM(SO_3H)][OTf]	13	81[e]
9				[TMG][EtOSO_3]	13	83[d]

10*				[BMIM(SO$_3$H)][OTf]/ [BMIM][PF$_6$]	15	84[c]
11				[BMIM(SO$_3$H)][OTf]	16	81[d]
12				[TMG][CF$_3$COO]	16	86[c]
13*				[BMIM(SO$_3$H)][OTf]/ [BMIM][PF$_6$]	18	76[d]
14				[BMIM(SO$_3$H)][OTf]	17	90[c]
15				[TMG][CF$_3$COO]	22	67[e]
16				[TMG][EtOSO$_3$]	20	70[e]
17				[BMIM(SO$_3$H)][OTf]	18	84[c]
18				[TMG][EtOSO$_3$]	22	86[c]

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[a]Reaction Condition: Nitrile (1 mmol), *tert*-Alcohol (2 mmol), IL (6-7 mL), Oil bath temperature (50-70 °C), [b]Isolated yield of pure product, [c]Yield employing fresh IL; [d]Yield using recycled IL (2nd cycle); [e]Yield using recycled IL (3rd cycle), *[BMIM(SO$_3$H)][OTf] (5-6 mL)/[BMIM][PF$_6$](2-3 mL).

Table 2: Regioselective Directed *Ortho*-Arylation of Benzamides[a]

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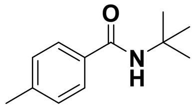
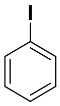
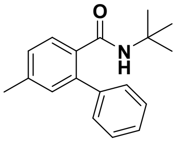
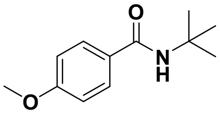
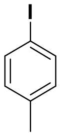
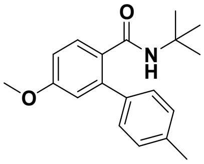
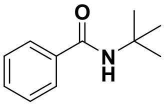
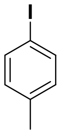
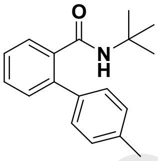
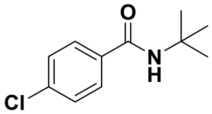
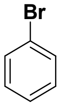
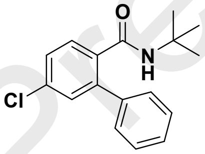
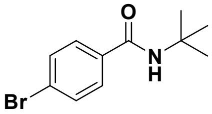
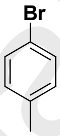
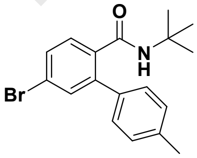
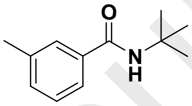
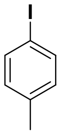
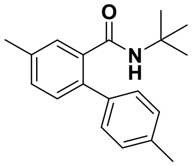
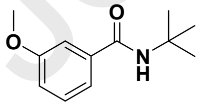
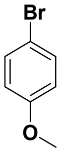
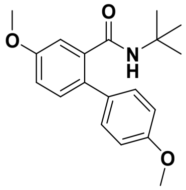
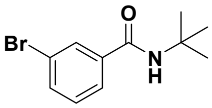
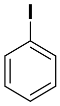
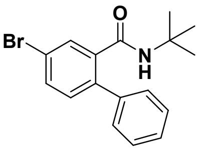
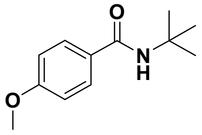
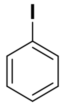
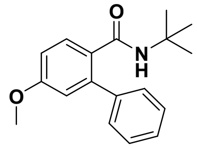
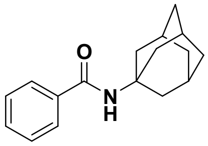
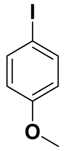
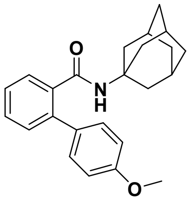
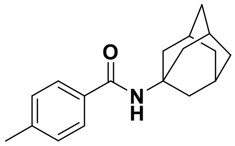
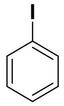
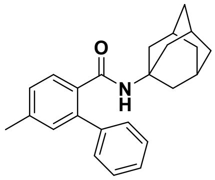
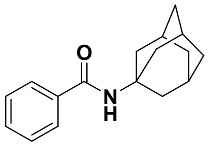
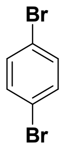
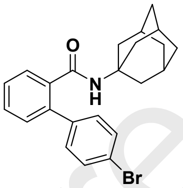
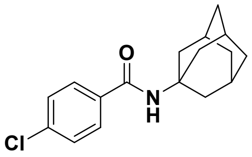
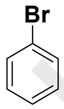
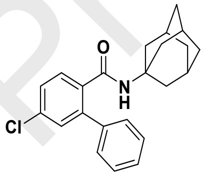
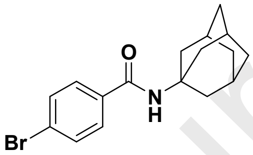
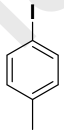
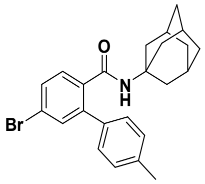
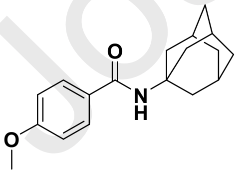
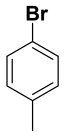
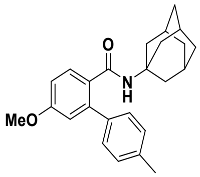
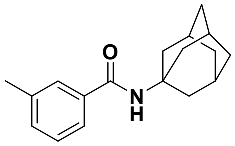
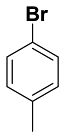
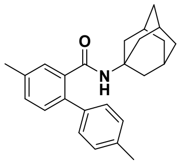
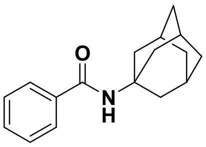
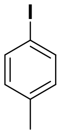
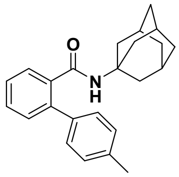
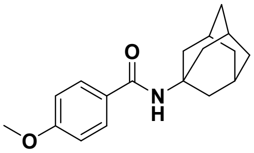
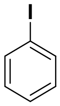
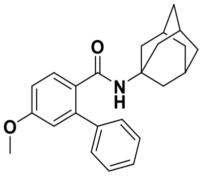
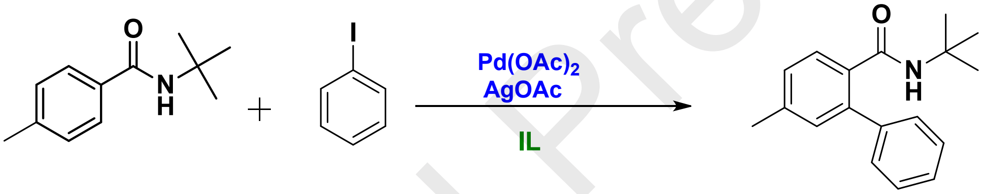
1				[BMIM(SO_3H)][OTf]	5	67[c]
2				[TMG][CF_3COO]	7	62[c]
3				[TMG][$EtOSO_3$]	10	55[d]
4				[TMG][CF_3COO]	19	56[d]
5*				[BMIM(SO_3H)][OTf]/ BMIM][PF_6]	21	49[d]
6				[TMG][$EtOSO_3$]	6	59[c]
7				[TMG][CF_3COO]	4	55[d]
8				[BMIM(SO_3H)][OTf]	19	65[c]

9				[TMG][CF$_3$COO]	8	62[c]
10*				[BMIM(SO$_3$H)][OTf]/ [BMIM][PF$_6$]	5	54[c]
11				[TMG][EtOSO$_3$]	8	60[c]
12				[TMG][EtOSO$_3$]	11	54[d]
13				[TMG][CF$_3$COO]	22	47[e]
14				[BMIM(SO$_3$H)][OTf]	20	56[d]
15				[BMIM(SO$_3$H)][OTf]	18	53[e]
16				[TMG][EtOSO$_3$]	9	46[e]

17				[TMG][CF_3COO]	10	49[e]
18*				[BMIM(SO_3H)][OTf] /[BMIM][PF_6]	8	44[e]

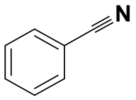
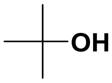
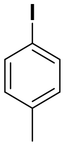
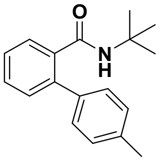
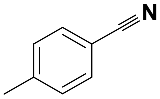
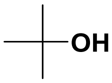
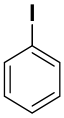
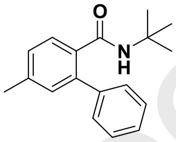
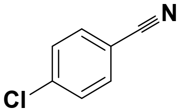
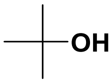
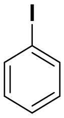
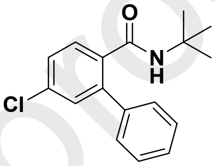
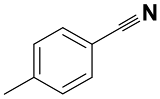
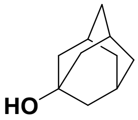
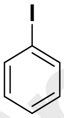
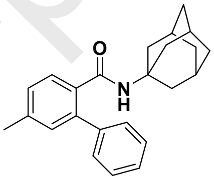
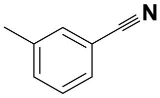
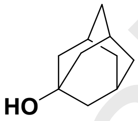
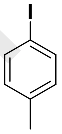
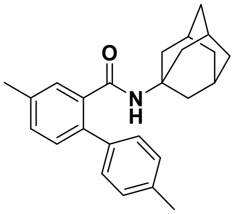
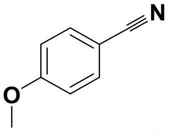
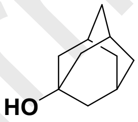
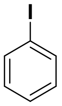
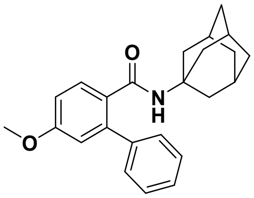
[a]Reaction Condition: Benzamide (1 mmol), Aryl Halide (1.2 mmol), IL (5-7 mL), AgOAc (2 equiv.), $Pd(OAc)_2$ (5 mol %), Oil bath temperature (80-90 °C),[b]Isolated yield of pure product, [c]Yield employing fresh IL; [d]Yield using recycled IL (2nd cycle);[e]Yield using recycled IL(3rd cycle).*[BMIM(SO_3H)][OTf] (5-6 mL) + [BMIM][PF_6](2-3 mL).

Table 3: Survey of ILs Efficacy for the *ortho*-arylation step



Entry	BrønstedAcidic IL(%)	[BMIM][PF_6](%)	Time (h)	Yield (%)
1	**[BMIM(SO_3H)][OTf] (100)**	**--**	**9**	**67**
2	[TMG][CF_3COO] (100)	--	13	52
3	[TMG][$EtOSO_3$] (100)	--	12	55
4	--	100	10	NR
5	--	100	19	NR
6	**[BMIM(SO_3H)][OTf] (80)**	**20**	**11**	**60**
7	**[BMIM(SO_3H)][OTf] (60)**	**40**	**11**	**60**
8	[BMIM(SO_3H)][OTf] (50)	50	11	52
9	[BMIM(SO_3H)][OTf] (30)	70	11	39
10	[BMIM(SO_3H)][OTf] (20)	80	11	31
11	[BMIM(SO_3H)][OTf] (10)	90	11	19
12	[BMIM(SO_3H)][OTf] (10)	90	15	19

Table 4: Sequential Ritter Reaction/*ortho*-Arylation[a]

Entry	**Ar-CN**	**ROH**	**Aryl-X**	**Biaryl-benzamide**	**Time (h)**	**Yield[b] (%)**
1					25	47
2					15	45
3					24	42
4					23	41
5					27	39
6					24	40

[a] Reaction conditions: Ar-CN (1 mmol),ROH (2 mmol),Ar-X (1.2 mmol), $Pd(OAc)_2$ (5 mol %), AgOAc (2 equiv.),Oil bath temperature (80-90°C), $[BMIM(SO_3H)][OTf]$ (5-6 mL), $[BMIM][PF_6]$ (2-3 mL), [b] Isolated yield of pure product by using $BMIM\text{-}PF_6$ recovered from the 1st step.

Supplemental Information

Experimental procedures, analytical and spectral data for the products, recycling feasibility graphs, and DFT optimized structures for this article are gathered in the supplemental information file.

Acknowledgements

K. K. L. thanks University of North Florida for the Outstanding Faculty Scholarship and Presidential Professorship awards, Faculty scholarship and UNF Foundation Board grants, and the Dean's Leadership Council award. The authors at Karnatak Science College thank the University Sophisticated Instrument Center, KUD for IR, GC, and GC-MS, They also thank NMR Research Center, Indian Institute of Science, Bangalore for ^{1}H NMR and ^{13}C NMR. Financial assistance through Project No. VGST-RGS/F-GRD-742/2017-18/2018- 19 by Vision Group on Science and Technology, Govt. of Karnataka, Bangalore is gratefully acknowledged.

References

[1] Yeung, C. S.; Dong, V. M. *Chem. Rev*. **2011**, *111*, 1215–1292

[2] Yamaguchi, J; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 8960– 9009

[3] Hussain, I; Singh, T. *Adv.Synth. Catal*. **2014**, *356*,1661–1696**.**

[4] Li, D.-D.; Yuan, T.-T.; Wang, G.-W. *J. Org. Chem*. **2012**, *77*, 3341-3347

[5] Jaiswal, Y.; Kumar, Y.; Thakur, R.; Pal, J.; Subramanian, R.; Kumar, A. *J. Org. Chem*. **2016**, *81*, 12499-12505

[6] Reddy, M. D.; Blanton, A. N.; Watkins, E. B. *J. Org. Chem***. 2017**, *82*, 5080-5095

[7] Hu, Y.-H.; Xu, Z.; Shao, L.-Y.; Ji, Y.-F. *SynLett.* **2018**, *29*, 1875-1880

[8] Shen, Y.; Lee, W.-C. C.; Gutierrez, D. A.; Li, J. J. *J. Org. Chem*. **2017**, *82*, 11620-11625

[9] Zhao, S.; Zhan, B.-B.; Zhang, W.-D.; Shi, B.-F. *Org. Lett*. **2016**, *18*, 4586-4589

[10] Malunavar S. S.; Sutar, S. M.; Prabhala, P.; Kalkhambkar, R. G.; Laali, K. K. *Tetrahedron Lett*. **2020**, *61*, 151987-

[11] Malunavar, S. S.; Sutar, S. M.; Savanur, H. M.; Kalkhambkar, R. G.; Laali, K. K. *Tetrahedron Lett*. **2020**, *61*, 151509-

[12] Sutar, S. M.; Savanur, H. M.; Malunavar, S. S.; Prabhala, P.; Kalkhambkar, R. G.; Laali, K. K. *Eur. J. Org. Chem*. **2019**, 6088-6093

[13] Prabhala, P.;Savanur, H. M.; Kalkhambkar, R. G.; Laali, K. K. *Eur. J. Org. Chem*. **2019**, 2061-2064

[14] Savanur, H. M.; Kalkhambkar, R. G.; Laali, K. K. *Eur. J. Org. Chem*. **2018**, 5285-5288

[15] Savanur, H. M.; Kalkhambkar, R. G.; Laali, K. K. *Applied Catalysis, A: General* 2017, *543*, 150-161

[16] Savanur, H. M.; Kalkhambkar, R. G.; Laali, K. K. *Tetrahedron Lett.* **2016**, *57*, 663-667

[17] Srinivas Reddy, A.; Laali, K. K. *Tetrahedron Lett*. **2015**, *56*, 4807-4810

[18] Kalkhambkar, R. G.; Laali, K. K. *Tetrahedron Lett*. **2011**, *52*, 1733-1737

[19] Kalkhambkar, R. G.; Waters, S. N.; Laali, K. K. *Tetrahedron Lett*. **2011**, *52*, 867-871

Declaration of Interest Statement

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights

Synthesis of diverse libraries of biaryl-amides from aryl-nitriles

IL-mediated Ritter reaction followed by Pd-catalyzed directed *ortho*-arylation

Use of [BMIM(SO_3H)][OTf] (neat or diluted in BMIM-PF_6) and tetramethyl guanidinium-ILs [TMG][X] (X = CF_3COO, $EtOSO_3$) as dual catalysts/solvents

Feasibility for sequential reaction