Tetrahedron Letters 51 (2010) 2685–2689

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Flexible palladium-catalysed amidation reactions for the synthesis of complex aryl amides

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ARTICLE INFO

Article history:
Received 2 February 2010
Revised 26 February 2010
Accepted 12 March 2010
Available online 17 March 2010

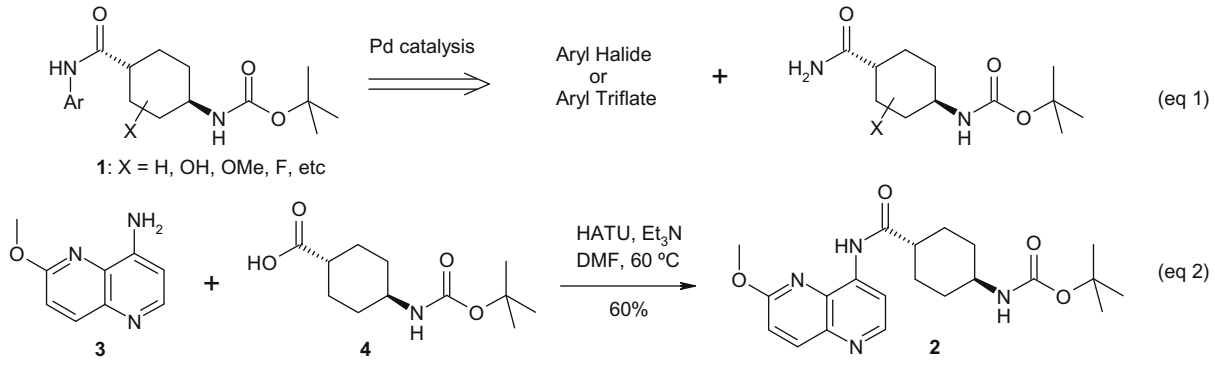
ABSTRACT

This Letter describes the synthesis of complex aryl amides using palladium-catalysed amidation reactions. Use of these conditions allowed for the coupling of a variety of aryl halides and triflates with a host of primary amides in high yields.

Since the early publications on palladium-catalysed amidation of aryl halides were reported (Buchwald, Shakespeare and Hartwig), there has been an increasing use of these transformations in academic and industrial groups.[1,2] In this Letter, we describe the use of this reaction for the formation of complex aryl-amides **1**, which we required for our medicinal chemistry programme (Scheme 1, Eq. 1). Amides of type **1** were used as intermediates towards compounds with anti-bacterial activity against a range of clinically relevant organisms.[3] For our initial work towards target **2**, we used a classical amide coupling strategy between amine **3** and carboxylic acid **4** (Scheme 1, Eq. 2). This coupling worked well although it required more forcing conditions than typical amide coupling reactions. However, this coupling depends on the availability of amine **3**. These amines generally derive from the corresponding aryl halide or triflate (Scheme 2) and all typically required a linear multi-step synthesis.[4] Of particular note is the formation of **3** *via* the reaction of a precursor triflate with propylamine hydrochloride under forcing conditions.[5]

We therefore decided to focus on an alternative disconnection which would allow for the use of more synthetically accessible aryl halides and/or triflates.

Another major issue in driving this change of approach was that efficient though the HATU coupling was, switching to α-hydroxy acids led to a complex mixture of products.



Scheme 1. Initial synthesis of aryl amides and the proposed retrosynthetic disconnection for more complex amides.

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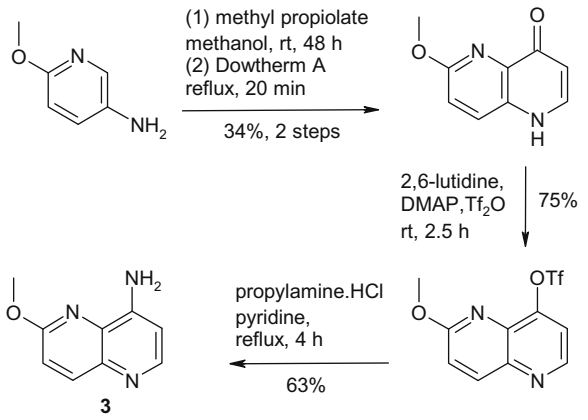
doi:10.1016/j.tetlet.2010.03.051



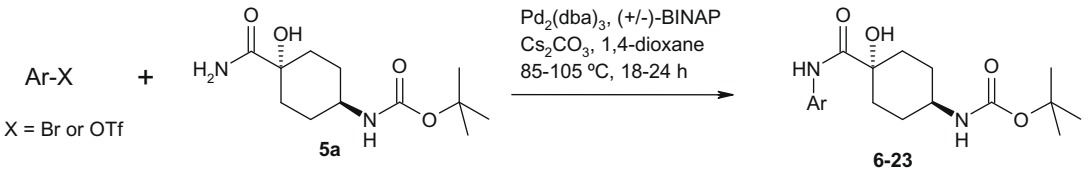
Scheme 2. A typical synthesis of a triflate and an amino-naphthyridine.

We believed that this additional functionality was hindering an already slow amide-coupling process allowing for numerous competitive side-reactions to take place instead. We therefore required a solution to our problem which would tolerate this functionality and provide more efficient access to our complex aryl amide targets.

After analysing the literature and following in-house experience we investigated coupling conditions using a palladium-BINAP complex formed in situ and caesium carbonate as a base. To our delight the coupling reaction proceeded cleanly and in high yield. These reactions were performed on a variety of scale from milligram to multigram, thus outlining their robust nature. For our first product **6**, the yield was essentially quantitative and standard column chromatography removed all relevant impurities.

To our knowledge, this was the first example of a palladium-catalysed coupling of an α-hydroxy amide in this manner.[6] Exam-

Table 1
Amidation of a variety of aryl halides and triflates using amide **5a**[a]



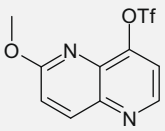
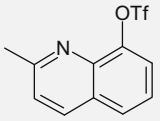
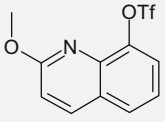
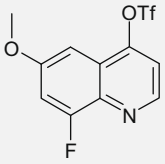
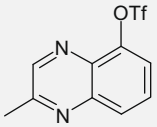
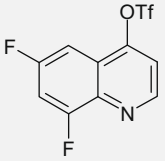
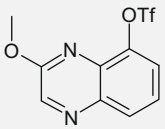
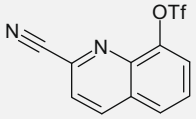
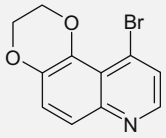
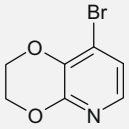
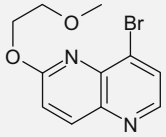
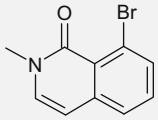
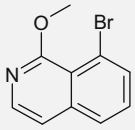
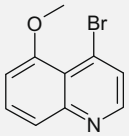
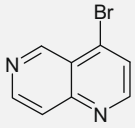
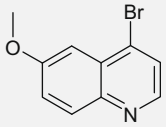
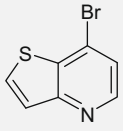
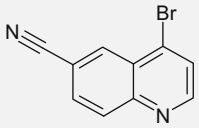
Entry	Ar-X	Product[b] (yield %)
1		**6** (>95)
2[c]		**7** (79)
3		**8** (65)
4		**9** (53)
5		**10** (72)
6		**11** (40)
7[c]		**12** (72)

Table 1 (*continued*)

Entry	Ar-X	Product[b] (yield %)
8		**13** (90)
9		**14** (25)
10		**15** (13)
11		**16** (>95)
12		**17** (92)
13		**18** (34)
14		**19** (18)
15		**20** (74)
16		**21** (94)
17		**22** (84)
18		**23** (94)

[a] Reaction conditions: aryl halide or triflate (1 equiv), amide (1.05 equiv), $Pd_2(dba)_3$ (3 mol %), (±)-BINAP (6 mol %), Cs_2CO_3 (2.5 equiv), 1,4-dioxane, 85–105 °C, 18–24 h.
[b] Isolated yield.
[c] Xantphos was used instead of (±)-BINAP.

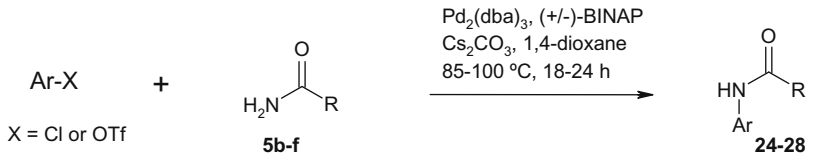
ination of the reaction mixtures showed no evidence of competing reactions such as arylation of the carbamate or hydroxy functionalities. We reasoned that the primary amide should be the most reactive functional group under typical palladium-catalysed amidation conditions, mostly due to steric reasons.

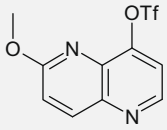
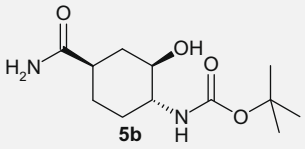
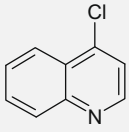
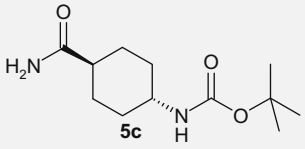
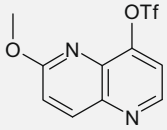
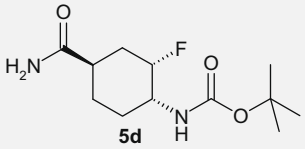
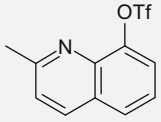
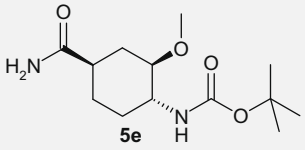
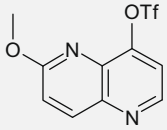
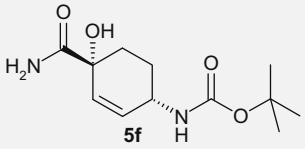
We decided to use amide **5a** as our standard amide coupling partner for medicinal chemistry reasons.[7]

These coupling conditions proved to be general for a host of diverse aryl halides and triflates (Table 1). This was extremely beneficial due to the wide availability of triflates (or their precursor phenols) and aryl halides.

The synthesis of aryl triflates and aryl halides has been described already and the preparation of primary amides of type **5a–f** will be fully described as the subject of a future Letter.[4,6]

Table 2
Amidation of a variety of aryl halides and triflates using amides **5b–f**[a]



Entry	Ar-X	Amide	Product[b] (yield %)
1			**24** (82)
2			**25** (60)
3			**26** (97)
4[c]			**27** (72)
5[d]			**28** (53)

[a] Reaction conditions: aryl halide or triflate (1 equiv), amide (1.05 equiv), $Pd_2(dba)_3$ (3 mol %), (±)-BINAP (6 mol %), Cs_2CO_3 (2.5 equiv), 1,4-dioxane, 85–100 °C, 18–24 h.
[b] Isolated yield.
[c] Xantphos was used instead of (±)-BINAP.
[d] Reaction temperature was kept at 60 °C.

The synthesis of these amides generally presented no more of an obstacle than that of the corresponding carboxylic acids.

As entries 1–18 show, this strategy successfully afforded α-hydroxy amides **6–23**.[8,9] In contrast to the HATU amide coupling conditions, a clean reaction to give the product was observed. Entries for aryl triflates (entries 1–8) show a similar range of yields to the aryl bromides (entries 9–18). In some cases a minor by-product was observed when using electron-withdrawing aryl triflates due to some triflate hydrolysis. Entries 2 and 7 also show that Xantphos was an equally efficient ligand for this process. As well as examining a range of substituted aryl halides and triflates, we also examined the effect of altering the primary amide.

We therefore looked at a series of primary amide variations, taking in fluoro, methoxy, and various hydroxy functionalities as dictated by our medicinal chemistry needs at the time (Table 2).

To our delight, the entries in Table 2 all showed reasonable yields and good purities. The reaction is tolerant of various functionalities on the amide synthon including hydroxy, methoxy, fluoro or alkene. No competing arylation of the carbamate, hydroxy group or alkene (via Heck reaction) was observed. A temperature of 60 °C was required in entry 5 in order to reduce the formation of uncharacterized impurities. As entry 2 shows, an aryl chloride was also suitable for this reaction.

In conclusion, we have described a very general method for the synthesis of α-hydroxy aryl amides and related aryl amides using a palladium-catalysed process, which may find future synthetic use.

Acknowledgements

Acknowledgment is given to Steve Richards for NMR support, Bill Leavens for mass spectroscopy support and all the chemists who have been involved in this work.

References and notes

1. For early intramolecular examples, see: (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *21*, 7525; (b) Yang, B. H.; Buchwald, S. L. *Org. Lett.* **1999**, *1*, 35; (c) He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc.* **1988**, *120*, 6417; For early intermolecular examples, see: (d) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035; (e) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101; (f) Hartwig, J. F.; Kawatsura, M.; Huack, S. L.; Shaughnessy, K. H.; Alcazar-Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575.
2. For recent related Letters, see (a) Fors, B. P.; Dooleweerdt, K.; Zeng, Q.; Buchwald, S. L. *Tetrahedron* **2009**, *65*, 6576; (b) Wallace, D. J.; Campos, K. R.; Shultz, C. S.; Klapars, A.; Zewge, D.; Crump, B. R.; Phenix, B. D.; McWilliams, J.; Krska, S.; Sun, Y.; Chen, C.; Spinder, F. *Org. Process Res. Dev.* **2009**, *13*, 84; (c) Hunag, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609; (d) Dallas, A. S.; Gothelf, K. V. *J. Org. Chem.* **2005**, *70*, 3321; (e) Manley, P. J.; Bilodeau, M. T. *Org. Lett.* **2004**, *6*, 2433.

3. (a) For the syntheses of these compounds and experimental details for the reactions in this Letter see: Brooks, G.; Davies, D. T.; Jones, G. E.; Markwell, R. E.; Pearson, N. D.; WO2003087098; *Chem. Abstr.* **2003**, *139*, 337959; (b) Axten, J. M.; Daines, R. A.; Davies, D. T.; Gallagher, T. F.; Jones, G. E.; Miller, W. H.; Pearson, N. D.; Pendrak, I.; WO2004002992; *Chem. Abstr.* **2004**, *140*, 94053; (c) Davies, D. T.; Elder, J. S.; Forrest, A. K.; Jarvest, R. L.; Pearson, N. D.; Sheppard, R. J.; WO20040014361; *Chem. Abstr.* **2004**, *140*, 199210
4. Aryl bromides were generally made from precursor quinolinones and naphthyridinones using PBr_3 in DMF.
5. For an example of this reaction, see: Radinov, R.; Khaimova, M.; Simova, D. *Synthesis* **1986**, *11*, 886.
6. This work originally appeared in the patents listed in references **3a**–**c**. Related copper-catalysed amidations have also been reported but have tended to require aryl iodides as the coupling partner and failed to give any of the desired product for our systems. For examples, see: (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421; (b) Franz, A. K.; Dreyfuss, P. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 1020; (c) Clive, D. L. J.; Peng, J.; Fletcher, S. P.; Ziffle, V. E.; Wingert, D. *J. Org. Chem.* **2008**, *73*, 2330; (d) Some palladium-catalysed couplings were also reported in the patent literature after our initial patent publications, see: Herold, P.; Mah, R.; Stutz, S.; Stojanovic, A.; Tschinke, V.; Jotterand, N.; WO2005061457; *Chem. Abstr.* **2005**, *143*, 115449; (e) Zhang, X. P; Chen, Y.; Gao, G.; US2005124596; *Chem. Abstr.* **2003**, *143*, 37557
7. A Letter detailing the multiple routes and methods to access amides of type **5**, is in preparation.
8. *General procedure for the palladium-catalysed amidation reaction*, (Table 1, entry 1). A mixture of amide (**5a**) (0.51 g) (1.05 equiv), caesium carbonate (0.818 g) (2.5 equiv), tris(dibenzylideneacetone)dipalladium(0) (38 mg) (3%) and *rac*-2,2′-[bis(diphenylphosphino)]-1,1′-binaphthyl (77.4 mg) (6%) in dry 1,4-dioxane (20 ml) under argon was sonicated for 10 min. 1,1,1-Trifluoro-methanesulfonic acid 6-methoxy-[1,5]-naphthyridin-4-yl ester (0.64 g) (1 equiv) was added, and the mixture was stirred at 85 °C for 18 h under argon. The mixture was cooled to room temperature, filtered and the filtrate was evaporated and chromatographed on silica gel, eluting with $CHCl_3$, then (1–2%) MeOH–CH_2Cl_2 to afford **6** as a white solid (0.85 g) (>95%); mp 165–167 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.39 (s, 9H), 1.49–1.60 (m, 2H), 1.63–1.74 (m, 4H), 1.84–1.91 (m, 2H), 3.24–3.30 (m, 1H), 4.10 (s, 3H), 6.10 (s, 1H), 6.83 (br d, *J* = 9 Hz, 1H), 7.33 (d, *J* = 9.5 Hz, 1H), 8.28 (d, *J* = 9.5 Hz, 1H), 8.44 (d, *J* = 6 Hz, 1H), 8.69 (d, *J* = 6 Hz, 1H), 11.10 (s, 1H).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 27.2, 28.3, 32.9, 48.5, 53.7, 73.8, 77.4, 109.6, 116.8, 131.5, 138.8, 140.7, 140.8, 149.0, 154.8, 161.0, 176.9. ESI-HRMS: *m/z* calcd for $C_{21}H_{29}N_4O_5$: 417.2138; found 417.2139 $[M+H]^+$.
9. *Selected analytical data*:
Compound **9**: White solid; mp 179–181 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.39 (s, 9H), 1.54–1.63 (m, 2H), 1.64–1.71 (m, 2H), 1.74–1.80 (m, 2H), 1.82–1.91 (m, 2H), 3.23–3.30 (m, 1H), 3.95 (s, 3H), 5.96 (s, 1H), 6.82 (br d, *J* = 9 Hz, 1H), 7.09 (d, *J* = 1.5 Hz, 1H), 7.40 (dd, *J* = 10.5, 1.5 Hz, 1H), 8.20 (d, *J* = 6 Hz, 1H), 8.70 (d, *J* = 6 Hz, 1H), 10.03 (s, 1H).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 27.3, 28.2, 32.8, 48.5, 55.9, 73.7, 77.3, 96.9, 106.1, 113.5, 123.1, 134.7, 139.8, 148.3, 154.8, 156.8, 158.2, 176.5. ESI-HRMS: *m/z* calcd for $C_{22}H_{29}FN_3O_5$: 434.2091; found 434.2087 $[M + H]^+$.
Compound **21**: White solid; mp 161–163 °C; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 1.39 (s, 9H), 1.55–1.64 (m, 2H), 1.65–1.71 (m, 2H), 1.75–1.80 (m, 2H), 1.84–1.90 (m, 2H), 3.24–3.30 (m, 1H), 3.94 (s, 3H), 5.96 (s, 1H), 6.82 (br d, *J* = 9.5 Hz, 1H), 7.33 (d, *J* = 3.5 Hz, 1H), 7.45 (dd, *J* = 9.0, 3.5 Hz, 1H), 7.93–7.96 (m, 2H), 8.66 (d, *J* = 6.5 Hz, 1H), 10.05 (s, 1H).
^{13}C NMR (151 MHz, DMSO-d_6): δ = 27.5, 28.4, 33.0, 48.6, 55.7, 73.9, 77.5, 100.2, 112.6, 121.6, 122.1, 131.3, 139.6, 144.6, 148.3, 155.0, 157.3, 176.6. ESI-HRMS: *m/z* calcd for $C_{22}H_{30}N_3O_5$: 416.2185; found 416.2191 $[M+H]^+$.